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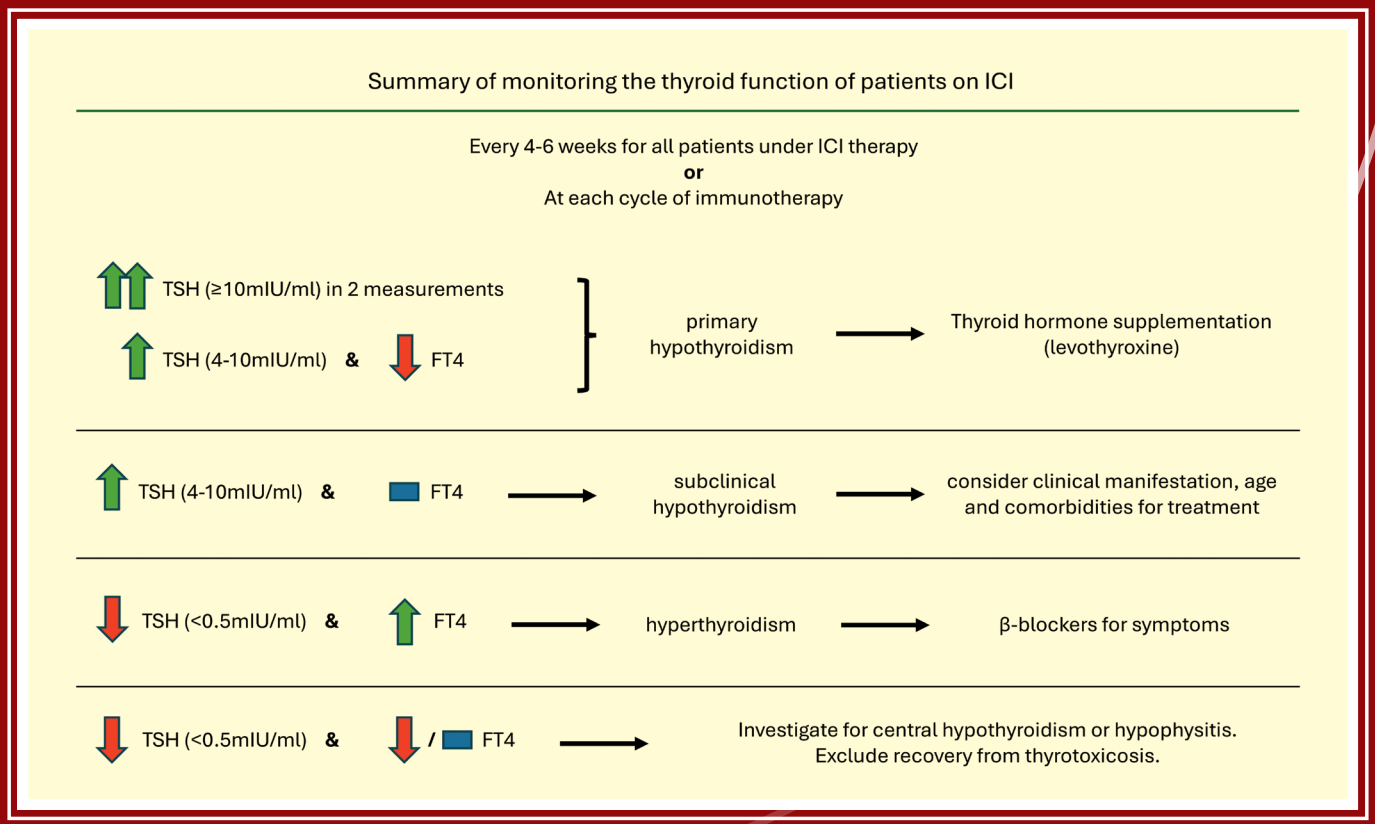

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ACHAIKI IATRIKI

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CONTENTS

Dear colleagues,

In the current issue, the editorial by Pastras et al. highlights recent advances in the understanding, diagnosis, and treatment of Autoimmune Pancreatitis (AIP). The article particularly emphasizes on emerging therapeutic strategies and the shift toward pathophysiology-driven, personalized care.

The current issue features four review articles. The first, authored by Kyriazoglou et al., discusses recent advances in the management of soft tissue sarcomas, focusing on the integration of neoadjuvant therapies, immunotherapy, and precision medicine strategies to improve patient outcomes. The review by Filippopoulou et al. examines the key factors contributing to difficult-to-treat rheumatoid arthritis and highlights the critical role of early identification in enhancing disease management and improving patient outcomes. The review by Chardalia et al. underscores the clinical importance of early diagnosis of immune checkpoint inhibitor-induced colitis emphasizing management strategies aligned with the latest evidence-based guidelines, while also exploring emerging therapeutic approaches. Finally, the review by Kyriakopoulos et al. studies the significance of immune checkpoint inhibitor-induced thyroid dysfunction, highlighting its clinical patterns, underlying mechanisms, diagnostic methods, and management strategies.

Lastly, this issue features a case report by Ndidiamaka Onyiriuka Daniel, which discusses the psychosocial impact of childhood vitiligo on both the patient and her family. It emphasizes the importance of addressing the concerns of parents and reviews the recommended treatment guidelines for childhood vitiligo, along with certain challenges associated with their application.

Yours sincerely,

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Understanding and Management of Autoimmune Pancreatitis

Ploutarchos Pastras, Ioanna Aggeletopoulou, Christos Triantos

INTRODUCTION

Autoimmune pancreatitis (AIP) is a chronic, benign inflammatory disease of the pancreas, characterized by autoimmune mechanisms. Unlike other pancreatic diseases, AIP responds dramatically to glucocorticoid therapy [1]. Although it is considered rare, it accounts for approximately 2% of chronic pancreatitis cases [2].

The clinical presentation of AIP varies widely, ranging from asymptomatic cases to symptoms such as obstructive jaundice, weight loss, chronic abdominal pain, fever, and acute pancreatitis episodes. AIP can present as a diffuse pancreatic process, which is pathognomonic, or as a focal pancreatic mass that can mimic pancreatic cancer. Histological confirmation may be necessary, with findings typically including pancreatic lymphoplasmacytic infiltration and fibrosis.

Diagnosing autoimmune pancreatitis is based on clinical features, serological markers, imaging findings from computed tomography (CT) or magnetic resonance imaging (MRI), and the classification of AIP type. Endoscopic ultrasound (EUS) with pancreatic biopsy is often crucial to rule out pancreatic cancer [3] and may also assist in determining the AIP subtype.

AIP is classified into two types: type I (lymphoplasmacytic sclerosing pancreatitis) and type II (idiopathic duct-centric pancreatitis) [1]. Each subtype differs in clinical presentation, histological features, and associated systemic involvement, necessitating tailored diagnostic and therapeutic approaches.

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Autoimmune Pancreatitis Subtypes

Type I AIP (Lymphoplasmacytic Sclerosing Pancreatitis - LPSP)

Type I AIP is the most common subtype, accounting for approximately 80% of AIP cases. It is observed more frequently in Asia, particularly Japan, but its distribution is global. The mean age of onset is 60–70 years, and males are three times more likely to be affected than females. Clinically, type I AIP most often presents with painless obstructive jaundice (75%) and, less frequently, with abdominal pain. Imaging findings may include a diffuse pancreatic process or a focal pancreatic mass [4]. The hallmark feature is an elevated level of immunoglobulin G4 (IgG4)-positive plasma cells in the blood (≥2 times the upper limit of normal) and within the pancreatic parenchyma. Type I AIP is histologically defined as lymphoplasmacytic sclerosing pancreatitis (LPSP), according to the International Consensus Diagnostic Criteria (ICDC) [5]. This subtype often involves other organs beyond the pancreas and may present either as an isolated condition or as part of IgG4-related disease (IgG4-RD). Unlike type II AIP, type I has no association with inflammatory bowel disease (IBD). Relapses occur in up to 60% of cases following corticosteroid therapy [4].

Type II AIP (Idiopathic Duct-Centric Pancreatitis - IDCP)

Type II AIP is more prevalent in Europe and the United States compared to Asia, but it represents a minority of cases (approximately 20% of AIP patients). The mean age of onset is 40–50 years, and there is no significant gender predominance.

Patients with type II AIP commonly present with either obstructive jaundice or symptoms of acute pan-

Key words: *Autoimmune pancreatitis; subtypes; therapy; new treatment options*

creatitis at similar rates. Imaging frequently reveals a focal pancreatic mass (85%). Histologically, type II AIP is characterized as idiopathic duct-centric pancreatitis (IDCP), which features granulocyte epithelial lesions (GELs). Unlike type I, blood IgG4 levels are typically normal, and pancreatic tissue has very few IgG4-positive plasma cells. Type II AIP does not involve other organs but is strongly associated with IBD. Relapse is rare, occurring in less than 10% of cases [4].

Table 1 provides an overview of the key characteristics, prevalence, demographic trends, clinical features, and relapse rates associated with the different subtypes of AIP, highlighting the distinctions between type I and type II.

Other recorded disorders

Two additional disorders have been reported in the literature without being the primary classification of autoimmune pancreatitis. More specifically, AIP Not Otherwise Specified (AIP-NOS) refers to cases of AIP that do not meet the criteria for either type I or type II AIP. These patients typically lack elevated serum IgG4 levels, other organ involvement, IBD association, or histological confirmation. Evidence suggests that AIP-NOS shares similar clinical features with type II AIP, and a significant proportion of these patients are reclassified as type II AIP upon further follow-up [6].

Furthermore, Immune Checkpoint Inhibitor-Induced Pancreatic Injury is a recently described disorder, associated with immune-related adverse events caused by immune checkpoint inhibitors (ICIs). This iatrogenic pancreatic injury occurs due to a nonspecific immune response triggered by regulatory checkpoint blockade in patients undergoing treatment for advanced malignancies [7]. That condition typically manifests four–six months after initiating ICI therapy. While asymptomatic elevation of pancreatic enzymes (e.g., lipase) is the most common finding, a minority of patients may develop symptoms of chronic pancreatitis. Diagnosis relies on excluding alternative causes of pancreatitis and establishing a temporal correlation with ICI exposure, as radiological findings are often absent. Disorder is usually seronegative, and it lacks pathognomonic histopathological lesions [7].

Therapeutic Management and Follow-Up of Autoimmune Pancreatitis

It is not necessary to initiate treatment for all patients with AIP immediately. The decision to begin therapy is guided by specific clinical indications. Patients presenting with obstructive jaundice, abdominal pain, back pain, or other symptoms involving the pancreas or extrapancreatic organs (e.g., jaundice due to bile duct strictures in overlapping IgG4-related disease) should receive prompt treatment.

Additionally, asymptomatic patients with persistent pancreatic masses on imaging, irreversible pancreatic exocrine or endocrine dysfunction, persistent abnormalities in liver function tests, or progressive subclinical lesions in vital organs associated with (overlapping) IgG4-related disease should also be treated.

Conversely, patients without these characteristics typically do not require initial therapy. This approach is supported by evidence showing recurrence rates without a definitive cure in 25–55% of AIP cases [8].

The primary treatment for AIP patients with clinical indications is prednisone at an initial dose of 40 mg per day for four–six weeks. After this induction period, repeat clinical evaluation and imaging studies (e.g., CT or MRI) are performed. Patients who demonstrate clinical and radiological improvement undergo a gradual tapering of prednisone over two months until discontinuation. Most patients with AIP (80–99%) respond to this initial corticosteroid therapy.

In cases where patients fail to respond to corticosteroids, it is crucial to re-evaluate the diagnosis and

Table 1. *Summary Table of Autoimmune Pancreatitis Subtypes.*

Subtype	Prevalence	Age Range	Gender Predominance	Key Features	Relapse Rate
Type I	~80%	60–70 years	Male > Female (3:1)	Elevated IgG4 levels, lymphoplasmacytic infiltration, systemic involvement, no IBD association	Up to 60%
Type II	~20%	40–50 years	Male ≈ Female	Normal IgG4 levels, granulocyte epithelial lesions, no systemic involvement, associated with IBD	<10%

exclude other conditions in the differential diagnosis [8]. For patients with contraindications to corticosteroid use, treatment with rituximab should be initiated or continued. Additionally, for certain AIP populations with co-existing IgG4-sclerosing cholangitis (IgG4-SC) as part of IgG4-RD, biliary stenting may be warranted depending on individual risk factors [9].

Follow-Up Care

After completing primary treatment, AIP patients should be monitored regularly by a physician. The suggested follow-up schedule includes clinical and serological evaluations every six months and radiological examinations initially at 4–6 weeks post-treatment, followed by a six-month interval thereafter [10].

Patients do not require maintenance therapy during follow-up, unless they experience a relapse or are considered at high risk for relapse. High-risk relapse characteristics include [8]:

1. Type I AIP with diffuse pancreatic enlargement.
2. Involvement of two or more extra-pancreatic organs or proximal IgG4-SC before treatment.
3. Delayed radiologic remission with corticosteroid therapy.
4. Persistently elevated serum IgG4 levels (>2 times the upper limit of normal) after treatment.

Maintenance Therapy

Patients experiencing relapse or identified as high risk for relapse require maintenance therapy during follow-up. The choice of maintenance therapy depends on the presence or absence of IgG4-RD:

- In AIP without IgG4-RD:
  - Azathioprine: 2 mg/kg per day (first-line therapy).
  - Alternative options:
    - Prednisone: 2.5–10 mg per day for one–three years or indefinitely.
    - Mycophenolate mofetil: 750 mg twice daily.
- In AIP with IgG4-RD:
  - Rituximab: 1 g IV on days 0 and 14 (maintenance therapy) [11].

It is important to recognize the increased risk of diabetes mellitus in AIP patients due to extensive pancreatic parenchymal atrophy. Proactive management of this risk should be considered during follow-up [12].

Potential New Treatment Options

Recent studies have explored the pathophysiology of AIP to identify new potential treatment options. Eotaxin, a chemokine involved in the recruitment of inflammatory cells, has emerged as a promising therapeutic target, and efforts to develop targeted anti-eotaxin therapies are ongoing [13]. Regarding type II AIP, a case series has reported that colchicine may be an effective treatment option due to its ability to inhibit neutrophils and reduce the formation of pathognomonic granulocytic epithelial lesions [14]. Additionally, some patients with type II AIP and coexisting IBD have responded effectively to ustekinumab, a monoclonal antibody targeting interleukin-12 and interleukin-23 [15]. For type I AIP, several targeted therapies have been proposed, including inhibitors of B-cell activating factors such as ianalumab and inebilizumab (anti-CD19), as well as agents targeting other pathways, including simtuzumab (anti-LOX2), abatacept (anti-CD80/86), elotuzumab (anti-SLAMF7), and daratumumab (anti-CD38) [16]. More specifically, a recent study published in the New England Journal of Medicine (N.E.J.M.) with 135 IgG4-related disease (IgG4-RD) participants showed that inebilizumab reduced the risk of flares and increased the likelihood of flare-free complete remission at one year [17].

