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Editorial

Continuity, Modernization, and Editorial Responsibility

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Running title: Modernizing Rheumatology (Bulgaria)

Rheumatology (Bulgaria) enters a new stage in its development. Editorial transitions are natural moments of reassessment, not of rupture. They provide an opportunity to reaffirm principles while refining structures.

For more than a decade, the Journal was led by Professor Rumen Stoilov. During that period, it preserved its institutional role and remained a stable scientific platform for Bulgarian rheumatology. Continuity is valuable in academic publishing, particularly in smaller scientific communities where sustainability cannot be taken for granted.

At the same time, the environment in which medical journals operate has evolved rapidly. Scientific output has expanded exponentially. Digital dissemination has replaced traditional distribution models [1]. Evaluation metrics increasingly depend on transparency, indexing visibility, and methodological rigor [2]. In this context, modernization is not optional; it is structural.

Over the past years, the Journal has undergone a process of digital consolidation. We are now completing the transition to an entirely online format. Printed editions have been discontinued in order to focus resources on digital infrastructure, discoverability, and production quality. The Journal operates on an upgraded publishing platform, with improved workflow management, archiving standards, and metadata integration. These technical adjustments are not cosmetic; they define how efficiently and transparently a manuscript moves from submission to publication.

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We have also introduced structured submission templates within the Instructions for Authors. These templates align manuscripts with internationally accepted reporting standards and facilitate both peer review and editorial consistency. Clear formatting, explicit methodological reporting, and standardized reference style are practical tools for improving quality and reducing unnecessary delays.

A dedicated Publishing Coordinator has been appointed to oversee production workflow, author communication, and technical coordination. Predictability in correspondence, clarity of revision requests, and professional copyediting are essential components of editorial credibility [3]. Academic publishing depends not only on scientific merit but also on procedural reliability.

The Editorial Board is being expanded and restructured to ensure active participation rather than symbolic affiliation. Membership implies engagement in peer review, strategic guidance, and promotion of the Journal's standards. A board should be functional and accountable.

Maintaining inclusion in Scopus remains a priority. At the same time, we are working toward broader indexing and improved citation visibility. Indexing is not pursued for prestige alone. It ensures that research originating from our region is integrated into global scientific discourse and accessible to clinicians and investigators beyond national boundaries.

What will not change is our commitment to rigor and clinical relevance. Rheumatology is a discipline in which published evidence can directly influence patient care. Statistical robustness, transparent methodology, and ethical compliance are therefore non-negotiable.

The Journal belongs to its authors, reviewers, and readers. Constructive critique, intellectual honesty, and professional respect remain the foundation of its work. The objective is not transformation for its own sake, but steady advancement built on continuity.

The responsibility is shared. The opportunity is real. The standard must remain high.

Declarations

Author Contributions

T.G. conceived the editorial, drafted the manuscript, and approved the final version for publication.

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Conflicts of Interest

The authors declare no conflict of interest.

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Original article

Clinical Outcomes after Switching from Originator Infliximab to the Biosimilar Ixifi in Patients with Axial Spondyloarthritis: A Single-Center Study from Türkiye

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Running title: Switching from Originator to Biosimilar

Abstract

Background: Biosimilar infliximab agents are increasingly used in the management of axial spondyloarthritis (axSpA), primarily driven by cost considerations. While clinical outcomes after switching from originator infliximab (INF) to several biosimilars have been reported, real-world data regarding switching to Ixifi remain limited. Objectives: To evaluate clinical outcomes, treatment retention and safety following non-medical switching from originator INF to the biosimilar Ixifi in patients with axSpA. Methods: This single-center observational cohort study included adult patients with axSpA who were transitioned from originator INF to Ixifi for non-medical reasons. Clinical assessments and laboratory parameters were recorded at baseline and at 3 and 6 months after switching. Disease activity was evaluated using ASDAS, BASDAI and BASFI. Safety outcomes and treatment discontinuation were systematically recorded. Results: 72 patients were included. Inflammatory markers, including C-reactive protein and erythrocyte sedimentation rate, remained stable over 6 months ($p>0.05$ for all), as did ASDAS scores ($p>0.05$). In contrast, BASDAI and BASFI showed modest but statistically significant improvements at month 6 ($p=0.008$ and $p=0.002$, respectively). 2 serious infections (2.8%) and 2 infusion reactions (2.8%) were observed. Treatment discontinuation occurred in 13.9% of

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patients, exclusively due to loss of efficacy. The estimated 6-month treatment retention rate was 86.1%. Conclusion: In this real-world cohort, non-medical switching from originator infliximab to Ixifi in axSpA was associated with maintained short-term clinical stability, acceptable treatment retention and a favorable safety profile. However, the absence of a control group limits causal interpretation of these findings. Larger studies with longer follow-up are warranted to confirm long-term outcomes.

