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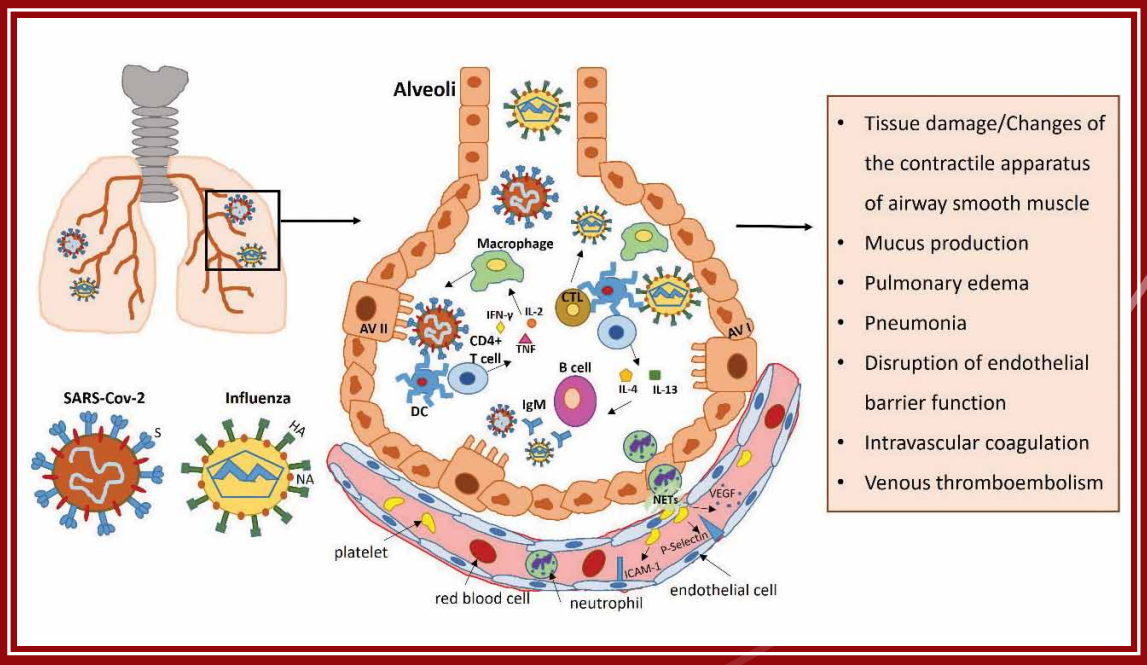

Host immunity of SARS-Cov-2 co-infection with influenza viruses and pathophysiology

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CONTENTS

Dear colleagues,

In the current issue, the editorial by Tourkochristou et al. discusses the immunopathology of SARS-Cov-2 co-infection with influenza virus, providing details on the host background immune responses related to these viruses. The editorial by Tsounis et al. provides an update on the recent reports of severe acute hepatitis of unknown aetiology in previously healthy children across multiple countries. The editorial by Pastras et al. summarizes the clinical characteristics of monkeypox outbreak and discusses the main therapeutic options in this setting. The editorial by Kyrousi et al. describes the role of brain organoids as a model system for studying human-specific mechanisms of brain development and disease.

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Lastly, this issue includes a case report by Topis et al. which depicts an unusual case of complicated pyosalpinx and peritonitis after a hysterosalpingography examination and the treatment which was employed.

Yours sincerely

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The immunopathology of SARS-Cov-2 co-infection with influenza virus

Evanthia Tourkochristou[1], Markos Marangos[2]

INTRODUCTION

The emergence of Covid-19 in the influenza season has posed a new challenge to the healthcare system, regarding the clinical impact of a potent co-infection on disease severity and health-service demand. Covid-19 and seasonal influenza can be detrimental for the same high-risk groups, including persons of older age, persons with chronic co-morbidities and residents of long-term care facilities [1,2]. Pulmonary immunopathology is the leading cause of mortality in both SARS-Cov-2 and influenza infections, as the host's response to viral invasion could be deleterious and contribute to severe disease phenotypes. There is experimental evidence, reporting that pre-infection with influenza virus significantly promotes SARS-CoV-2 virus entry and infectivity in cells and animals [3]. However, investigation of the impact of SARS-Cov-2 and influenza co-existence on clinical outcomes, immunopathology and tissue repair following viral lower respiratory tract infection is still ongoing. The understanding of the mechanisms underlying the pathologic interaction between SARS-Cov-2 and influenza virus is of high clinical significance to inform treatment and control strategies for the effective management of all sets of patients.

An overview of SARS-Cov-2 and influenza viruses

Influenza viruses are enveloped segmented, single-stranded, negative sense RNA viruses of the Orthomyxoviridae family, which includes four genera, influenza virus A–D (IAV, IBV, ICV and IDV) [4,5]. Coronaviruses are enveloped single-stranded non-segmented RNA viruses of the Coronaviridae family, which are classified into four genera (alphacoronaviruses, betacoronaviruses, gammacoronaviruses and deltacoronaviruses) [6]. Respiratory epithelial cells (types I and II alveolar epithelial cells) are the primary targets of both influenza and SARS-Cov-2 viruses, which use specific surface receptors to enter host cells. Considering that these two viruses can infect the same types of respiratory cells, SARS-Cov-2 co-infection with influenza viruses could have a negative impact on disease course and clinical outcomes. The haemagglutinin (HA) and neuraminidase (NA) glycoproteins of influenza viruses bind to epithelial cell surface sialosaccharides (SA) and the spike protein of SARS-Cov-2 uses the transmembrane angiotensin converting enzyme 2 (ACE2) receptor for epithelial cell entry. HA and spike protein are processed by specific host proteases to initiate virus-host cell fusion. Other types of epithelial cells, including the intestinal epithelial cells, endothelial cells and renal parenchymal cells are also infected by SARS-Cov-2. Thus, SARS-Cov-2 shows extensive extrapulmonary complications compared to influenza viruses, which affect mainly the upper and lower respiratory tract [7]. Years of prior influenza exposure and national implementation of influenza vaccination policies that contribute to a significant level of population immunity seem to be responsible for a lower influenza R0 (1.28) compared to SARS-Cov-2 R0 (3.6-6.1), as pre-existing immunity to SARS-Cov-2 is lacking [8,9]. Elucidation of viral dynamics and immune-encountering through time, could provide useful guidance to the investigation of the disease course and effective management of SARS-Cov-2 co-infection with influenza viruses.

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Host background immunity of SARS-Cov-2 co-infection with influenza viruses and pathophysiology

Common immune responses initiate after invasion of both SARS-Cov-2 and influenza viruses into the host cells. Respiratory epithelial cells, after encountering the SARS-Cov-2 and influenza viruses produce antiviral and chemotactic molecules, which recruit innate effector cells, including natural killer cells, monocytes, dendritic cells (DCs) and neutrophils. Pathogen recognition receptors (PRRs) present on innate immune cells, recognize the viral particles by binding to viral conserved components called pathogen associated molecular patterns (PAMPs), initiating a signaling cascade that results in the activation of transcription factors (NF-Kβ, IRFs) and induction of gene expression of pro-inflammatory cytokines and anti-viral peptides. Production of pro-inflammatory cytokines by host cells is associated with infection with IAV or SARS-CoV-2 [10]. Elevated inflammatory cytokines may be involved in the induction of endothelial leak and contribute to pathogenesis. A systemic inflammatory response with the excessive activation of immune cells and proinflammatory mediators such as IFN-α, IL-1β, and IL-6, that lead to lung injury and respiratory failure characterizes the COVID-19- associated severe cases [11]. High levels of cytokines have been observed in the lung of SARS-Cov-2 and influenza infected patients and side effects could be attributed to abnormal levels of specific cytokines [12]. SARS-Cov-2 and influenza virus infection of the alveolar capillary endothelium could contribute to pulmonary edema and venous thromboembolism, probably through cytokine-induced endothelial activation or cell death. Activated neutrophils in the respiratory epithelium release neutrophil extracellular traps (NETs). NETs have been associated with tissue damage, hypercoagulability, and thrombosis, as they directly cause endothelial and epithelial cell death, promote thrombosis by acting as a scaffold and activating platelets, recruit pro-coagulation factors, bind von Willebrand factor (vWF) and fibrin to recruit platelets, and enhance production of inflammatory cytokines by immune cells [13]. Enhanced adhesion and activation of platelets during both influenza and SARS-CoV-2 infection could amplify the inflammatory response, resulting in further endothelial activation, vascular leak and disseminated intravascular coagulation. Activated platelets can release inflammatory cytokines and chemokines, which induce endothelial expression of cell adhesion molecules such as ICAM-1, VCAM-1, E-Selectin, and P-Selectin and pro-inflammatory cytokines and chemokines such as IL-6, IL-8 and MCP-1 (CCL2). Many inflammatory mediators such as vascular endothelial growth factor (VEGF) can induce the phosphorylation and endocytosis of major protein of endothelial adherents junctions, thereby disrupting endothelial barrier function [13] (Figure 1).

Initiation of adaptive immune responses is crucial for an effective coordinated immune response against the virus and achievement of immune homeostasis. Adaptive immunity begins when naïve and memory T lymphocytes recognize SARS-Cov-2 and influenza viral antigens presented by major histocompatibility complex (MHC) proteins on the surface of DCs, migrated from lungs to T-cell zone of the draining lymph nodes. In particular, T helper cells (CD4+ T cells, Th) are activated through binding to viral peptides on MHC-II molecules and differentiate into Th subpopulations with separate functions. Th1 cells express antiviral cytokines, such as IFN-γ, TNF, and IL-2 and activate alveolar macrophages to phagocyte viral particles, whereas Th2 cells produce IL-4 and IL-13 to promote B cell responses and antibody production. T regulatory cells play a major role in modulating immune responses, establishing the immune homeostasis. CD8+ T cells are also activated by DCs and differentiate into cytotoxic T lymphocytes (CTLs), which produce cytokines and effector molecules to restrict viral replication and kill virus-infected cells [10,14]. In severe Covid-19 disease secretion of IL-4, IL-5, IL-13, and IL-10 cytokines by Th2 cells delays clearance of the virus via inhibition of anti-viral responses. In mild Covid-19 Th1 responses and activated macrophages, CTLs and B cells play major role in viral clearance. TNF-α and IFN-γ induce antiviral responses directly through their receptors on the epithelial surfaces of the lung [12]. In influenza infection, tissue damage, pathogen removal and the inflammatory response processing the acute lung injury infection are under the effect of T helper polarization. TNF-α and IFN-γ cytokines induce antiviral responses in the lung and IL-1 increases IgM antibody responses. Th2 cells by secreting IL-4, IL-5 and IL-13 suppress antiviral immune responses, activate natural killer T cells, eosinophil, macrophage, and mast cells and contribute to elevating eosinophil infiltration in the lungs, resulting in changes of the contractile apparatus of airway smooth muscle, macrophage polarization, following mucus production, and elevating aryl hydrocarbon receptor (AHR) and goblet cell metaplasia [12] (Figure 1).

Although SARS-Cov-2 and influenza viruses induce common immune responses, understanding of their

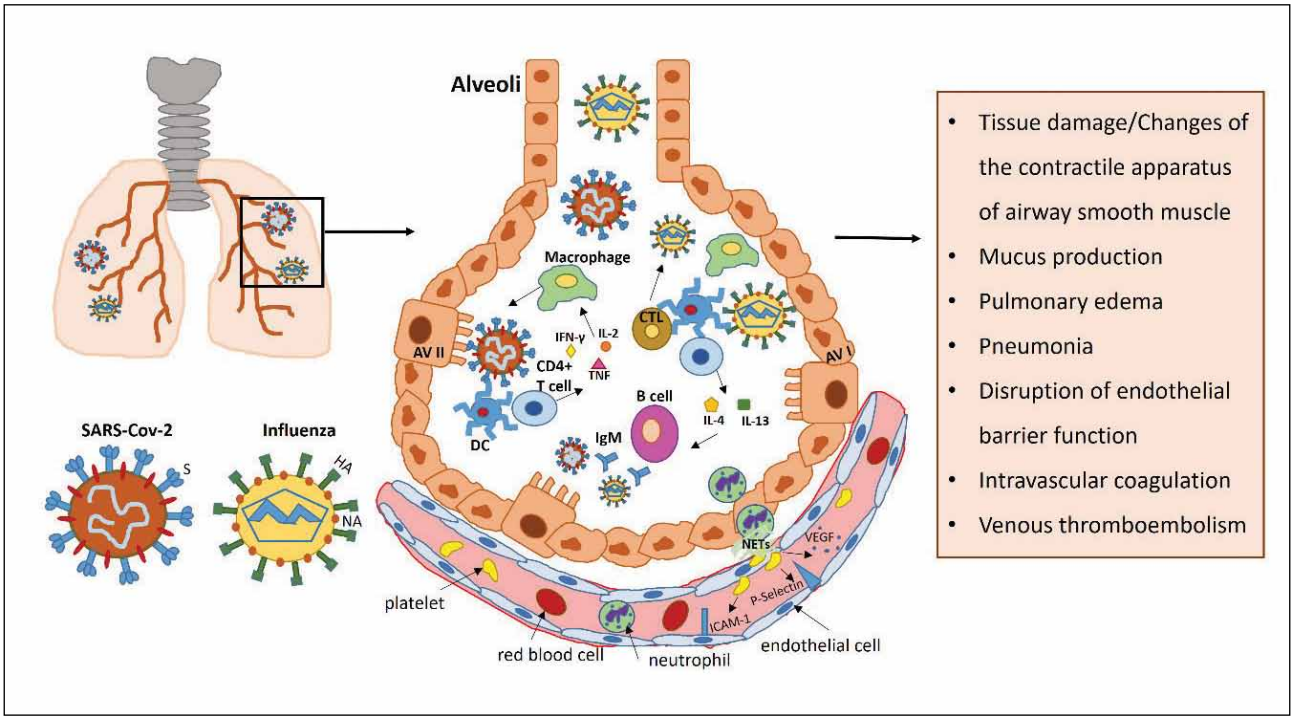

Figure 1. Host immunity of SARS-Cov-2 co-infection with influenza viruses and pathophysiology. Haemagglutinin (HA) and neuraminidase (NA) glycoproteins of influenza viruses bind to epithelial cell surface sialosaccharides (SA) and spike (S) protein of SARS-Cov-2 relies on transmembrane angiotensin converting enzyme 2 (ACE2) receptor for epithelial cell entry. Respiratory epithelial cells (alveolar type I and alveolar type II cells), after encountering with the SARS-Cov-2 and influenza viruses produce antiviral and chemotactic molecules, which recruit innate effector cells, including natural killer cells, monocytes, dendritic cells (DCs) and neutrophils. Cytokine-induced endothelial activation or cell death could contribute to pulmonary edema and venous thromboembolism. Activated neutrophils in the respiratory epithelium release neutrophil extracellular traps (NETs), leading probably to tissue damage, hypercoagulability, and thrombosis, as they directly cause endothelial and epithelial cell death, promote thrombosis by acting as a scaffold and activating platelets and recruit pro-coagulation factors. Activated platelets can release inflammatory cytokines and chemokines, which induce endothelial expression of cell adhesion molecules such as ICAM-1, P-Selectin. Many inflammatory mediators such as vascular endothelial growth factor (VEGF) can disrupt endothelial barrier function. T helper cells (CD4+ T cells, Th) are activated by DCs, express antiviral cytokines (IFN-γ, TNF, IL-2) that activate alveolar macrophages to phagocyte viral particles and CD4+ T cells also produce IL-4 and IL-13 to promote B cell responses and antibody production. Cytotoxic T lymphocytes (CTLs) produce cytokines and effector molecules to restrict viral replication and kill virus-infected cells. In mild Covid-19 Th1 responses and activated macrophages, CTLs and B cells play major role in viral clearance. In influenza infection, TNF-α and IFN-γ cytokines induce antiviral responses in the lung and IL-1 increases IgM antibody responses. Th2 cells by secreting IL4, IL-5 and IL-13 suppress antiviral immune responses, contribute to elevating eosinophil infiltration in the lungs, resulting in changes of the contractile apparatus of airway smooth muscle and mucus production.

correlation is still ongoing. A possible impact of influenza specific T cell immunity on immune responses to SARS-CoV-2 has been suggested. Influenza HIN1 antigen specific $CD4^+$ T cells have been found in 92% COVID+ and 76% COVID- subjects and exhibited a strong direct correlation with SARS-CoV-2 specific $CD4^+$ T cells [15]. A potent interaction between the immune components of both infections should be further investigated to provide useful information regarding the dynamics of SARS-Cov-2 and influenza virus co-existence. In literature there are two sides of the coin, about how aggravating a SARS-Cov-2 co-infection with influenza virus could be for disease course. SARS-Cov-2 co-infection with IAV has been associated with a prolonged primary virus infection period, increased immune cell infiltration and inflammatory cytokine levels in bronchoalveolar lavage fluid which led to severe pneumonia and lung damage compared to SARS-Cov-2 and IAV monoinfections. Moreover, severe lymphopenia in peripheral blood, resulting in reduced total IgG, neutralizing antibody titers, and CD4+ T cell responses against each virus has been linked to co-infection [16]. Similar patterns of symptoms and clinical outcomes have been observed among patients with SARS-CoV-2 infection only and

patients with SARS-CoV-2/IFV-A co-infection in a retrospective cohort study. An increased expression of serum cytokines (interleukin-2R [IL-2R], IL-6, IL-8, and tumor necrosis factor-α) and cardiac troponin I, and higher incidence of lymphadenopathy were observed in patients with SARS-CoV-2 infection only. Male patients and patients aged less than 60 years in the SARS-CoV-2 infection group also had significantly higher computed tomography scores than patients in the co-infection group, indicating that co-infection with IFV-A had no effect on disease outcome but alleviated inflammation in certain populations of COVID-19 patients [17]. Further observational studies with systematic analysis of clinical outcomes in co-infected patients compared with those mono-infected are needed to elucidate whether SARS-Cov-2 and influenza co-existence contributes to increased disease severity, regarding mortality, incidence of shock, being admitted to an intensive care unit (ICU) or requiring ventilatory support. Knowledge of pathogenic interactions between SARS-CoV-2 and influenza virus is limited so far. A better understanding of the host immune responses and immunopathological features that distinguish the two infections will provide useful guidance for the design of effective therapeutic approaches and vaccine development.

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REFERENCES

1. Petrilli CM, Jones SA, Yang J, Rajagopalan H, O'Donnell L, Chernyak Y, et al. Factors associated with hospital admission and critical illness among 5279 people with coronavirus disease 2019 in New York City: prospective cohort study. BMJ. 2020; 369:m1966..
2. Danis K, Fonteneau L, Georges S, Daniau C, Bernard-Stoecklin S, Domegan L, et al. High impact of COVID-19 in long-term care facilities, suggestion for monitoring in the EU/EEA, May 2020. Euro Surveill. 2020;25(22): 2000956.
3. Bai L, Zhao Y, Dong J, Liang S, Guo M, Liu X, et al. Coinfection with influenza A virus enhances SARS-CoV-2 infectivity. Cell Res. 2021;31(4):395-403.
4. Hause BM, Collin EA, Liu R, Huang B, Sheng Z, Lu W, et al. Characterization of a novel influenza virus in cattle and Swine: proposal for a new genus in the Orthomyxoviridae family. mBio. 2014;5(2):00031-14.
5. WHO. Influenza (Seasonal). https://wwwwhoint/news-room/fact-sheets/detail/influenza-(seasonal) 2018.
6. Payne S. Family Coronaviridae. Viruses. Elsevier; 2017.
7. Flerlage T, Boyd DF, Meliopoulos V, Thomas PG, Schultz-Cherry S. Influenza virus and SARS-CoV-2: pathogenesis and host responses in the respiratory tract. Nat Rev Microbiol. 2021;19(7):425-41.
8. Biggerstaff M, Cauchemez S, Reed C, Gambhir M, Finelli L. Estimates of the reproduction number for seasonal, pandemic, and zoonotic influenza: a systematic review of the literature. BMC Infect Dis. 2014;14(480):1471-2334.
9. Ke R, Romero-Severson E, Sanche S, Hengartner N. Estimating the reproductive number R0 of SARS-CoV-2 in the United States and eight European countries and implications for vaccination. Journal of theoretical biology. 2021;517:110621.
10. Shah VK, Firmal P, Alam A, Ganguly D, Chattopadhyay S. Overview of Immune Response During SARS-CoV-2 Infection: Lessons From the Past. Front Immunol. 2020;11: 1949.
11. Li X, Geng M, Peng Y, Meng L, Lu S. Molecular immune pathogenesis and diagnosis of COVID-19. J Pharm Anal. 2020;10(2):102-8.
12. Aleebrahim-Dehkordi E, Molavi B, Mokhtari M, Deravi N, Fathi M, Fazel T, et al. T helper type (Th1/Th2) responses to SARS-CoV-2 and influenza A (H1N1) virus: From cytokines produced to immune responses. Transpl Immunol. 2022;70: 101495.
13. Latreille E, Lee WL. Interactions of Influenza and SARS-CoV-2 with the Lung Endothelium: Similarities, Differences, and Implications for Therapy. Viruses. 2021;13(2): 161.
14. Chen X, Liu S, Goraya MU, Maarouf M, Huang S, Chen JL. Host Immune Response to Influenza A Virus Infection. Front Immunol. 2018;9: 320.
15. Pallikkuth S, Williams E, Pahwa R, Hoffer M, Pahwa S. Association of Flu specific and SARS-CoV-2 specific CD4 T cell responses in SARS-CoV-2 infected asymptomatic heath care workers. Vaccine. 2021;39(41):6019-24.
16. Kim EH, Nguyen TQ, Casel MAB, Rollon R, Kim SM, Kim YI, et al. Coinfection with SARS-CoV-2 and Influenza A Virus Increases Disease Severity and Impairs Neutralizing Antibody and CD4(+) T Cell Responses. J Virol. 2022;96(6):01873-21.
17. Cheng Y, Ma J, Wang H, Wang X, Hu Z, Li H, et al. Co-infection of influenza A virus and SARS-CoV-2: A retrospective cohort study. J Med Virol. 2021;93(5):2947-54.

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Acute hepatitis of unknown etiology in children: Many clues but few clear answers

Efthymios P. Tsounis[1], Christos Triantos[1]

INTRODUCTION

Six hundred and fifty probable cases of acute hepatitis of unknown etiology in children have been reported to the World Health Organization (WHO) between 5 April and 26 May 2022 [1]. The absence of any link between these cases and the currently known hepatitis agents has prompted the investigation of this emergent condition to elucidate its possible etiology, pathogenesis, and outcome. One of the alarming features of acute non-HepA-E hepatitis in children appears to be the unusually high proportion of severe cases that necessitated liver transplantation in a fraction of the affected cases [1]. In this editorial, we summarize the latest evidence on this topic and discuss the most possible pathogenetic mechanisms.