Furthermore, therapies like anifrolumab and sifalimumab (anti-IFN-I), as well as etokimab (anti-IL-33), which have been successfully used in systemic lupus erythematosus, have been suggested for type I AIP. These therapies target interferon-I and interleukin-33, which are known to drive chronic inflammation and fibrosis in this subtype [18]. The role of the gut microbiome in AIP pathogenesis has also been highlighted, particularly in type I AIP. Studies in mice have shown that gut sterilization reduces the accumulation of pathognomonic plasmacytoid dendritic cells in the pancreas, suggesting that modulation of the gut microbiome could be a potential therapeutic strategy. Future approaches may include probiotics, prebiotics, symbiotics, or fecal microbiota transplantation as prophylactic or adjunctive treatments to mitigate pancreatic inflammation and fibrosis [19].

CONCLUSION

Response to corticosteroids is a hallmark characteristic of AIP. Most patients achieve remission through induction or maintenance therapy, and relapse rates remain relatively low. While some studies are exploring and proposing novel therapies for different AIP subtypes, the majority of current clinical trials are focused on improving diagnostic methods. This emphasis reflects the greater challenge physicians face in accurately diagnos-

ing AIP in daily clinical practice. Among potential new treatment options, inebilizumab is a promising choice because the participants it tested included patients with AIP.

These trends suggest that research priorities in AIP are shifting toward a deeper understanding of its pathophysiology to facilitate the development of more precise and effective diagnostic tools. A better comprehension of the underlying mechanisms could not only improve diagnostic accuracy but also pave the way for identifying novel therapeutic approaches that enhance treatment outcomes for AIP patients.

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New Trends in the Management of Soft Tissue Sarcoma

Anastasios Kyriazoglou, Anna Boulouta

Abstract

Soft tissue sarcomas (STS) are a heterogeneous group of tumors originating from connective tissues. The management of STS has historically been challenging due to their rarity, heterogeneity, and complex anatomical locations. Surgical excision remains the standard treatment for localized STS, often supplemented by radiotherapy and chemotherapy to control recurrence and metastasis. Recent advancements in the era of immunotherapy and precision medicine have introduced novel therapeutic strategies, including neoadjuvant combination treatments and immune checkpoint inhibitors. Neoadjuvant therapies incorporating chemotherapy agents and tyrosine kinase inhibitors (TKIs), often combined with radiotherapy and regional hyperthermia, have improved surgical outcomes and survival rates. In metastatic STS, immune checkpoint inhibitors have shown promising efficacy, particularly in specific histologic subtypes. The identification of biomarkers such as tumor mutational burden (TMB) and tertiary lymphoid structures (TLS) has the potential to guide and personalize immunotherapy, improving prognostic accuracy and treatment efficacy. This review highlights these emerging trends, emphasizing the importance of integrating novel therapeutic approaches and precision medicine in the management of STS to optimize patient outcomes.

Key words: *Soft tissue sarcoma; treatment; chemotherapy; radiotherapy; immunotherapy; pathologic complete response.*

INTRODUCTION

Soft tissue sarcomas (STS) are a heterogeneous group of malignant tumors originating in connective tissues, including muscles, fat, blood vessels, nerves, and fibrous tissues, and accounting for approximately 1% of malignant tumors in adults [1]. Historically, the management of STS has been challenging due to their rarity, heterogeneity, and the complex anatomical locations they often involve. Surgical excision remains the standard treatment for early disease. However, due to high recurrence rates, the addition of perioperative systemic therapies and/or radiotherapy (RT) has been integrated [2,3]. RT has been a standard adjunct to surgery, particularly for high-grade and large tumors, aiming to control local disease. Chemotherapy plays a well-established role in managing metastatic disease and serves as a perioperative treatment for certain high-risk patients [2]. With the advent of immunotherapy and precision medicine, significant advances have been made in the management of STS, such as neoadjuvant combination treatments and immune checkpoint inhibitors. New trends in STS therapeutics emphasize improving treatment efficacy and tailoring therapeutic strategies to individual patients.

MATERIALS AND METHODS

This review aims to highlight and evaluate the emerging trends and advancements in the management of STS, including an analysis of novel therapeutic approaches, the role of precision medicine, and the integration of multimodal treatment strategies. To achieve this, we conducted a bibliographic search of the PubMed database using the following terms: "Soft

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tissue sarcoma" AND ("treatment") AND ("chemotherapy" OR "radiotherapy" OR "hyperthermia" OR "TKI") AND ("neoadjuvant" OR "adjuvant" OR "perioperative"). We included phase I, II or III clinical trials, reviews, as well as the ESMO–EURACAN–GENTURIS Clinical Practice Guidelines for diagnosis, treatment and follow-up of soft tissue and visceral sarcomas.

RESULTS

Early disease

Surgery is the standard treatment for all patients with localized STS, with en-bloc excision with R0 margins being the standard procedure [3]. For high-grade tumors, RT is the classic adjunct treatment. While it was historically preferred postoperatively, it is nowadays used as a preoperative treatment with or without chemotherapy [5]. Neoadjuvant treatment for STS can facilitate surgical resection and lower rates of local relapse and distant metastases, compared to adjuvant treatment. There is no standard neoadjuvant chemotherapy treatment for STS, however, among expert centers, a combination of doxorubicin and ifosfamide is preferred [3].

Radiotherapy and hyperthermia

For patients with localized high-risk STS, incorporating regional hyperthermia (RHT) into neoadjuvant therapy has led to improved survival rates and better local progression-free survival. Therefore, for those eligible for neoadjuvant therapy, adding RHT to the treatment regimen may be beneficial [6]. Another issue that is under investigation is the hypofractionation of RT, meaning an RT schedule that is given over a shorter period of time than standard RT. The standard-of-care preoperative RT dose regimen for STS remains 25 × 2 Gy [7]. Recent studies on moderate hypofractionation and ultra-hypofractionation for STS have demonstrated that these alternative schedules generally achieve comparable local control outcomes to the conventional RT regimen [8]. In addition, a phase II study of hypofractionated RT combined with chemotherapy for extremity STS resulted in a disease-free survival (DFS) of 72%, with a median follow-up of 29 months [9].

Chemotherapy and TKIs

A chemotherapeutic agent that has demonstrated promising activity in the neoadjuvant treatment of STS, especially in myxoid liposarcoma (MLS), is trabectedin. In a recent phase II clinical trial, 51% of patients treated with preoperative trabectedin combined with RT achieved over 90% necrosis in the tumor specimen [10]. Another agent showing promising results in combination with RT is pazopanib. In the ARST1321 randomized phase II trial, the addition of pazopanib to neoadjuvant chemoradiotherapy improved the rate of pathologic complete response, increasing to 58% compared to 22% [11]. A similar study of neoadjuvant pazopanib plus chemotherapy in patients with high-grade localized soft tissue sarcoma more than double the historical pathologic complete response (pCR) rates observed with neo-adjuvant RT alone [12].

Pathologic complete response

pCR is a marker that is used in daily clinical practice in other neoplasms, such as breast and urothelial cancers. Even though it is not yet integrated into the therapeutic approach of STS, there are recent data that indicate a correlation between pCR and clinical outcomes in these patients. A study of neoadjuvant RT for STS had shown a positive correlation between the rate of pCR and distant recurrence-free survival (DRFS) [13]. The RTOG 9514 and RTOG 0630 trials of neoadjuvant chemoradiotherapy proved that pCR after preoperative treatment is correlated with a superior five-year overall survival (OS) [14,16]. Additionally, a study evaluating neoadjuvant chemotherapy versus chemoradiotherapy for retroperitoneal STS, concluded in a superior five-year disease specific survival (DSS) in the group of patients that achieved pCR [15]. The above results show that pCR is a marker that needs to be investigated further and utilized in therapeutic decisions for localized STS.

Metastatic disease

Immunotherapy

Several immune checkpoint inhibitors have been, and are currently being, investigated, showing promising results in certain subtypes of STS.

The SARC028 phase II trial enrolled 84 patients with both bone sarcoma (BS) and soft tissue sarcoma (STS). The STS group included patients with undifferentiated pleomorphic sarcoma (UPS), liposarcoma (LPS), leiomyosarcoma (LMS), and synovial sarcoma (SS). All participants were administered pembrolizumab at a dose of 200 mg every 21 days. There was a notably high objective response rate (ORR) in the UPS subgroup, with one patient achieving a complete response and two others achieving partial responses. Additionally, 20% of patients with LPS exhibited partial responses. The median progression-free survival (mPFS) was 30 weeks for UPS and 25 weeks for LPS [17].

The AcSe trial, a phase II multicenter study, also evaluated the effectiveness of pembrolizumab monotherapy across different sarcoma subtypes. The updated results demonstrated an ORR of 6.2%, with a mPFS of 2.8 months and a median OS of 19.7 months. There was notable heterogeneity in responses among different histotypes, with alveolar soft part sarcoma (ASPS) and SMARCA4-deficient sarcoma or malignant rhabdoid tumor showing favorable outcomes, achieving partial response rates of 50% and 25%, respectively. One patient with ASPS (7%) and one patient with epithelioid sarcoma (17%) achieved complete responses [18].

A phase II study investigating the effect of atezolizumab in patients with ASPS reported an ORR of 37%, including one complete response and 18 partial responses. The mPFS was 20.8 months. Interestingly, seven patients discontinued treatment after two years and their responses were maintained [19].

In a Chinese phase I clinical trial, toripalimab was administered to patients with advanced or refractory tumors, including 12 with ASPS. Among the ASPS patients, the ORR was 25.0%, the mOS was 34.7 months and the mPFS was 11.1 months [20].

The randomized Alliance A091401 trial demonstrated that the combination of nivolumab and ipilimumab was more effective for treating metastatic, locally advanced, or unresectable sarcomas compared to nivolumab alone. The study's primary endpoint was met, with a response rate of 16%. Responses to the combination therapy were noted in patients with ASPS, UPS, LMS, myxofibrosarcoma (MFS), and angiosarcoma (AS), with five (12%) partial responses and two (5%) complete responses [21].

Immune checkpoint inhibitors and TKI combinations

In the phase Ib/II IMMUNOSARC trial, nivolumab plus sunitinib was tested in 16 patients with STS. The ORR was 21%, while the 18-month OS was 100% for patients who had an objective response and 75% for those who had stable disease. One patient with AS achieved a complete response, while two patients with ASPS, one with AS, one with SS, and one with extraskeletal myxoid CS experienced a partial response [22].

A phase II, single-arm clinical trial of pembrolizumab combined with axitinib for advanced soft tissue sarcoma, including ASPS, showed a three-month progression-free survival of 65.6% for all evaluable patients, with a three-month progression-free survival being 72.7%, especially for patients with ASPS [23].

Alliance A091902 is a multicenter phase II study of cabozantinib plus nivolumab for patients with advanced AS previously treated with a taxane. Preliminary data from this trial show an ORR of 62%, with 11 partial responses and two complete responses. Median PFS was 9.6 months, and OS 20.5 months [24].

Recently, the combination of durvalumab plus pazopanib was tested in metastatic and/or recurrent STS. The ORR was 30.4%, meeting the prespecified endpoint and the median PFS was 7.7 months [25].

Biomarkers for immunotherapy response

PD-L1 is known to predict responses to immune checkpoint inhibitors in several solid tumors. However, its role as a prognostic and predictive biomarker in STS is controversial [26]. A marker that has shown a stronger correlation with ICI response is tumor mutational burden (TMB). High TMB values are observed in UPS, LMS, and SS [27].

Tertiary lymphoid structures (TLS), which include T cells, follicular dendritic cells, and B cells, are part of the tumor microenvironment and appear to be better predictors of prognosis and response to therapy. Recent findings from the PEMBROSARC trial showed that STS rich in TLS and intratumoral plasma cells exhibited a better response to pembrolizumab [28].

DISCUSSION

The management of soft tissue sarcomas (STS) has evolved significantly over the past decades, with advancements in surgical techniques, the incorporation of multimodal therapies, and the advent of precision medicine and immunotherapy. This review has highlighted several key trends and innovations in the treatment of STS, particularly focusing on the roles of neoadjuvant therapies, hyperthermia, and immune checkpoint inhibitors, as well as the exploration of biomarkers to guide therapy. These trends represent a move towards more personalized, precise, and effective management of soft tissue sarcomas, aimed at improving outcomes and quality of life for patients. Future research should focus on refining these therapeutic strategies and validating biomarkers to further improve clinical outcomes for patients with soft tissue sarcomas. The continued collaboration between clinical researchers, oncologists, and multidisciplinary teams will be essential in translating these advancements into standard practice, ultimately enhancing the prognosis and quality of life for patients with STS. Table 1 summarizes the new therapeutic options in the management of STS.

Table 1.

Therapeutic option	Sarcoma type	Disease stage	Outcome
Neoadjuvant RT +/- Chemotherapy	All STS	Locally advanced	Lower rates of local relapse and distant metastases [5]
Neoadjuvant Hypofractionated RT + Chemotherapy	All STS	Locally advanced	Increased DFS [8,9]
Neoadjuvant regional hyperthermia	All STS	Locally advanced	Increased survival rates and local PFS [6]
Neoadjuvant trabectedin + RT	MLS	Locally advanced	Increased tumor necrosis [10]
Neoadjuvant pazopanib + RT	All STS	Locally advanced	Increased tumor necrosis [11,12]
Pembrolizumab	All STS	Recurrent/Metastatic	High ORR, mPFS, mOS [18]
Atezolizumab	ASPS	Recurrent/Metastatic	High ORR, mPFS [19]
Toripalimab	All STS	Recurrent/Metastatic	High ORR, mOS, mPFS in ASPS patients [20]
Nivolumab/Ipilimumab	All STS	Locally advanced/Metastatic/Unresectable	High ORR [21]
Nivolumab/Sunitinib	All STS	Recurrent/Metastatic	High ORR [22]
Pembrolizumab/Axitinib	All STS	Recurrent/Metastatic	High 3-month PFS [23]
Nivolumab/Cabozantinib	AS	Recurrent/Metastatic previously treated with taxane	High ORR, mPFS, mOS [24]
Durvalumab/Pazopanib	All STS	Recurrent/Metastatic	High ORR [25]

CONCLUSION

The landscape of STS management is rapidly evolving, with significant advancements in both neoadjuvant and metastatic disease treatments. The integration of new radiotherapy regimens, hyperthermia, novel chemotherapeutic agents, TKIs, immune checkpoint inhibitors and combinations of the above, have enhanced the efficacy of traditional treatment regimens. Moreover, the identification of predictive biomarkers for therapy response represents a significant step towards personalized medicine in STS.