Keywords: Ankylosing spondylitis; Spondyloarthritis; Infliximab; Biosimilar pharmaceuticals; Drug switching; Treatment outcome

1. Introduction

Tumor necrosis factor alpha inhibitors constitute a cornerstone in the management of inflammatory rheumatic diseases by effectively suppressing disease activity and preventing structural and functional damage [1]. Among these agents, originator infliximab (Remicade) has been widely used for over two decades, with robust evidence supporting its efficacy and well-established safety profile across multiple indications [2]. However, the high cost of biologic therapies and the chronic nature of these diseases have imposed a substantial financial burden on healthcare systems, thereby accelerating the adoption of biosimilar agents in routine clinical practice [3].

Biosimilars are biological products that demonstrate a high degree of similarity to their reference product in terms of quality characteristics, pharmacokinetics, efficacy, safety and immunogenicity [4]. For infliximab (INF) biosimilars, randomized controlled trials conducted in patients with rheumatoid arthritis (RA) and other inflammatory conditions have consistently shown comparable clinical efficacy and safety outcomes when compared with the originator molecule [5]. Beyond initial equivalence studies, increasing attention has been directed toward the clinical consequences of switching stable patients from originator INF to biosimilar INF, commonly referred to as non-medical switching [6]. The NOR-SWITCH trial, a large multicenter randomized non-inferiority study including several immune mediated inflammatory diseases, demonstrated that switching from originator INF to the biosimilar CT-P13 was not associated with a higher risk of disease worsening [7]. These findings were further corroborated by the open label extension phase, which showed sustained efficacy and comparable safety following the switch [8]. Large observational cohorts have reported generally stable disease activity following mandatory or voluntary transitions from originator INF to biosimilars,

although slightly increased treatment discontinuation rates have been observed in some studies [9].

In addition to rheumatologic diseases, observational studies in inflammatory bowel disease (IBD) populations have similarly indicated that switching from reference INF to biosimilar is not associated with clinically meaningful deterioration in disease control or increased adverse events [10]. Despite the growing body of evidence supporting INF biosimilars, real-world data evaluating switches to specific biosimilar molecules remain limited. In particular, clinical experience with switching from originator INF to Ixifi, a biosimilar approved based on extrapolation of indications is scarce in the literature [11]. Therefore, additional cohort studies assessing clinical outcomes, treatment persistence and safety following such switches are warranted.

In this context, the present study aims to evaluate the clinical course and treatment outcomes of patients transitioned from originator INF to Ixifi in a real-world rheumatology setting for axial spondyloarthritis patients (axSpA).

2. Materials and Methods

Study design and patient selection

This single-center observational cohort study included adult patients with axSpA who were transitioned from originator infliximab (Remicade) to the biosimilar Ixifi. Patients were eligible for inclusion if they had received at least one infusion of Ixifi following the switch and had available baseline and follow up clinical and laboratory data. Demographic characteristics and disease related variables were recorded at baseline prior to the switch. Patients were consecutively recruited between 2022 and 2026 at the rheumatology outpatient clinic. Individuals with incomplete follow up data or who discontinued treatment immediately after switching were excluded. Given the retrospective design, no imputation methods were applied, and analyses were conducted using available data only.

Treatment protocol and switching strategy

The switch from originator INF to Ixifi was performed for non-medical reasons in accordance with institutional practice [12]. Ixifi was administered using the same dosing regimen and infusion intervals as the originator INF. No changes in concomitant therapies were routinely

mandated at the time of switching. Patients were followed within routine outpatient visits at 3 and 6 months after the switch.

Data collection, outcome measures and safety assessment

Clinical and laboratory parameters were assessed at baseline and during follow up visits at month 3 and month 6. Disease activity was evaluated using the Ankylosing Spondylitis Disease Activity Score (ASDAS), Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and Bath Ankylosing Spondylitis Functional Index (BASFI) where applicable. Laboratory assessments included inflammatory markers, liver enzymes, renal function parameters, urinalysis findings and hematological indices.

Safety outcomes were evaluated throughout the follow up period. Adverse events were recorded at each visit and classified according to type and severity. Serious adverse events were defined as events requiring hospitalization or leading to treatment discontinuation. Infusion reactions, infections, laboratory abnormalities and cardiovascular events were specifically monitored. Reasons for treatment discontinuation and follow up completion status were documented. Treatment discontinuation due to loss of efficacy was based on the treating physician's clinical judgment, supported by worsening of disease activity parameters, including ASDAS and/or BASDAI scores, as well as persistent or increasing inflammatory markers (CRP, ESR) where available.