Timeline

During October 2021–February 2021, clinicians at a children's hospital in Alabama identified nine pediatric patients with severe hepatitis of unknown etiology and adenovirus viremia upon admission. Three patients developed acute liver failure, two of whom were transferred to a different medical facility and underwent liver transplantation [2]. On 31 March 2022, Public Health Scotland was notified of 5 cases of acute hepatitis of unknown origin, which were referred to the Glasgow children's hospital within a period of 3 weeks [3]. Apparently, this cluster significantly exceeded the expected number of cases of pediatric hepatitis of unknown etiology, which was estimated to be fewer than 4 per year across Scotland [4]. Subsequently, the WHO was notified of 10 cases of severe acute hepatitis of unknown etiology in previously healthy children in Scotland, on 5 April 2022 [5]. A multi-disciplinary team of experts was formed to review the epidemiological and clinical data of this initial cohort. All children required hospitalization, while one patient underwent liver transplantation [3]. Additional investigations identified 64 further cases (*i.e.,* a total of 74 cases) across the UK from 1 January up until 8 April 2022. In light of this evidence, the WHO published an alert, regarding cases of severe acute hepatitis of unknown origin in children, on 15 April 2022 [5].

Definitions and current status

Following this announcement, an increasing number of cases has been reported in several countries across the globe. The WHO and the European Centre for Disease Prevention and Control (ECDC) elaborated the currently applied working case definitions: (i) **Confirmed case**: not available at present; (ii) **Probable case**: a person presenting with an acute hepatitis (non-hepatitis viruses A, B, C, D, E) with serum transaminase >500 IU/L (AST or ALT), who is 16 years and younger, since 1 October 2021; **Epi-linked case**: a person presenting with an acute hepatitis (non-hepatitis viruses A, B, C, D and E) of any age who is a close contact of a probable case, since 1 October 2021. If the criteria are fulfilled but serology results for hepatitis A-E are awaited, these cases can be reported and shall be classified as "pending classification". Cases of hepatitis with a known underlying condition should not be reported under this protocol. Cases with other explanations for their clinical presentation are discarded [1,6,7].

According to the aforementioned criteria, 650 probable cases and 99 cases pending classification from 33 countries have been reported to the WHO as of 26

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May 2022. The majority of them have been identified in European countries (n=374; 58%) and, particularly, in the UK and Northern Ireland (n=222; 34%), while probable cases have also risen in USA (n=216; 33%) [1]. In Greece, at least 9 probable cases have been reported according to the National Public Health Organization [8]. Most of the reported cases are not epidemiologically linked and thorough investigations are ongoing to recognize common exposures, risk factors, or links between patients.

Clinical Presentation and Associated Pathogens

The mainly affected population are young children with no comorbidities. The majority of the cases reported through the European Surveillance System (TESSy) are children <5 years of age (75.4%), while the median age of the patients is 3 years according to reports from case series in the US and the UK [2,9]. The most common manifestation appears to be jaundice (68.8%), followed by vomiting episodes during the preceding weeks (57.6%). The presence of pale stools (42.7%) and lethargy (48.6%) are also frequently reported symptoms. At presentation, many children experience gastrointestinal symptomatology, such as diarrhea (43.1%), nausea (25.7%), or abdominal pain (36.1%). Interestingly, fever (28.5%) or respiratory symptoms (18.1%) are less commonly recognized [9].

Out of the 650 probable cases, at least 38 (6%) children required liver transplantation and 9 (1%) died according to the WHO [1]. Out of 156 cases registered *via* TESSy with hospitalization data available, 13.6% of the children were admitted to intensive care unit and 10.7% underwent liver transplantation [7]. Intriguingly, positive testing for human adenovirus (HAdV) infection among affected patients was reported to be as high as 68.6% in whole blood specimens, suggesting a potential role for HAdV in disease pathogenesis. Adenovirus characterization in a subgroup of 35 patients revealed that HAdV serotype F 41 was the predominant type (77%) [9]. Most of the patients had not received COVID-19 vaccination (84.7%), while SARS-CoV-2 was detected in 11.8% of the cases [7]. A range of other pathogens of uncertain significance, including adenovirus-associated virus (AAV) and human herpes virus 6 (HHV6), were identified in a low proportion of children [9].

Working hypotheses: Spotlight on Adenovirus

Although hAdV infection alone is rarely associated with fulminant hepatitis in immunocompetent patients, the most plausible hypothesis continues to encompass the role of adenovirus, considering its high prevalence among affected children [6,9]. hAdVs are nonenveloped, double-stranded, linear DNA viruses, and consist of 7 different species (HAdV A–G); they can be further classified into >100 types using whole-genome sequencing [10]. Inhalation of aerosolized droplets, fecal-oral spread, and direct exposure to infected tissue or blood represent the principal routes of transmission. The most common method to establish diagnosis is polymerase chain reaction (PCR) testing of respiratory secretions, plasma, stool, or urine samples [6]. Adenovirus infections can occur throughout the year. Following an incubation period that ranges from 2 to 14 days, hAdVs typically cause self-limited infections, which, depending on the cell tropism of the serotype, can affect the upper or lower respiratory tracts (mainly serotypes 1-5, 7, 14, and 21), the conjunctiva (serotypes 8, 19, and 37), or the GI tract (notably serotypes 40 and 41) [11]. Indeed, 5-10% of pediatric febrile illnesses have been attributed to hAdV-associated infections [6]. In addition, hAdVs have been reported to cause disseminated infection or acute hepatitis, leading to increased mortality, in immunocompromised patients [12,13]. Supportive care is the main therapeutic option for hAdV infections, while evidence supporting the administration of antivirals is scarce [11].

In the UK, the number of adenoviral infections among children aged 1 to 4 years from November 2021 to April 2022 has not only returned to pre-pandemic levels, but has spiked drastically and surpassed the expected number as estimated from the reported cases in the previous 5 years [9]. Interestingly, this period coincides with the emergence of cases of acute hepatitis of unknown origin in children, implicating a detrimental effect of adenovirus in this setting [6,14,15]. Indeed, hAdV 41 is associated with GI-related symptoms, such as vomiting, nausea, or abdominal pain, which are consistent with the symptomatology preceding the manifestation of acute hepatitis. However, even though adenoviruses may induce liver injury in immunosuppressed or less frequently in healthy children, hAdV 41 is not among the serotypes exhibiting features of hepatotropism [11,16]. In addition, histopathologic examination of liver biopsies in 6 cases did not yield findings indicative of adenovirus or other viral hepatitis [2].

It is hypothesized that other contributing factors, which undermine the host's defense mechanisms and alter the course of a typical hAdV infection, could induce

liver injury through a complementary manner [6,9,15]. First, lower circulation of hAdV and other pathogens, due to COVID-19 restrictions, has precluded the exposure of children to relevant stimuli [17]. As counties worldwide are starting to lift public health measures, a delayed exposure could elicit vigorous immune system responses precipitating hepatic damage in a subset of children [9]. In parallel, this delayed epidemiological peak of naturally occurring adenovirus infections could have possibly revealed a sporadic, albeit underrecognized, complication of hAdV infection [6,9]. Furthermore, a prior or concomitant infection with SARS-CoV-2, or another infectious agent might lead to increased susceptibility or impaired immune response to hAdV [6,9]. In fact, SARS-CoV-2 has been detected in a subset of children with acute hepatitis of unknown etiology [7], while hepatic involvement has been previously described in pediatric COVID-19 cases [18]. Nevertheless, it typically occurs as asymptomatic/mild hepatitis with preserved liver function, whereas severe acute hepatitis can rarely be presented as a complication of COVID-19-associated multisystem inflammatory syndrome [18]. Nishiura et al. have shown that countries reporting hepatitis cases experienced a significantly higher burden of Omicron cases, suggesting that previous exposure to SARS-CoV-2 Omicron variant may entail a risk for the development of post-infectious severe hepatitis among children [19]. However, further cofactor studies with serology tests will be required to clarify the effect of consecutive or coincidental infections with hAdV and SARS-CoV-2, or other pathogens.

Other theories suggest that the current outbreak may be due to the emergence of novel hAdV or SARS-CoV-2 variants that exhibit potent liver tropism with or without the contribution of the aforementioned cofactors [6,9,15]. However, data to corroborate this assumption are lacking, and the results of whole genome sequencing studies from numerous cases are eagerly awaited. At present, COVID-19 vaccination as a triggering event for hepatitis can be safely excluded, considering that most affected children had not received vaccination [1,6,15]. Finally, toxins, drugs, or other environmental stimuli leading to liver injury, alone or in combination with another cofactor, have not been identified, but cannot be entirely excluded yet [6].

CONCLUSIONS

The etiology of this seemingly rare but threating condition remains elusive. It is possible that liver injury occurs as a consequence of a "double-hit" process, in which adenovirus infection imparts a detrimental role. However, the association between cases and hAdV could be overestimated due to increased community transmission and enhanced laboratory testing. Outbreak risk assessment requires further epidemiological, clinical, laboratory, histopathological, and toxicological investigations of all the possible cause(s) of these cases. A methodical approach using standardized definitions, common diagnostic algorithms, and exchange of information as well as multinational collaboration need to be implemented to achieve a rapid and effective global response.

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REFERENCES

1. World Health Organization. Disease outbreak news: acute hepatitis of unknown aetiology in children - Multi-country. 27 May 2022. Available at: https://www.who.int/emergencies/disease-outbreak-news/item/DON-389. [Accessed 6 June 2022].
2. Baker JM, Buchfellner M, Britt W, Sanchez V, Potter JL, Ingram LA, et al. Acute Hepatitis and Adenovirus Infection Among Children — Alabama, October 2021–February 2022. MMWR Morb Mortal Wkly Rep 2022; 71(18):638–40.
3. Marsh K, Tayler R, Pollock L, Roy K, Lakha F, Ho A, et al. Investigation into cases of hepatitis of unknown aetiology among young children, Scotland, 1 January 2022 to 12 April 2022. Euro Surveill. 2022; 27(15):2200318.
4. Braccio S, Irwin A, Riordan A, Shingadia D, Kelly DA, Bansal S, et al. Acute infectious hepatitis in hospitalised children: a British Paediatric Surveillance Unit study. Arch Dis Child. 2017; 102(7):624-8.
5. World Health Organization. Disease outbreak news: acute hepatitis of unknown aetiology - the United Kingdom of Great Britain and Northern Ireland. 15 April 2022. Available at: https://www.who.int/emergencies/disease-outbreak-news/item/2022-DON368. [Accessed 6 June 2022].
6. Mücke MM, Zeuzem S. The recent outbreak of acute severe hepatitis in children of unknown origin - what is known so far. J Hepatol. 2022; S0168-8278(22):00271-9.
7. European Centre for Disease Prevention and Control/WHO

Regional Office for Europe. Hepatitis of Unknown Aetiology in Children, Joint Epidemiological overview. 31 May 2022. Available at: https://cdn.ecdc.europa.eu/novhepsurveillance/ [Accessed 6 June 2022].
8. National Public Health Organization. Επιδημιολογική έκθεση οξείας ηπατίτιδας αγνώστου αιτιολογίας. 8 June 2022. https://eody.gov.gr/epidimiologiki-ekthesi-oxeias-ipatitidas-agnostoy-aitiologias-3/ [Accessed 13 June 2022].
9. UK Health Security Agency Technical briefing. Investigation into acute hepatitis of unknown aetiology in children in England. Version 3. 19 May 2022. Available at: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1077027/acute-hepatitis-technical-briefing_3.pdf [Accessed 6 June 2022].
10. Seto D, Chodosh J, Brister JR, Jones MS; Members of the Adenovirus Research Community. Using the whole-genome sequence to characterize and name human adenoviruses. J Virol. 2011; 85(11):5701-2.
11. Lynch JP 3rd, Kajon AE. Adenovirus: Epidemiology, Global Spread of Novel Serotypes, and Advances in Treatment and Prevention. Semin Respir Crit Care Med. 2016; 37(4):586-602.
12. Gu J, Su QQ, Zuo TT, Chen YB. Adenovirus diseases: a systematic review and meta-analysis of 228 case reports. Infection. 2021; 49(1):1-13.
13. Ronan BA, Agrwal N, Carey EJ, De Petris G, Kusne S, Seville MT, Blair JE, Vikram HR. Fulminant hepatitis due to human adenovirus. Infection. 2014; 42(1):105-11.
14. Hakim MS. The recent outbreak of acute and severe hepatitis of unknown etiology in children: A possible role of human adenovirus infection? J Med Virol. 2022; doi:10.1002/jmv.27856.
15. Sallam M, Mahafzah A, Şahin GÖ, on behalf of ESCMID Study Group for Viral Hepatitis—. Hepatitis of Unknown Origin and Etiology (Acute Non HepA-E Hepatitis) among Children in 2021/2022: Review of the Current Findings. Healthcare. 2022; 10(6):973.
16. Munoz FM, Piedra PA, Demmler GJ. Disseminated adenovirus disease in immunocompromised and immunocompetent children. Clin Infect Dis. 1998; 27(5):1194-200.
17. Groves HE, Piché-Renaud PP, Peci A, Farrar DS, Buckrell S, Bancej C, et al. The impact of the COVID-19 pandemic on influenza, respiratory syncytial virus, and other seasonal respiratory virus circulation in Canada: A population-based study. Lancet Reg Health Am. 2021; 1:100015.
18. Perez A, Cantor A, Rudolph B, Miller J, Kogan-Liberman D, Gao Q, et al. Liver involvement in children with SARS-COV-2 infection: Two distinct clinical phenotypes caused by the same virus. Liver Int. 2021; 41(9):2068-75.
19. Nishiura H, Jung SM, Hayashi K. High population burden of Omicron variant (B.1.1.529) is associated with the emergence of severe hepatitis of unknown etiology in children. Int J Infect Dis. 2022; S1201-9712(22):00290-9.

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Monkeypox outbreak: A clinical and therapeutic overview

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INTRODUCTION

Monkeypox has historically caused sporadic endemics in Central and West Africa in proximity to tropical rainforests [1]. However, since 13 May 2022, and as of 2 June 2022, the World Health Organization (WHO) has been notified of 780 laboratory-confirmed cases of monkeypox identified in 27 non-endemic countries [2]. The pattern of the current outbreak differs considerably from previous outbreaks outside of Africa, in which monkeypox was almost exclusively diagnosed in people with a history of travel to endemic countries, or with direct contact to infected exotic animals [3]. As epidemiological and laboratory information is still missing and many chains of transmission remain undetected, the number of cases is possibly underestimated [2]. This sudden and unprecedented rise in cases, simultaneously, in numerous non-endemic countries should raise the awareness of clinicians, especially in areas, where they may have never encountered a monkeypox case in the past.

Monkeypox at a glance

Monkeypox is an enveloped, double-stranded, DNA (dsDNA) virus belonging to the *Orthopoxvirus* genus of the *Poxviridae* family [4]. Monkeypox is a zoonotic disease transmitted to people through bite, scratch, handling wild game, or use of products made from various infected wild mammals including rope squirrels, tree squirrels, and Gambian pouched rats. Human-to-human transmission is possible after direct physical contact with skin lesions or body fluids of an infected person, direct contact with contaminated materials such as bedding or after prolonged face-to-face contact through respiratory droplets. [3]. Its clinical presentation resembles that of smallpox; however, symptoms tend to be milder. Following an incubation period of 5-21 days, monkeypox begins with a combination of the following symptoms: fever, headache, swollen lymph nodes, myalgia, and exhaustion. Lymphadenopathy can be either generalized or localized (submandibular, cervical, axillary, or inguinal) and facilitates distinguishing monkeypox from other smallpox-like syndromes [4]. The onset of general symptoms typically precedes 1-3 days of the development of skin lesions. The lesions vary from a few to several thousand and mostly affect the face (95% of the cases) and the extremities (75%), rather than the torso. Other commonly affected areas include oral mucous membranes (in 70% of cases), genitalia (30%), and conjunctivae (20%). The rash evolves sequentially through four stages, namely macular, papular, vesicular, and pustular, followed by exfoliation and resolution of the lesions [4]. In the current outbreak, a significant proportion of patients are men who have sex with men (MSM), who were diagnosed at sexually transmitted infection (STI) clinics or other primary, or secondary health services, suggesting a novel route of transmission *via* sexual intercourse [2,5]. In parallel, a peculiar clinical presentation of the disease has been described. In particular, sore throat and genital or perianal lesions are frequently recognized, apart from fever and lymphadenopathy. Interestingly, anogenital rash is reported to evolve before the development of general symptoms and without consistently spreading to other parts of the body [2].

In most cases, monkeypox is a self-limited disease

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lasting from 2 to 4 weeks. Secondary infections, bronchopneumonia, encephalitis, sepsis, and corneal infection, leading to loss of vision, are among the most serious disease complications. The case fatality ratio is reported to be as high as 3-6%, while certain strain variations, such as the West African clade, appear to be less virulent with a mortality rate of <1% [2,6].

Patient management: who to treat?

Most patients with monkeypox experience mild symptoms and recover without requiring any medical support. Supportive care and intravenous hydration should be considered in those patients at risk for dehydration (vomiting, nausea, geriatric patients) [7]. Treatment should be considered in three categories of patients: (a) those with severe disease (hemorrhagic disease confluent lesions, sepsis, encephalitis or other severe complications), (b) those at high risk of severe disease, including immunocompromised individuals (e.g. patients with HIV-1 infection, hematologic or generalized solid organ malignancy, autoimmune diseases with immunodeficiency, hematopoietic stem cell or solid-organ transplant recipients, and those on immunosuppressive therapy), children < 8 years old, pregnant or breastfeeding women, patients with atopic dermatitis or other active exfoliative skin conditions, and (c) those with aberrant infections that include accidental implantation in eyes, mouth, or other anatomical sites where monkeypox might constitute a special hazard. [7-9]. There is no specific antiviral drug for monkeypox; however, certain antivirals approved for the treatment of smallpox are expected to be equally effective against human monkeypox. The efficacy of antiviral agents may be lessened in immunosuppressed patients. In general, tecovirimat is considered the treatment of choice, although some specialists support the administration of dual-combination therapy with tecovirimat and cidofovir in seriously ill patients [7].

Treatment and immunization

Tecovirimat

Tecovirimat (TPOXX®) is a potent inhibitor of the highly conserved among orthopoxviruses VP37 envelope protein, which is essential for the generation of egress-competent virions, and thereby, hinders the dissemination of the infectious particles into host circulation [10]. In July 2018, tecovirimat was the first agent to be approved for the treatment of smallpox in the USA and can be administered in adults or pediatric patients weighting at least 3kg [11]. It is important to note that this approval was based on experimental data from animal or dose-escalation studies in healthy volunteers [10,11]. Clinical trials would be very challenging to conduct considering accessibility and security issues in areas where monkeypox thrives, so this procedure is justified in the interest of public health security. Tecovirimat is available in oral (capsules of 200mg) or intravenous formulations and the recommended dosage depends upon the weight of the patient [7]. Treatment with tecovirimat was effective in non-human primates with smallpox and well-tolerated in humans over a period of 14 days [10]. In an expanded safety trial recruiting 361 healthy adults, administration of tecovirimat was not followed by any increase in adverse events, while the most common side effects were reported to be headache, abdominal discomfort, and nausea [10]. In a small retrospective study, tecovirimat appeared to reduce the duration of viral shedding [12].

Cidofovir/Brincidofovir

Cidofovir (Vistide®) is a monophosphate nucleotide analog that displays broad-spectrum antiviral activity by inhibiting viral DNA polymerase [13]. It was first approved in 1996 as an intravenous therapy against cytomegalovirus retinitis in patients with AIDS [13]. Importantly, cidofovir exhibits remarkable anti-poxvirus activity *in vitro* and prevents lethal monkeypox infection in animal models. However, evidence supporting its efficacy on human monkeypox infection is lacking, while its administration has been associated with significant adverse events, including nephrotoxicity [7,14].

Brincidofovir (Tembexa®) is an optimized, orally available, lipid conjugate of cidofovir. The lipid conjugation leads to higher intracellular concentrations of the active metabolite (cidofovir diphosphate), enhancing, thus, its antiviral efficacy against dsDNA virus, and lower plasma concentrations of cidofovir, preventing from drug-induced toxicity [15]. In June 2021, brincidofovir was approved by the US FDA for the treatment of smallpox in adult and pediatric patients [16]. Remarkably, the decision was once again based on animal studies and *in vitro* data supporting its potent activity against orthopoxviruses [15,16]. The safety profile of brincidofovir derived from clinical trials of the drug in the context of non-smallpox infections. The most frequently reported side effects were GI-related, such as diarrhea, vomiting, nausea, or abdominal pain [16]. The duration of brincidofovir therapy should be closely

monitored, since an increased risk for mortality was observed, when used for a longer than recommended period [16]. Brincidofovir yielded discouraging results in a UK case series study. In three monkeypox patients, the administration of brincidofovir was not associated with any convincing clinical benefit; instead, it induced derangement of liver function tests leading to treatment discontinuation [12].

Smallpox immunization

Previous vaccination against smallpox prevents the acquisition of monkeypox virus and, in case of infection, significantly improves symptoms and clinical outcomes [17-19]. According to a population-based surveillance study in Africa, individuals with prior smallpox vaccination presented a fivefold lower risk to be infected with monkeypox in comparison to unvaccinated persons (0.78 vs. 4.05 per 10,000) [17]. In another study investigating 2278 close contacts of 203 primary monkeypox infections, the secondary attack rate (SAR) was highly influenced by prior immunization status against smallpox (1.3% versus 9.3% among vaccinated and unvaccinated household contacts, respectively) [18].

ACAM2000® and Jynneos® are the two currently approved vaccines to prevent smallpox in the USA [19]. ACAM2000® is administered as a live vaccinia virus formulation that is inoculated into the skin and entails a risk of spreading to other parts of the body or even to other people. The newer-generation Jynneos® vaccine is based on a live, attenuated, replication-incompetent, vaccinia virus (Modified Vaccinia Ankara). The CDC recommends that individuals with occupational exposure to orthopoxviruses receive a vaccination with either ACAM2000 or JYNNEOS as pre-exposure prophylaxis (PrEP) [19]. Post-exposure vaccination of close contacts has efficiently limited transmission in past outbreaks and can be considered in certain cases. According to the CDC, vaccination within 4 days from the date of exposure can effectively prevent monkeypox transmission, and, if delivered within days 4 to 14 from exposure, it can alleviate the symptoms of the disease [19]. Intravenous administration of Vaccinia Immune (VIGIV) is an alternative measure for post-exposure prophylaxis, in cases in which small immunization is contraindicated, e.g., immunosuppression [7].