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Difficulties in treating Rheumatoid Arthritis until nowadays

Alexandra Filippopoulou

Abstract

Rheumatoid arthritis (RA), mainly affecting women, is the most frequent rheumatic disease with different phenotypes. In recent years, despite the development of new therapies, clinical remission is not always achieved by all patients. Disease activity remains high or moderate and corticosteroids cannot be tapered, despite the use of conventional synthetic Disease-Modifying Antirheumatic Drugs (csDMARDs) and/ or at least two different biologic agents. The difficult to treat RA and the consequent decreased quality of life, remain an intractable problem in everyday clinical practice. Specific genetic factors are reported to be potentially involved, whereas comorbidities, including obesity, osteoarthritis and/or fibromyalgia may aggravate the uncontrolled disease. Moreover, atherosclerosis and malignancies are more frequently presented in cases of refractory RA, often leading to limited therapeutic options. Patients with difficult-to-treat arthritis are additionally prone to infections, occasionally pausing their treatment. Pregnancy and lactation may complicate the disease by imposing specific precautions, also involving the period before conception. Consequently, only allowable therapy is indicated in all cases. Furthermore, several environmental factors, including smoking, coffee consumption and lack of physical exercise, may negatively affect disease activity, despite treatment. Patients' quality of life may additionally deteriorate because of pharmacologically induced adverse events, such as osteoporosis, particularly following steroids administration. Finally, lower adherence to treatment, frequently related to patients' lower educational and financial situation, combined with the absence of only one standardized tool for assessing patient's perception of the severity of their condition, may also lead to difficult-to-treat disease. It is worth noting that the RA population is not treated uniformly worldwide, since drug prescription and administration vary across different areas, according to local economic regulations. For all the above reasons, early recognition of poor prognostic factors is essential to prevent disease flares and hence, therapy escalation, with controversial outcomes.

Key words: *Rheumatoid arthritis; difficult-to-treat; high disease activity; complications*

INTRODUCTION

Rheumatoid arthritis (RA) is one of the most common autoimmune inflammatory diseases, mainly affecting the joints of upper or/and lower extremities in a symmetrical pattern. Extra-articular manifestations, including pleuritis, pericarditis and formation of rheumatoid nodules may also occur. Different phenotypes are not uncommon in everyday clinical practice, since

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Abbreviations: *RA = Rheumatoid Arthritis, EULAR = European League Against Rheumatism, DMARD = Disease-Modifying Antirheumatic Drugs, csDMARDs = conventional synthetic Disease-Modifying Antirheumatic Drugs, bDMARDs = biologic Disease-Modifying Antirheumatic Drugs, ACPA = Anti- Citrullinated Protein Antibody, DAS-28 = Disease Activity Score-28, TNFi = Tumor Necrosis Factor Inhibitor, BMI = Body Mass Index, tsDMARDs = synthetic targeted Disease-Modifying Antirheumatic Drugs, jakinh = Jak inhibitor, RCT = Randomized Control Trial, TNFa =Tumor Necrosis Factor a, IL 6 = Interleukin 6*

several patients may present with early joint destruction, whereas others exhibit milder symptoms at baseline [5]. Epidemiologically, RA is estimated to affect 1 % of the worldwide population [1,2] with females being twice as likely to be affected, according to most studies [3].

The last decades, the evolution of therapy has been proven to be beneficial for the majority of patients. Clinical remission or low disease activity is achieved through new therapeutic approaches, according to the European League Against Rheumatism (EULAR) recommendations. However, 5- 20% of patients remain difficult to treat, failing to reach treatment targets [4]. Unachievable corticosteroid tapering, usually accompanied by the failure of two or more conventional synthetic Disease-Modifying Antirheumatic Drugs csDMARDs and/or biologic Disease-Modifying Antirheumatic Drugs (bDMARDs) or targeted synthetic DMARDs (tsDAMRDs), also known as Jak inhibitors (Jakinh), is often considered as difficult-to-treat RA. Therefore, despite the treat-to-target strategy, refractory disease is frequently identified [5,6]. Under these circumstances, the concurrent presence of comorbidities, fatigue and /or extra-articular manifestations, is frequent [4]. Additionally, the variant response to treatment, commonly observed in everyday clinical practice, is considered multifactorial.

Main text

Genetic risk factors may lead to the presence of heterogeneous clinical phenotypes; however, no specific genetic factor has been strongly associated with a better response to treatment [4]. Positivity for various alleles, such as HLA DR1 and HLA DR4, is prone to the development of RA [6]. Anti–citrullinated protein antibodies (ACPAs), the most specific autoantibodies for the disease [7,6], are more frequently present in HLA DR1 positive patients. Therefore, radiological damage, accompanied by higher inflammatory markers in sera and more swollen joints in clinical examination, is often observed [7-9]. According to De Rooy et al, the presence of SNPs located near TNF receptor-associated factor 1 (TRAF1) is highly associated with aggravation of radiographic damage, indicating that SNPs may play an important role in difficult to treat RA cases [10]. Conigliaro et al report that exacerbation of RA is associated with several SNPs, such as PSORS1C (psoriasis susceptibility 1 candidate 1, PTPN2 (protein tyrosine phosphatase non-receptor type 2, FOXO3A (Forkhead Box O3A) [4]. The methylation of DNA may also affect the synovium cells of the joint and is frequently associated with the development of a more severe and aggressive RA phenotype and consequently more difficult to treat [4,11]. The last decades the use of DMARDs, and more specifically of bDMARDs, aiming at better management and treatment of RA, is proven to be promising [15]. On the other hand, bDMARDs are not always successful, despite their increased use. According to Schipper et al, positive predictors for rapid reach of low disease activity include male gender, younger age and low Disease Activity Score-28 (DAS28) at baseline [12]. These predictors often require early diagnosis. Unfortunately, delays in identifying RA are not uncommon. It is reported that the time lag between onset of symptoms and diagnosis ranges from one month to ten years [58], increasing the risk for a more difficult to treat disease. However, refractory RA is frequently associated, not only with delayed diagnosis, but also with the presence of comorbidities. Despite the use of biologic agents and more specifically Tumor Necrosis Factor inhibitors (TNFi), disease remission may not occur, as revealed by an Italian cohort of 308 patients [13,14]. Generally, clinical outcomes in RA are often influenced by the presence of comorbidities; hence it is highly recommended that patients should be monitored for co- or pre- existing comorbidities [26]. Among them, obesity plays an important role in difficult to treat patients. Concurrent osteoarthritis, in conjunction with depression, is often associated with exacerbation of fibromyalgia and consequently chronic pain, have a negative impact on clinical remission [16]. The assessment of DAS28 score, widely used for the estimation of disease activity in RA, may not be accurate in cases of obesity, since obese patients are frequently considered to have more swollen joints during clinical examination. For that reason, the use of ultrasound (not available in all rheumatology outpatient clinics) may be beneficial in patients with a higher BMI (Body Mass Index) [17]. Furthermore, obesity is also associated with a worse clinical response to treatment with TNFi, when compared to patients with normal BMI [18,19]. Therefore, non-TNFi administration, including abatacept or tocilizumab, is considered to be more beneficial in overweighed RA subjects, whose sera have higher amounts of IL 6, frequently resulting in exacerbation of inflammation [20-22]. The pro- inflammatory cytokine IL 6, especially in high levels, is also associated with cardiovascular diseases and atherosclerosis. Many studies report that RA patients have an increased risk for cardiovascular events, especially in high levels of inflammation [23-25].

According to an observational cohort-study with

combinatorial data from Norway and Sweden, the increased RA disease activity is correlated with higher risk for acute coronary syndrome. These results indicate the imperative need for close monitoring of these patients, who are prone to remain in a continuous non-remission state, despite treatment [25]. Additionally, Oral Surveillance survey revealed an increased risk for major adverse cardiovascular events (MACE), also concerning malignancies, in RA patients under treatment with tofacitinib (the first approved jak inhibitor in RA), compared to subjects under TNFi administration [58]. The survey results raise suspicions for the safe use of Jak inhibitors (jakinh) in RA, and inflammatory diseases in general. Consequently, the use of jakinh is recommended after risk assessment [59] and as a result, several patients may be excluded from this kind of therapeutic options by their rheumatologists. Nonetheless post hoc analysis did not reveal significant danger for these events after jakinh administration [60], indicating that there is no real contraindication for their use. However, it is worth noting that comorbidities, including cardiovascular disease, may lead to contraindications concerning the use of several approved for RA drugs, resulting in a sustainable active disease.

Malignacies are another major problem in RA patients. An increased rate of lymphoma and lung cancer is observed among them [62-64], due to immune dysregulation and/or chronic inflammation, that often result in cell proliferation, mutagenesis, oncogene activation and angiogenesis [65]. Although it was initially believed that bDMARDs, and mainly TNFi, were potentially involved in carcinogenesis, meta-analyses, observational studies and post marketing surveillance, indicated that early use of these drugs is safe, not increasing the overall risk for malignancies [66]. Data remain controversial, reporting that patients receiving treatment for RA, especially rituximab, have a greater risk for all cancers, compared to general population [67]. The recent ORAL surveillance study also detected an increased risk for carcinogenesis after tofacitinib (jakinh) administration compared to TNFi [58]. Burmester et al, however, did not report a higher risk of malignancy, excluding NMSC, in RA patients after a 5.45 year administration of another jak inhibitor, upadacitinib [69].

Nonetheless, managing patients with RA and concurrent cancer is a non-rare complex problem for both rheumatologists and oncologists, often resulting in a difficult to treat disease. In patients with a history of malignancy, bDMARDs, and specifically TNFi, are not commonly preferred as therapeutic tools, while an increased use of rituximab is noticed in most cases [68]. Nowadays, treatment with TNFi in patients with prior cancer (except in cases of lymphoma or melanoma), is considered to be safe after a mean follow-up of five years, since no significant cancer recurrence is reported, under these circumstances [70]. However, since no robust data from randomized clinical trials (RCTs) exist, the therapeutic management of RA patients during the first five years after malignancy diagnosis still remains an ongoing question.

An increased rate of infections (both outpatient and those requiring hospitalization), is observed in patients with refractory disease [28]. Serious infections, especially under treatment with bDMARDs or jakinh, are common in RA population with high disease activity, especially during the first year after treatment initiation [27,72]. Bacterial infections are more commonly observed in these patients. Interestingly, in case of sepsis, a lower risk of death is noted in subjects treated with bDMARDs, compared to subjects, who are on therapy with conventional synthetic DMARDs (csDMARDs) (71). CsDMARDs, initially administered after the diagnosis of RA and frequently in combination with low daily doses of glucocorticosteroids (5–7.5 mg), are generally considered safe [71-74]. Risk factors for severe infections among RA patients include older age (> 65 years), high disease activity and disability score (as defined by DAS-28 and HAQ score, respectively), presence of comorbidities (chronic lung or kidney disease), higher doses of glucocorticoids (> 7.5 mg/day), history of previous serious infections and previous DMARDs failures and, finally, current immunosuppressive therapy [71]. Infectious complications should be taken into consideration, because in case of infection, according to general recommendations in everyday clinical practice, patients with autoimmune diseases, including RA, are advised to temporarily suspend their immunosuppressive therapy. This practice, however, often results in a non remission state, especially when pausing is frequent.

Pregnancy is another factor that may cause difficulties in treating RA. Since women are mainly affected by the disease, the periods of pregnancy and puerperium, especially with concomitant lactation, are critical. Although 60 % of pregnant RA women (particularly without positive RF and/or ACPAs in the serum) are reported to be in remission during pregnancy [29-30], treatment in this period remains challenging. Contraindications for the use of several drugs are the

major problem for rheumatologists. Methotrexate, the basic and most widely used DMARD in rheumatology, is known for its teratogenic effects on the fetus. The drug is also combined with an increased rate of abortion [31]. Generally, for safety reasons, the discontinuation of methotrexate is recommended, three months prior to scheduled conception [34,35].

Taking into consideration that 40% of pregnancies are unintended worldwide [32], women diagnosed with RA in their reproductive age, should be advised for contraception measures, and if they still express the desire to conceive in near future, only conventional medications can be prescribed, including: glucocorticoids (prednisolone is particularly selected, since, due to its lower transpacental transfer, earlier fetal lung maturation is avoided), hydroxychloroquine, azathioprine, cyclosporine and sulfasalazine [4,33]. Those drugs are also compatible with breastfeeding, except from sulfasalazine that is not recommended in case of premature or ill infants [34]. However, several of them are occasionally proven to be inadequate in controlling disease activity and therefore bDMARDs should be used. During pregnancy the most widely used bDMARD is certolizumab pegol, a PEGylated, Fc-free anti-TNF agent with a high safety profile. In 1,137 prospectively reported pregnancies with maternal exposure to the drug, neither teratogenesis, nor increased rate of fetal death was found [35]. Data from gastroenterology indicate that adalimumab may also be a safe choice for pregnant patients with autoimmune diseases [37]. Additionally, there are no reports linking etanarcept to unfavorable outcomes during pregnancy and lactation, indicating that etanercept may be administered, if necessary [39].

Congenital abnormalities are not referred to in cases of compatible TNFi administration during the first half of pregnancy [4]. However, there are several concerns about the potential affection of infants' immune system after birth, and consequently live vaccines are contraindicated for the first 12 months of life [38]. As far as the newer therapies with targeted synthetic therapies (tsDMARDs or jakinh) are concerned, no clear evidence to this date exist regarding their safety during pregnancy. Due to their small size, these molecules are considered capable of crossing the placenta; therefore, their use is not indicated in pregnant women [40].

Environmental factors may also play an important role in unsuccessful treatment in RA. Smoking increases the risk of ACPA-positive RA [41]. Seropositive RA (as defined by positive ACPA and/ or RF in patients' serum) is known to be more severe than seronegative disease and therefore more difficult to treat. The administration of the most widely used bDMARDs, such as TNFi, is negatively correlated with smoking [46]. Smoking is also associated with radiographic progression in RA. According to Rydell et al, other risk factors for rapid joint destruction are seropositivity, presence of erosions, and high disease activity at baseline; maintenance of active disease at one year after diagnosis is additionally considered dangerous for the development of novel erosions [47]. Therefore, cigarette smoking may be related to a more severe and often refractory disease, with limited response to treatment options.