Statistical analysis

Continuous variables were assessed for normality and are presented as median and interquartile range (IQR). Comparisons between baseline and follow up measurements were performed using the Wilcoxon signed-rank test. Paired categorical variables were compared using McNemar's test. All statistical analyses were conducted using two-sided tests, and a p value <0.05 was considered statistically significant. Kaplan-Meier analysis was used to estimate treatment retention, and 95% confidence intervals were calculated. Censoring was applied to patients who completed follow-up without discontinuation.

The study was conducted in accordance with the principles of the Declaration of Helsinki. Ethical approval was obtained from the local ethics committee (approval number: 2025.184.10.19, approval date: 30 October 2025). Due to the retrospective observational design of the study, the use of anonymized data and the absence of any direct patient intervention, the

requirement for written informed consent was waived by the local ethics committee.

3. Results

A total of 72 patients with axSpA who were switched from originator INF to Ixifi were included in the analysis. Baseline demographic and clinical characteristics are summarized in Table (see Table 1).

Table 1. Baseline demographic and clinical characteristics of the study population

Variable	Value
Age (years), median (IQR)	49.0 (41.5–57.3)
Sex, female, n (%)	32 (44.4)
Symptom duration (years), median (IQR)	12.0 (10.0–18.0)
Age at diagnosis (years), median (IQR)	37.0 (29.0–45.0)
Duration of prior infliximab exposure (years), median (IQR)	4.0 (2.0–5.0)
Ever smoker, n (%)	40 (55.6)
HLA-B27 positivity, n (%)	50 (69.4)
Concomitant therapies, n (%)	
On-demand NSAID use	72 (100)
csDMARDs (sulfasalazine)	14 (19.4)
Glucocorticoids	10 (13.9)

Values are presented as median (interquartile range, IQR) unless otherwise stated. Categorical variables are expressed as number (percentage). NSAIDs were used on demand. csDMARDs refer to sulfasalazine. IQR, interquartile range; HLA-B27, human leukocyte antigen B27.

Inflammatory markers including C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), did not show a statistically significant change over the 6 month follow up period. Disease activity assessed by the ASDAS also remained stable after switching. Functional and disease activity indices demonstrated small but statistically significant improvements over time. Median BASDAI scores decreased from baseline to month 6 (p=0.008), and a similar improvement was observed in BASFI scores (p=0.002).

With regard to laboratory safety parameters, liver and renal function tests remained largely stable throughout follow up. A statistically significant change was observed in aspartate aminotransferase levels between baseline and month 6 (p=0.004), however, values remained within the normal reference range. Platelet counts also showed a statistically significant difference over time (p=0.018). Despite statistical significance, these changes were not considered clinically relevant. No significant changes were observed in hemoglobin levels, white blood cell counts,

creatinine or estimated glomerular filtration rate. The prevalence of hematuria and proteinuria on urinalysis did not differ significantly between baseline and follow-up assessments. Changes in clinical and laboratory parameters are presented in Table 2 (see Table 2).

Table 2. Changes in laboratory parameters and disease activity indices from baseline to month 6

Parameter	Baseline	Month 3	Month 6	p value (Baseline vs Month 6)
Laboratory parameters				
CRP (mg/L), median (IQR)	4.20 (1.23–9.61)	3.98 (1.42–9.98)	2.96 (1.15–6.20)	0.447
ALT (U/L), median (IQR)	18.81 (15.90–23.55)	21.00 (16.55–26.25)	20.00 (15.00–25.00)	0.279
AST (U/L), median (IQR)	18.05 (13.97–20.25)	19.90 (15.28–22.00)	19.15 (16.85–23.38)	**0.004**
Creatinine (mg/dL), median (IQR)	0.84 (0.72–0.98)	0.82 (0.70–0.97)	0.90 (0.74–1.01)	0.503
GFR (mL/min), median (IQR)	94.25 (80.97–107.29)	95.80 (83.75–108.42)	93.80 (79.75–108.13)	0.831
ALP (U/L), median (IQR)	75.00 (66.00–93.25)	77.50 (63.50–95.00)	76.50 (64.75–92.25)	0.986
GGT (U/L), median (IQR)	23.00 (14.00–32.00)	22.50 (16.00–32.75)	26.00 (14.75–38.25)	0.452
Hemoglobin (g/dL), median (IQR)	14.05 (12.40–14.90)	13.53 (11.95–14.60)	13.85 (12.35–14.90)	0.844
WBC ($\times 10^3/\mu L$), median (IQR)	7305 (6405–8970)	7095 (5575–8955)	7030 (6348–7993)	0.213
Platelet ($\times 10^3/\mu L$), median (IQR)	252 (204–288)	248.5 (209–296.5)	256 (231.8–293.0)	**0.018**
ESR (mm/h), median (IQR)	11.00 (6.00–20.00)	14.50 (8.00–22.25)	13.00 (6.00–18.25)	0.316
Hematuria present urinalysis, n %)	6 (8.3)	6 (8.3)	8 (11.1)	0.500
Proteinuria present urinalysis, n (%)	6 (8.3)	6 (8.3)	8 (11.1)	0.500
Clinical and disease activity indices				
ASDAS score, median (IQR)	1.00 (0.50–1.60)	1.20 (0.60–1.52)	0.90 (0.40–1.40)	0.761
BASDAI, median (IQR)	3.20 (2.77–3.52)	3.10 (2.50–3.52)	3.00 (2.49–3.40)	**0.008**
BASFI, median (IQR)	3.20 (2.77–3.73)	3.20 (2.60–3.70)	3.20 (2.60–3.42)	**0.002**