CONCLUSIONS

The scientific community has focused on unraveling the changing epidemiology of this monkeypox outbreak in communities outside of Africa. In the meantime, containment efforts are relied on enhanced case identification, isolation, and contact tracing. Primary care physicians, dermatologists, and those working in STI clinics should maintain a high degree of clinical suspicion. The monkeypox outbreak does not have the characteristics that could lead to a new viral pandemic since transmission occurs mainly after symptom(s) onset through visible skin lesions, therefore protection measures can be undertaken by both the patient and its potential contacts, and there is no airborne transmission. It is imperative that effective interventions and medications are already available and affordable in monkeypox-endemic low-income countries. Finally, this monkeypox outbreak should not lead to stigmatization of already vulnerable groups; instead, the real culprit is the neglect of diseases that affect the most impoverished populations.

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REFERENCES

1. Nalca A, Rimoin AW, Bavari S, Whitehouse CA. Reemergence of monkeypox: prevalence, diagnostics, and countermeasures. Clin Infect Dis. 2005; 41(12):1765-71.
2. World Health Organization. Multi-country monkeypox outbreak: situation update. 4 June 2022. Available at: https://www.who.int/emergencies/disease-outbreak-news/item/2022-DON390. [Accessed 11 June 2022]
3. Parker S, Nuara A, Buller RM, Schultz DA. Human monkeypox: an emerging zoonotic disease. Future Microbiol. 2007; 2(1):17-34.
4. McCollum AM, Damon IK. Human monkeypox. Clin Infect Dis. 2014; 58(2):260-7.
5. Heskin J, Belfield A, Milne C, Brown N, Walters Y, Scott C, et al. Transmission of monkeypox virus through sexual contact - A novel route of infection. J Infect. 2022; S0163-4453(22):00335-8.
6. Huhn GD, Bauer AM, Yorita K, Graham MB, Sejvar J, Likos A, et al. Clinical characteristics of human monkeypox, and risk factors for severe disease. Clin Infect Dis. 2005; 41(12):1742-51.

7. Centers for Disease Control and Prevention (CDC). Interim Clinical Guidance for the Treatment of Monkeypox. 10 June 2022. Available at: https://www.cdc.gov/poxvirus/monkeypox/treatment.html [Accessed 11 June 2022].
8. Jezek Z, Szczeniowski M, Paluku KM, Mutombo M. Human monkeypox: clinical features of 282 patients. J Infect Dis. 1987; 156(2):293-8.
9. Cono J, Cragan JD, Jamieson DJ, Rasmussen SA. Prophylaxis and treatment of pregnant women for emerging infections and bioterrorism emergencies. Emerg Infect Dis. 2006; 12(11):1631-7.
10. Grosenbach DW, Honeychurch K, Rose EA, Chinsangaram J, Frimm A, Maiti B, et al. Oral Tecovirimat for the Treatment of Smallpox. N Engl J Med. 2018; 379(1):44-53.
11. Hoy SM. Tecovirimat: First Global Approval. Drugs. 2018; 78(13):1377-1382.
12. Adler H, Gould S, Hine P, Snell LB, Wong W, Houlihan CF, et al; NHS England High Consequence Infectious Diseases (Airborne) Network. Clinical features and management of human monkeypox: a retrospective observational study in the UK. Lancet Infect Dis. 2022; S1473-3099(22):00228-6.
13. Safrin S, Cherrington J, Jaffe HS. Clinical uses of cidofovir. Rev Med Virol. 1997; 7(3):145-56.
14. Ortiz A, Justo P, Sanz A, Melero R, Caramelo C, Guerrero MF, et al. Tubular cell apoptosis and cidofovir-induced acute renal failure. Antivir Ther. 2005; 10(1):185-90.
15. Florescu DF, Keck MA. Development of CMX001 (Brincidofovir) for the treatment of serious diseases or conditions caused by dsDNA viruses. Expert Rev Anti Infect Ther. 2014; 12(10):1171-8.
16. U.S. Food and Drug Administration. FDA approves drug to treat smallpox. 6 April 2022. Available at: https://www.fda.gov/drugs/news-events-human-drugs/fda-approves-drug-treat-smallpox [Accessed 11 June 2022].
17. Rimoin AW, Mulembakani PM, Johnston SC, Lloyd Smith JO, Kisalu NK, Kinkela TL, et al. Major increase in human monkeypox incidence 30 years after smallpox vaccination campaigns cease in the Democratic Republic of Congo. Proc Natl Acad Sci U S A. 2010; 107(37):16262-7.
18. Fleischauer AT, Kile JC, Davidson M, Fischer M, Karem KL, Teclaw R, et al. Evaluation of human-to-human transmission of monkeypox from infected patients to health care workers. Clin Infect Dis. 2005 Mar 1;40(5):689-94.
19. Centers for Disease Control and Prevention (CDC). Monkeypox and Smallpox Vaccine Guidance. 2 June 2022. Available at: https://www.cdc.gov/poxvirus/monkeypox/clinicians/smallpox-vaccine.html [Accessed 11 June 2022].

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The role of brain organoids as model system for human disease

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The human cerebral cortex represents the most highly developed part of the brain. It plays a vital role in processing and integrating information, modulating social and motor behaviors, planning and organization and thus it determines intelligence and personality in humans. Hence, the series of events resulting in its development must be tightly coordinated and regulated. Smaller or bigger changes or disruptions in the regulation of proliferation, differentiation, and migration of cells in the developing central nervous system may lead to malformations of the brain affecting its structure and function. This can cause a wide range of physiological and functional consequences, provoking brain-related diseases such as neurodevelopmental disorders. The main characteristics of such disorders are developmental delay, intellectual disability, and epilepsy. They can also be associated with psychiatric disorders affecting individuals from early postnatal life and throughout adulthood. Given the high societal and economic burden that such disorders impose, defining the pathophysiological mechanisms underlying their manifestation will help to better diagnose and will accelerate treatment. For this reason, over recent years scientists have made a significant effort to model brain diseases.

Mouse models revealed many aspects of the mechanism underlying proper cortical development, as well as the appearance of cortical malformations; however, their use is limited due to structural and functional differences between mice and humans. The latest advances in stem cell technology and the generation of induced pluripotent stem cells (iPSCs) offer a promising way to derive human cells of any tissue of interest from patients and control individuals to study the phenotype of patients affected by disease-causing mutations. The originally developed protocols yielded two-dimensional (2D) monolayer cultures of human neural progenitors and neurons, and were a big step forward in identifying human-specific molecular and cellular mechanisms related to brain development and disease. However, they did not allow insights into the effects of three-dimensional (3D) tissue context on cellular processes, a key feature that determines brain function, while the lack of cellular and molecular diversity was profound in such cultures. On the other hand, organoids offer a possibility to overcome these problems since they represent 3D, embryonic structures that reflect the 3D structure of organs. Brain organoids have been shown to reflect the 3D organization, cell-type composition, and transcriptional footprints of the developing human brain. For these reasons, in the past decade, such brain organoid protocols have been used to model many diseases and they are now representing a promising model system [1].

Brain organoids are characterized by high complexity in terms of cellular composition, as they consist of neural progenitors, neurons, astrocytes, and oligodendrocytes, by structural diversity, as they are organized in different cellular layers and by a higher degree of maturation than 2D cultures. All of these features allow regional interconnectivity and function similar to those observed in the human brain. Several different protocols

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for generating brain organoids have been published in the past decade. They are based either on intrinsic properties of neural progenitor cells to self-organize into 3D aggregates, or on guided differentiation programs engineering the external environment of the 3D aggregates which is achieved through the addition of morphogens mimicking endogenous patterning events. The first approach leads to the production of various cellular lineages yielding brain organoids composed of multiple regional identities of the brain within the same organoid. This allows the holistic modeling of brain structure, but it was reported to show increased variability between batches [2]. On the contrary, the second approach drives neural progenitors to acquire a specific brain region identity, which was proposed to reduce the variability between different organoid batches. However, they can be used only for specific applications because they lack complexity [2]. Over the last few years, different modifiers, namely small molecules, have been used to produce forebrain organoids (dorsal and ventral), midbrain organoids, hypothalamic or thalamic organoids, hippocampal organoids, spinal cord organoids, cerebellum organoids, and choroid plexus organoids, reviewed in [3]. In parallel, differently patterned organoids have been fused creating more complex models of the developing human nervous system leading to modeling interconnectivity in a tightly regulated approach [3] and they have been used as an alternative method of the intrinsic protocols. Nevertheless, these basic differences between these approaches need to be considered when choosing the appropriate 3D model to study different brain diseases.

These protocols were used to model early human CNS development, neuronal survival and maturation, human brain evolution, and human brain diseases [1]. Indeed, since the publication of the first intrinsic brain organoid protocol [4], numerous studies have been published modeling a great variety of different brain-related diseases. Amongst the first diseases that have been modeled were the malformations of cortical development (MCDs), such as microcephaly, macrocephaly, cortical heterotopias, and lissencephaly. Interestingly, structural defects of the developing cortex are among the main clinical phenotypes in the previously mentioned diseases. Using mainly the intrinsic protocols for generating brain organoids, a human-specific mechanism involving the proper regulation of the mitotic spindle orientation in the transition from apical radial glial cells to basal radial glial cells, the novel neural progenitors responsible for the neuronal expansion observed in the human cortex, was described in patients with microcephaly following mutations in genes such as CDK5RAP2 [4] and ASPM [5] or after zika virus infection [6]. Besides, macrocephaly was also modeled using brain organoids as well as disorders implicating alterations in the gyrification index of the brain scrutinizing the human-specific function of genes including PTEN, LIS1 and YWHAE [7-9]. Finally, neuronal heterotopias were also extensively studied using brain organoids contributing to our limited knowledge of the involvement of intrinsic and extrinsic signaling on neural progenitors' function, and neuronal migration profile in the formation of the human cortex. These studies have shown that the morphology, position, and function of neural progenitors, as well as the migration behavior of human neurons during cortical development, are regulated amongst others by DCHS1, FAT4, and LGALS3BP [10,11] contributing to the establishment of human cortical complexity.

Besides cortical malformations, other brain-related neurodevelopmental disorders have been modeled including αutism spectrum disorder (ASD) [12,13], Rett syndrome [14], and Timothy syndrome [15]. Using brain organoids, the hypothesis of the excitatory/inhibitory imbalance in autistic brains has been tested and the involvement of genes such as FOGX1 and CHD8 has been shown. Additionally, using assembloids, interneuron migration defects were suggested as one of the causing mechanisms of Timothy syndrome, while brain organoids harboring mutations in the gene MECP2 showed defects such as increased proliferation and decreased differentiation potentials of neural progenitors suggesting a novel mechanism for Rett Syndrome. Lastly, although brain organoids were shown to recapitulate early steps of brain development, modified protocols have been used for modeling neurodegenerative disorders including Alzheimer's disease (AD) [16], Amyotrophic lateral sclerosis (ALS) [17], Parkinson's disease (PD) [18] schizophrenia [19] and others. This enabled the modeling of these genetic neurodegenerative diseases in a human cellular context, highlighting for example i) the cellular mechanisms involved in the accumulation of amyloidogenic Aβ peptides in AD, ii) the impaired motor features upon neuronal degradation in ALS and iii) the decreased neurite length of dopaminergic neurons in LRRK2 mutant (PD) organoids. Of note, these cellular systems have highlighted potential developmental deficits underlined classical neurodegenerative disor-

ders. For instance, in schizophrenia cellular mechanisms, such as cell cycle control dysregulation of the key neural progenitor type, the radial glial cells, were described as a consequence of the disruption of DISC1 and NDEL1 interaction. This could shape a novel understanding of the causes of neurodegenerative disorders that may contribute to changes in diagnosis and therapeutic strategies in the future.

From all the above, it is clear that with the use of brain organoids we were able to describe human-specific mechanisms that upon disruption lead to MCDs, neurodevelopmental or neurodegenerative disorders. Nevertheless, it is not always easy to estimate where the limitations of the organoids lie. Even though many studies have shown remarkable similarities between brain organoids and the fetal brain, it is also clear that not all aspects of brain development are accurately reflected in these *in vitro* cultures. For instance, it has been reported that the proportion of several cell types is altered in organoids compared to the primary tissue. Indeed, single-cell-RNA-sequencing, immunofluorescence, and FACS analysis from several labs have shown that the proportion of glial cells – astrocytes and oligodendrocytes – is lower, same as the ratio of apical and basal progenitors in the neurogenic zones. Furthermore, endothelial cells are missing and white matter regions are also very much underrepresented within the organoids. In addition, due to the absence of vascularization, the organoid's nutrient and oxygen supply are suboptimal and thus their size and stochasticity of developmental fate choices remain limited. These limitations are the driving force for future improvements of organoid cultures. Attempts for such improvement are already in line, such as the addition of microfilaments and scaffolding components or the generation of the "organoids on a chip", micro-engineered promising models that will allow the control and manipulation of fluid flow with a high degree of accuracy [20]. These will assist the improvement of the morphology and nutrient support of organoids, which ultimately will ameliorate organoid cultures and will ensure the high quality of this model. Regardless of the remaining limitations from the use of organoids, it is widely accepted that they represent one of the best models so far for studying human-specific mechanisms of brain development and disease and constitute an evolutionary approach which opens new avenues in the diagnosis and treatment of brain-related disorders.

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REFERENCES

1. Kyrousi C, Cappello S. Using brain organoids to study human neurodevelopment, evolution and disease. Wiley Interdiscip Rev Dev Biol. 2020;9(1):e347.
2. Yoon SJ, Elahi LS, Paşca AM, Marton RM, Gordon A, Revah O, et al. Reliability of human cortical organoid generation. Nat Methods. 2019;16(1):75-8.
3. Bhattacharya A, Choi WWY, Muffat J, Li Y. Modeling developmental brain diseases using human pluripotent stem cell-derived brain organoids - progress and perspective. J Mol Biol. 2022;434(3):167386.
4. Lancaster MA, Renner M, Martin CA, Wenzel D, Bicknell LS, Hurles ME, et al. Cerebral organoids model human brain development and microcephaly. Nature. 2013;501(7467):373-9.
5. Li R, Sun L, Fang A, Li P, Wu Q, Wang X. Recapitulating cortical development with organoid culture in vitro and modeling abnormal spindle-like (ASPM related primary) microcephaly disease. Protein Cell. 2017;8(11):823-33.
6. Qian X, Nguyen HN, Jacob F, Song H, Ming GL. Using brain organoids to understand Zika virus-induced microcephaly. Development. 2017;144(6):952-7.
7. Li Y, Muffat J, Omer A, Bosch I, Lancaster MA, Sur M, et al. Induction of Expansion and Folding in Human Cerebral Organoids. Cell Stem Cell. 2017;20(3):385-96.e3.
8. Bershteyn M, Nowakowski TJ, Pollen AA, Di Lullo E, Nene A, Wynshaw-Boris A, et al. Human iPSC-Derived Cerebral Organoids Model Cellular Features of Lissencephaly and Reveal Prolonged Mitosis of Outer Radial Glia. Cell Stem Cell. 2017;20(4):435-49.e4.
9. Iefremova V, Manikakis G, Krefft O, Jabali A, Weynans K, Wilkens R, et al. An Organoid-Based Model of Cortical Development Identifies Non-Cell-Autonomous Defects in Wnt Signaling Contributing to Miller-Dieker Syndrome. Cell Rep. 2017;19(1):50-9.
10. Klaus J, Kanton S, Kyrousi C, Ayo-Martin AC, Di Giaimo R, Riesenberget S, al. Altered neuronal migratory trajectories in human cerebral organoids derived from individuals with neuronal heterotopia. Nat Med. 2019;25(4):561-8.
11. Kyrousi C, O'Neill AC, Brazovskaja A, He Z, Kielkowski P, Coquand L, et al. Extracellular LGALS3BP regulates neural progenitor position and relates to human cortical complexity. Nat Commun. 2021;12(1):6298.
12. Mariani J, Coppola G, Zhang P, Abyzov A, Provini L, Tomasini L, et al. FOXG1-Dependent Dysregulation of GABA/Glutamate Neuron Differentiation in Autism Spectrum Disorders. Cell. 2015;162(2):375-90.
13. Wang P, Mokhtari R, Pedrosa E, Kirschenbaum M, Bayrak C, Zheng D, et al. CRISPR/Cas9-mediated heterozygous

knockout of the autism gene CHD8 and characterization of its transcriptional networks in cerebral organoids derived from iPS cells. Mol Autism. 2017;8:11.
14. Mellios N, Feldman D, Sheridan S, Ip JPK, Kwok S, Amoah SK, et al. Human cerebral organoids reveal deficits in neurogenesis and neuronal migration in MeCP2-deficient neural progenitors. Mol Psychiatry. 2018;23:791.
15. Birey F, Andersen J, Makinson CD, Islam S, Wei W, Huberet N, et al. Assembly of functionally integrated human forebrain spheroids. Nature. 2017;545(7652):54-9.
16. Gonzalez C, Armijo E, Bravo-Alegria J, Becerra-Calixto A, Mays CE, Soto C. Modeling amyloid beta and tau pathology in human cerebral organoids. Mol Psychiatry. 2018;23(12):2363-74.
17. Osaki T, Uzel SGM, Kamm RD. Microphysiological 3D model of amyotrophic lateral sclerosis (ALS) from human iPS-derived muscle cells and optogenetic motor neurons. Sci Adv. 2018;4(10):eaat5847.
18. Kim H, Park HJ, Choi H, Chang Y, Park H, Shin J, et al. Modeling G2019S-LRRK2 Sporadic Parkinson's Disease in 3D Midbrain Organoids. Stem Cell Reports. 2019;12(3):518-31.
19. Ye F, Kang E, Yu C, Qian X, Jacob F, Yu C, et al. DISC1 Regulates Neurogenesis via Modulating Kinetochore Attachment of Ndel1/Nde1 during Mitosis. Neuron. 2017;96(5):1204.
20. Qiao H, Zhang YS, Chen P. Commentary: Human brain organoid-on-a-chip to model prenatal nicotine exposure. Front Bioeng Biotechnol. 2018 ;6:138.

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IBD patients' psychosocial functioning during the first COVID-19 lockdown

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Abstract

Background: The COVID-19 outburst and the following lockdown had a drastic effect on the Greek general population's mental health and especially in chronic disease patients. The aim of the current study was to assess the psychological burden of inflammatory bowel disease (IBD) patients during the first COVID-19 lockdown in Greece.

Methods: IBD outpatients of the Division of Gastroenterology of the University General Hospital of Patras were enrolled to the study. Participants were administered the Hospital Anxiety and Depression Scale at two time points, before and during the lockdown, and the Impact of Event Scale-Revised and the Short-Form-36 Health Survey at one time point, during the lockdown.

Results: Twenty-two (22) patients entered the study, 15 (68.2%) females with a mean age of 43.2 years old (SD:12.5). Eleven (11) patients were diagnosed with ulcerative colitis and 11 with Crohn's disease. During the lockdown, 30% of participants reported clinically significant anxiety symptoms, 50% reported clinically significant depression symptoms and 59.1% reported clinically significant post-traumatic stress symptoms. During the lockdown, we observed a significant rise in depression symptoms in the whole sample (p=0.038) and in female patients (p=0.006) compared to the pre-lockdown period.

Conclusion: During the first COVID-19 lockdown in Greece, we detected a significant percentage of post-traumatic stress disorder in IBD patients and a significant increase in depression levels compared to the pre-lockdown period, especially in females.

Key words: *IBD; psychological functioning; COVID-19 lockdown*

INTRODUCTION

The SARS-CoV-2 infection rapidly spread around the globe affecting all aspects of human living including economy, social relationships, lifestyle and people's physical and mental health [1]. During the first pandemic wave, most administrations implemented strict lockdown measures in order to control viral transmission [2]. Several studies worldwide have shown that during lockdown measures people experienced increased psychosocial suffering, mostly anxiety, depression and post-traumatic stress and reported impaired quality of life [3-5]. COVID-19 quarantine measures seem to have exerted an even greater impact on chronic disease patients' well-being, mainly because these populations reported greater fears regarding their health and experienced reduced access to standard medical care due to the allocation

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of healthcare resources to the management of the pandemic [6].

Inflammatory bowel disease (IBD) is a chronic autoimmune gastrointestinal disorder which is associated with increased levels of psychological distress, impaired quality of life and significant limitations in everyday functioning [7]. The majority of IBD patients receive immunosuppressive or immunomodulative treatment, thus being considered a high-risk group regarding the SARS-CoV-2 infection [6,8]. In addition, there is a growing body of research showing that IBD patients experienced intense feelings of fear and isolation and reported increased prevalence of anxiety, depression and stress symptoms following the outburst of the pandemic [2,6,9,10]. In this context, the aim of the current prospective study was to evaluate the impact of the first lockdown imposed throughout Greece in spring 2020 on IBD patients' psychological functioning. To our knowledge, this is the first study focusing on this issue in Greek IBD patients.

MATERIALS AND METHODS

The current prospective study was performed at the Division of Gastroenterology of the Internal Medicine Department of the University Hospital of Patras in Greece with the collaboration of the Department of Psychiatry. The study was conducted from April 10th to May 4th 2020, a period during which the whole country was under strict lockdown measures in an attempt to control SARS-CoV-2 transmission. The study protocol conformed to the principles of the Helsinki Declaration and was approved by the Institutional Review Board of the University Hospital of Patras. IBD patients recruited from the IBD Outpatients Department of the University Hospital of Patras were initially approached by phone and were invited to enroll to the study after being thoroughly informed regarding its aim and methods. These participants were selected because they had been enrolled a few months prior to the COVID-19 pandemic to another research protocol and had completed the Hospital Anxiety and Depression Scale at that time. Two members of the research team (GK and MK) contacted by phone or video call those patients who consented to participate and administered the study questionnaires by interview.

Psychometric instruments

Post-traumatic stress (PTS) symptoms related to the COVID-19 epidemic were assessed with the use of the Impact of Event Scale-Revised (IES-R), which is a 22-item scale. Respondents were asked to indicate how much they were distressed or bothered during the past week by each "difficulty" listed in regards with the epidemic outbreak. Each item was rated on a 5-point scale ranging from 0 ("not at all") to 4 ("extremely"). The IES-R yields a total score (ranging from 0 to 88) and subscale scores can also be calculated for the Intrusion, Avoidance, and Hyperarousal subscales. A cut-off score of 24 was used for the detection of clinically relevant post-traumatic stress symptoms [11].