Coffee consumption is also associated with higher risk for RA development and mainly for a seropositive, and consequently more difficult to treat, disease [42]. However, inflammatory responses are influenced by caffeine and its metabolite paraxanthine. Caffeine has been shown to suppress chemotaxis of monocytes and neutrophils, as well as the production of pro – inflammatory cytokines, including TNFα [49], indicating the existence of contradictory data concerning caffeine consumption in RA patients [4]. The lack of physical exercise may also exacerbate disease activity. Due to inflammatory mechanisms, lower bone mineral density and aggravation of joint mobility may occur [43]. More specifically, Th1 cell production is reported to be decreased after physical activity. IL 6 is also secreted inducing the production of anti- inflammatory cytokines, including IL 1ra, IL 10 and TNF receptor (TNF-R) [48]. Furthermore, lack of physical activity may also increase the cardiovascular risk. Patients with RA, due to uncontrolled systemic inflammation, are prone to atherosclerotic cardiovascular diseases [50], as already mentioned. Consequently, they are advised for a healthier way of living, including aerobic exercise, as well as strength and resistance training, as a main part of their therapy, according to EULAR recommendations published in 2018, concomitantly aiming at a better quality of life [44,45,51]. However, nowadays, the maintenance of good physical condition is limited by the new way of urban living. The concurrent long-term use of steroid agents may also easily lead to muscle weakness and osteoporosis [4]. Systemic inflammation, as observed in RA, is often associated with bone loss. Osteoclastic activity may also be activated, resulting in a reduced bone mineral density (BMD) [52]. Osteoporosis is estimated to be found in 30–50% of patients with RA, mainly in cases of high disease activity [53]. However, the prolonged use of corticosteroids, a major cornerstone

in the treatment of RA patients, may increase the risk for bone loss and, consequently, fractures. As a result, anti-osteoporotic treatment is also recommended in RA patients, contributing to polypharmacy and frequently poor treatment compliance [53,54].

Considering all the above, the use of several commonly preferred drugs for RA treatment, may be present challenges and, therefore, inevitably not prescribed for several patients. Comorbidities and adverse drug reactions may not be compatible with the administration of DMARDs, leading to refractory disease, difficult to treat [55]. Furthermore, lower adherence to treatment in RA is mainly observed in patients with higher disease activity. in addition, factors such as lower education level and worse financial situation of several patients further result in non- compliance and, therefore, poor disease outcomes [54]. In order to calculate disease activity, several tools are often used, taking into consideration the Patient Global Assessment (PGA), too. PGA is a widely used self-report measure reflecting patients' own assessment of the severity of their condition. However, since many versions of PGA world widely exist, its standardization remains a major problem, indicating the necessity for validity and reliability [56]. Since patients' lives are undoubtedly affected by the disease in every aspect of their everyday activities, the development for new patient – centered tools, capable of incorporating the symptoms and consequences is imposed.

Finally, the high cost of several treatment options (especially bDMARDs) may influence the physician's prescription. Rheumatologists should lean on robust data for better disease control, but financial obstacles may influence the therapy that is administered in their patients [61], especially in different regions with different economic laws.

CONCLUSION

Despite the treat-to-target strategy in combination with novel drugs in RA, some patients may still fail to respond. Difficult-to-treat RA remains a major problem in everyday clinical life of rheumatologists, indicating the need for early recognition of poor prognostic factors in order to avoid disease flares and hence therapy escalation, resulting in controversial outcomes. Refractory disease may require better management of comorbidities and environmental factors, which, combined with the different pathways, molecules, and cells involved in the pathogenesis of RA, may in part justify the lack of response of some patients.

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Immunotherapy - Induced Colitis

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Abstract

The introduction of Immune Checkpoint Inhibitors (ICIs) entirely altered the landscape of the oncologic therapeutic approach. The immunotherapy agents administered to date have been proven to be efficient and improve overall survival even in advanced malignancies, whose prognosis was poor before the emergence of ICIs. Nevertheless, the immune system's overresponsive activity may lead to toxic consequences, gastrointestinal adverse events being the most frequently reported. Their clinical manifestations range from mild, self-restricted diarrhea to fatal complications such as intestinal perforation. Few studies have been conducted to detect the susceptibility factors leading to the development of immune-checkpoint inhibitor-mediated colitis (IMC) and clinicians remain incapable of identifying high-risk patients in time. Management of IMC principally includes corticosteroids, showing favorable outcomes and remission in a significant percentage of patients. However, refractory disease cases still require biologic agents such as Infliximab or Vedolizumab. This review aims to highlight the clinical importance of diagnosing IMC promptly and treating it according to the latest evidence-based guidelines, while discussing promising management approaches.

Key words: *Immune checkpoint inhibitors; diarrhea; colitis; immune-related adverse events*

INTRODUCTION

Immunity checkpoint inhibitors (ICIs) have dramatically transformed the current treatment approach of malignancies. Since their incorporation into oncology, there has been a revolution in the management of cancers of all grades. The improvement of both overall survival and quality of life for patients represents a significant scientific breakthrough of the 21st century [1]. It is well acknowledged that tumor cells employ mechanisms to escape the immunosurveillance system. Hence, scientists developed the ICIs, monoclonal antibodies targeting three critical molecules of this process: the cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4), the programmed cell death protein-1 (PD-1) and its ligand PD-L1 (PD-L1). These proteins consist of inhibitory receptors of the immune system, suppressing the T-cell-mediated activity against the tumor. Consequently, the ICIs, by blocking these receptors, lead to enhanced T cell activity in order to eliminate the tumor cells [2].

The introduction of immunotherapy as an additional tool against cancer has not only resulted in favorable outcomes, but has also posed challenges. Unfortunately, the overresponse of T cells has a potentially harmful effect on almost every healthy tissue, imitating the entities of autoimmune diseases, known as immune-related adverse events (irAEs) [3]. One of the most common irAEs implicates the gastrointestinal tract, with clinical presentation ranging from diarrhea to severe colitis leading even to fatal perforation [4]. Its prevalence in the population receiving ICIs ranges from 1 to 25%, depending on several parameters [5]. Wang et al. [6], in their meta-analysis, reported that the incidence of colitis across all grades varies depending on the type of immunotherapy administered. More specifically, the percentage of patients who presented ICIs-induced colitis was 1.4% for anti-PD1 agents, 1% for anti-PDL1 agents, and 9.1% for anti-CTLA4 agents. It is noteworthy that the combination of two types of agents, Nivolumab and Ipilimumab, is linked to even higher incidence [7].

This review aims to highlight the importance of

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promptly diagnosing Immune-checkpoint inhibitor-mediated colitis (IMC), differentiating it from other forms of colitis and effectively managing it according to the latest guidelines.

Pathophysiology

The precise mechanism underlying IMC remains obscure. Nevertheless, three events play a pivotal role in its pathology: the excessive activation of T effector cells (Teff), the lymphocyte infiltration of the intestinal mucosa, and the increased circulation of T memory cells [8-10].

CTLA-4 is a critical checkpoint inducing the suppressive function of CD4+ regulatory T cells (Tregs) [11]. Hence, the inhibition of CTLA-4 may contribute to the development of autoimmune diseases such as IMC. In addition, Luoma et al. [12] proposed that one of the initiating events of IMC is the conversion of resident CD8+ T memory cells in the intestinal mucosa into cytotoxic effector T cells (CTLs), overproducing inflammatory cytokines such as IL-17, IFN-γ, and TNF-α. Furthermore, the upregulation of chemokine receptors CXCR3, 6, 9/10, 16, and integrin receptors a4b7/aEb7 appears to enhance the T cell activity [13].

The role of gut microbiota is also in the spotlight of researchers of irAEs as an imbalance in the intestinal mucosa's flora can affect both the patient's response to immunotherapy and severity of IMC [14]. In most patients receiving ICIs, species such as *Bacteroides fragilis, Burkholderiales, and Lactobacillus reuteri* are decreased, while bacteria from the *Faecalibacterium prausnitzii* genus are enriched [13]. This dysbiosis in gut microbiota may play a predictive role in patients' antitumor response and their likelihood of developing IMC.

Risk factors

Since the emergence and recognition of the IMC entity as an irAE, researchers have sought to identify the main parameters defining the level of patient's susceptibility in developing IMC. As mentioned above, the type of immunotherapy agents administered must be considered as a risk factor. CTLA4 inhibitors are associated with a higher incidence of colitis compared to both anti-PD1 and anti-PDL1 agents [6]. Notably, Ascierto et al. [15], in their randomized, double-blind, multicenter study, concluded that patients with advanced melanoma who received higher doses of Ipilimumab were more susceptible to developing colitis in comparison with the patient group receiving lower Ipilimumab doses. Hence, this finding establishes Ipilimumab, an anti-CTLA4 factor, as the only demonstrating dose-dependent predisposition to colitis.

In the largest study examining the epidemiology of IMC, Farha et al. [16] were the first to identify the characteristics associated with increased susceptibility to developing IMC. Accordingly, it was discussed that female gender, Caucasian ancestry, alcoholism, obesity, and age over 65 years are the primary underlying risk factors to consider when administering immune checkpoint inhibitors. Furthermore, the same cohort study demonstrated that patients with a background of autoimmune disease have an elevated risk of developing colitis. The presence of preexisting autoimmune disease in patients with IMC was found to be 24.6%, with rheumatoid arthritis being the most prevalent, affecting 9.8% of the population studied. In addition, on a genetic basis, HLA-DQB1*03:01 was found to be associated with gastrointestinal adverse events [17].

Patients with a history of Inflammatory Bowel Disease (IBD) have a significantly higher median risk of developing IMC compared to those without an IBD background (41% vs 11%, respectively; $P < .001$) [18]. Therefore, clinicians should maintain a high level of suspicion in such cases but always consider the differential diagnosis with an exacerbation of IBD, as the clinical manifestations may overlap [19].

Clinical presentation and differential diagnosis

Based on clinical manifestations, the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) provides classification systems for both diarrhea and colitis in order to assess disease severity and guide proper management (Table 1) [20]. The classification of diarrhea is based on the number of daily bowel movements above the patient's baseline. Diarrhea is often the first alarming sign of IMC and requires thorough examination [21]. Specifically, Grade 1 diarrhea is defined as fewer than four stools above baseline per day, while Grade 2 is characterized by four to six additional stools per day above baseline. Severe cases where the number of stools exceeds seven above baseline are classified as Grade 3. Grade 4 indicates life-threatening conditions requiring urgent intervention, such as hemodynamic collapse. Finally, both diarrhea and colitis classifications designate Grade 5 as death.

Regarding the classification of colitis, Grade 1 corresponds to asymptomatic patients, while Grade 2 refers to patients with a recent history of or currently receiving

Table 1. *The CTCAE classification of diarrhea and colitis [20].*

CLASSIFICATION	DIARRHEA	COLITIS
Grade 1	Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline	Asymptomatic, pathologic or radiographic findings only
Grade 2	Increase of 4 – 6 stools per day over baseline; moderate increase in ostomy output compared to baseline	Abdominal pain; mucus or blood in stool
Grade 3	Increase of ≥7 stools per day over baseline; severe increase in ostomy output compared to baseline	Abdominal pain, fever, change in bowel habits with ileus; peritoneal signs
Grade 4	Life-threatening consequences (e.g., hemodynamic collapse)	Life-threatening consequences (e.g., perforation, bleeding, ischemia, necrosis, toxic megacolon)
Grade 5	Death	Death

immunotherapy who present with abdominal pain, and bloody or mucousy diarrhea. Concomitant presentations that raise suspicion of IMC include fever, severe pain, signs of peritoneal irritation (Grade 3), or even life-threatening conditions (Grade 4) such as perforation, ischemia, bleeding, necrosis, and toxic megacolon [19]. Additionally, common clinical manifestations include hematochezia, vomiting, and nausea, while patients may also report less typical symptoms such as weight loss or loss of appetite [13]. Furthermore, IMC may also involve upper gastrointestinal symptoms, including dyspepsia, heartburn, and regurgitation. Clinicians must be mindful of the potential coexistence of immunotherapy-induced gastritis alongside IMC [22].

The diagnosis of IMC is based on exclusion, as other forms of colitis or clinical entities (Figure 1) may present with the same manifestations and may even share comparable laboratory, imaging, or histological findings [23].

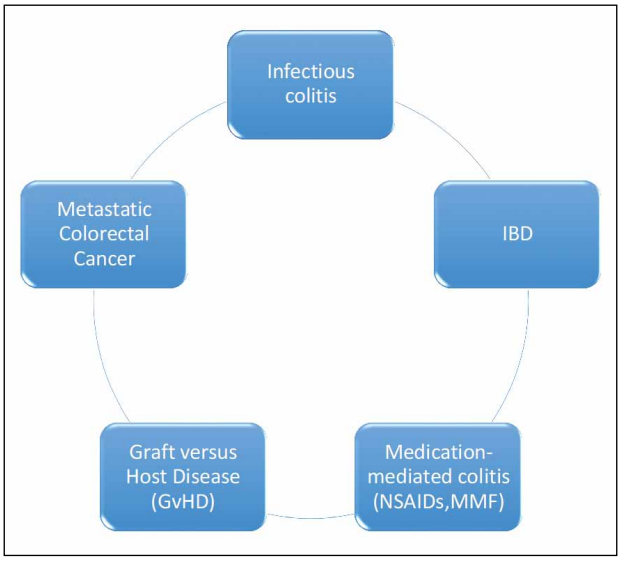

Figure 1. Differential Diagnosis of Immune-checkpoint inhibitor-mediated colitis (IMC) [23].

Diagnosis

Clinical manifestations suggestive of IMC should prompt clinicians to undertake a thorough investigation to establish a timely diagnosis. A detailed patient history and physical examination play a crucial role in the initial assessment and in determining the grade of colitis. Moreover, a complete blood count and biochemical panel should be performed, as along with a measurement of C-reactive protein (CRP) and Erythrocyte Sedimentation Rate (ESR) [24]. Infectious causes of colitis should be ruled out from the beginning, and therefore, it is recommended to obtain stool cultures for detecting pathogens such as *Clostridioides difficile*. It may also be prudent to conduct a supplemental viral check and parasite test in patients residing in regions with a high prevalence of viruses and parasites known to cause colitis. Further investigation could include stool inflammatory markers such as lactoferrin and calprotectin. The American Gastroenterological Association (AGA) recommends the detection of these markers as they identify patients with Grade 1 colitis as being at high-risk for further endoscopic assessment. Regarding Grade 2 or higher colitis, their detection is strongly recommended, though not strictly required, before proceeding to endoscopy [25]. Furthermore, exocrine pancreatic insufficiency is a rare complication of ICIs, but it must still be excluded from the differential

diagnosis by measuring fecal pancreatic elastase [26]. Additionally, the possibility of new-onset celiac disease following immunotherapy should be considered, and tissue transglutaminase immunoglobulin A (IgA) and total IgA tests should be ordered [27].