CRP, C-reactive protein; ASDAS, Ankylosing spondylitis disease activity score; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GFR, glomerular filtration rate; ALP, alkaline phosphatase; GGT, gamma glutamyl transferase; WBC, white blood cell count; ESR, erythrocyte sedimentation rate; BASDAI, Bath ankylosing spondylitis disease activity index; BASFI, Bath ankylosing spondylitis functional index; IQR, interquartile range. Continuous variables are presented as median (IQR); p values represent comparisons between baseline and month 6 measurements using the Wilcoxon signed-rank test; paired categorical variables were compared using McNemar's test; p values <0.05 were considered statistically significant.

During the follow up period, adverse events were infrequent. 2 patients (2.8%) experienced an infection classified as a serious adverse event, which led to treatment discontinuation. 2 infusion reactions (2.8%) were observed. No cases of transaminase elevation, hematological abnormalities or cardiovascular adverse events were recorded. Overall, 10 patients (13.9%) discontinued Ixifi during follow up, all due to loss of efficacy, occurring at a mean duration of 4.2 months. Among the 10 patients who discontinued treatment, discontinuations occurred predominantly within the first 3 months after switching (n=6), with fewer events at months 4 and 6. Although baseline clinical and laboratory parameters varied among these patients, no clear distinguishing pattern was identified. Given the limited number of discontinuations, detailed subgroup analysis was not feasible. No discontinuations related to patient preference, access issues, or remission were observed. A total of 62 patients (86.1%) completed the 6 month follow up period (see Table 3).

Table 3. Adverse events, safety outcomes, and reasons for treatment discontinuation

Adverse events and safety outcomes			
Adverse event type	**n (%)**	**Serious adverse event, n**	**Related to drug discontinuation, n (%)**
Infection (upper respiratory / pneumonia / other)	2 (2.8)	2	2 (2.8)
Transaminase elevation	0 (0.0)	0	0 (0.0)
Hematological (anemia, leukopenia, thrombocytopenia)	0 (0.0)	0	0 (0.0)
Infusion reaction	2 (2.8)	0	0 (0.0)
Hypertension / heart failure exacerbation	0 (0.0)	0	0 (0.0)
Reasons for treatment discontinuation and follow up status			
Reason	**n (%)**	**Mean duration (months)**	

Loss of efficacy	8 (11.1)	4.2
Patient preference / access issues	0 (0.0)	—
Discontinuation due to remission	0 (0.0)	—
Total discontinuations	10 (13.9)	4.2
Completed 6 months, n (%)	62 (86.1)	—

Adverse events are presented as number (percentage). Pneumonia was classified as a serious adverse event. 2 adverse events led to treatment discontinuation. Treatment discontinuation was exclusively driven by insufficient clinical or laboratory response, occurring at a mean of 4.2 months. No patient discontinued therapy due to remission.

Kaplan-Meier analysis demonstrated an estimated 6-month treatment retention rate of 86.1%, with most discontinuations occurring within the first 3 months after switching (see Figure 1).