Psychological functioning was evaluated with the use of the validated Greek version of the Hospital Anxiety and Depression Scale (HADS), which comprises seven items for anxiety and seven items for depression. Each item is rated on a 4-point scale (0-3) and each subscale is scored from 0 to 21. Higher scores indicate greater symptom severity. We used a cut-off score of 8 to detect clinically significant anxiety and depression symptoms according to the instructions of the initial validation study [12,13].

Health-related quality of life was assessed with the validated Greek version of the Short-Form-36 Health Survey (SF36), which is a self-reported, generic HRQOL validated instrument. It includes 8 multi-item scales (36 items) that evaluate the extent to which an individual's health limits his or her physical, emotional, and social well-being. More specifically, it covers 8 domains of HRQOL, namely physical functioning, role limitations due to physical problems, bodily pain, general health perception, vitality, social functioning, role limitations due to emotional problems, and mental health. Scores on each subscale range from 0 to 100, with higher scores indicating a better HRQOL results [14]. The Greek version of the SF-36 provides population-based normative data which make possible the calculation of norm-based scores for each sub-scale. Norm-based scores below 50 indicate impaired functioning compared to the general population [15,16].

Statistical analysis

Statistical analysis was performed with the SPSS package for Windows (release 22.0). Numerical data were expressed as means and standard deviations (SD), and categorical data as counts and percentages. Due to the small sample size we used Mann-Whitney U-tests to perform between-group comparisons in HADS, SF36 and IES-R scores by gender and disease type. We also used repeated measures to compare anxiety

and depression levels prior and during the lockdown for the whole sample and separately by gender and disease type.

RESULTS

Twenty-two (22) IBD patients, 15 (68.2%) females, were approached by phone and agreed to enter the study. 11 patients were diagnosed with ulcerative colitis (UC) and 11 patients were diagnosed with Crohn's Disease (CD). Participants' mean age was 42.3 years (SD: 12.5).

During the COVID-19 lockdown, 30.0% of subjects reported clinically significant anxiety symptoms, 50.0% reported clinically significant depressive symptoms and 59.1% reported clinically significant COVID-19 related post-traumatic stress symptoms (Fig.1). As far as quality-of-life scores are concerned, participants scored below the Greek general population in all sub-scales of the SF36 with the exception of the Physical Functioning sub-scale. Figure 2 depicts comparisons between our sample's SF36 subscale scores and the Greek general population's scores.

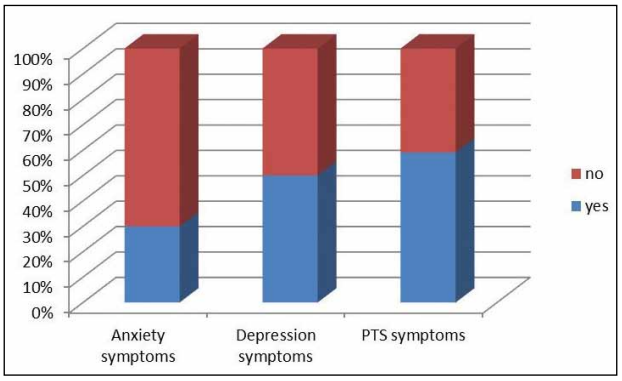

Figure 1. Clinically significant anxiety, depression and PTS symptoms.

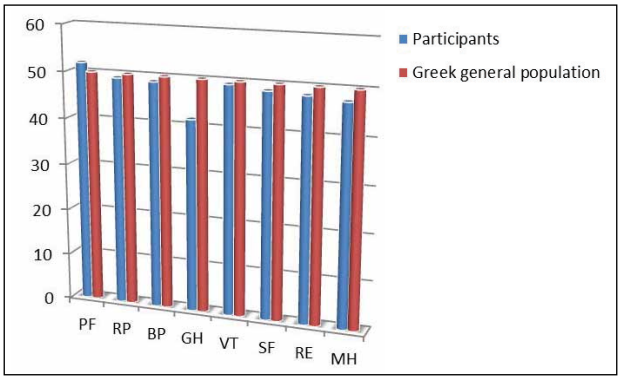

Figure 2. Participants' norm-based SF36 subscale scores vs Greek general population's scores.

No significant differences were observed between males and females in anxiety (p=0.603), depression (p=0.936), total PTS (p= 0.121), intrusion (p=0.243) and avoidance (p=0.216) symptoms, however there was a significant difference in hypervigilance symptoms (p=0.048) reported during the COVID-19 lockdown. Likewise, no significant differences were observed between UC and CD patients in anxiety (p=0.848), depression (p=0.759), total PTS (p=0.411), intrusion (p=0.429), avoidance (p=0.767) and hypervigilance (p=0.391) symptoms reported during the COVID-19 lockdown. In a similar way, no difference was observed in any of the SF36 sub-scales between males and females and between UC and CD patients. Table 1 presents HADS, IES-R and SF36 scores during the COVID-19 lockdown by gender and disease group.

Comparing HADS scores prior to and during the lockdown measures, we observed a significant increase in depression symptoms (p=0.038), while no significant effect was observed in anxiety symptoms (p=0.259) (Fig. 3). We then proceeded to separate data analyses by gender. In females, there was a significant increase in depression scores (p=0.006) during the lockdown compared to the pre-quarantine period (Fig.4). No significant changes in anxiety (p>0.999) or depression (p=0.884) scores compared to the pre-lockdown period were observed in males.

DISCUSSION

Our study revealed that during the first lockdown period in Greece, IBD patients reported increased levels of depression and post-traumatic stress symptoms and experienced impairment in most sub-domains of quality of life. These findings corroborate recent studies originating from various countries, including the Netherlands, Japan, Australia, UK, Spain, USA [2,4,10, 17,18,19] suggesting that during the COVID-19 lockdowns IBD patients experienced intense stress, increased health-related worries and depressive and anxious symptomatology. The fact that our sample was already enrolled in another research protocol and had been evaluated for anxiety and depression symptoms prior to the lockdown measures, provided us with the unique opportunity to assess prospectively the impact of the quarantine. The current analysis revealed a significant increase in depression symptoms during the lockdown which represents solid evidence regarding the negative

Table 1. *HADS, IES-R and SF36 scores (medians and IQR) by gender and disease type.*

	Males	Females	p	UC	CD	P
HADS-A	5 (4, 6)	5 (3.5, 11.5)	0.603	5 (3, 9)	5 (4.5, 6.5)	0.848
HADS-D	7 (4, 10)	8 (5.5, 9.5)	0.936	8 (6, 9)	6 (3.5, 10)	0.759
IES-R total	20 (2, 32)	30 (14, 40)	0.121	30 (18, 40)	20 (9, 35)	0.411
Intrusion	6 (0, 10)	10 (3, 12)	0.243	10 (3, 12)	6 (2, 11)	0.429
Avoidance	9 (1, 11)	12 (4, 14)	0.216	11 (8, 13)	9 (2, 14)	0.767
Hypervigilance	4 (1, 8)	8 (5, 13)	0.048*	8 (5, 13)	6 (3, 9)	0.391
Physical functioning	75 (67.5, 95)	92.5 (81.3, 100)	0.285	90 (72.5, 97.5)	90 (71.3, 100)	0.696
Role physical	100 (25, 100)	100 (75, 100)	0.859	100 (75, 100)	87.5 (25, 100)	0.448
Bodily pain	41 (36.5, 92)	73 (63.8, 84)	0.424	72 (46.5, 84)	73 (46, 96)	0.846
General Health	52 (35, 64.5)	38.5 (30, 64.3)	0.792	37 (30, 64.5)	54.5 (30.3, 63)	0.772
Vitality	75 (57.5, 85)	70 (40, 85)	0.557	80 (47.5, 85)	70 (40, 82.5)	0.592
Social Functioning	87.5 (63.5, 100)	100 (34.4, 100)	0.723	100 (56.3, 100)	93.8 (43.8, 100)	0.666
Role emotional	100 (83.3, 100)	100 (8.3, 100)	0.292	100 (33.3, 100)	100 (41.7, 100)	0.955
Mental Health	72 (54, 80)	56 (41, 80)	0.672	72 (44, 82)	68 (38, 78)	0.498

HADS: Hospital Anxiety Scale; IES-R: Impact of Event Scale-Revised; SF36: Health Survey 36 Short Form; IQR: Intraquartile range

psychological effects of social distancing and isolation on this patient population. We also found an increase in anxiety scores, although it did not reach statistical significance, probably due to the small sample size.

According to most relevant research, female patients appeared more vulnerable to the negative mental health consequences of the quarantine [4,6,10,19]. In our study, no significant differences were detected in anxiety, depression, overall PTS symptoms and quality of life scores between males and females at time point T2, during the quarantine. However, we found that female patients experienced a significant worsening in depression symptoms after the pandemic outburst, suggesting a higher vulnerability towards the quarantine-related adverse psychological consequences. General population studies have shown that women

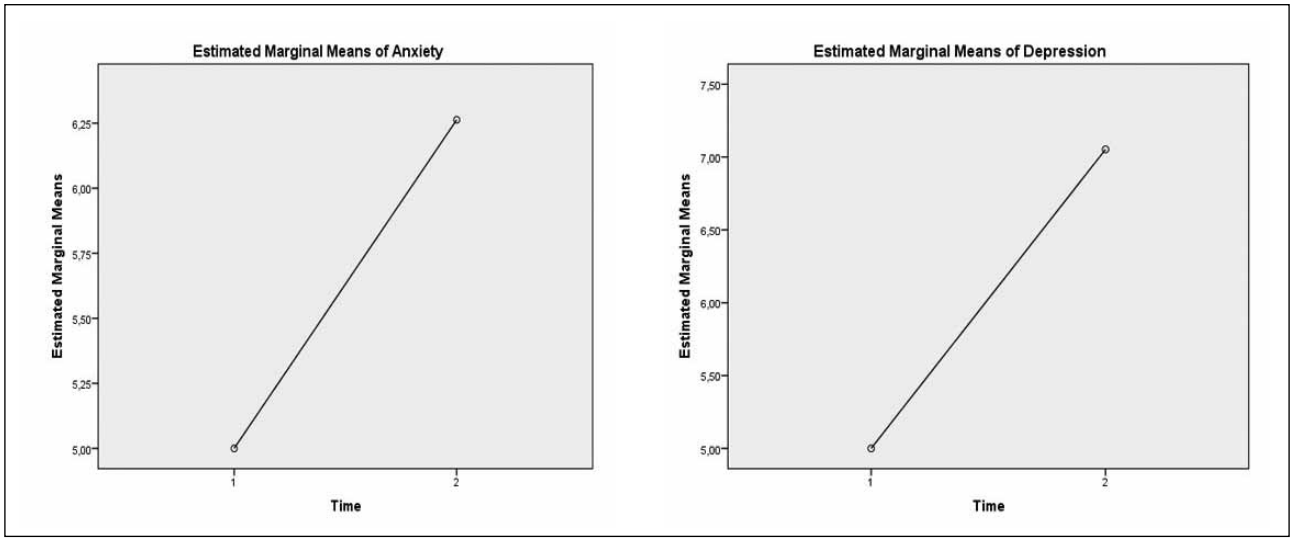

Figure 3. Changes in HADS-A and HADS-D scores for the whole sample pre- and post- lockdown measures.

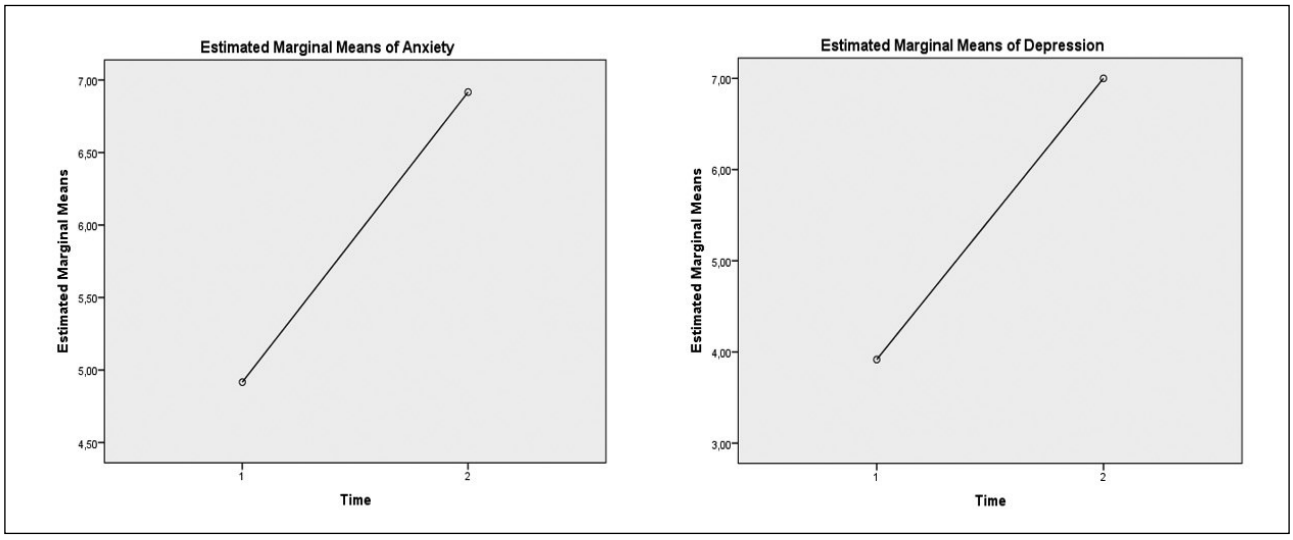

Figure 4. Changes in HADS-A and HADS-D scores for female patients pre- and post- lockdown measures.

experienced more intensely the psychosocial impact of the pandemic [5,20] and this vulnerability has been mainly attributed to increased childcare demands and greater occupational and financial difficulties during the lockdown period [21]. The current study's design did not allow us to detect potential mediators of women's psychological burden, however our results suggest that female IBD patients' mental health needs require extra attention and care not only during the pandemic but also in the upcoming post-pandemic era.

A major limitation of this study was the small sample size which probably did not allow us to detect more significant associations between the studied parameters.

In conclusion, our study confirmed that IBD patients commonly experience increased psychological distress and poor quality of life and their mental health was adversely affected during the first COVID-19 lockdown period. Female patients appeared more vulnerable to the quarantine's negative psychosocial consequences and their needs should be prioritized during the process of healthcare resources allocation, given that the upcoming post-pandemic period is anticipated to be characterized by a dramatic increase in psychosocial difficulties especially within high-risk populations.

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Author contributions: *KK conceived the idea, analyzed data and wrote the manuscript; GK and MK conducted the study and collected data; TL, TK, GD and GT recruited patients and collected data; KA and KT reviewed the manuscript and provided expert opinion; CT conceived the idea, reviewed and approved the final version of the manuscript*

REFERENCES

1. Wang C, Horby PW, Hayden FG, Gao GF. A novel coronavirus outbreak of global health concern. Lancet. 2020; 395(10223):470-3.
2. Nishida Y, Hosomi S, Fujimoto K, Nakata R, Sugita N, Itani S, et al. Impact of the Lockdown Due to the COVID-19 Pandemic on Patients With Inflammatory Bowel Disease. Front Med (Lausanne). 2021; 8:649759.
3. Wang C, Pan R, Wan X, Tan Y, Xu L, Ho CS, et al. Immediate psychological responses and associated factors during the initial stage of the 2019 coronavirus disease (COVID-19) epidemic among the general population in China. Int J Environ Res Public Health. 2020; 17(5):1729.
4. Planchuelo-Gómez Á, Odriozola-González P, Irurtia MJ, de Luis-García R. Longitudinal evaluation of the psychological impact of the COVID-19 crisis in Spain. J Affect Disord. 2020; 277:842-9.
5. Karaivazoglou K, Konstantopoulou G, Kalogeropoulou M, Iliou T, Vorvolakos T, Assimakopouloset K, al. Psychological distress in the Greek general population during the first COVID-19 lockdown. BJPsych Open. 2021;7(2):e59
6. Hernández Camba A, Ramos L, Madrid Álvarez MB, Pérez-Méndez L, Nos P, Hernández V, et al. Psychosocial impact of the COVID-19 pandemic on patients with inflammatory bowel disease in Spain. A post lockdown reflection. Gastroenterol Hepatol. 2021; S0210-5705(21): 00252-1.
7. Cao Q, Huang YH, Jiang M, Dai C. The prevalence and risk factors of psychological disorders, malnutrition and quality of life in IBD patients. Scand J Gastroenterol. 2019;

54(12):1458-66.
8. Mao R, Liang J, Shen J, et al. Chinese Society of IBD, Chinese Elite IBD Union; Chinese IBD Quality Care Evaluation Center Committee. Implications of COVID-19 for patients with pre-existing digestive diseases. Lancet Gastroenterol Hepatol. 2020; 5(5):425-7.
9. Cheema M, Mitrev N, Hall L, Tiongson M, Ahlenstiel G, Kariyawasam V. Depression, anxiety and stress among patients with inflammatory bowel disease during the COVID-19 pandemic: Australian national survey. BMJ Open Gastroenterol. 2021 ;8(1):e000581.
10. de Bock E, Filipe MD, Meij V, Oldenburg B, van Schaik FDM, Bastian OW, et al. Quality of life in patients with IBD during the COVID-19 pandemic in the Netherlands. BMJ Open Gastroenterol. 2021; 8(1):e000670.
11. Weiss DS, Marmar CR. The Impact of Event Scale – Revised. In Assessing Psychological Trauma and PTSD (eds Wilson JP, Keane TM): 399–411. Guilford Press, 1997.
12. Zigmond AS, Snaith RP. The Hospital Anxiety and Depression Scale. Acta Psychiatr Scand. 1983; 67(6):361–70.
13. Michopoulos I, Douzenis A, Kalkavoura C, Christodoulou C, Michalopoulou P, Kalemi G, et al. Hospital Anxiety and Depression Scale (HADS): validation in a Greek general hospital sample. Ann Gen Psychiatry. 2008; 7:4.
14. Ware JE, Kosinski M and Gandek B (eds). SF-36 Health Survey manual and interpretation guide. Lincoln, RI: QualityMetric Incorporated, 2004. 15.
15. Pappa E, Kontodimopoulos N, Niakas D. Validating and norming of the Greek SF-36 Health Survey. Qual Life Res. 2005; 14(5):1433–8.
16. Anagnostopoulos F, Niakas D, Pappa E. Construct validation of the Greek SF-36 Health Survey. Qual Life Res. 2005;14(8):1959-65.
17. Harris RJ, Downey L, Smith TR, Cummings JRF, Felwick R, Gwiggner M. Life in lockdown: experiences of patients with IBD during COVID-19. BMJ Open Gastroenterol. 2020; 7(1):e000541.
18. Sempere L, Bernabeu P, Cameo J, Gutierrez A, Laveda R, García MF, et al. Evolution of the emotional impact in patients with early inflammatory bowel disease during and after Covid-19 lockdown. Gastroenterol Hepatol. 2022; 45(2):123-33.
19. El-Dallal M, Saroufim A, Systrom H, Ballou S, Farhoud A, Pasam RT, et al. Assessing the repercussions of COVID-19 pandemic on symptoms, disease management, and emotional well-being in patients with inflammatory bowel disease: a multi-site survey study. Scand J Gastroenterol. 2022;57(4):406-14.
20. Luo M, Guo L, Yu M, Jiang W, Wang H. The psychological and mental impact of coronavirus disease 2019 (COVID-19) on medical staff and general public - a systematic review and meta-analysis. Psychiatry Res. 2020; 291:113190.
21. Yerkes MA, André SCH, Besamusca JW, Kruyen PM, Remery CLHS, van der Zwan R, et al. 'Intelligent' lockdown, intelligent effects? Results from a survey on gender (in)equality in paid work, the division of childcare and household work, and quality of life among parents in the Netherlands during the Covid-19 lockdown. PLoS One. 2020; 15(11): e0242249.

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Surgical management of early-stage breast cancer

Ioannis Chaveles[1]

Abstract

The management of breast cancer patients is multidisciplinary and requires the combined strengths of modern surgery, radiation therapy and oncological systemic treatments to yield the current excellent results. From initial diagnosis to long-term follow-up, new evidence continuously adds to our understanding regarding optimal treatment. As such, there is no "one size fits all" type of recommendation for the various types of breast cancer. In this review, the most recent guidelines are presented from the breast surgeon's point of view and the most significant new data anticipated are mentioned. With the vast majority of women surviving breast cancer, communication with patients and taking into account their wishes regarding their treatment is of paramount importance in modern practice.

Key words: *Early-stage breast cancer; breast cancer surgery; breast cancer management; SLNB; oncoplastic surgery; neoadjuvant chemotherapy*

INTRODUCTION

Breast cancer is by far the most common form of cancer among women. However, despite its high incidence, implementation of rigorous screening programs, increased awareness and improved diagnosis and treatment have contributed to significant reduction in breast cancer (BC) mortality rates. Increased survivability indicates that extra care should be taken by clinicians to ensure BC survivors' quality of life. Patients are more knowledgeable nowadays and clinician needs to be able to communicate facts and include them in the decision-making process.

Modern treatment is multidisciplinary and multimodal, including surgery, radiotherapy and systemic treatment. The goal is to determine the optimal combination of the aforementioned interventions which will offer oncological safety while de-escalating treatment and caring for patient preference at the same time.

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Diagnostic work-up in early breast cancer patients

The surgeon plays a pivotal role in the initial diagnosis and work-up of BC patients. Alongside medical history, menopausal status, clinical examination of the breasts and axillae, the surgeon has to request radiological assessment of the primary tumor including mammography, ultrasound of the breast and lymph nodes, as well as magnetic resonance imaging (MRI) of the breast in selected cases. MRI indications include family history of BC or known genetic mutations, lobular BC, extremely dense breasts, large discrepancy between clinical examination and imaging, presence of implants, suspicion of multifocal or multicentral disease, occult primary tumor, need for neoadjuvant chemotherapy (NAC) [1,2]. Tissue samples for complete histological assessment need to be taken, in the form of core biopsies for the primary tumor and core biopsy or fine needle aspiration biopsy for any suspicious nodes. Assessment of metastatic disease with whole body computed tomography imaging, bone scintigram and blood tumor markers measurement is reserved for patients with suspicious symptoms, high disease burden and aggressive tumor biology on the biopsy. Genetic testing should be offered to high-risk

patients such as those with a strong family history and BC diagnosis before the age of 50 [1].

Breast surgery in early-stage breast cancer

Breast conservation versus mastectomy

Both mastectomy and breast conserving surgery (BCS) combined with radiotherapy (RT) have been shown to be oncologically safe and bearing comparable results in multiple randomized clinical trials with a patient follow-up of up to 20 years. Local recurrence (LR) seems to vary predominantly according with tumor subtype and systemic therapy, rather than disease burden and type of surgery (BCS or mastectomy), thus, biologically aggressive cancers need not to be treated more aggressively from a surgical point of view [2]. The selection between BCS or mastectomy depends on tumor size compared to the size of the breast, anticipated aesthetic results, availability of oncoplastic techniques, patient's candidacy for RT, and, ultimately, patient's choice [1-4].