Endoscopic assessment through colonoscopy or sigmoidoscopy is the gold standard for diagnosing IMC. In patients receiving Ipilimumab, sigmoidoscopy could be considered a first-choice diagnostic procedure because the rectum and the sigmoid colon are the principal colon segments affected [10]. Random biopsies should always be performed, as 33% of patients with IMC undergoing colonoscopy show normal-appearing intestinal mucosa [28]. This subgroup of patients tends to have better clinical outcomes and a lower risk of developing refractory disease or biologic therapies [29]. Abnormal endoscopic findings may include loss of vascular patterns, erythema, ulcerations, edema, necrosis and friable mucosa, which are associated with a worse prognosis [30]. Furthermore, the biopsies obtained can be used to rule out microscopic colitis or infectious colitis caused by *Clostridioides difficile* or cytomegalovirus (CMV) [31]. Notably, endoscopy plays a multi-dimensional role in the management of IMC. Clinicians should be aware of indications for repeat endoscopy applied in Grade 2 and above, such as lack of response to immunosuppressive treatment, deterioration of symptoms despite initial improvement, and evaluation of the intestinal mucosa before resuming immunotherapy agents following temporary discontinuation [5].

Computed tomography (CT) has also proven useful in assessing probable IMC cases, especially if there is a high clinical suspicion index of life-threatening events such as toxic megacolon or perforation, which necessitate immediate surgical intervention [32]. Findings such as diffuse or segmental colitis patterns on CT cannot establish a definite diagnosis of IMC as CT is characterized by low sensitivity and a high rate of false negatives [33]. Consequently, in early-stage patients, combining sigmoidoscopy with CT may be beneficial [32].

Histopathologic findings from the biopsies obtained are suggestive of the diagnosis of IMC. Remarkably, histological differences have been noted depending on the ICI administered. For instance, CTLA-4-associated colitis is linked to lamina propria expansion and lymphocytic intraepithelial infiltration, along with cryptic apoptosis or occasional prevalence of eosinophils in the lamina propria [34]. Concurrently, the lamina propria expansion by lymphoplasmacytic infiltration may be a histologic feature of anti-PD1/anti-PDL1-associated colitis. In addition, neutrophils are the prominent inflammatory cells found, while they can also form cryptic abscesses [35,36]. Ischemic or collagenous colitis have also been described [37]. Most of the patients' biopsies, in both CTLA-4 and anti-PD1/anti-PDL1-induced colitis, show acute inflammatory changes that are indicative of IMC, while chronic inflammatory alterations of the intestinal submucosal tissue are found in approximately 50% of patients [33,37]. However, it is noteworthy that these histologic findings are not pathognomonic for IMC and have been described in other clinical entities that mimic IMC, such as infectious colitis, IBD, and GvHD [38]. Consequently, the final diagnosis must be made by integrating the patient's history, physical examination, laboratory work-up, and both endoscopic and histopathologic findings [32].

Management

Early-stage colitis, assessed as Grade 1, is typically managed conservatively. Specifically, liquid supplementation is imperative in case of dehydration and electrolyte imbalances, which should be corrected. Anti-diarrheal agents such as loperamide may be used, but they are only approved for patients with Grade-1 colitis [39]. Foods containing a high percentage of fat and lactose should be avoided in order to prevent secondary lactose intolerance or deterioration of the disease [40]. Moreover, the immunotherapy agent may be temporarily ceased or, depending on the patient's tolerance, continued. At this stage of IMC, discontinuing ICIs is not usually considered. However, this decision should be made after a multidisciplinary discussion involving oncologists and gastroenterologists, who will assess the patient's performance status, comorbidities, and clinical presentation [41]. Persisting Grade-1 colitis for more than 14 days may lead to the addition of oral budesonide [42], which has been shown to improve colitis symptoms and prevent the immunotherapy discontinuation [43]. Despite its efficacy, budesonide was tested in two randomized trials as possible prophylactic treatment for patients receiving Ipilimumab, but no statistically significant benefit was demonstrated [44,45]. Systemic corticosteroids could be an alternative option in persisting colitis of Grade 1, but clinicians should assess their effectiveness within the first few days of administration and, in case of a positive reciprocation, taper them throughout four to six weeks [46]. Furthermore, patients should be evaluated for stool

inflammatory markers in order to determine whether they are low- or high-risk, with the latter requiring assessment with an endoscopy [25].

The therapeutic management of Grade-2 IMC differs as systemic corticosteroids intravenously (IV) should be initiated from the outset (preferably prednisone or methylprednisolone in doses of 1-2 mg/kg/day). If improvement is noted after introducing IV corticosteroids, the patient may transition to oral corticosteroids [47]. Abdominal CT and endoscopy should always be performed for further evaluation [13]. In addition, patients receiving CTLA4 inhibitors should likely discontinue treatment permanently, while anti-PD1 and anti-PDL1 agents may be temporarily withheld and reintroduced when clinical improvement is achieved [48]. Biologic agents such as Infliximab, an anti-TNFa antibody or Vedolizumab, an integrin blocker, can be administered in case of corticosteroid refractory disease, whose incidence may reach 40% [49]. Early initiation of such biologic agents typically leads to better results, including fewer hospitalizations, earlier disease remission and reduced corticosteroid requirements [50].

Grade-3 colitis necessitates hospitalization of all patients, with close monitoring of hydration level and electrolytes. Therapeutic management does not differ significantly from Grade 2. Discontinuation of CTLA-4 inhibitors is mandatory, while anti-PD1/PDL-1 agents can be temporarily withheld. Systemic corticosteroids should be administered intravenously at high doses but if there is no immediate clinical improvement (after three to five days), escalation therapy with the biologic agents discussed should be initiated [39]. The recommended dosages are the same as those used in IBD patients: 5 mg/kg for Infliximab and 300mg for Vedolizumab [51]. The responsiveness after the biologic agent's infusion is typically rapid within the first week [52]. Notably, a single infusion may be adequate for complete remission of clinical manifestations with either Infliximab or Vedolizumab used, though there is a higher risk of relapse compared to 3 infusions [50]. Furthermore, there is currently no evidence to suggest whether either of the two biologic factors predominate. Clinicians should decide based on the availability or any contraindications that may arise [53].

Grade-4 colitis is managed similarly to Grade 3; however, in this case, immunotherapy agents are permanently discontinued regardless of the factor administered and reintroduction is not reconsidered (Table 2). CT imaging must be performed as life-threatening events such as intestinal necrosis, perforation or toxic megacolon may have occurred, potentially requiring further intervention or surgery [19].

According to the treatment algorithm of IMC (Figure 2), biologic agents, particularly Infliximab and Vedolizumab, play an indispensable role in the therapeutic arsenal considering their efficacy [54]. Besides their role as an escalation therapy, the multidisciplinary modified Delphi consensus [55] recommended their introduction as a first-line treatment in patients with high-risk endoscopic findings, including large ulcerations and extensive colitis [50]. Furthermore, in case of no significant clinical improvement after administering one of these two commonly used biologic agents, the introduction of the other is strongly recommended [24]. Nonetheless, in case of Infliximab and Vedolizumab refractory disease the American Society of Clinical Oncology (ASCO) suggests the introduction of Tofacitinib, a Janus kinase (JAK) inhibitor or Ustekinumab, an antibody blocking interleukin-12 (IL-12) [56].

Management of IMC can be particularly challenging for clinicians, as refractory disease is common, even with the use of biologic agents [57]. In response, researchers are conducting trials to discover alternative and more effective treatments. Specifically, the correlation between gut microbiome composition and the IMC, as well as the influence of gut microbiota on the efficacy of ICIs against tumor cells, has led scientists to explore the potential of fecal microbiota transplantation (FMT) [58-62]. The first two patients receiving FMT due to refractory IMC were reported by Wang et al. in 2018 [62]. Notably, the second patient underwent two cycles of FMT to achieve complete remission of colitis. Since these

Table 2. *ASCO and NCCN Guidelines on discontinuation rules of ICIs [46,56].*

Grade 1	No consideration of discontinuation.
Grade 2	Discontinuation of ICIs. A resume may be considered after the improvement of symptoms to Grade 1 or less, completion of steroid tapering, review of risks and benefits and achievement of endoscopic/histologic remission.
Grade 3	Same principles as in Grade 2. If CTLA-4 was the ICI agent previously administered, permanent discontinuation is strongly recommended. A resume with an anti-PD-1/PD-L1 agent after the resolution of toxicity may be considered.
Grade 4	Permanent discontinuation of ICIs.

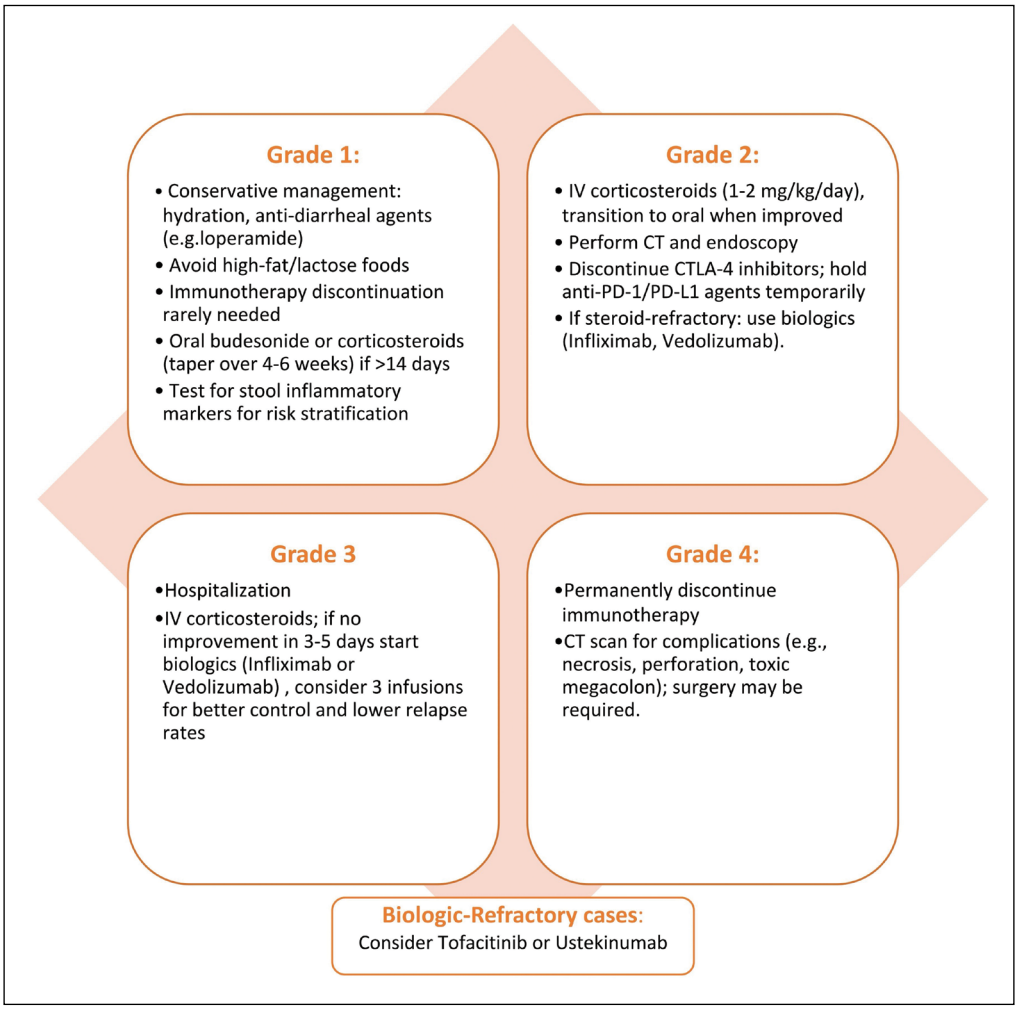

Figure 2. Practical Guide for Immune-checkpoint inhibitor-mediated colitis (IMC) management [46,56].

initial case reports, other researchers have applied FMT in refractory cases with favorable outcomes, rendering it an extremely promising treatment option [63-65].

CONCLUSION

Checkpoint inhibitors are among the most revolutionary oncologic treatments to date. However, they can result in various forms of toxicity, with IMC being one of the most frequently encountered adverse events. Clinicians must be aware that this side effect can arise even months after immunotherapy has been discontinued. Evaluating patients' risk factors is essential for assessing susceptibility to developing IMC. Clinical manifestations are nonspecific, as many pathologies mimic IMC, necessitating a thorough investigation, including laboratory workup, imaging and endoscopic procedures. The management of these patients must be meticulous, with collaboration between oncologists and gastroenterologists being essential. Stratifying patients and defining the colitis grade is the first step in managing this irAE. Corticosteroids remain the cornerstone of treatment, but unfortunately, the rate of steroid-refractory disease is high. Hence, the use of biologic agents plays a crucial role and is associated with favorable outcomes. However, despite their efficacy, some patients fail to respond to this approach, prompting researchers to introduce new treatments aimed at achieving complete disease remission. Notably, FMT is one of the most promising alternatives, but further trials are needed to embed it as a safe and effective treatment in the management guidelines algorithm. Consequently, IMC is an adverse event that significantly affects a patient's quality of life, requiring prompt diagnosis and evidence-based management to ensure optimal remission.

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Immunotherapy-induced thyroid dysfunction

George C. Kyriakopoulos

Abstract

Immune checkpoint inhibitors (ICIs) are a groundbreaking class of drugs that significantly advance cancer treatment by leveraging the immune system against cancer cells. However, their efficacy as anti-cancer agents is accompanied by a broad range of immune-related adverse effects (irAEs), including endocrinopathies. Thyroid dysfunction is among the most common endocrinopathies induced by ICI therapy, making it a major concern. The pathophysiology typically involves destructive thyroiditis, leading to the common patterns of thyrotoxicosis followed by hypothyroidism or isolated hypothyroidism. Diagnosis relies mostly on clinical presentation and laboratory tests. Treatment varies from levothyroxine substitution to the use of beta blockers, based on the severity of thyroid dysfunction. As immunotherapy evolves, recognizing and managing ICI-induced thyroid dysfunction is essential for improving patient safety and outcomes. This review aims to explore the significance of ICI-induced thyroid dysfunction, detailing the patterns, mechanisms, diagnostic approaches, and treatment strategies.

Key words: *Immunotherapy; adverse effects; thyroid dysfunction; hypothyroidism; hyperthyroidism*

INTRODUCTION

In recent years, immune checkpoint inhibitor (ICI) therapy has become a promising advancement in cancer treatment. This innovative approach utilizes the body's immune system to target cancer cells, offering patients new therapeutic options and improved survival rates. Initially used for treating malignant melanoma and lung cancer, this therapy involves administering monoclonal antibodies that target specific cell proteins, such as cytotoxic T lymphocyte-associated protein 4 (CTLA-4), programmed cell death protein 1 (PD-1), and its ligand (PD-L1), thereby inducing T cell activation against neoplasms [1].