Oncoplastic breast conserving surgery

The blending of traditional breast oncologic surgery via wide local excision (WLE) and plastic surgery techniques, called oncoplastic BCS are increasingly being used by specially trained breast surgeons or teams of breast and plastic surgeons. These techniques have made possible BCS in the case of large tumors otherwise warranting mastectomy. Despite the additional disease burden in these patients, in a recent meta-analysis of all major relevant studies oncoplastic BCS has been proved safe in the setting of oncology when compared to both 'traditional' WLE and mastectomy [1,5].

Resection margins

In the excision of invasive disease, the "no-tumor on ink" guideline is universally accepted, regardless of patient characteristics, tumor histology or surgical technique employed [1,3,6]. For ductal carcinoma in situ (DCIS) a minimum clear margin of 2 mm is required, with wider margins not reducing the risk of LR [1,6,7]. When striving to achieve negative margins at the initial operation and reduce the reoperation rate for re-excisions, oncoplastic BCS has proven valuable, allowing for larger tissue resection volumes without compromising the cosmetic outcomes [1,6].

Mastectomy with or without reconstruction

For patients having to undergo mastectomy, the operation of choice is no longer straightforward, as nowadays there is a wide range of reconstructive techniques available. Beyond simple mastectomy, skin and/or nipple areola complex sparing mastectomy is employed, in the immediate or delayed setting, as well as autologous or not techniques, all with comparable oncologic safety and a significant advantage for quality of life [2,6]. The choice among the above operations is made after careful consideration of patient's expectations, her general health and potential comorbidities, tumor location, availability of genetic screening, pursuit of risk reducing surgery and overall cost of the procedure(-s). More specifically, nipple sparing operations require tumor to nipple distance of at least 1cm, detailed review of the imaging for retroareolar intraductal calcifications and intraoperative frozen section pathology of retroareolar biopsy to ensure major duct integrity [2,6].

Contralateral Prophylactic Mastectomy

It has been shown that women with unilateral sporadic BC do not gain significant oncological benefit when undergoing contralateral prophylactic mastectomy (CPM), apart from a marked decrease in the incidence of future contralateral BC (96%). However, the absolute benefit remains very low, given that for every 1000 women treated with CPM, only 2-3 CBCs will be avoided. Among women without a family history or genetic predisposition, factors that favor CPM are young age, white race, higher education and economic status/private security. What fuels the rise in CPM is the more widespread availability of skin/nipple-sparing mastectomy (SNSM) with immediate reconstruction. Indeed, women having bilateral simultaneous SNSMs will end up with increased symmetry and breast satisfaction. However, there is a cost in the form of a 2.7-fold increase in major surgical complications following CPM. These could lead to delays in the onset of adjuvant chemotherapy, which is of great importance especially for high-risk patients. The increased financial burden associated with CPM and its potential complications is of note and should be taken into account. Surgeons need to be prepared for a comprehensive and unbiased conversation with patients interested in CPM [8].

Postmastectomy radiotherapy

Postmastectomy radiotherapy (PMRT) for early-stage breast cancer is a quite controversial issue, as LR rates have decreased due to more comprehensive modern systemic treatment. The decision to proceed with PMRT

should be multidisciplinary, taking into account various factors determining the risk of recurrence (age, life expectancy and disease burden in both the breast and the axilla [2,9]. PMRT is especially critical as it poses a very significant threat to implant-based reconstruction (IBR), especially immediate IBR. The radiation of the reconstructed breast causes increased infection rates, implant loss and severe capsular contracture leading to reconstructive failure. Even when trying to address this problem with two-stage reconstruction with expander, reconstructive failure remains higher [6,10].

Axillary surgery in early-stage breast cancer

Sentinel lymph node biopsy

Axillary surgery for breast cancer plays a dual role, both therapeutic, as well as staging and prognostic. Initially axillary lymph node dissection (ALND) regardless of disease burden has been the norm. However, ALND comes with significant morbidity, such as arm lymphedema, sensory nerve damage and paresthesia, restriction of arm mobility and weakness, seroma formation and, rarely, chyle leak [6,11]. With an increasing understanding of tumor biology and the availability of constantly improving adjuvant treatments, it became clear that de-escalation was needed for patients without obvious lymph node involvement. Hence, in the 1990s multiple randomized clinical trials compared ALND to sentinel lymph node biopsy (SLNB)-only for node negative patients. SLNB has been the standard of care ever since its validation [1,3,6,11,12].

DCIS and SLNB

Currently, SLNB in patients with DCIS is not routinely performed in all patients. Women with DCIS undergoing mastectomy are offered SLNB because in case of upgrade to invasive disease the sentinel nodes will not be detectable following mastectomy. Other patients at high risk of pathological upgrade such as clinical presence of mass lesion or area of DCIS of >5cm, may be offered SLNB [11].

Omission of ALND in low axillary disease burden

In 2013, ALND was shown not to provide any advantage in patients with micrometastatic disease in the SLNB (one or more foci of <2mm), as there was no impact on survival [13-15].

The 2010s saw a further significant de-escalation of axillary surgery, in patients with limited macrometastatic disease. The 2011 American College of Surgeons Oncology Group (ACOSOG) Z0011 trial [16] and the 2014 European multicenter AMAROS trial [17] demonstrated that clinically node negative patients with limited positivity in the sentinel lymph nodes (1-2 positive SLNs) have similar axillary disease control whether being spared ALND or not. Radiotherapy and systemic treatment will still be applied appropriately. The ACOSOG Z0011 trial reports good outcome results even without radiotherapy to the axilla, consequently criteria have been proposed for the recommendation of radiotherapy: (1) tumor size ≥3 cm; (2) lymphovascular invasion at tumor pathology; (3) SLNs with extracapsular extension of the metastasis [11,18].

Breast surgery after neoadjuvant chemotherapy (NAC) in early-stage breast cancer

NAC has been the standard of care for locally advanced, inflammatory and metastatic breast cancers. It has been used to render inoperable tumors rejectable. More recently NAC has been used with the intent to downstage large tumors so that BCS becomes feasible [2,3]. However, nowadays NAC is being increasingly used in the setting of early-stage breast cancer, being suggested by the St. Gallen International Consensus Guidelines for the treatment of early breast cancer 2021 for stage II and III HER2-positive disease and triple negative breast cancers (TNBCs) [3]. Pathological complete response (pCR) is an excellent prognostic factor with a significant impact on overall survival (OS) and recurrence-free survival, especially in biologically more aggressive subtypes of BC.

Breast Conserving Surgery post-NAC

BCS post-NAC can be performed whether there is a radiological complete response (rCR) or residual disease, as long as it is technically possible. BCS in the setting of oncology is safe, with comparable LR rates disease free survival (DFS) and OS to patients treated with mastectomy [6,19].

Breast Imaging post-NAC

Breast MRI is required both before the onset of NAC, as well as upon completion preoperatively [2,6] and is the major determinant of rCR and the extent of excision during the operation [20].

Moreover, localization of the tumor bed is imperative for BCS post-NAC, usually by means of radiopaque clips inserted after diagnosis and subsequent wire localization before surgery [21].

Axillary surgery after NAC in early-stage breast cancer

The management of the axilla after NAC is an area of actively ongoing research. Some cases are uncontroversial: Patients with clinically positive axillary nodes post-NAC will undergo ALND. Also, patients downstaged to node-negative by the NAC are candidates for SLNB and in the case of significant positivity in the pathology, ALND is performed [2,3,6,11]. However, there was a concern that false negative rates (FNR) could be too high for post-NAC SLNB to offer a satisfactory result. This has been addressed in a few major studies: ACOSOG Z1071 (22), SENTINA (23) and SN FNAC [24] which highlight the importance of excision of at least 3 lymph nodes for the FNR to be kept below the acceptable 10% [2,3,6,11]. Another concern was whether the known positive node was actually sampled during the SLNB. This issue was addressed in the ACOSOG Z1071 [22,25] with the use of tailored axillary surgery (TAD). With this technique the proven positive node is marked and removed specifically, with a further reduction of FNR at 6.8%.

Controversy remains as to whether clinically negative patients with residual low burden disease in the SLNB can be spared ALND in favor of axillary radiotherapy, as per the Z0011 patients at upfront surgery. This is being addressed in the Alliance A011202 trial, expected to end in 2024.

Special considerations

BC management in the young patient

Young women under the age of 40 constitute a special subset of patients due to the following reasons: Formal breast cancer screening will not have started at this age; thus, they will usually present with palpable disease, i.e., higher stage of disease than the screen-detected older counterparts. In addition, it is more likely that women in this age group will suffer from more aggressive BC subtypes, such as TNBC, higher grade or HER2+ disease. As such, even young women at high risk for BC who are indeed under surveillance, will routinely present with interval cancers [26].

Genetic predisposition is another major issue within this age group, regardless of the presence of positive family history. It is believed that every BC patient under the age of 45 years should undergo genetic testing for BRCA1, BRCA2, PALB2, ATM, p53 and CHEK 2 genes. Ideally the testing needs to be completed prior to the surgical treatment, as the results may influence the surgical plan by dictating the need for a risk reducing operation [26]. BC patients under 40 years of age have been shown to have increased local recurrence rates, however this does not impact overall survival. As a consequence, in the absence of genetic predisposition, breast surgery principles in young women are identical to their older counterparts [26].

Of note is the assessment of the patients' wishes for a future pregnancy, as fertility preservation may be required. This may be in the form of gonadotropin-releasing hormone agonist administration for ovarian protection during pregnancy or may include embryo and/or oocyte preservation [2].

Breast cancer during pregnancy

One of the most challenging forms of BC is BC during pregnancy. Its current incidence is one case every 1000 pregnancies; however, this is expected to rise due to the social trend of increasing age at first pregnancy. In terms of BC biology, TNBC and HER2+ types seem to be dominant and a higher presence of tumor-infiltrating lymphocytes (TILs) is noted. The worse prognosis associated with BC in pregnancy can be attributed to late/delayed diagnosis, inability of optimal staging and the possibility of suboptimal treatment if an expert multidisciplinary team is not involved. Surgical treatment is considered safe to be applied for the whole duration of the pregnancy. The limiting factor for operation choice is the absolute contraindication of radiotherapy during pregnancy, the delay of which will lead to increased rates of LR after breast conserving surgery. As a consequence, there is a bias towards performing a mastectomy, especially if the operation takes place at the initial stages of the pregnancy. In this case, performing immediate reconstruction with a tissue expander is not contraindicated. Axillary surgery in pregnant women is a point of controversy. ALND is routinely performed, however recent studies have shown that SLNB can be offered utilizing Technetium-99m by the one-day protocol only. In these cases, the identification rate is high and is not accompanied by increased axillary LR rates [27].

Neo-adjuvant Endocrine Treatment (NET)

A less common modality for neo-adjuvant treatment is endocrine treatment alone. It is used as a tool to preoperatively downstage ER+/HER2- disease with treatment duration of 4-6 months, as well as to maintain oncologic safety when surgery needs to be delayed (e.g., COVID-19-induced delays). A recent meta-analysis of available data shows that when paired with OncotypeDX©

Recurrence Score (RS) assessment on the diagnostic core tissue biopsy samples, NET can yield satisfactory results. Patients with low (<18) or intermediate (18-30) RS were found to be four times more likely to respond than high risk patients and this cohort of patients will simultaneously be spared overtreatment in the form of NAC. Nonetheless, it should be noted that pCR is rarely achieved in the settings of NET (2.8%) [28].

Multifocal or multicentric breast cancer

Multifocal or multicentric (MF/MC) presents a surgical challenge and the implementation of BCT remains a point of controversy, especially in the case of MC disease. Further complicating treatment decisions, rarely, MF/MC presents with heterogeneous histology for different foci. The main concern is local recurrence (LR) after BCT. A recent meta-analysis showed that while LR after breast conserving surgery (BCS) for MF/MC BCs is higher than LR after BCS for unifocal BCs, interestingly there is no significant difference when comparing LR for MF/MC BCs treated with BCS versus mastectomy [29]. Consequently, the use of BCS for MF/MC disease has to be considered an equally efficacious alternative approach, as far as a pleasing cosmetic outcome can be achieved given disease size, patient characteristics and surgeon's oncoplastic expertise [30].

Inflammatory breast cancer

Inflammatory breast cancer (IBC) is a distinct subtype of BC characterized by rapid progression and early occurrence of distant disease. Notoriously difficult to treat in the past, 5-year overall survival rates still remain less than 71%, with triple negative variants being as low as 44%. The diagnosis of IBC will be based upon core biopsy tissue samples from the main tumor (when present) or skin punch biopsy samples showing dermal lymphatic invasion. Surgeons need to be aware that 25% of punch biopsies will miss the dermal cancer and only show lymphedema. This leaves the rapidity of symptoms onset (<6 months) as the main diagnostic criterion. Use of MRI and PET/CT are optimal for local and systemic staging. The mainstay of IBC treatment is the tri-modality approach: Preoperative systemic treatment, surgery and post-operative radiotherapy. During systemic treatment clinicians need to re-examine the patient for the detection of disease progression despite treatment. Surgery for IBC usually comes in the form of mastectomy including previously involved skin and ALND of levels 1 and 2. If primary closure cannot be achieved due to the extent of skin excision, a latissimus dorsi or abdominal flap has to be considered. Breast conserving surgery and skin sparing reconstruction techniques are contraindicated. As systemic treatment evolves and cPR rates increase, less aggressive surgical approaches will have to be considered, tailored to individual patients' needs [1,31].

Occult breast cancer

This rare occurrence of BC (<0.5% of all BCs) presents with axillary lymph node disease without an apparent primary tumor at the breast. A breast MRI needs to be performed, in search of the breast primary site, as well as a PET-CT for the exclusion of any other primary site. Surgical treatment usually comprises mastectomy and ALND, however axillary radiotherapy after SLNB with low disease burden is still a valid option and whole breast radiotherapy is a valid alternative to mastectomy. Systemic treatment is administered accordingly [1].

Surgery for locally recurrent breast cancer

Local recurrence (LR) on the chest wall after mastectomy can be excised if focal and not extending beyond the pectoralis muscles. Depending on the extent of skin involvement, local flaps may be required for skin closure. When multifocal or infiltrating the ribcage, systemic treatment and radiotherapy may be a better solution. LR after BCS is usually treated with completion mastectomy, since radiotherapy to the breast cannot be repeated when initially performed. However, small recurrent tumors <2 cm with a long time to relapse from initial surgery (>48 months) have been treated with redo BCS successfully. Lastly, redo BCS should not be considered in high-risk patients such as carriers of genetic mutations. LR in the axilla after SLNB warrants ALND of levels 1 and 2. LR after ALND is treated with axillary exploration for removal of the disease [32].

Male breast cancer

Approximately only 1% of breast cancers occur in men, so, unsurprisingly, research is focused on female BC. Men are often diagnosed at a later stage, with almost half presenting with locally advanced or distant disease. From the point of view of surgery, it is very common for male patients to undergo mastectomy (due to nipple or skin involvement) and SLNB (or ALND when obvious disease is present in the axilla). BCS is seldom used and, in these cases, it usually applies to T1 disease. Surgery is followed by radiotherapy to the chest wall and axilla

as appropriate. Most BCs in men express ER, PR and AR receptors, so endocrine treatment is used. Tamoxifen is the treatment of choice, as aromatase inhibitors can cause an unwanted increase in androgens, but significant side effects impacting quality of life, such as hot flushes and lowered sex drive, lead to a quarter (25%) of patients discontinuing their treatment [33].

CONCLUSIONS

We live in the era of de-escalation and personalization of breast cancer treatment. Significant advances are in the works. TAD is being assessed as a completely personalized and least invasive means of axillary surgery [34]. Elimination of surgery after pCR is a sensible goal, however much remains to be addressed regarding adequacy of tissue sampling, minimizing FNRs and optimal patient follow-up [35]. From the point of view of breast surgery, oncoplastic techniques are essential, as are reconstruction techniques that are continuously requested by women today [36]. These requirements highlight the need for highly specialized and qualified breast surgeons alongside all other members of the multidisciplinary team, always cognizant of the latest advances in this everchanging field.

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REFERENCES

1. Cardoso F, Kyriakides S, Ohno S, Penault-Llorca F, Poortmans P, Rubio I, et al. Early breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2019;30(8):1194-220.
2. Moo T-A, Sanford R, Dang C, Morrow MJPc. Overview of breast cancer therapy. PET Clin. 2018;13(3):339-54.
3. Burstein H, Curigliano G, Thürlimann B, Weber W, Poortmans P, Regan M, et al. Customizing local and systemic therapies for women with early breast cancer: the St. Gallen International Consensus Guidelines for treatment of early breast cancer 2021. Ann Oncol. 2021;32(10):1216-35.
4. Waks AG, Winer EPJJ. Breast cancer treatment: a review. JAMA. 2019;321(3):288-300.
5. Campbell EJ, Romics L. Oncological safety and cosmetic outcomes in oncoplastic breast conservation surgery, a review of the best level of evidence literature. Breast Cancer (Dove Med Press). 2017;9:521.
6. Riis M. Modern surgical treatment of breast cancer. Ann Med Surg (Lond). 2020;56:95-107.
7. Houssami N, Macaskill P, Marinovich ML, Morrow M. The association of surgical margins and local recurrence in women with early-stage invasive breast cancer treated with breast-conserving therapy: a meta-analysis. Ann Surg Oncol. 2014;21(3):717-30.
8. Montagna G, Morrow M. Contralateral prophylactic mastectomy in breast cancer: what to discuss with patients. Expert Rev Anticancer Ther. 2020;20(3):159-66.
9. Recht A, Comen EA, Fine RE, Fleming GF, Hardenbergh PH, Ho AY, et al. Postmastectomy radiotherapy: an american society of clinical oncology, american society for radiation oncology, and society of surgical oncology focused guideline update. Pract Radiat Oncol. 2016;6(6):e219-e34.
10. Ricci JA, Epstein S, Momoh AO, Lin SJ, Singhal D, Lee BT. A meta-analysis of implant-based breast reconstruction and timing of adjuvant radiation therapy. J Surg Res. 2017;218:108-16.
11. Magnoni F, Galimberti V, Corso G, Intra M, Sacchini V, Veronesi P, editors. Axillary surgery in breast cancer: an updated historical perspective. Seminars in oncology; 2020: Elsevier.
12. Chang JM, Leung JW, Moy L, Ha SM, Moon WK. Axillary nodal evaluation in breast cancer: state of the art. Radiology. 2020;295(3):500-15.
13. Galimberti V, Cole BF, Zurrida S, Viale G, Luini A, Veronesi P, et al. Axillary dissection versus no axillary dissection in patients with sentinel-node micrometastases (IBCSG 23–01): a phase 3 randomised controlled trial. Lancet Oncol. 2013;14(4):297-305.
14. Galimberti V, Cole BF, Viale G, Veronesi P, Vicini E, Intra M, et al. Axillary dissection versus no axillary dissection in patients with breast cancer and sentinel-node micrometastases (IBCSG 23-01): 10-year follow-up of a randomised, controlled phase 3 trial. Lancet Oncol. 2018;19(10):1385-93.
15. Solá M, Alberro JA, Fraile M, Santesteban P, Ramos M, Fabregas R, et al. Complete axillary lymph node dissection versus clinical follow-up in breast cancer patients with sentinel node micrometastasis: final results from the multicenter clinical trial AATRM 048/13/2000. Ann Surg Oncol. 2013;20(1):120-7.
16. Giuliano AE, Hunt KK, Ballman KV, Beitsch PD, Whitworth PW, Blumencranz PW, et al. Axillary dissection vs no axillary dissection in women with invasive breast cancer and sentinel node metastasis: a randomized clinical trial. JAMA. 2011;305(6):569-75.
17. Donker M, van Tienhoven G, Straver ME, Meijnen P, van de Velde CJ, Mansel RE, et al. Radiotherapy or surgery of the axilla after a positive sentinel node in breast cancer (EORTC 10981-22023 AMAROS): a randomised, multicentre, open-label, phase 3 non-inferiority trial. Lancet Oncol. 2014;15(12):1303-10.
18. Morrow M. Management of the node-positive axilla in breast cancer in 2017: selecting the right option. JAMA Oncol. 2018;4(2):250-1.
19. Sun Y, Liao M, He L, Zhu C. Comparison of breast-conserving surgery with mastectomy in locally advanced breast cancer after good response to neoadjuvant chemotherapy: A

PRISMA-compliant systematic review and meta-analysis. Medicine (Baltimore). 2017;96(43).
20. Dialani V, Chadashvili T, Slanetz PJ. Role of imaging in neoadjuvant therapy for breast cancer. Ann Surg Oncol. 2015;22(5):1416-24.
21. Newman LA, Buzdar AU, Singletary SE, Kuerer HM, Buchholz T, Ames FC, et al. A prospective trial of preoperative chemotherapy in resectable breast cancer: predictors of breast-conservation therapy feasibility. Ann Surg Oncol. 2002;9(3):228-34.
22. Boughey JC, Suman VJ, Mittendorf EA, Ahrendt GM, Wilke LG, Taback B, et al. Sentinel lymph node surgery after neoadjuvant chemotherapy in patients with node-positive breast cancer: the ACOSOG Z1071 (Alliance) clinical trial. JAMA. 2013;310(14):1455-61.
23. Kuehn T, Bauerfeind I, Fehm T, Fleige B, Hausschild M, Helms G, et al. Sentinel-lymph-node biopsy in patients with breast cancer before and after neoadjuvant chemotherapy (SENTINA): a prospective, multicentre cohort study. Lancet Oncol. 2013;14(7):609-18.
24. Boileau J-F, Poirier B, Basik M, Holloway CM, Gaboury L, Sideris L, et al. Sentinel node biopsy after neoadjuvant chemotherapy in biopsy-proven node-positive breast cancer: the SN FNAC study. J Clin Oncol.2015;33(3):258-64.
25. Boughey JC, Ballman KV, Le-Petross HT, McCall LM, Mittendorf EA, Ahrendt GM, et al. Identification and resection of the clipped node decreases the false negative rate of sentinel lymph node surgery in patients presenting with node positive breast cancer (T0-T4, N1-2) who receive neoadjuvant chemotherapy–results from ACOSOG Z1071 (Alliance). Ann Surg. 2016;263(4):802.
26. Subhedar PD, McLaughlin SA. Breast cancer in the young patient: review of therapy and treatment considerations. Breast Cancer Manag. 2020;9(2):BMT39.
27. Poggio F, Tagliamento M, Pirrone C, Soldato D, Conte B, Molinelli C, et al. Update on the management of breast cancer during pregnancy. Cancers (Basel). 2020;12(12):3616.
28. Davey M, Ryan É, Boland M, Barry M, Lowery A, Kerin MJ. Clinical utility of the 21-gene assay in predicting response to neoadjuvant endocrine therapy in breast cancer: A systematic review and meta-analysis. Breast. 2021;58:113-20.
29. Fang M, Zhang X, Zhang H, Wu K, Yu Y, Sheng Y. Local control of breast conservation therapy versus mastectomy in multifocal or multicentric breast cancer: a systematic review and meta-analysis. Breast Care (Basel).2019;14(4):188-93.
30. Corso G, Magnoni F, Provenzano E, Girardi A, Iorfida M, De Scalzi AM, et al. Multicentric breast cancer with heterogeneous histopathology: a multidisciplinary review. Future Oncol. 2020;16(8):395-412.
31. Baker JL, Hegde J, Thompson CK, Lee MK, DiNome M. Locoregional Management of Inflammatory Breast Cancer. Curr Breast Cancer Rep. 2020; 12:326–35.
32. Goel A, Agarwal VK, Nayak V, Yogsrivas R, Gulia A. Surgical Management of Locoregional Recurrence in Breast Cancer. Indian J Surg Oncol. 2021;12(3):616-23.
33. Gucalp A, Traina TA, Eisner JR, Parker JS, Selitsky SR, Park BH, et al. Male breast cancer: a disease distinct from female breast cancer. Breast Cancer Res Treat. 2019;173(1):37-48.
34. Henke G, Knauer M, Ribi K, Hayoz S, Gérard M-A, Ruhstaller T, et al. Tailored axillary surgery with or without axillary lymph node dissection followed by radiotherapy in patients with clinically node-positive breast cancer (TAXIS): study protocol for a multicenter, randomized phase-III trial. Trials. 2018;19(1):1-28.
35. Heil J, Kuerer H, Pfob A, Rauch G, Sinn H, Golatta M, et al. Eliminating the breast cancer surgery paradigm after neoadjuvant systemic therapy: current evidence and future challenges. Ann Oncol. 2020;31(1):61-71.
36. Jonczyk MM, Jean J, Graham R, Chatterjee A. Surgical trends in breast cancer: a rise in novel operative treatment options over a 12 year analysis. Breast Cancer Res Treat. 2019;173(2):267-74.

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Dementia management in the COVID-19 crisis era

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Abstract

The COVID-19 crisis has perplexed the management of dementia. Repetitive confinement and quarantine measures, the high vulnerability of older adults to severe acute respiratory syndromes and the difficulties of healthcare systems to cope with the overwhelming care needs, have placed people with dementia at even greater disadvantage compared to the pre-crisis period. Here, data on the particularities of the treatment of COVID-19 infections in older adults with dementia, COVID-19 crisis-related changes in dementia management and the increase of caregiver burden are succinctly presented. Moreover, light is shed on the ramifications of ageist attitudes and on the challenges of allocating limited healthcare resources, which threaten clinicians with moral injury. Despite not being a one size fits all strategy, telemedicine services seem to embody a pragmatic way to overcome, at least partially, the effects of the reduction or even suspension of non-emergency diagnostic and therapeutic in-person dementia care services during the COVID-19 crisis. In addition, increasing awareness among medical and non-medical professionals about the principles of healthcare ethics, transparent decision- making and implementation of distress-mitigating interventions for hospital workforces could facilitate moral injury prevention and sufficient coping with moral stress in the field of dementia care in the COVID-19 crisis and beyond it.

Key words: *COVID-19; dementia treatment; caregiver burden; moral injury; telemedicine*

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INTRODUCTION

The COVID-19 crisis

It has already been almost two years since the World Health Organization declared Coronavirus disease 2019 (COVID-19) a pandemic. The term coronavirus disease 2019 (COVID-19) refers to an acute respiratory infection which is caused by the novel RNA virus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1,2]. The clinical impact of the new virus ranges from asymptomatic phenotypes to acute respiratory distress syndrome, metabolic acidosis, liver, kidney and heart failure, but has also implications for mental health [3–5]. These clinical uncertainties in conjunction with the appearance of new virus variants being increasingly transmissible and the detrimental socioeconomic effects of draconic measures (e.g. con-

finement, quarantine) have created a stressful healthcare and public terrain that encumbers public health, global economy and social cohesion [6]. Coronavirus disease cannot be approached as a healthcare challenge solely concerning infectious disease specialists and pneumonologists as it co-exists or even interacts with other morbidities that continue to affect individuals. Interestingly, vertical and primary focus on preventing and containing COVID-19, seems to have led to disruptions in healthcare service provision-, access- and supply chains. Of note, older adults with dementia have paid an enormous death toll since the outbreak of the COVID-19 crisis, since they are particularly vulnerable to its detrimental effects [7,8].

Dementia symptoms and treatment

Dementia embodies a complex phenotype and a therapeutic challenge. The term dementia denotes a syndrome that is characterized by a triad of symptom groups: persistent deterioration of cognitive function upon a relatively stable level of consciousness (e.g. memory-, attention-, language deficits), behavioural and psychological (neuropsychiatric) symptoms such as apathy, depressive mood, anxiety, agitation, irritability, hallucinations, and disturbances in complex and basic activities of daily living [9]. Dementia can be caused by various diseases. Neurodegenerative diseases- including Alzheimer disease (AD) and Lewy bodies disease, and cerebrovascular disease constitute the most common causes of dementia [10]. The pharmacological treatment of dementia in Europe is based on medications, which ideally mildly ameliorate or stabilize cognitive symptoms, as well as on psychopharmacological agents in order to treat neuropsychiatric symptoms [11,12]. The other backbone of dementia management encompasses non-pharmacological interventions, such as cognitive training, occupational therapy and physical exercise, counselling services for patient caregivers and environmental modifications aiming to help people with dementia and their families to deal with the multifaceted ramifications of patient's functional decline [13]. Due to the lack of one-size-fits-all therapy, dementia management embodies a quite challenging task.

COVID-19 crisis and dementia symptoms

The drastic measures imposed by governments to keep the pandemic at bay, as for instance those of home confinement and social distancing, significantly affect the mental health of older adults living with dementia. Their outdoor and social activities, physical contact with their families and friends, visits to their doctors or day-care centres have been significantly diminished. In this context, there are indications of cognitive, neuropsychiatric and functional worsening in people with dementia during the confinement period [8,14–18]. Higher prevalence and severity of neuropsychiatric symptoms, such as agitation, apathy, depression, anxiety and changes in appetite, were shown to correlate closely with the duration of confinement and lower cognitive function, while an overall worsening of cognitive symptoms with or without a decrease of functional independence was observed during confinement in parts of the studied samples [15,16,19–21]. It should be underscored that most of these studies included relatively small cohorts, they did not consider longitudinal changes in dementia symptoms and they were conducted over the telephone. Despite these limitations, such studies shed light on the negative effects of the COVID-19 crisis on the mental health of older adults with dementia.

COVID-19 symptoms in people with dementia

People with dementia are at high risk for becoming seriously infected with COVID-19. Their difficulties to firmly grasp the dangers related to the COVID-19 crisis and adhere to the necessary preventive measures, as well as the residence of a part of them at nursing homes, where the chance of transmission is higher, make older adults with dementia particularly vulnerable to COVID-19 infection [20–23]. Moreover, older adults suffering from chronic diseases such as dementia develop more serious and lethal forms of COVID-19 [14]. They are more vulnerable to the development of severe neuropsychiatric phenotypes, including delirium, stroke, seizures and encephalitis-like presentations [24,25], which are associated with poor prognosis. Risk factors include old age, dementia and multiple drug use. The consequences of COVID-19, such as organ failure, electrolyte abnormalities and sepsis, may also contribute to the presence of delirium. The association between dementia and serious COVID-19 symptoms does not exclusively stem from the well-studied increased mortality rate of dementia; it may also mirror the consequences of ageist approaches in allocating healthcare resources in exceptional resource-limited constellations such as those of significant surges in COVID-19 cases [26,27]. A further factor that may underpin this association is the common initial manifestation of the infection in older adults with atypical symptoms such as altered mental

status without cough or fever which can stymie early diagnosis and initiation of the appropriate therapeutic interventions [21,23,28].

The aim of this review is to succinctly capture the challenges related to dementia management which confront medical and non-medical professionals and caregivers in the complex context of the COVID-19 crisis. The following lines point to the necessity of paving the way towards pragmatic strategies, in order to optimally meet the healthcare needs of people with dementia, ease the burden of their caregivers and improve the quality of life of both.

Pharmacological treatment of individuals with dementia and COVID-19 infection

Respiratory system

COVID-19 infection affects a wide range of organs and systems and subsequently may lead to alterations of drug pharmacokinetics as well as to a higher vulnerability to adverse effects related to psychotropics commonly prescribed to people with dementia [29–31]. Frequently affected in symptomatic COVID-19 cases, the respiratory system may be suppressed by psychotropics such as benzodiazepines, despite their crucial role in alleviating symptoms of anxiety in contexts with severe pneumonia or acute respiratory distress syndrome. Moreover, certain antipsychotics, such as risperidone and olanzapine, have been shown to be related to respiratory distress [32–35]. Individuals on clozapine, such as patients suffering from dementia due to Parkinson's disease or Lewy bodies [36], deserve particular attention, since this atypical antipsychotic might lead to serious pneumonia [37–40]. In the absence of guidelines regarding the use of benzodiazepines and antipsychotics in patients with COVID-19, clinicians are called to carefully weigh in each individual case the risks and benefits of initiating or continuing such medications and to properly adjust their dosages.

Cardiovascular system

Even though no final conclusions have been drawn with regard to the impact of arterial hypertension and cardiovascular diseases on the outcome of COVID-19 infection, the effects of psychotropic medication on cardiovascular system should be taken into account in the treatment of patients infected by COVID-19 [41]. Antipsychotics are associated with severe cardiovascular adverse effects, e.g. ventricular arrhythmia with subsequent corrected-QT (QTc) prolongation and sudden cardiac death [42]. Particularly, the mortality rate of older adults with dementia, being under antipsychotic therapy, is significantly high [43]. Moreover, tricyclic antidepressants (TCAs) exert cardiotoxic effects [44]. They pertain to increased risk for arrhythmias, tachycardia and coronary heart disease and are contraindicated in older adults. Finally, because of the high risk for QTc prolongation, upper limits for the selective serotonin reuptake inhibitors (SSRIs) citalopram and escitalopram dosing in older adults have been recommended, although scientific evidence is not solid yet [45].

Haematological changes

In many cases of COVID-19, lymphopenia and leukopenia have been reported [46, 47]. These findings are associated with unfavourable prognosis, mainly because they increase the risk of further infections. Therefore, medications affecting white blood cell production should be prescribed with caution or be avoided, if possible. For instance, the initiation of a treatment with clozapine, which can lead to blood dyscrasia with severe agranulocytosis [48] and subsequently increase the risk for pneumonia and further complications [49], should be carefully determined even in patients with dementia due to Lewy bodies who suffer from psychotic symptoms. Furthermore, COVID-19, along with immobilization and hypoxia pertains to increased risk of deep vein thrombosis [50]. Certain antipsychotics, such as clozapine, quetiapine and risperidone, might further increase this possibility, too [51]. On the other hand, SSRIs have been shown to be related to higher risk for gastrointestinal tract bleeding and intracranial bleeding [52].

Hepatic and renal function alterations

COVID-19 can lead to acute liver and kidney injury [53]. Acknowledging that psychotropics rely on hepatic metabolism and/or renal excretion, dosage adjustments are likely to become inevitable. TCAs, atypical antipsychotics and lithium, which have been accused of hepatotoxicity or nephrotoxicity, should be avoided in patients with acute liver and/or kidney injury.

Neuropsychiatric side effects of suggested COVID-19 treatments (Table 1)

Remdesivir

Remdesivir is an antiviral agent which inhibits the RNA-dependent-RNA-polymerase of SARS-CoV-2 and subsequently decreases viral load [54]. No neuropsy-

Table 1. *Potential side effects of suggested COVID-19 treatments on mental health of people with dementia*

Suggested Covid-19 Treatments	Potential Neuropsychiatric Side Effects
Remdesivir	Rare side effects including excessive sweating and shivering may mimic panic attack symptoms Drug-drug interactions with psychotropic medication
Chloroquine and hydroxychloroquine	Delirium, agitation, suicidality, personality changes, depression, sleep disturbances, psychotic symptoms Drug-drug interactions with psychotropic medication
Corticosteroids	Agitation, depression, anxiety, euphoria, hypomania, insomnia, irritability, delirium, psychotic symptoms, cognitive deterioration Drug-drug interactions with psychotropic medication
Colchicine	Delirium, seizures
Monoclonal antibodies	None

chiatric side effects of remdesivir have been reported so far [55]. Rare side effects including excessive sweating and shivering may be erroneously interpreted as symptoms of a panic attack. However, remdesivir may elevate the levels of hepatic enzymes and perplex the use of hepatically metabolized or hepatotoxic psychotropic drugs.

Chloroquine and hydroxychloroquine

Chloroquine, an anti-malarian drug, and hydroxychloroquine, its derivative compound that is widely used in rheumatology, had initially emerged as a potential treatment of COVID-19. However, the use of (hydroxy)chloroquine is currently not recommended in patients with COVID-19. Both chloroquine and hydroxychloroquine are associated with various neuropsychiatric side effects, such as delirium, agitation, suicidality, personality changes, depression, sleep disturbances and psychotic symptoms, to which people with dementia are particularly sensitive [55,56]. They are metabolized by CYP3A4, which is either inhibited or induced by many psychotropics, while chloroquine and hydroxychloroquine inhibit CYP2D6, pertain to QTc prolongation and decrease seizure threshold. Thus, treating people with dementia and COVID-19 infection with (hydroxy)chloroquine exposes them to drug-drug interactions, resulting in lower effectiveness and higher risk for cardiovascular, neurological and other side effects.

Corticosteroids

Since SARS-CoV-2 provokes an excessive inflammatory response, corticosteroids were proposed as potential treatment, as they have anti-inflammatory effects. Nonetheless, since corticosteroid use in individuals with COVID-19 infection is related to delayed viral clearance and did not convincingly improve survival in all patients, corticosteroids should be used with extreme caution in the treatment of COVID-19 [57]. Their well-known neuropsychiatric and cognitive side-effects such as agitation, depression, anxiety, euphoria, hypomania, insomnia, irritability, delirium, psychosis and cognitive deterioration may complicate a dementia syndrome [58]. Moreover, corticosteroids induce CYP3A4 and CYP2C19, so potential drug-drug interactions should be also taken into account [59].

Colchicine

Due to its anti-inflammatory features, colchicine has been proposed as a treatment against COVID-19 infection [60]. Toxic levels of colchicine are related to delirium or seizures, which occur with higher incidence in individuals with dementia than in the general population [61,62]. Clinicians should be aware of the possible drug-drug interactions of colchicine, as its metabolism and excretion may be affected by drugs, such as clarithromycin, cyclosporine, ketoconazole, ritonavir, azithromycin [63,64].

Monoclonal antibodies

Three monoclonal antibody products have received Emergency Use Authorizations (EUAs) from the Food and Drug Administration (FDA) for the treatment of mild to moderate COVID-19 so far, mainly

bamlanivimab plus etesevimab, casirivimab plus imdevimab and sotrovimab [65–67]. The former two can additionally be prescribed as post-exposure prophylaxis (PEP) for individuals who are at high risk of acquiring COVID-19. No neuropsychiatric side effects or negative effects on cognitive function of the aforementioned monoclonal antibody products have been reported yet.

Nonpharmacological management of dementia in the era of the COVID-19

Social distancing- and generalized lockdown measures led to the reduction or even to the suspension of non-emergency diagnostic and therapeutic healthcare services for older adults with dementia (e.g. reduction of the size of therapy groups at Day Care Centres) and deprived people with dementia of in-person mental healthcare services. 'Telemedicine' provides a model of care provision, based on new technologies, which has proven valuable in mitigating the detrimental effects of the COVID-19 crisis on traditional care of older adults with dementia [68–70]. Telephone-calls and video conferences using platforms available online like WhatsApp, Zoom, FaceTime and Teams facilitate ongoing follow-up and management of patients with dementia. They even enable assessment of cognitive functions of older adults with cognitive complaints, since online audio-visual versions of popular neurocognitive instruments such as the Mini-Mental State Examination (MMSE) and the Montreal Cognitive Assessment (MoCA) have been developed [71]. Moreover, the use of electronic health record systems through online platforms like Google Forms and e-mails notifying patients of necessary diagnostic examinations or medical prescriptions have greatly contributed to all this effort.

To a large extent, the daily schedule of Dementia Day Care Centres went on-line [69,70]. Webinars and podcasts on the COVID-19 crisis were organised. Videos with recommendations on strategies to minimize the risk of virus transmission, on physical activity at home, on exercises for cognitive stimulation and speech/swallowing interventions for people with dementia are publicly available via websites of such centres and further institutions for dementia and ageing. Moreover, every day real-time group sessions were carried out online for people with dementia to boost their memory and physical condition and individualized psychotherapeutic sessions via phone-calls or online were offered. Cognitive and physical enhancement exercises and videos were also sent to the email address of caregivers on a regular basis [69]. In cases of caregiver-patient dyads with no access to the internet, virtual illiteracy or disabilities impeding their participation in the aforementioned programs, or absolute absence of a supportive social network, healthcare professionals (social workers, nurses, psychologists) conducted home visits following all necessary preventive measures for COVID-19 transmission. They not only provided psychosocial support, cognitive stimulus exercises, information guides for COVID-19 written in a simple and comprehensive way, but also tried to familiarize older adults with the use of the internet, video conference applications, so that after a few visits they could participate in online sessions.

New technologies also facilitated the operation of long-term care facilities for people with dementia in the COVID-19 crisis. Videoconferences were employed for observing and addressing the behavioural symptoms of patients with dementia living in long-term care facilities and curbed the rates of their hospital admissions [72]. Devices like smartphones and tablets have enabled the communication of older people living in such facilities with their families and friends, since visiting has been radically restricted or even suspended [73]. Video calling formed an alternative way to remain in touch with relatives and friends during the crisis, avoid social isolation and affective destabilization, while smart devices provide the opportunity to listen to music and download useful apps for stimulus memory games [73–75].

The integration of telemedicine and technological devices into dementia management is not a straightforward process. Important barriers have been brought into light by healthcare professionals, people with dementia and their caregivers [72]. First of all, older adults and even more older adults with dementia may face great difficulties to become familiar with the operation of technological devices or internet services, the use of which may be hampered by the lack of the necessary resources (smartphones, tablets, webcams) or low connection quality particularly in rural or remote areas [69,72]. Of note, visual and/or auditory sensory impairments related to ageing may set up further barriers. What is more, successful participation in therapeutic video conference sessions mostly depends on the motivating and supporting endeavours of the

caregiver and is rarely possible in cases of patients left alone during such sessions, while increasing severity of cognitive deficits undermines their participation in telemedicine [76].

Dementia caregiver challenges in the era of the COVID-19

Caregivers of people with dementia are very prone to developing depression and anxiety symptoms as well as to report low quality of life [77], since caring for people with dementia embodies a chronic stressor [78]. Caregiver burden mainly depends on patients' needs for support in activities of daily living, their neuropsychiatric symptoms and their memory- and executive function deficits. It is also contingent on the physical and emotional resilience of the carer [79]. Resilience is related to the degree of dependence caring, the presence of depressive and anxiety symptoms and the health-related quality of life of the caregiver [80]. Therefore, both caregiver-related and patient-related factors influence caregiver's burden.

Caregivers of people with dementia belong to the hidden victims of the outbreak of the COVID-19 pandemic. Confinement measures increased caregivers' stress independently of the severity of symptoms of the individual with dementia, but the more severe the symptoms were, the higher the stress experienced by the caregiver [81]. Decline in cognition, communication, affective symptoms, movement disturbances and low compliance with the measures imposed by governments during the COVID-19 crisis were associated with increased caregivers' psychological and physical burden, particularly where the available support sources were limited [82–84]. Despite the lack of general agreement [85], confinement duration seems to correlate with the severity of caregiver depressive symptoms. This association may be attributed to the detrimental effects of social distancing and mobility restrictions on psychological support of caregivers [86]. Interestingly, even in the absence of significant changes in neuropsychiatric symptoms of patients before and after the outbreak of COVID-19 pandemic, caregiver distress severity during the confinement period was influenced not only by memory deficits and neuropsychiatric symptoms of patients, but also by caregiver hyperarousal and avoidance symptoms, reflecting the traumatic dimension of the pandemic, and worries directly linked to the COVID-19 crisis [78]. Quite unexpectedly, caregivers with high resilience were shown to be more vulnerable to significant increase in anxiety levels during lockdown than caregivers with low resilience [86]. Furthermore, tension and stress in families which had been called to replace the main caregiver because of COVID-19 infection have been reported due to the subsequent changes in the roles of family members and their relationships [87]. Hence, there is an urgent need for psychotherapeutic interventions, so that levels of depression, anxiety and caregiver burden are reduced.

Strategies for easing caregiver burden include avoiding isolation, attending group support meetings and sharing the burden of care with other family members and other caregivers [88]. As the access to community services providing mental healthcare for people with dementia and their caregivers has been restricted during the COVID-19 crisis, caregivers have taken advantage of telemedicine services. Webinars and podcasts for caregivers providing useful information, support, self- help guidance and ways of enriching the daily routine of people with dementia with creative activities, while being obliged to stay at home, were organized and are still available on demand [89]. In addition, video conferences promote a more direct interaction which encompasses not only verbal but also non- verbal communication. In this way, telemedicine embodies a feasible strategy to support caregivers and families of older adults with dementia [90].

Further factors perplexing dementia management during the COVID-19 crisis: Ageism and moral injury

The COVID-19 pandemic has given rise to ethical issues related to healthcare of older adults which challenge and can morally injure healthcare providers in acute phases of the crisis. In such phases, geriatric patients tend to be treated as a lower priority for healthcare systems. Older age pertains to a less favourable pathophysiological response to COVID-19 infection, higher proneness to severe symptoms, drug side effects and a higher fatality ratio compared to younger individuals [91]. This evidence underpins ageist attitudes which may contaminate clinical practice. Ageism is defined by the World Health Organisation (WHO) as the 'stereotyping, prejudice and discrimination against people on the basis of their age' [92,93]. Clinical syndromes like dementia are considered to be a reason for older adults' stigma because of their impaired cognitive and functional performance and

potential and partial loss of agency. Ageism correlates with adverse health in multiple ways, as well as with impaired memory and depression [91,94,95].