However, despite its benefits, ICI therapy is associated with various adverse effects, with thyroid disorders being among the most common endocrine complications. Thyroid dysfunction can appear as either primary hypothyroidism or thyrotoxicosis. The most common type of thyroid abnormality is destructive thyroiditis, which initially causes a phase of thyrotoxicosis followed by permanent hypothyroidism. Rarely, Graves' disease could also occur. The pathophysiology is primarily linked to destructive thyroiditis caused by a T cell-mediated acute autoimmune response [2]. Additionally, research consistently points to the role of autoantibodies against thyroglobulin (Tg), thyroid peroxidase (TPO), and thyroid-stimulating hormone (TSH) receptor, as well as the role of cytokines in the disease's pathogenesis [3]. Consequently, laboratory tests measuring TSH, free thyroxine (fT4), and antibodies are crucial for accurate diagnosis and for monitoring before and during ICI therapy. ICI-induced thyroidopathy can range from asymptomatic cases to severe conditions, including fatalities. Addressing these complications requires prompt diagnosis and therapeutic strategies customized to the clinical manifestations and their severity. Close monitoring and collaboration between

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oncologists and endocrinologists are essential to manage these effects effectively [4,5].

Possible mechanisms of immunotherapy-induced adverse effects

The immune activation responsible for most immune-related adverse events (irAEs) may be linked to the mechanisms driving antitumor immune responses. This tumor-specific hypothesis is supported by the consistent positive correlation between therapeutic responses and the incidence of irAEs [6–8]. Correlative studies offer further evidence of this association, showing shared T cell receptor sequences and upregulated organ-specific transcripts between tumors and non-malignant tissues affected by toxicities [9,10]. Additionally, the development of vitiligo, an autoimmune response targeting melanocytes, serves as a reliable indicator of ICI antitumor activity, particularly in melanoma patients. This suggests a mechanistic link between irAEs and antitumor immunity [11]. If both the beneficial and adverse outcomes stem from the same processes, long-term responders might face a higher risk of chronic toxicities compared to those who do not benefit from the therapy.

Evidence also suggests that certain irAEs may emerge from mechanisms unrelated to antitumor activity, including factors such as the microbiome and viral or tissue-specific elements [12–15]. The diversity of irAEs likely reflects distinct and varied mechanisms for each type of event. Different cell types are implicated as dominant drivers in various preclinical models and biopsy samples from affected tissues. For instance, tissue-resident memory CD8+ T cells were predominant in colon biopsy samples from patients with ICI-induced colitis, while cytotoxic activated memory CD4+ T cells were most prevalent in the brain of a patient with fatal encephalitis [13,16–18]. Targeted inhibition of specific cytokines, such as IL-6, could potentially separate antitumor from antihost immune responses in preclinical models [19,20]. Ultimately, a single mechanistic explanation for irAEs is unlikely; they probably result from both tumor-related and tumor-unrelated factors. Additionally, the mechanisms distinguishing acute versus chronic irAEs remain poorly understood.

The mechanism underlying immune checkpoint inhibitor (ICI)-induced thyroid disorders also remains unclear. In a study conducted by Osario et al., among ten patients who developed thyroid dysfunction following pembrolizumab administration, eight patients were found to have antithyroglobulin or antimicrosomal antibodies [21]. Another study reported ten cases of thyroiditis following anti-PD-1 treatment. Among these cases, six patients experienced transient thyrotoxicosis followed by hypothyroidism, while four patients developed hypothyroidism without a preceding thyrotoxic phase. All patients tested positive for antithyroid antibodies [22]. Iyer et al. also observed that thyroid peroxidase and thyroglobulin antibodies were present in 44.7% and 33% of patients, respectively, after ICI therapy [23]. However, other immune pathways, involving T-cells, natural killer cells, and monocytes might also contribute to thyroid dysfunction during anti-PD-1 therapy, independent of antibody presence [24]. Interestingly, positron emission tomography (PET) scans of patients affected by thyroid irAEs frequently show a diffuse increase in 18-fludeoxyglucose (18-FDG) uptake, suggesting it may serve as a better biomarker for thyroid irAEs. Thyroid antibodies, on the other hand, might indicate the severity and increased risk of needing hormone replacement [25]. Finally, certain cytokines are associated with thyroid irAEs. Elevated levels of cytokines, such as IL-1β, IL-2, and GM-CSF, and lower levels of IL-8, G-CSF, and MCP-1, indicating a shift in the Th1/Th2 balance, may be linked to the development of these immune-related thyroid disorders [26].

Risk factors for immunotherapy-induced thyroid dysfunction

Patients undergoing ICI therapy are exposed to several risk factors that may predispose them to thyroid dysfunction and other endocrine-related adverse effects (Table 1). One significant risk factor is gender, as women are more likely to develop thyroid dysfunction during ICI therapy compared to men. Age is another critical factor, with younger patients being at a higher risk for

Table 1. *Risk factors for immunotherapy-induced thyroid dysfunction.*

Female	
Younger age	
Elevated anti-TPO or anti-TG antibodies before starting ICI	
Higher baseline TSH levels	
High number of immunotherapy cycles	
Obesity	
Race:	Caucasians and Latinos (hypothyroidism)
	African Americans (thyrotoxicosis)

thyroid-related issues [27,28]. The presence of elevated anti-TPO or anti-TG antibodies before starting ICI therapy is another important risk factor. Patients with higher levels of these antibodies have an increased likelihood of developing thyroid dysfunction. Additionally, higher baseline TSH levels at the commencement of therapy are associated with a greater risk of experiencing thyroid problems during treatment [29–31]. The number of immunotherapy cycles a patient undergoes also influences the risk, with a higher number of cycles correlating with an increased incidence of thyroid and other endocrine issues. Obesity further compounds this risk, as it has been identified as a significant factor in the development of thyroid dysfunction during ICI therapy [30,32]. Finally, racial background impacts the type of thyroid dysfunction experienced. Caucasians and Latinos are more prone to developing hypothyroidism as a result of ICI therapy, whereas African Americans are more likely to experience thyrotoxicosis [33]. Recognizing these risk factors can aid healthcare providers in monitoring and managing potential endocrine side effects more effectively in patients undergoing ICI therapy.

Thyroid disorders induced by immunotherapy

Thyroid dysfunction is one of the most common endocrinopathies following therapy with immune checkpoint inhibitors (ICIs). The clinical spectrum ranges from overt hypothyroidism to overt thyrotoxicosis, with destructive thyroiditis being the common underlying pathophysiological mechanism. Thyroid dysfunction is more frequently observed in patients treated with anti-PD-1 agents or a combination of ipilimumab and nivolumab, and less commonly in those treated with anti-CTLA-4 or anti-PD-L1 monotherapies [34–37].

More specifically, primary hypothyroidism affects 6%-9% of patients undergoing anti-PD-1 and/or anti-PD-L1 therapy, 4% of those on anti-CTLA-4 therapy, and approximately 16% of patients receiving a combination of anti-PD(L)1 and anti-CTLA-4 therapies (Figure 1) [38]. It can be preceded by a hyperthyroid state, which may be subclinical. Most cases arise within the first three months of treatment initiation, but onset can occur at any time during the therapy [39].

On the other hand, Immune-related (IR) hyperthyroidism occurs less frequently. It is reported in approximately 2%-5% of patients treated with immune checkpoint inhibitor (ICI) monotherapy and in about 10% of those receiving a combination of anti-PD(L)1 and anti-CTLA-4 therapies (Figure 1) [38]. Transient thyroiditis remains the most common cause of IR hyperthyroidism. Among these cases, around 40% are present with symptomatic thyrotoxicosis, while 60% manifest as subclinical thyrotoxicosis, which is usually followed by hypothyroidism [40]. Primary hyperthyroidism due to Graves-like disease is rarely reported. When it occurs, persistent hyperthyroidism, diffuse goiter, and ophthalmopathy may indicate this diagnosis (41). Thyroid dysfunction typically emerges within a few weeks of ICI initiation and can occur after a single dose (42). Median onset time ranges from 18 to 123 days, but cases have been reported as early as seven days or as late as three years after initiation [34–37]. The dysfunction often starts as painless thyroiditis, beginning with a transient thyrotoxic phase that is usually mild or asymptomatic, lasting a few weeks before transitioning to euthyroidism or hypothyroidism. Symptoms are generally nonspecific, such as fatigue and weight loss, but can include tremor, anxiety and heat intolerance [43,44]. Physical examination may reveal tachycardia or warm, smooth skin, although severe thyrotoxicosis (thyroid storm) is rare [45,46].

The median time for progression to euthyroidism or hypothyroidism is four-seven weeks [24,42]. In some cases, hypothyroidism, whether subclinical or clinical, is the initial presentation and may be transient or permanent. Symptoms are usually mild and nonspecific, including fatigue and weight gain, but may also involve bradycardia, cold skin, constipation, and cold intolerance [43,44]. Myxedema coma, a complication resulting from untreated hypothyroidism, is very rare [47].

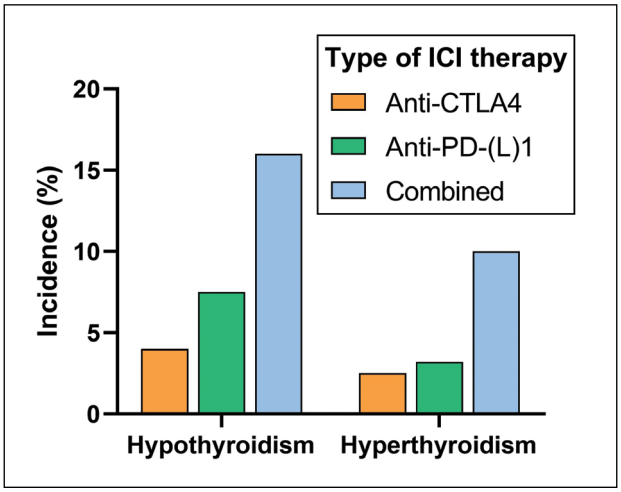

Figure 1. Incidence of thyroid adverse events in patients treated with ICIs.

Elevated autoantibodies against thyroid peroxidase (anti-TPO) and thyroglobulin (anti-Tg) are found in some patients developing thyroid dysfunction after ICI therapy [34–37]. High titers of these antibodies prior to therapy appear to be related to ICI-induced thyroid dysfunction, though they are not necessary but represent a risk factor [26]. Stimulating autoantibodies for the TSH receptor (TRAb or TSI) were negative in most patients, though in rare cases, TRAb positivity suggests co-existing Graves' disease [34–37,48,49].

Measurement of TSH, FT4, and occasionally T3 levels is typically sufficient for diagnosis. In thyrotoxicosis due to thyroiditis, FT4 levels are more elevated compared to T3 levels due to the release of stored thyroxine (T4) into the bloodstream. In hyperthyroidism, T3 levels are higher due to stimulation of the thyroid gland. Differentiating between primary and central hypothyroidism is crucial, as hypophysitis should be considered in these patients [43,44,50,51]. More detailed information can be found in Table 2.

Monitoring and management of immune-related hypothyroidism

The management of endocrine adverse events related to immunotherapy, specifically thyroid dysfunction, follows a structured approach based on the assessment of thyroid function tests (TFTs). For patients with asymptomatic or subclinical hypothyroidism, it is recommended to monitor TSH and free T4 every four-six weeks. If TSH is elevated, the next steps depend on the levels of TSH and free T4. If TSH levels range between 4 and less than 10 mIU/ml, the patient is asymptomaticwith normal free T4 levels, the patient should continue immunotherapy and regular monitoring of TFTs. If TSH exceeds 10 mIU/ml but free T4 is normal, immunotherapy can continue, and the consideration of levothyroxine treatment is advised. In cases where TSH is normal or low and free T4 is low, it is important to investigate for central hypothyroidism or hypophysitis and exclude recovery from thyrotoxicosis [50,51].

For patients with clinical (overt) primary hypothyroidism, TSH should be monitored every four-six weeks. Management includes continuing immunotherapy and considering endocrine consultation. Thyroid hormone supplementation with levothyroxine should be initiated, and TSH levels should be reassessed in four-six weeks to guide dosing adjustments. Additionally, it is essential to exclude concomitant adrenal insufficiency by checking the morning cortisol level. This approach ensures that thyroid dysfunctions are identified and managed effectively without discontinuing necessary immunotherapy, thus maintaining the therapeutic benefits while mitigating adverse endocrine effects (Figure 2) [50,51].