The management of the COVID-19 crisis has often exceeded the capacities of healthcare systems, as indicated by deficiencies in intensive care unit beds and ventilators. In the battle of resource allocation procedures, older adults and even more older adults with dementia seem to be placed at disadvantage as a consequence of a widespread implicit bias [96], arising from the conviction that older adults should or even wish to "make way" for younger people in the current deep crisis [97]. Moreover, the necessary modifications in healthcare services, so that the increasing treatment needs of patients with COVID-19 are adequately met, may undermine the proper operation of non-urgent healthcare services, from which the overall health of older people mostly benefits [91,98].

Many critical questions arise as clinicians are confronted with the challenges of allocation of limited healthcare resources. Dealing with these challenges is not always based on fair and transparent criteria. Triage protocols considering non- medical criteria like age and disability status of the patient in decision-making may result in the exclusion of older adults with dementia from proper diagnostic endeavours and therapeutic interventions [99]. Furthermore, clinicians are called upon to take crucial decisions in demanding practice environments, while clinical practice guidelines are not always clear-cut. The difficulties in shared decision-making in cases of individuals with dementia being partially or totally incapable of participating in decision-making [100] is further complicated by difficulties in the communication with patients' families due to mobility restrictions and the immense physical and emotional burden of clinicians serving on the frontline during the current severe pandemic crisis [101]. These circumstances form a terrain of moral stress and ethical dilemmas [102] on which medical and non-medical healthcare professionals treating patients with dementia are frequently bound to make decisions directly contrasting those they would make in a less stressful and demanding setting.

Moral injury refers to the psychological distress which occurs in individuals who are exposed to traumatic or unusually stressful events that transgress their moral values or ethical code. Morally injurious events include perpetration, omission or being a witness of acts that violate moral and predictive expectations and/or betrayal by a trusted authority [103–105]. The core symptoms of moral injury encompass shame, guilt, spiritual/existential conflict and loss of trust in self, others, and/or transcendental beings. Moral injury in healthcare workers is closely associated with frustration, burnout, thoughts, or decision to quit the profession. These symptoms are commonly accompanied by physical symptoms, such as headaches, muscle tension, gastrointestinal and sleep disturbances [106,107]. Of note, moral injury does not embody a mental disorder, even though it shares symptoms with post-traumatic stress disorder (PTSD). Nevertheless, moral injury can contribute to or even trigger the development of a variety of mental health problems, such as adjustment disorder, depression, burnout and PTSD [103,107,108], which deprive healthcare services of workforces with moral sensitivity, empathy and prosocial behaviour, characteristics particularly desired in the field of dementia care [109,110]. Healthcare providers with symptoms of moral injury may benefit from an amalgamation of validated psychological treatments, such as cognitive behavioural therapy (CBT), compassion focused therapy and psycho-education sessions with family members [103,111]

Conclusionary remarks: The way ahead

The outbreak of the COVID-19 pandemic crisis has further perplexed the complex management of dementia. The puzzle of the new setting consists of pieces with variable characteristics. It includes (i) the high vulnerability of older adults with dementia to severe phenotypes of the COVID-19 infection, which may be negatively affected by psychotropic medication (e.g. suppressive effects of benzodiazepines on respiratory function, cardiotoxic effects of antipsychotics and older antidepressants), (ii) the neuropsychiatric side effects of COVID-19 treatment, (iii) the reduction or even suspension in acute phases of the pandemic of non-emergency diagnostic and non-pharmacological therapeutic care services for individuals with dementia, (iv) the increasing caregiver burden and (v) medical- and nonmedical healthcare providers frustrated by physical exhaustion, ethical dilemmas and moral injury, pertaining for instance to pursuing non-medical criteria (e.g. age, disability status) for allocating limited healthcare resources. Healthcare providers of older adults with dementia are called to cope with highly demanding circumstances and deal with tasks which at least partially seem to be sisyphean.

Pragmatic, albeit not one size fits all strategies such as telemedicine services and boosting the resilience of healthcare professional have been proposed and implemented as ways to alleviate the detrimental effects of the COVID-19 crisis on dementia management. Despite the initial enthusiasm, online and telephone healthcare services do not efficiently facilitate the establishment of physician-patient therapeutic alliance and interpersonal engagement compared to face-to-face services [69,90], while inaccuracies because of non-standardized conditions of the virtual encounter and the insufficiently validated transfer of cognitive screening tools from paper-based mode to a virtual setting undermine diagnostic procedures. Moreover, there is a need for targeted training of professionals and organizational support [112,113], so that healthcare services can benefit from the use of new technologies. Mental healthcare services based on new technologies may more adequately be understood as services complementing and enriching traditional face-to-face care provision, rather than distinct and independent healthcare services [74,75]. Interestingly, tele-psychogeriatrics has been proposed as a platform for connecting primary health care centres in remote areas, which provide face-to-face care, with highly specialized university psychogeriatric clinics [114].

Practical steps could facilitate moral injury prevention and efficient coping with moral stress. Practical courses on becoming aware of the principles of healthcare ethics and transparent decision- making can minimise biased exclusion criteria during the triage and resource allocation procedures, which otherwise may place older adults with dementia at a disadvantage. Such courses are not bound to provide specific 'right answers' to the ethical issues confronting dementia care providers, but they are supposed to highlight productive lines of thought in navigating such issues [115,116]. In addition, effective (online) listening and communication with supervisors, easily accessible professional support (e.g. web- or telephone based hotlines, hospital-based teams providing counselling on handling stress), models such as the structured forum Schwartz rounds [117], (one-to-one) peer support and last but not least organizational adjustments (e.g. shortened shifts, staff involvement in organisational decisions), may pave the way towards enhanced resilience against moral injury during the COVID-19 pandemic surge and beyond it [103,106,108,118].

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REFERENCES

1. Anastasopoulou S, Mouzaki A. The biology of SARS-CoV-2 and the ensuing COVID-19. Ach Iatr. 2020;39(1):29-35.
2. Hu B, Guo H, Zhou P, Shi Z-L. Characteristics of SARS-CoV-2 and COVID-19. Nat rev Microbiol. 2021;19(3):141-54.
3. Karaivazoglou K, Konstantopoulou G, Kalogeropoulou M, Iliou T, Vorvolakos T, Assimakopoulos K, et al. Psychological distress in the Greek general population during the first COVID-19 lockdown. BJPsych Open. 2021;7(2):e59.
4. Alexopoulos P, Roukas D, Efkarpidis A, Konstantopoulou G, Soldatos R, Karaivazoglou K, et al. Hospital workforce mental reaction to the pandemic in a low COVID-19 burden setting: a cross-sectional clinical study. Eur Arch Psychiatry Clin Neurosci. 2022;272(1):95–105.
5. Forte G, Favieri F, Tambelli R, Casagrande M. COVID-19 Pandemic in the Italian Population: Validation of a Post-Traumatic Stress Disorder Questionnaire and Prevalence of PTSD Symptomatology. Int J Environ Res Public Health. 2020;17(11):4151.
6. Kaimann D, Tanneberg I. What containment strategy leads us through the pandemic crisis? An empirical analysis of the measures against the COVID-19 pandemic. PloS one. 2021;16(6):e0253237.
7. Korczyn AD. Dementia in the COVID-19 Period. J Alzheimers Dis. 2020;75(4):1071–2.
8. Alexopoulos P, Soldatos R, Kontogianni E, Frouda M, Loanna Aligianni S, Skondra M, et al. COVID-19 Crisis Effects on Caregiver Distress in Neurocognitive Disorder. J Alzheimers Dis. 2021;79(1):459–66.
9. Alexopoulos P, Frounta M, Perneczky R. The multidimensional beneficial effect of physical exercise on symptoms of neurocognitive disorder. Int Psychogeriatr. 2021; 34(2):109-112.
10. Livingston G, Huntley J, Sommerlad A, Ames D, Ballard C, Banerjee S, et al. Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. Lancet. 2020;396(10248):413-46.
11. Arvanitakis Z, Shah RC, Bennett DA. Diagnosis and Management of Dementia: Review. JAMA. 2019;322(16):1589–99.
12. Wolinsky D, Drake K, Bostwick J. Diagnosis and Management of Neuropsychiatric Symptoms in Alzheimer's Disease. Curr Psychiatry Rep. 2018;20(12):117.
13. Meyer C, O'Keefe F. Non-pharmacological interventions for people with dementia: A review of reviews. Dementia (London). 2020;19(6):1927-54.

14. Wang QQ, Davis PB, Gurney ME, Xu R. COVID-19 and dementia: Analyses of risk, disparity, and outcomes from electronic health records in the US. Alzheimers Dement. 2021;17(8):1297–306.
15. Boutoleau-Bretonnière C, Pouclet-Courtemanche H, Gillet A, Bernard A, Deruet AL, Gouraud I, et al. The Effects of Confinement on Neuropsychiatric Symptoms in Alzheimer's Disease During the COVID-19 Crisis. J Alzheimers Dis. 2020;76(1):41–7.
16. Canevelli M, Valletta M, Toccaceli Blasi M, Remoli G, Sarti G, Nuti F, et al. Facing Dementia During the COVID-19 Outbreak. J Am Geriatr Soc. 2020;68(8):1673-1676.
17. Padala KP, Parkes CM, Padala PR. Neuropsychological and Functional Impact of COVID-19 on Mild Cognitive Impairment. Am J Alzheimers Dis Other Demen. 2020;35:1533317520960875.
18. Simonetti A, Pais C, Jones M, Cipriani MC, Janiri D, Monti L, et al. Neuropsychiatric Symptoms in Elderly With Dementia During COVID-19 Pandemic: Definition, Treatment, and Future Directions. Front Psychiatry. 2020;11:579842.
19. Barguilla A, Fernández-Lebrero A, Estragués-Gázquez I, García-Escobar G, Navalpotro-Gómez I, Manero RM, et al. Effects of COVID-19 Pandemic Confinement in Patients With Cognitive Impairment. Front Neurol. 2020;11:589901.
20. Borges-Machado F, Barros D, Ribeiro Ó, Carvalho J. The Effects of COVID-19 Home Confinement in Dementia Care: Physical and Cognitive Decline, Severe Neuropsychiatric Symptoms and Increased Caregiving Burden. Am J Alzheimers Dis Other Demen. 2020;35:1533317520976720.
21. Alonso-Lana S, Marquié M, Ruiz A, Boada M. Cognitive and Neuropsychiatric Manifestations of COVID-19 and Effects on Elderly Individuals With Dementia. Front Aging Neurosci. 2020;12:588872.
22. Wang H, Li T, Barbarino P, Gauthier S, Brodaty H, Molinuevo JL, et al. Dementia care during COVID-19. Lancet. 2020;395(10231):1190-1.
23. Hariyanto TI, Putri C, Situmeang RF v, Kurniawan A. Dementia is a predictor for mortality outcome from coronavirus disease 2019 (COVID-19) infection. Eur Arch Psychiatry Clin Neurosci. 2021;271(2):393-5.
24. Hawkins M, Sockalingam S, Bonato S, Rajaratnam T, Ravindran M, Gosse P, et al. A rapid review of the pathoetiology, presentation, and management of delirium in adults with COVID-19. J Psychosom Res: 2021;141:110350.
25. Oliveira R, Sotero FD, Teodoro T. NeuroCOVID: critical review of neuropsychiatric manifestations of SARS-CoV-2 infection. Ir J Med Sci. 2021;190(2):851-2.
26. Cesari M, Proietti M. COVID-19 in Italy: Ageism and Decision Making in a Pandemic. J Am Med Dir Assoc. 2020;21(5):576–7.
27. Kornadt AE, Albert I, Hoffmann M, Murdock E, Nell J. Perceived Ageism During the Covid-19-Crisis Is Longitudinally Related to Subjective Perceptions of Aging. Front Public Health. 2021;9:679711.
28. Bianchetti A, Rozzini R, Guerini F, Boffelli S, Ranieri P, Minelli G, et al. Clinical Presentation of COVID19 in Dementia Patients. J Nutr Health Aging. 2020;24(6):560–2.
29. Bilbul M, Paparone P, Kim AM, Mutalik S, Ernst CL. Psychopharmacology of COVID-19. Psychosomatics. 2020;61(5):411–27.
30. Seifert J, Heck J, Eckermann G, Singer M, Bleich S, Grohmann R, et al. Psychopharmakotherapie in Zeiten der COVID-19-Pandemie. Nervenarzt. 2020;91(7):604–10.
31. Ostuzzi G, Papola D, Gastaldon C, Schoretsanitis G, Bertolini F, Amaddeo F, et al. Safety of psychotropic medications in people with COVID-19: evidence review and practical recommendations. BMC Med. 2020;18(1):215.
32. Mouallem M, Wolf I. Olanzapine-induced respiratory failure. Am J Geriatr Psychiatry. 2001;9(3):304–5.
33. Yagmur F, Ulusoy HB, Buyukoglan H, Kaya MG. Acute respiratory distress due to antipsychotic drugs. Pharmacopsychiatry. 2010;43(3):118–9.
34. Wang M-T, Tsai C-L, Lin CW, Yeh C-B, Wang Y-H, Lin H-L. Association Between Antipsychotic Agents and Risk of Acute Respiratory Failure in Patients With Chronic Obstructive Pulmonary Disease. JAMA Psychiatry. 2017;74(3):252–60.
35. Wilson H, Ridley S. Antipsychotic drugs and the acute respiratory distress syndrome. Br J Anaesth. 2007;99(2):301–2.
36. Kyle K, Bronstein JM. Treatment of psychosis in Parkinson's disease and dementia with Lewy Bodies: A review. Parkinsonism Relat Disord. 2020;75:55–62.
37. Gurrera RJ, Perry NL. Clozapine-Associated Aspiration Pneumonia: Case Series and Review of the Literature: Reply. Psychosomatics. 2019;60(1):103.
38. Gurrera RJ, Parlee AC, Perry NL. Aspiration pneumonia: An underappreciated risk of clozapine treatment. J Clin Psychopharmacol. 2016;36(2):174–6.
39. Kaplan J, Schwartz AC, Ward MC. Clozapine-Associated Aspiration Pneumonia: Case Series and Review of the Literature. Psychosomatics. 2018;59(2):199–203.
40. Cranshaw T, Harikumar T. COVID-19 infection may cause clozapine intoxication: Case report and discussion. Schizophr Bull. 2020;46(4):751.
41. Tadic M, Cuspidi C, Mancia G, Dell'Oro R, Grassi G. COVID-19, hypertension and cardiovascular diseases: Should we change the therapy? Pharmacol Res; 2020;158:104906.
42. Friedrich ME, Winkler D, Konstantinidis A, Huf W, Engel R, Toto S, et al. Cardiovascular Adverse Reactions During Antipsychotic Treatment: Results of AMSP, A Drug Surveillance Program Between 1993 and 2013. Int J Neuropsychopharmacol. 2020;23(2):67–75.
43. Maust DT, Kim HM, Seyfried LS, Chiang C, Kavanagh J, Schneider LS, et al. Antipsychotics, other psychotropics, and the risk of death in patients with dementia: number needed to harm. JAMA Psychiatry. 2015;72(5):438–45.
44. Kahl KG. Direct and indirect effects of psychopharmacological treatment on the cardiovascular system. Horm Mol Biol Clin Investig. 2018;36(1).
45. Crépeau-Gendron G, Brown HK, Shorey C, Madan R, Szabuniewicz C, Koh S, et al. Association between citalopram, escitalopram and QTc prolongation in a real-world geriatric setting. J Affect Disord. 2019;250:341–5.

46. Huang W, Berube J, McNamara M, Saksena S, Hartman M, Arshad T, et al. Lymphocyte Subset Counts in COVID-19 Patients: A Meta-Analysis. Cytometry A. 2020;97(8):772–6.
47. Frater JL, Zini G, d'Onofrio G, Rogers HJ. COVID-19 and the clinical hematology laboratory. Int J Lab Hematol. 2020;42 Suppl 1:11–8.
48. Mijovic A, MacCabe JH. Clozapine-induced agranulocytosis. Ann Hematol. 2020;99(11):2477–82.
49. Ostuzzi G, Papola D, Gastaldon C, Schoretsanitis G, Bertolini F, Amaddeo F, et al. Safety of psychotropic medications in people with COVID-19: evidence review and practical recommendations. BMC Med. 2020;18(1):215.
50. Pancani R, Villari L, Foci V, Parri G, Barsotti F, Patrucco F, et al. Lower limb deep vein thrombosis in COVID-19 patients admitted to intermediate care respiratory units. Thromb Res. 2021;197:44–7.
51. Campion P, Campion G, Anbarasan D. Changes in Neutrophil Count After Antipsychotic Prescription Among a Retrospective Cohort of Patients With Benign Neutropenia. J. Clin. Psychopharmacol.. 2017;37(4):456–8.
52. Yuet WC, Derasari D, Sivoravong J, Mason D, Jann M. Selective Serotonin Reuptake Inhibitor Use and Risk of Gastrointestinal and Intracranial Bleeding. JAOA. 2019;119(2):102–11.
53. Gupta A, Madhavan M v., Sehgal K, Nair N, Mahajan S, Sehrawat TS, et al. Extrapulmonary manifestations of COVID-19. Nat. Med. 2020;26(7):1017–32.
54. Kokic G, Hillen HS, Tegunov D, Dienemann C, Seitz F, Schmitzova J, et al. Mechanism of SARS-CoV-2 polymerase stalling by remdesivir. Nat. Commun. 2021;12(1):279.
55. Ticinesi A, Cerundolo N, Parise A, Nouvenne A, Prati B, Guerra A, et al. Delirium in COVID-19: epidemiology and clinical correlations in a large group of patients admitted to an academic hospital. Aging Clin Exp Res. 2020;32(0):2159–66.
56. Borah P, Deb PK, Chandrasekaran B, Goyal M, Bansal M, Hussain S, et al. Neurological Consequences of SARS-CoV-2 Infection and Concurrence of Treatment-Induced Neuropsychiatric Adverse Events in COVID-19 Patients: Navigating the Uncharted. Front. Mol. Biosci. 2021;8:627723..
57. Wang J, Yang W, Chen P, Guo J, Liu R, Wen P, et al. The proportion and effect of corticosteroid therapy in patients with COVID-19 infection: A systematic review and meta-analysis. PloS one .2021;16(4):e0249481..
58. Sacks O, Shulman M. Steroid dementia: an overlooked diagnosis? Neurology. 2005;64(4):707–9.
59. Warrington TP, Bostwick JM. Psychiatric adverse effects of corticosteroids. Mayo Clin. Proc. 2006;81(10):1361–7.
60. Bilbul M, Paparone P, Kim AM, Mutalik S, Ernst CL. Psychopharmacology of COVID-19. Psychosomatics. 2020;61(5):411–27.
61. Fong TG, Davis D, Growdon ME, Albuquerque A, Inouye SK. The interface between delirium and dementia in elderly adults. Lancet Neurol .2015;14(8):823–32.
62. Beagle AJ, Darwish SM, Ranasinghe KG, LaL, Karageorgiou E, Vossel KA. Relative Incidence of Seizures and Myoclonus in Alzheimer's Disease, Dementia with Lewy Bodies, and Frontotemporal Dementia. J Alzheimers Dis. 2017;60(1):211-23.
63. Terkeltaub RA, Furst DE, Digiacinto JL, Kook KA, Davis MW. Novel evidence-based colchicine dose-reduction algorithm to predict and prevent colchicine toxicity in the presence of cytochrome P450 3A4/P-glycoprotein inhibitors. Arthritis Rheumatol. 2011;63(8):2226–37.
64. Villa Zapata L, Hansten PD, Horn JR, Boyce RD, Gephart S, Subbian V, et al. Evidence of Clinically Meaningful Drug-Drug Interaction With Concomitant Use of Colchicine and Clarithromycin. Drug Saf . 2020;43(7):661–8.
65. O'Brien MP, Forleo-Neto E, Musser BJ, Isa F, Chan K-C, Sarkar N, et al. Subcutaneous REGEN-COV Antibody Combination to Prevent Covid-19. N Engl J Med. 2021;385(13):1184-95.
66. Cohen MS, Nirula A, Mulligan MJ, Novak RM, Marovich M, Yen C, et al. Effect of Bamlanivimab vs Placebo on Incidence of COVID-19 Among Residents and Staff of Skilled Nursing and Assisted Living Facilities: A Randomized Clinical Trial. JAMA. 2021;326(1):46–55.
67. Weinreich DM, Sivapalasingam S, Norton T, Ali S, Gao H, Bhore R, et al. REGEN-COV Antibody Combination and Outcomes in Outpatients with Covid-19. N Engl J Med. 2021;385(23):e81.
68. Cuffaro L, di Lorenzo F, Bonavita S, Tedeschi G, Leocani L, Lavorgna L. Dementia care and COVID-19 pandemic: a necessary digital revolution. Neurol Sci. 2020;41(8):1977–9.
69. Tousi B. Dementia Care in the Time of COVID-19 Pandemic. J Alzheimers Dis. 2020;76(2):475-9.
70. Benaque A, Gurruchaga MJ, Abdelnour C, Hernandez I, Cañabate P, Alegret M, et al. Dementia Care in Times of COVID-19: Experience at Fundació ACE in Barcelona, Spain. J Alzheimers Dis. 2020;76(1):33-40.
71. Sorinmade OA, Kossoff L, Peisah C. COVID-19 and Telehealth in older adult psychiatry-opportunities for now and the future. Int. J. Geriatr. Psychiatry. 2020;35(12):1427–30.
72. Gosse PJ, Kassardjian CD, Masellis M, Mitchell SB. Virtual care for patients with Alzheimer disease and related dementias during the COVID-19 era and beyond. CMAJ. 2021;193(11):E371–7.
73. Hung L. Using virtual care interventions to provide person-centred care to hospitalised older people with dementia. Nurs Older People. 2020 Nov 11. doi: 10.7748/nop.2020.e1294.
74. Sorinmade OA, Kossoff L, Peisah C. COVID-19 and Telehealth in older adult psychiatry-opportunities for now and the future. Int J Geriatr Psychiatry. 2020;35(12):1427–30.
75. Danilewitz M, Ainsworth NJ, Bahji A, Chan P, Rabheru K. Virtual psychiatric care for older adults in the age of COVID-19: Challenges and opportunities. Int J Geriatr Psychiatry. 2020;35(12):1468–9.
76. Sander J, Bolinski F, Diekmann S, Gaebel W, Günther K, Hauth I et al. Online therapy: an added value for inpatient routine care? Perspectives from mental health care professionals. Eur Arch Psychiatry Clin Neurosci. 2022;272(1):107-18.
77. Ornstein KA, Gaugler JE, Devanand DP, Scarmeas N, Zhu CW, Stern Y. Are there sensitive time periods for dementia caregivers? The occurrence of behavioral and psychological symptoms in the early stages of dementia. Int Psychogeriatr.

2013;25(9):1453-62.
78. Alexopoulos P, Soldatos R, Kontogianni E, Frouda M, Loanna Aligianni S, Skondra M, et al. COVID-19 Crisis Effects on Caregiver Distress in Neurocognitive Disorder.J Alzheimers Dis.2021;79(1):459-66.
79. Seidel D, Thyrian JR. Burden of caring for people with dementia - comparing family caregivers and professional caregivers. A descriptive study. J Multidiscip Healthc. 2019;12:655–63.
80. Durán-Gómez N, Guerrero-Martín J, Pérez-Civantos D, López Jurado CF, Palomo-López P, Cáceres MC. Understanding Resilience Factors Among Caregivers of People with Alzheimer's Disease in Spain. Psychol Res Behav Manag 2020;13:1011-25.
81. Tuijt R, Frost R, Wilcock J, Robinson L, Manthorpe J, Rait G, et al. Life under lockdown and social restrictions - the experiences of people living with dementia and their carers during the COVID-19 pandemic in England. BMC Geriatr. 2021;21(1):301.
82. Borelli WV, Augustin MC, de Oliveira PBF, Reggiani LC, Bandeira-De-Mello RG, Schumacher-Schuh AF, et al. Neuropsychiatric Symptoms in Patients with Dementia Associated with Increased Psychological Distress in Caregivers During the COVID-19 Pandemic. J Alzheimers Dis. 2021;80(4):1705-12.
83. Tsapanou A, Papatriantafyllou JD, Yiannopoulou K, Sali D, Kalligerou F, Ntanasi E, et al. The impact of COVID-19 pandemic on people with mild cognitive impairment/dementia and on their caregivers.Int J Geriatr Psychiatry. 2020;36(4):583-7.
84. Tsapanou A, Zoi P, Kalligerou F, Blekou P, Sakka P. The Effect of Prolonged Lockdown Due to COVID-19 on Greek Demented Patients of Different Stages and on Their Caregivers. J Alzheimers Dis. 2021;83(2):907-13.
85. Sheth K, Lorig K, Stewart A, Parodi JF, Ritter PL. Effects of COVID-19 on Informal Caregivers and the Development and Validation of a Scale in English and Spanish to Measure the Impact of COVID-19 on Caregivers. J Appl Gerontol. 2020;40(3):235-43.
86. Altieri M, Santangelo G. The Psychological Impact of COVID-19 Pandemic and Lockdown on Caregivers of People With Dementia. Am J Geriatr Psychiatry. 2020;29(1):27-34.
87. Brown EE, Kumar S, Rajji TK, Pollock BG, Mulsant BH. Anticipating and Mitigating the Impact of the COVID-19 Pandemic on Alzheimer's Disease and Related Dementias. Am J Geriatr Psychiatry. 2020;28(7):712-21.
88. Cohen G, Russo MJ, Campos JA, Allegri RF. Living with dementia: increased level of caregiver stress in times of COVID-19. Int Psychogeriatr. 2020;32(11):1377-81.
89. Wang H, Li T, Barbarino P, Gauthier S, Brodaty H, Molinuevo JL, et al. Dementia care during COVID-19. Lancet. 2020;395(10231):1190-1.
90. Lai FH yin, Yan EW hung, Yu KK ying, Tsui WS, Chan DT hoi, Yee BK. The Protective Impact of Telemedicine on Persons With Dementia and Their Caregivers During the COVID-19 Pandemic. Am J Geriatr Psychiatry. 2020;28(11):1175-84.
91. D'cruz M, Banerjee D. "An invisible human rights crisis": The marginalization of older adults during the COVID-19 pandemic - An advocacy review. Psychiatry Res.2020;292:113369.
92. Lesser H. Ageism. Encyclopedia of Applied Ethics (Second Edition). 2012;79–85.
93. Asnaani A, Majeed I, Kaur K, Gutierrez Chavez M. Diversity and Cultural Perspectives. Reference Module in Neuroscience and Biobehavioral Psychology. 2021 doi: 10.1016/B978-0-12-818697-8.00081-9
94. Chang ES, Kannoth S, Levy S, Wang SY, Lee JE, Levy BR. Global reach of ageism on older persons' health: A systematic review. PLoS One. 2020;15(1):e0220857.
95. Colenda CC, Reynolds CF, Applegate WB, Sloane PD, Zimmerman S, Newman AB, et al. COVID-19 Pandemic and Ageism: A Call for Humanitarian Care. J Am Geriatr Soc. 2020;68(8):1627-8.
96. Fitzgerald C, Hurst S. Implicit bias in healthcare professionals: A systematic review. BMC Med Ethics. 2017;18(1):19.
97. Clarfield AM, Jotkowitz A. Age, ageing, ageism and "ageitation" in the Age of COVID-19: rights and obligations relating to older persons in Israel as observed through the lens of medical ethics.Isr J Health Policy Res. 2020;9(1):64.
98. Chehrehgosha M. The Unpreparedness of the Healthcare System for the Management of COVID-19 Pandemic Leading to the Mistreatment of the Elderly: A Newly Emerging Moral Dilemma. J Nutr Health Aging. 2020;24(9):973-4.
99. Rueda J. Ageism in the COVID-19 pandemic: age-based discrimination in triage decisions and beyond. Hist Philos Life Sci.2021;43(3):91.
100. Smebye KL, Kirkevold M, Engedal K. How do persons with dementia participate in decision making related to health and daily care? A multi-case study. BMC Health Serv Res. 2012;12:241.
101. Köther AK, Siebenhaar KU, Alpers GW. Shared Decision Making during the COVID-19 Pandemic. Med Decis Making. 2021; 41(4):430-8.
102. Donkers MA, Gilissen VJHS, Candel MJJM, van Dijk NM, Kling H, Heijnen-Panis R, et al. Moral distress and ethical climate in intensive care medicine during COVID-19: a nationwide study. BMC Med Ethics. 2021; 22(1):73.
103. Williamson V, Murphy D, Greenberg N. COVID-19 and experiences of moral injury in front-line key workers. Occup Med (Lond). 2020; 70(5):317-9.
104. 104. Shale S. Moral injury and the COVID-19 pandemic: reframing what it is, who it affects and how care leaders can manage it. BMJ Lead. 2020; 4(4):224–7.
105. Griffin BJ, Purcell N, Burkman K, Litz BT, Bryan CJ, Schmitz M, et al. Moral Injury: An Integrative Review. J Trauma Stress. 2019; 32(3):350-62.
106. Williams RD, Brundage JA, Williams EB. Moral Injury in Times of COVID-19. J Health Serv Psychol. 2020;46(2):65-9.
107. Jinkerson JD. Defining and assessing moral injury: A syndrome perspective. Traumatology. American Psychological Association Inc. 2016;22(2):122–30.
108. Tracy DK, Tarn M, Eldridge R, Cooke J, Calder JDF, Greenberg

N. What should be done to support the mental health of healthcare staff treating COVID-19 patients? Br J Psychiatry. 2020;217(4):537-9.
109. Teófilo TJS, Veras RFS, Silva VA, Cunha NM, Oliveira J dos S, Vasconcelos SC. Empathy in the nurse–patient relationship in geriatric care: An integrative review. Nurs Ethics. 2019;26(6):1585-600.
110. Suazo I, Pérez-Fuentes MDC, Molero Jurado MDM, Martos Martínez Á, Simón Márquez MDM, Barragán Martín AB, et al. Moral Sensitivity, Empathy and Prosocial Behavior: Implications for Humanization of Nursing Care. Int J Environ Res Public Health. 2020;17(23):8914.
111. Williamson V, Greenberg N, Murphy D. Moral injury in UK armed forces veterans: a qualitative study. Eur J Psychotraumatol. 2019;10(1):1562842.
112. Weißenfeld MM, Goetz K, Steinhäuser J. Facilitators and barriers for the implementation of telemedicine from a local government point of view - a cross-sectional survey in Germany. BMC Health Serv Res. 2021;21(1):919.
113. Zhang T, Mosier J, Subbian V. Identifying Barriers to and Opportunities for Telehealth Implementation Amidst the COVID-19 Pandemic by Using a Human Factors Approach: A Leap Into the Future of Health Care Delivery? JMIR Hum Factors. 2021;8(2):e24860.
114. Alexopoulos P, Novotni A, Novotni G, Vorvolakos T, Vratsista A, Konsta A, et al. Old age mental health services in Southern Balkans: Features, geospatial distribution, current needs, and future perspectives. Eur Psychiatry. 2020;63(1):e88.
115. Cousins E, de Vries K, Dening KH. Ethical care during COVID-19 for care home residents with dementia. Nurs Ethics. 2020;28(1):46-57.
116. Parker J. Ethical issues in the care of people with dementia. InnovAiT. 2020;13(6):374–81.
117. Gleeson D, Arwyn-Jones J, Awan M, White I, Halse O. Medical Student Schwartz Rounds: A Powerful Medium for Medical Student Reflective Practice. Adv Med Educ Pract. 2020;11:775–80.
118. Alexopoulos P, Roukas D, Efkarpidis A, Konstantopoulou G, Soldatos R, Karaivazoglou K, et al. Hospital workforce mental reaction to the pandemic in a low COVID-19 burden setting: a cross-sectional clinical study. Eur Arch Psychiatry Clin Neurosci. 2021; 272(1):95-105.

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Pyosalpinx after hysterosalpingography examination: A case report

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Abstract

In this case report we will discuss the complication of pyosalpinx and peritonitis after a hysterosalpingography examination of a 38-year-old woman and the treatment used in our hospital. Pyosalpinx is an inflammatory reaction that affects the uterus, fallopian tubes and other intra-abdominal organs. The main bacterial species that are responsible are Neisseria gonorrhoeae, Chlamydia trachomatis, Mycoplasma genitalium and E. coli. Complications after hysterosalpingography examination are pelvic infection, loss of consciousness, spotting and iodine allergy and may occur in less than 1% of cases. We are reporting a rare case of pyosalpinx diagnosed at the district hospital of Tripolis and successful management.

Key words: *Pyosalpinx; fallopian tube; hysterosalpingography; peritonitis*

INTRODUCTION

Pyosalpinx is an inflammatory reaction that affects the uterus, fallopian tubes and other intra-abdominal organs. It can be acute or chronic and lead to female infertility [1]. Approximately 1-2% of women aged 16-25 with high-risk sexual behavior have fallopian tube infection. Except for free sexual intercourse, there are other risk factors such as intrauterine device and invasive techniques (dilatation and curettage, hysterosalpigography and hysteroscopy). The main bacterial species that are responsible are Neisseria gonorrhoeae, Chlamydia trachomatis, Mycoplasma genitalium and E. coli [1,5]

Hysterosalpingography is a common invasive radiological examination which is used to view the interior of the cervix, uterus, and fallopian tubes. Radiolucent fluid is injected from the cervical os into the endometrial cavity in order to investigate the patency of the fallopian tubes [2, 3]. During the passage of the fluid, shots are taken through an X-ray monitor. The process is repeated 3-4 times in order to examine the full course of the liquid. Hysterosalpingography is performed on the 10th-11th day of the cycle, before ovulation and antibiotics are always given in advance [6, 9]. Although this technique is considered a safe procedure, complications such as pelvic infection, loss of consciousness, spotting and iodine allergy may occur in less than 1% of cases [10].

There are other techniques to evaluate tubal patency such as chromopertubation and sonohysterosalpigography [10]. Chromopertubation is a laparoscopy assisted procedure where a dilute dye is injected transcevically in order to check tubal patency and surrounding pelvic anatomy. Sonohysterosalpingography is a similar technique but in this case tubal patency is examined via ultrasound.

CASE PRESENTATION

A 38-year-old patient came to the emergency department of the Panarkadiko General Hospital of Tripolis with reported fever (up to 39.5 degrees Celsius) onset of 48h and abdominal pain which persisted with movement,

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nor did it relieve with analgesia. She reported no episodes of vomiting, dysuric disorders, sexually transmitted diseases or other gastrointestinal disorders. The medical history of the patient was free without health problems, surgeries or allergies. From her gynecological history, she mentioned menstrual cycle without irregularities, with last menstruation 12 days ago and had never been pregnant. She had undergone a hysterosalpingography exam 5 days ago for investigation of subfertility. During the clinical examination the patient's abdomen was soft, easy to press with sensitivity in the abdomen, positive (+) intestinal sounds, positive (+) rebound tenderness, peer bilateral wheezing, negative (-) Giordano sign, and tenderness on the right gynecological examination. Her vital signs were: Blood Pressure 110 / 70mmHg, pulses 78 bpm, $Sp0_2$ 98%, GCs 15/15, temperature 38.5°C. In the laboratory workup, elevated inflammatory markers were observed namely Leukocytosis 18.4 and CRP 14.98 (the rest laboratory values were within normal range), the pregnancy test was negative as well as the chest radiological examination. The findings of the intravaginal ultrasound were: a uterus with anterior flexion of 7.2cm x 5,5cm and a cystic mass near the right fallopian tube (6,5cm x 5,5cm x 4.8cm) (Figure 1, Figure 2) with low-medium fluidity fluid with no rupture points, next to the right ovary the colored Doppler showed peripheral vascularity. Therefore, a right ovarian cyst with findings of tubal infection had to be differentiated from tubo-ovarian abscess, ruptured ectopic, ruptured hemorrhagic cyst, ovarian torsion, pelvic inflammatory disease, appendicitis with absence [4].

The patient was admitted to the Obstetrics / Gynecology Clinic of the Panarkadiko General Hospital of Tripolis where she was administered 3lt of fluids (D / W, N / S, R / L), gastroprotection, paracetamol and 2-fold antibiotic treatment (cephalosporin β΄ generation 750g x 3, metronidazole 500g x 3). Two days after admission, the patient's clinical condition deteriorated, with clinical signs of peritonitis and ileus. On physical examination, she demonstrated increased abdominal wall rigidity, with sparse bowel sounds and vomiting, while laboratory test results were also indicative of an infection (Leukocytosis 13.7, CRP 24.4 and hypoalbuminemia 5.4). It was decided to proceed to an exploratory laparotomy on the same day. During the operation, free purulent fluid was found in the peritoneal cavity with dilated intestinal bowel, and so the cavity was washed. The right fallopian tube was ruptured and purulent fluid was found in the Douglas space (localized peritonitis). Various intestine-uterine and tubo-ovarian adhesions were found and adhesiolysis was performed. The right fallopian tube was then ligated, excised (right salpingectomy) and sent for histological examination (Figure 3).

The histological examination revealed

- Macroscopic findings: distended fallopian tube (cystic mass) 7cm length and 4cm diameter with wall thickness up to 0.5 cm.
- Microscopic findings: acute salpingitis, with no neoplastic or atypal cells.

The patient's postoperative course ran with no complications, with a soft abdomen and positive bowel activity. Laboratory test results clearly improved including inflammatory markers (L 9.9 and CRP 11.57). The patient was discharged on the 3rd postoperative day in hemodynamically stable condition, without any discomfort and a 2-fold per os antibiotic regimen

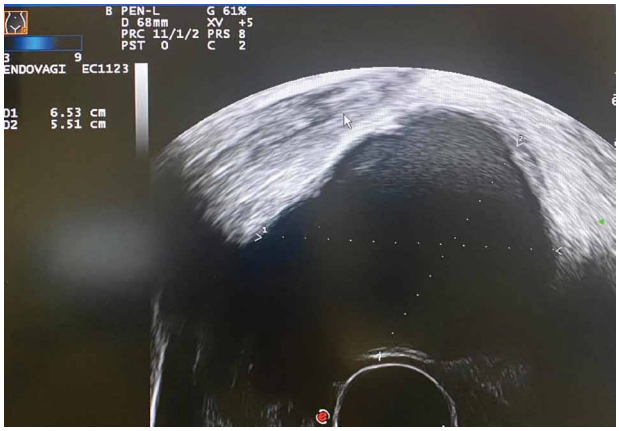

Figure 1. Cystic formation 6,5cm x 5,5cm.

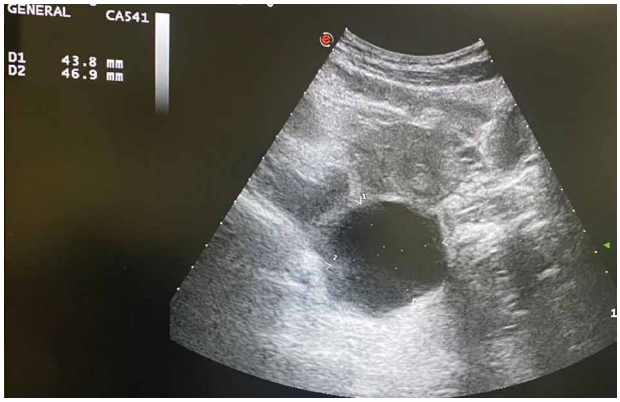

Figure 2. Cystic Formation 4,3cm x 4,7cm.

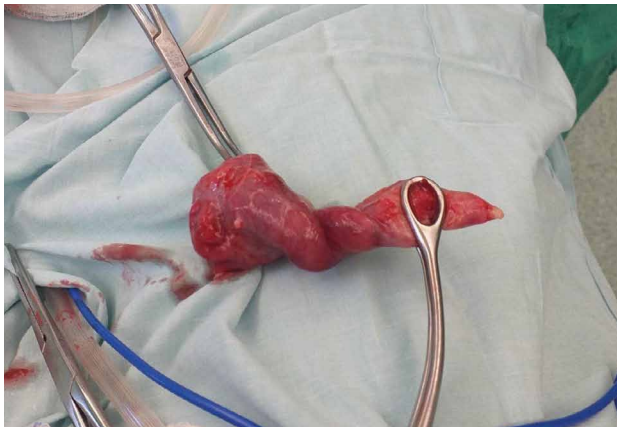

Figure 3. Excised Right Fallopian tube.

(doxycycline 100g x 2 and cephalosporin β΄ generation 750g x 2) was prescribed for 14 days at home.

DISCUSSION

As already mentioned, pyosalpinx is a condition that presents either with very specific symptoms (abdominal pain, fever and findings in gynecological examination) or with a silent clinical picture [1]. About 50% of women present with the typical clinical picture of the disease, which is important for diagnosis. It is necessary to know the exact medical history of the patient as it will help us to rule out diseases during differential diagnosis. In this case, we do not know what caused the peritonitis, whether there was a pre-existing fallopian tube infection or rupture of an ovarian cyst during the hysterosalpingography or the pyosalpinx was created through this invasive procedure. The ultrasound exam is useful, because it provides information about internal genitalia and helps us reach a diagnosis. Thus, the finding of a cystic mass near the ovary should be evaluated appropriately in order to exclude other diseases such as endometriosis, hemorrhagic ovarian cyst, extrauterine pregnancy, etc. When there is a differential diagnostic problem, it would be recommended to perform other auxiliary radiological examinations such as MRI which shows all lower abdomen structures with greater clarity and reliability. Disease management varies depending on the severity of each case from intravenous antibiotic treatment to surgical resection of the diseased organ followed by histological examination as in the current case. Pelvic inflammation (defined as Pelvic Inflammatory Disease - PID) is caused, as already reported, by sexually transmitted diseases that spread from the vagina to the cervix and through the uterus to the adnexa. The main bacteria responsible for the disease are Chlamydia trachomatis and Neisseria gonorrhea. PID is a condition with high morbidity and mortality if left untreated.

In literature, there is a similar case report [11] from a non-tertiary hospital where a 29-year-old woman presented with pyosalpinx after hysterosalpigography for infertility evaluation. Although her medical history was complicated (HIV positive, PID with pelvic and perihepatic adhesions), management was approximately the same with our case. Salpingectomy was performed in both cases through different surgical approaches (laparoscopy vs laparotomy). The antibiotic treatment during hospital stay in the first case [11] was ofloxacin 400mg x 2 + metronidazole 500mg x 2, whereas in the second was cephalosporin β' generation 750mg x 2 + metronidazole 500mg x 3. Despite the differences mentioned above, both patients were discharged 72h postoperative without complications.

CONCLUSION

In conclusion, it is challenging for every specialist in ob/gyn to make the diagnosis of acute abdomen due to tubal infection based on medical history and patient's clinical picture. This way the appropriate treatment plan will be developed. It turns out that any invasive examination of the internal genitals should be done with great precision, abiding by all sterilization protocols, as this complication that we analyzed may be considered rare, but it may be life-threatening for patients. Every patient with PID has lower chances of natural conception and high risk of ectopic pregnancy. More specifically, our patient was advised to in vitro fertilization for getting pregnant due to the fact that an extra factor was added in her infertility investigation process which is a major surgery (salpingectomy and pelvic adhesions).

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REFERENCES

1. Juvan V. Pyosalpinx. Jugosl Ginekol Opstet. 1978;18(5-6):397-403.
2. Parsons AK. Regarding the best approach to the pyosalpinx. Ultrasound Obstet Gynecol. 1996;7(6):398-400.
3. Chalazonitis A, Tzovara I, Laspas F, Porfyridis P, Ptohis N, Tsimitselis G. Hysterosalpingography: Technique and applications. Curr Probl Diagn Radiol. 2009;38(5):199-205.
4. Sendy S, Abuy A, Sendy Wd, Baradwan S. Unusual presentation of bilateral pyosalpinx mimicking an ovarian torsion: A case report. Ann Med Surg (Lond). 2020;52:16-8.
5. Eschenbach DA. Acute pelvic inflammatory disease. Urol Clin North Am. 1984;11(1):65-81.
6. Bramki TA. Hysterosalpingography. Fertil Steril. 2005;83(6):1595-606.
7. Taipale P, Tarjanne H, Ylostalo P. Transvaginal sonography in suspected pelvic inflammatory disease. Ultrasound Obstet Gynecol. 1995;6(6):430-4.
8. Stanto SL. Acute salpingitis. Br Med J (Clin Res Ed). 1987;295(6599):621-2.
9. Eng CW, Tang PH, Ong CL. Hysterosalpingography current applications. Singapore Med J. 2007;48(4):368-73; quiz 374.
10. Roest I, van Welie N, Mijatovic V, Dreyer K, Bongers M, Koks C et al. Complications after hysterosalpingography with oil- or water-based contrast: results of a nationwide survey. Hum Reprod Open. 2020;2020(1):hoz045.
11. Egbe TO, Kobenge FM, Arlette MMJ, Belley-Priso E. Pyosalpinges after hysterosalpingography in a patient with lower genital tract infection and managed by laparoscopic surgery in a resource low tertiary hospital case report and literature review. Fertil Res Pract. 2018;4:2.

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- Materials and Methods
- Results
- Discussion

Define abbreviations at first mention in text and in each table and figure.

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