Monitoring and management of immune-related hyperthyroidism

For patients experiencing thyrotoxicosis induced by immunotherapy, the management process is detailed and depends on specific thyroid function test

Table 2. *Evaluation and monitoring of patients on ICIs for possible immune-related thyroid dysfunction.*

Before ICI administration (Baseline)	Clinical evaluation for symptoms: Extreme weakness, unusual headache patterns, increased sweating, rapid heartbeat, weight loss or weight gain, mood changes, constipation or diarrhea, nausea or vomiting, abdominal pain
	Laboratory evaluation: Morning TSH, FT4, cortisol
Every 4-6 weeks (incl. 4-6 weeks after the last cycle)	Clinical evaluation for symptoms
	Laboratory evaluation: Morning TSH, FT4, cortisol
Additional tests	
If hypothyroidism suspected	anti-TPO, anti-TG
If hyperthyroidism suspected	T3
	TSH, FT4, T3 every 2-3 weeks to diagnose persistent hyperthyroidism or hypothyroidism (due to destructive thyroiditis)

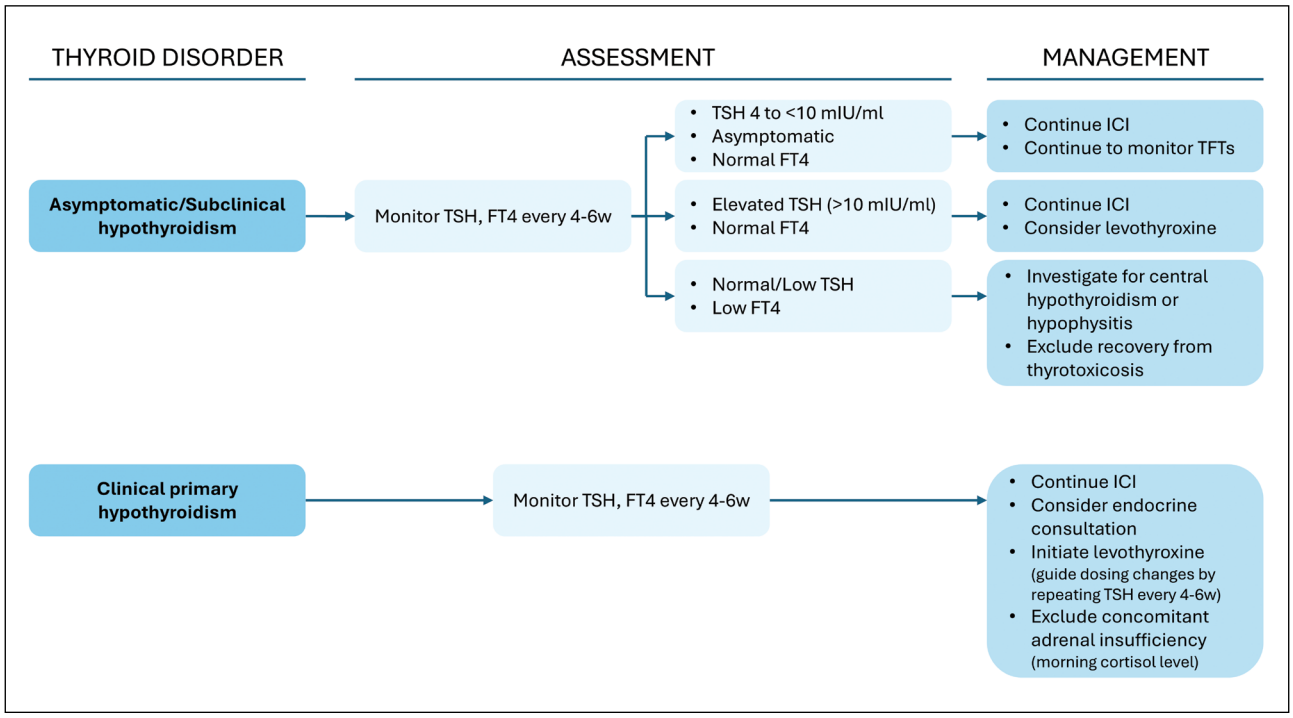

Figure 2. Monitoring and management of immune-related hypothyroidism.

(TFT) results. Immunotherapy-induced thyrotoxicosis is typically caused by transient or evolving painless thyroiditis. Antithyroid medications such as methimazole or propylthiouracil are not recommended for this condition. When thyrotoxicosis is identified, indicated by low or suppressed TSH levels and high free T4/total T3, an endocrine consultation should be considered if the patient is symptomatic. If the patient is asymptomatic, immunotherapy can continue. Symptomatic patients may be treated with propranolol (10–20 mg every 4–6 hours as needed) or atenolol or metoprolol until thyrotoxicosis resolves. TFTs should be repeated every 4–6 weeks. If thyrotoxicosis resolves, no further therapy for thyrotoxicosis is necessary. However, it often evolves into hypothyroidism in 50%–90% of cases, requiring treatment with thyroid hormone replacement, as mentioned above. Rarely, painful thyroiditis can occur, and in such cases, prednisolone 0.5 mg/kg should be prescribed [50]. If thyrotoxicosis persists, an evaluation for Graves' disease should be considered (Figure 3) [50,51].

Role of glucocorticoids in immunotherapy-induced thyroid dysfunction

Even though thyroid disorders have emerged as

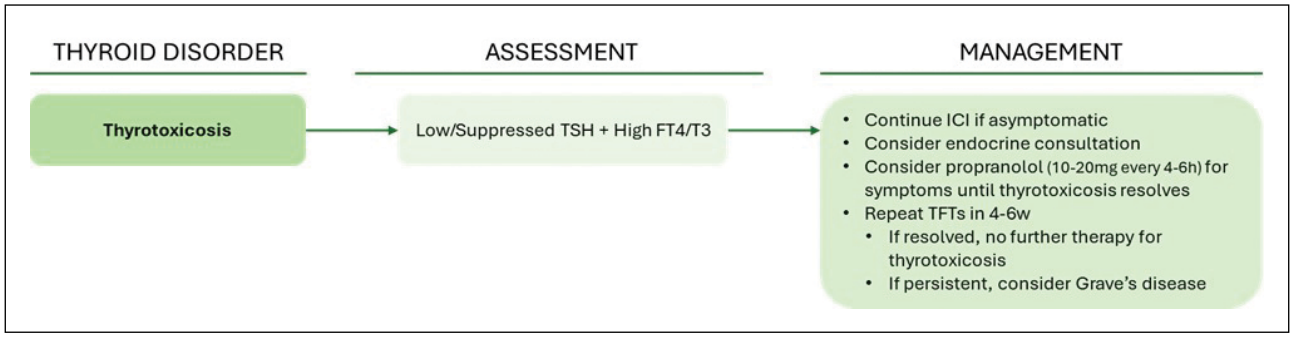

Figure 3. Monitoring and management of immune-related hyperthyroidism.

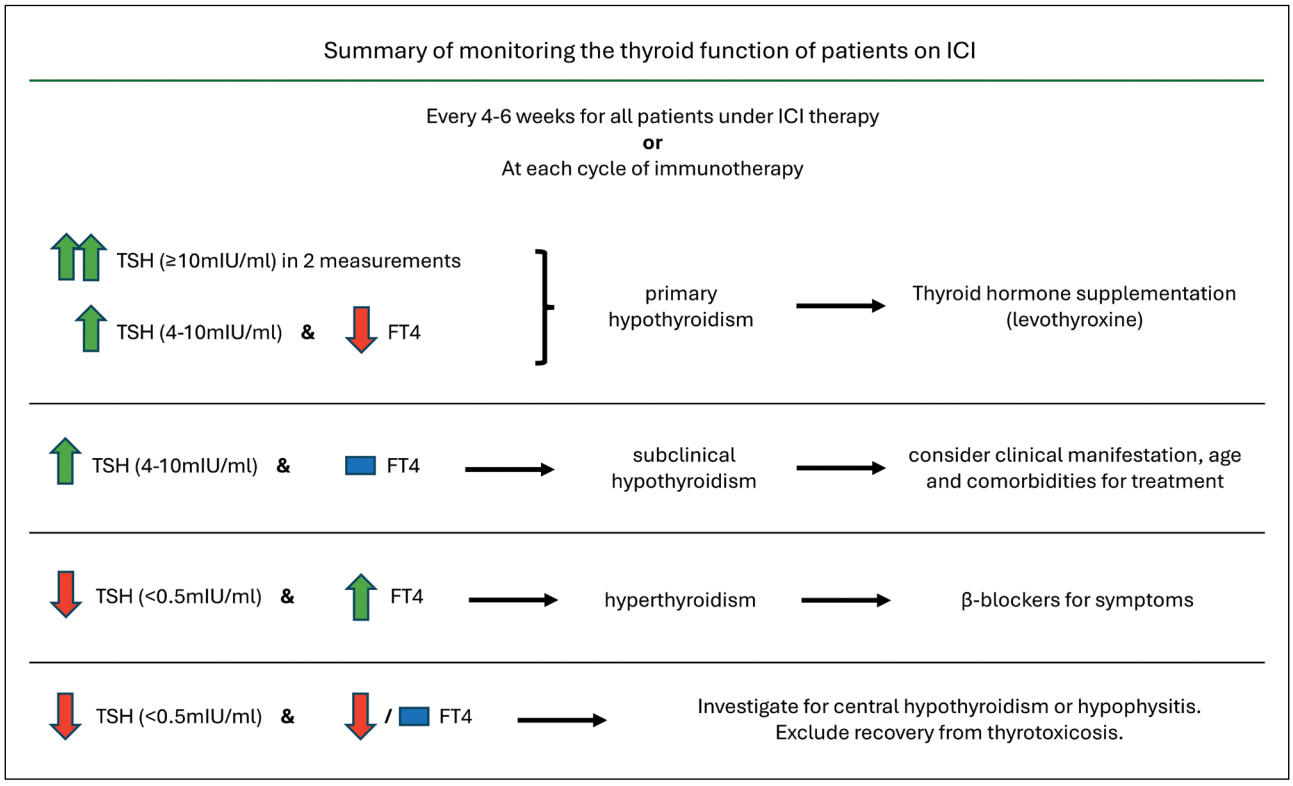

Figure 4. Summary of monitoring the thyroid function of patients on ICI therapy.

one of the most common immune-related adverse events (irAE) associated with immunotherapy, optimum management strategies and predictive biomarkers for vulnerable individuals remain to be fully explored. High-dose glucocorticoid (HDG) therapy is routinely recommended for irAEs [52,53]. However, a systematic analysis of the impact of glucocorticoid therapy on the outcome of immune-checkpoint inhibitor (ICI)-induced thyroid disorders is lacking. In a study analyzing 151 patients with or without ICI-related thyroid disorders, the patients with ICI-related thyroid disorders were divided into two subgroups: those receiving HDG treatment and those not. The results showed no significant differences between the HDG and no HDG groups in terms of the median duration of thyrotoxicosis (28 vs 42 days), the median time to conversion from thyrotoxicosis to hypothyroidism (39 vs 42 days), the median time to onset of hypothyroidism (both 63 days), and the median maintenance dose of levothyroxine (1.5 vs 1.3 mg/kg/day). The median pretreatment TSH was higher in patients with ICI-related thyroid disorders compared to those without (2.3 vs 1.7 mIU/L). Baseline TSH was significantly higher in patients who developed ICI-related thyroid disorders. Subgroup analysis revealed significantly higher baseline TSH in male patients with ICI-induced thyroid dysfunction, but not in female patients. This study concluded that HDG treatment did not improve the outcome of ICI-related thyroid disorders [54].

CONCLUSIONS

Immune checkpoints targeted by ICIs are crucial for maintaining immunological self-tolerance, making these therapies capable of triggering autoimmune adverse effects. Among the most common are thyroid disorders, as well as other endocrine complications like hypophysitis, diabetes mellitus, and primary adrenal insufficiency. Physicians managing such patients need to be well-informed about ICI-related endocrine adverse events, including their clinical presentation, laboratory findings, frequency, and severity. Effective screening and management require close collaboration between oncologists and endocrinologists. As survival rates improve, the monitoring and management of long-term consequences have become increasingly crucial, highlighting the necessity for joint clinics to provide comprehensive care.

To summarize, the management of thyroid-related adverse events from immunotherapy involves structured monitoring and intervention based on thyroid function tests (TFTs). For asymptomatic or subclinical hypothyroidism, TSH and free T4 levels should be monitored every four-six weeks. If TSH is elevated (ranging from 4 and less than 10 mIU/ml with normal free T4), immunotherapy may proceed with regular TFT monitoring. If TSH exceeds 10 mIU/ml, consideration of levothyroxine alongside ongoing immunotherapy is advised. In overt primary hypothyroidism, TSH is monitored similarly, with initiation of levothyroxine and adrenal insufficiency exclusion. Immune-related thyrotoxicosis management involves symptom-driven use of beta-blockers, ongoing immunotherapy if asymptomatic, and periodic TFT checks, anticipating potential transition to hypothyroidism. Persistent thyrotoxicosis may prompt evaluation for Graves' disease. This approach ensures thyroid dysfunctions are effectively managed without interrupting essential immunotherapy, balancing therapeutic benefits with managing adverse endocrine effects [50,51]. A summary can be found in Figure 4.

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Childhood vitiligo: Report of a case associated with psychiatric morbidity in the patient's mother and an approach to differential diagnosis

Daniel A. Ndidiamaka Onyiriuka

Abstract

This report describes the case of an adolescent 13-year-old Nigerian girl, diagnosed with the non-segmental variant of vitiligo, specifically the acrofacial subtype. She exhibited some clinical features of psychological disturbance as a result of her current depigmentation skin disorder. She developed the tendency to avoid strangers due to a fear of being talked about, which could potentially lead to social isolation. Although the patient's mother did not have vitiligo herself, she expressed anxiety regarding her daughter's skin disorder. In this context, her major concern was how the disorder might affect her daughter's eligibility for marriage as she approached the age of marriage, as well as whether the disease was curable. Thus, childhood vitiligo is a common skin disorder with significant cosmetic concern on the patient and psychosocial impact on both the patient and primary caregiver. Attention should be given to parents of children with vitiligo, because they may suffer quality of life impairment, requiring psychosocial support to promote better treatment outcomes. In addition, this report highlights the recommended guidelines for managing childhood vitiligo and points out some drawbacks regarding their application.

Key words: *Childhood vitiligo; depigmentation; differential diagnosis; parents; psychosocial impact*

INTRODUCTION

Vitiligo is an acquired, chronic and non-contagious disease characterized by depigmentation, resulting from selective immunologic destruction of epidermal melanocytes [1], causing achromatic macules or spots. Pigment cells of the skin, hair follicles and mucous membranes are commonly involved in the destructive process. Reports of recent translational research has linked key mechanisms of the disease to cellular stress, innate immune activation, T-cell mediated elimination of melanocytes from the skin, resulting in clinically obvious white spots, as well as stem cell regeneration that reverses established lesions [2]. Vitiligo can appear at sites of trauma or sunburn (Koebner's phenomenon). In older children and adolescents, vitiligo may occur as a component of certain hereditary syndromes such as Vogt-Koyanagi-Harada and Alezzandrini syndromes [3]. In both syndromes, vitiligo appears later and is usually persistent, despite therapy.

Worldwide, the prevalence of vitiligo ranges from 0.5% to 2.0%, with approximately 50% appearing before the age of 20 and 25% of cases starting before the age of 10 [1,4]. A hospital-based study of childhood dermatoses in Ile Ife and Ilesha, Nigeria, reported a vitiligo preva-

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lence of 5.3% [5]. The median onset age of childhood vitiligo is 5-10 years [6]. Vitiligo affects people of all ages, genders and races and may be presented anytime from neonatal period to adolescence. In one-third of cases, there is either a positive family history of vitiligo or a halo nevi or premature graying of the hair [7]. It presents as depigmented, well-defined, milk-white macules and patches of different configurations and variable sizes with an unpredictable disease course. With regard to its evolution, vitiligo can change and exhibit three distinct behaviors: stability, progression or regression. Vitiligo is described as stable or inactive if no new lesions have developed over the last 12 months, or an existing lesion shows no sign of progression. It is considered progressive or unstable when new lesions form or develop within 12 months, or when a pre-existing lesion grows larger. Vitiligo is referred to as regressive when spontaneous re-pigmentation of an existing lesion occurs [6]. Childhood vitiligo differs in its clinical characteristics and response to treatment, when compared to adults. The differences in clinical characteristics include higher rates of instability, re-pigmentation, female preponderance and a rarer frequency of association of other autoimmune and endocrine disorders in children compared to adults [4,8]. The frequency of relapses is lower in children than adults.

Childhood vitiligo is classified into two major clinical forms: segmental (SV) and non-segmental (NSV) [4,8]. The NSV is further sub-divided into generalized, acrofacial, universal, mucosal and mixed types. In the USA, Patel et al [9] reported that out of 9,118 eligible children and adolescents with vitiligo, two-thirds had the NSV subtype based on clinician-adjudicated prevalence. Similarly, a systematic review and meta-analysis study, involving 17 studies from different countries to evaluate the clinicoepidemiological features of childhood vitiligo conducted by Faradjzadeh et al. [10], found that non-segmental variant was the most common pattern of presentation. On the other hand, two separate studies in Brazil and China found that the SV is a more frequent pattern of presentation of childhood vitiligo [11,12]. Also in Nigeria, Anaba et al [13] found that the segmental variant was more common than the non-segmental variant. These conflicting findings suggest that there may be differences in the patterns of presentation across geographic regions. This view is reinforced by Faradjzadeh et al [10], who stated that the clinicoepidemiological pattern of childhood vitiligo varies from one geographical region to another.

The diagnosis of childhood vitiligo is primarily based on clinical examination, as the lesions have a typical appearance [8]. Wood's light examination enhances the contrast between pigmented and non-pigmented skin, particularly in light-skinned individuals. Based on severity/extent of body surface area involved, vitiligo can be categorized into four as follows: limited (< 10% involvement), moderate (10-25% involvement), moderately severe (26-50% involvement) and severe (> 50% depigmentation) [14].

Although childhood vitiligo is not typically associated with physical discomfort, it causes great cosmetic concern, not only for the affected person, but also for the primary caregivers because of the associated stigma [15,16]. This concern is more pronounced in darker-skinned individuals, as the contrast between affected and unaffected areas is more noticeable. It has been shown that the psychological effect may persist in adulthood with a negative impact on social development [17]. Vitiligo has been reported to be associated with autoimmune disorders, such as thyroid conditions, type 1 diabetes mellitus, pernicious anaemia, Addison's disease and alopecia areata [18]. In India, Handa and Dogra [19] found that 1.3% of vitiligo cases in children were linked to an associated autoimmune disorder.

The differential diagnosis includes other causes of widespread acquired leukoderma. The three leading differential diagnoses of childhood vitiligo are: tinea versicolor, post inflammatory hypopigmentation and pityriasis alba [17,19]. The purpose of this case report is to raise awareness among physicians that a patient's primary caregiver, such as parents, may be affected psychologically and may need screening for adverse mental health impact.

Case Report

A 13-year-old Nigerian post-menarcheal girl presented with a history of whitish skin lesions. They were first noticed five years earlier in the scalp near the forehead, accompanied by a depigmentation of the hair (poliosis). One year later, similar lesions appeared on her face. Over the next two years, the lesions spread to both hands and feet. Parents have applied some cream, but there has been no improvement. In addition, fluid extracted from certain herbs was also applied to the lesions. The lesion was not associated with itching, pain, or a burning sensation and there was no loss of superficial sensation. The patient expressed anxiety as a result of her clinical condition, and she tends to avoid

strangers to prevent discussions about her appearance. Her mother's major concern was her child's eligibility for marriage and the possibility of a cure. In addition, her mother sometimes feels embarrassed despite the small size of the lesion. Historically, there was no identifiable precipitating factor and there is no history of seizures or intellectual disability.

Physical examination revealed macular depigmented patches on the face, hands and feet. The lesions were milk-white in color, with distinct margins. The lesion in the scalp showed poliosis (leucotrichia) (Figure 1). She had vitiligo lesions on her face, hands and feet (Figures 1 and 2). The extent of skin involvement was less than 5% of body surface area. On palpation of the lesion, there was no change in texture between unaffected skin and depigmented patches. No underlying atrophy or induration was observed, and the overlying surface was not scaly. The patient did not have halo nevi or goitre. Based on clinical presentation and physical examination, a diagnosis of non-segmental childhood vitiligo with the acrofacial subtype was made.

Figure 1. Vitiligo lesions on the forehead and face.

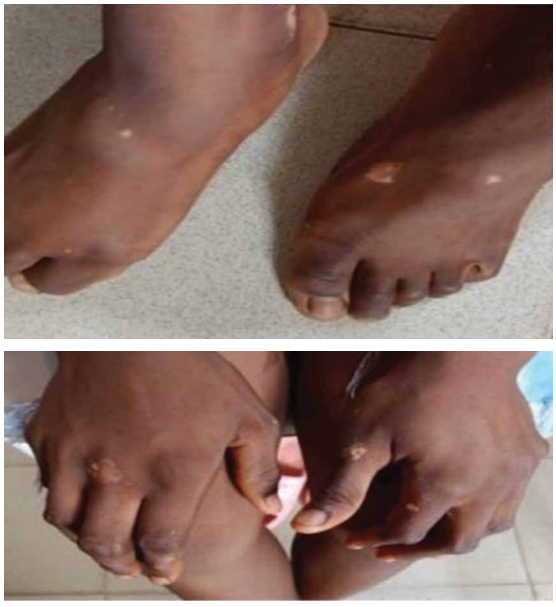

Figure 2. Vitiligo lesion on the feet and hands.

DISCUSSION

The index patient presented with non-segmental vitiligo (NSV) of the acrofacial subtype. This form of vitiligo is characterized by sparse lesions that generally appear bilaterally over the face and distal extremities. As in the index patient, truncal lesions are usually not seen in the initial stages but may develop over time as acrofacial variants evolve into generalized vitiligo [20]. In line with the findings of several studies [4-7,21,22], the diagnosis of childhood vitiligo in the index patient was based entirely on clinical evaluation, as the lesions have a typical appearance. With regard to severity, the index patient had a limited form of vitiligo as less than 10% of her body surface area was involved [14]. The patient's skin lesion was progressive, starting from the forehead, and spreading to the face, followed by the limbs (Figures 1 and 2). The progressive pattern demonstrated in the index patient aligns with non-segmental vitiligo (NSV), whereas segmental vitiligo (SV) is known to usually stabilize within six months to two years [8,23]. However, some SV may progress to generalized vitiligo over time. Considering that Mazereeuw-Hautier et al [24] reported that vitiligo-associated-autoimmune disorders in childhood occur largely in children with NSV, we determined the patient's fasting blood glucose, thyroid function tests and full blood count. All the results were within normal limits, supporting the reported low incidence of vitiligo-associated-autoimmune disorders in childhood [6,23]. In this context, Handa and Dogra in India found a prevalence of only 1.3% [19].

Regarding the differential diagnosis of childhood vitiligo, clinicians must recognize conditions with similar presentation to avoid misdiagnosis. The common acquired clinical conditions in the differential diagnoses of childhood vitiligo are tinea versicolor, post-inflammatory hypopigmentation and pityriasis alba [25]. Vitiligo is probably the most common disorder of skin pigmentation encountered by primary care physicians. Therefore, a simplified approach to differential diagnosis may be helpful. The common differential diagnoses of childhood vitiligo are presented in tabular form (Table 1). Other

Table 1. *Differential diagnosis of childhood vitiligo.*

Disorder	Clinical differentiating point from childhood vitiligo
Childhood vitiligo	Acquired skin depigmentation. The lesion is completely amelanotic, non-scaly, chalky-white macule with well-defined margin. Absence of induration, atrophy, bruising and itch/pain in the lesion is characteristic. On Wood's light examination, it emits bright blue-white fluorescence. May be associated with autoimmune and endocrine comorbidities.
Tinea versicolor	Asymptomatic skin infection caused by yeast *Malassezia furfur.* Characterized by hypopigmented scaly macules mainly over the face in children but the upper trunk in adults. On Wood's light examination, it emits orange fluorescence. Light microscopy of skin scrapings prepared with 10% potassium hydroxide (KOH) may reveal round yeast forms (spores) and short hyphae (referred to as "apples and bananas"). The most appropriate therapy is topical azole or terbinafine. Whitefield's ointment applied twice daily for 3 weeks is also effective.
Postinflammatory Hypopigmentation	History of active skin lesions in the past. Hypopigmented lesion. May occur as sequelae of impetigo, chicken pox infection, onchocerciasis, insect bites or physical trauma. Often retains the shape and size of the original skin lesion. Self-resolution is common
Pityriasis alba	Common in prepubertal children with personal or family history of atopy. Characterized by ill-defined hypopigmented macules with fine scaling; mostly over the face and upper arm. History of pruritus and irritation, especially at the borders may be present. It does not progress and is self-limited. On Wood's light examination, it emits off-white glow with non-circumscribed edges. Low-potency topical corticosteroids may help decrease the inflammatory component and lead to faster return of normal pigmentation. Healthy skin barrier can be achieved with the application of emollients. No associated comorbidities.

significant differential diagnoses include the ash-leaf macule of tuberous sclerosis (lesions typically present at birth or early in infancy) and morphea (the skin of the lesion is usually smooth, thickened and has shiny appearance), whereas vitiligo lesions maintain the same texture as the surrounding skin.

The index patient was an adolescent girl aged 13 years and manifested some clinical features of psychological disturbance as a result of her current skin disorder. As previously reported, in India [26], the index patient developed the tendency to avoid strangers to prevent discussions about her. This behavior often drives patients into social isolation and introversion, particularly when the condition affects the exposed parts of the body. It is known that adolescence is a critical period for developing self-identity and self-esteem [15]. Developmentally, the patient belongs to an age group where self-image is being formed, and social acceptance is of great importance. Thus, the patient's skin disorder has negatively affected her self-confidence and social interactions, leading to diminished quality of life. Despite the fact that the patient's mother did not have vitiligo, she expressed anxiety regarding her daughter's skin disorder. In this context, the mother's major concern was its potential in affecting her daughter's eligibility for marriage, as she approaches the age of marriage. As highlighted in previous reports [16,26,27], parents of children with vitiligo are often considered hidden victims of this relatively common childhood skin disorder. The mother who represents the closest and most caring relationships to her affected daughter becomes a hidden victim. In consideration of the psychological impact of the patient's skin disorder on the mother, it is important to recognize parental quality of life impairment and provide psychological support to promote treatment adherence and decrease the family burden of chronic skin disorder. The patient was accompanied only by her mother during clinic visits, which indicates higher maternal concern regarding the condition. This observation suggests that mothers may be more distressed than the father with regard to the child's skin disorder. A similar observation has been alluded to in the report by Ameer et al [16] in China. The report of some previous studies suggested that because of the cosmetic concern in vitiligo, patients/parents tend to seek medical attention early [28,29]. In contrast, the mother of the index patient sought medical attention five years after the first lesion appeared, despite its progressive nature and involvement of the face in the index case, suggesting poor health-seeking behavior,

is probably due to a lack of symptoms in the patient.

The natural history of vitiligo involves periods of remission and exacerbation, with complete spontaneous re-pigmentation being unusual. Partial or temporary re-pigmentation has been reported in children, particularly for lesions of less than two years' duration and during summer. The re-pigmentation process is slow, with the face and trunk typically responding better than the dorsa of hands and feet [30]. In the case of the index patient, the duration of the lesion was five years (exceeding the two-year threshold associated with re-pigmentation), potentially making spontaneous re-pigmentation less probable.

The treatment of vitiligo in children is very challenging, as many of available modalities of therapy cannot be applied to them. The two main goals of therapy of childhood vitiligo are (i) stabilization of active disease and (ii) promotion of re-pigmentation [31]. Factors influencing the choice of treatment plan include the patient's age, disease duration, extent and severity of the condition, presence of Koebner phenomenon and the association of other autoimmune conditions [31]. Other factors include the socio-economic status of the patient's family and availability of treatment options. According to the 2021 guidelines of the British Association of Dermatologist, the first-line option for managing vitiligo is topical non-steroid therapy [32]. In this regard, the use of tacrolimus is considered the first-line option in the treatment of childhood vitiligo because of the delicate nature of children's skin, which exposes them to a higher risk of skin atrophy from the use of topical corticosteroids (TCs). Additionally, the surface area-to-volume ratio in children increases the risk of the occurrence of adverse effects of steroids. Oral corticosteroids can interfere with growth in children; therefore, their use requires caution. Regarding therapy for childhood vitiligo, Raju et al [33] suggested that moderately potent topical corticosteroids (TCs) are considered as first-line therapy in children with localized vitiligo. Topical calcineurin inhibitors (TCIs) such as tacrolimus/pimecrolimus are good alternative to TCs and are recommended localized forms of vitiligo, as well as for areas with thin skin like eyelids where potential side effects of corticosteroids are high. TCIs cannot be used in children less than two years old because of the risk of skin cancer and lymphoma. In addition, TCIs are expensive and are not readily available in the environment where we practice. A synthetic vitamin D3 analogue (calcipotriol) though less effective than topical corticosteroids can stimulate melanogenesis and inhibit the destruction of melanocytes by T-cells. The combination of phototherapy (NB-UVB), psoralen and UAV (PUAV) is considered a second-line treatment option. Phototherapy acts as an immunosuppressant

Table 2. *Various treatment modalities of childhood vitiligo [31].*

Topical medical therapy	Systemic medical therapy	Surgical therapy
Corticosteroids	**1. Corticosteroids** (OMP with betamethasone/ethylprednisolone)	**1. Conventional**
Tacrolimus/pimecrolimus		Mini-punch graft
Calcipotriol	**2. Phototherapy**	Suction blister epidermal Graft
Pseudocatalase	Topical PUVA	Thin Thiersch graft
Combination (corticosteroids and tracolimus)	NB-UVB	
	Systemic PUVA (> 12 years)	**3. Newer cellular transplantation techniques**
	Phenyalanine + PUVA	Epidermal cell suspension
	Excimer laser (308nm)/targeted NB-UVB phototherapy	Cultured melanocyte Suspension
		Cultured epidermis

NB-UVB = Narrow Band Ultraviolet B.

and stimulates melanocyte activity [34]. The third-line treatment option is surgical therapy. Though not commonly used in children, suction blister epidermal grafting is preferred. Surgical procedures are not performed in very young children because segmental or stable focal lesions in younger children extend proportionate to their body growth. In addition, success of many surgical procedures depends on post-operative immobility of the operated part which is more difficult to achieve in young children [31]. Other potential treatment modalities of childhood vitiligo are displayed in Table 2.

Other modalities of treatment include (i) cosmetic camouflage (ii) Total depigmentation, using 20% Monobenzyl ether of hydroquinone (MBEH) [31].

In summary, a practical conclusion from this report is that increasing the use of psychiatric screening questionnaires might enhance recognition of psychiatric morbidity and the adverse mental health impact on mothers of children with vitiligo, ultimately leading to early intervention.

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