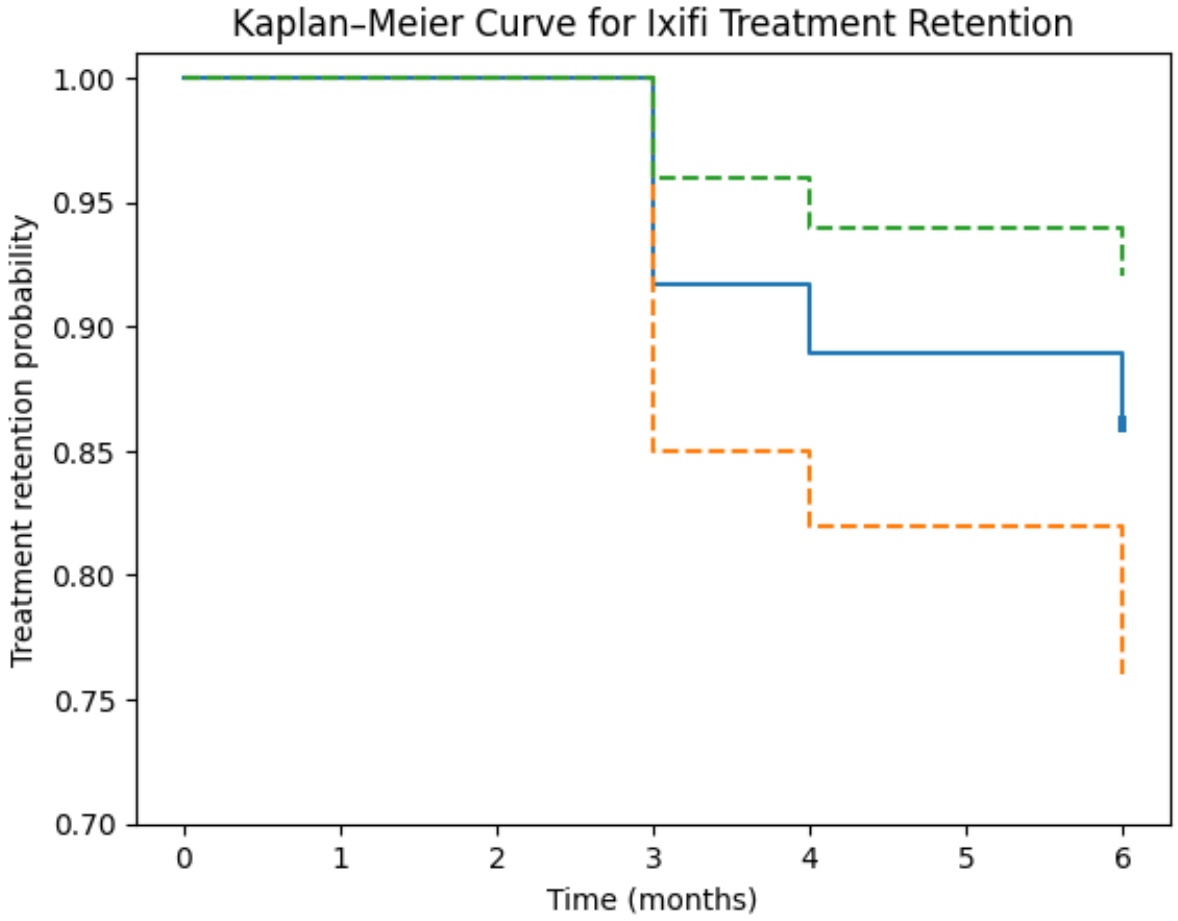


Figure 1. Kaplan-Meier curve showing treatment retention after switching from originator INF to Ixifi. The estimated 6-month treatment retention rate was 86.1% (95% CI: 76–92%). Tick marks indicate censored observations. The number of patients at risk at each time point is shown below the x-axis.

4. Discussion

To our knowledge, there are no previously published cohort studies from Türkiye evaluating clinical outcomes after switching from originator INF to the biosimilar Ixifi. Previous Turkish data have mainly focused on transitions to other INF biosimilars or utilization patterns of INF products [13]. These gaps highlight the novelty and regional contribution of the present analysis.

Randomized evidence from the NOR-SWITCH trial demonstrated that switching from originator INF to CT-P13 was not inferior to continued originator treatment across several indications, although the study was not powered for non-inferiority within each individual disease subgroup [7]. The subsequent extension study supported maintained effectiveness and a comparable safety profile in patients who switched, reinforcing the overall feasibility of switching strategies in stable patients [8]. While current study lacked a parallel originator continuation arm, the absence of meaningful deterioration in inflammatory markers and ASDAS after switching is directionally consistent with these randomized findings [7, 8].

Within SpA specifically, controlled and observational data have generally suggested that switching from reference INF to biosimilars does not lead to clinically relevant loss of disease control. In AxSpA, the PLANETAS extension reported comparable efficacy and safety after switching from reference INF to CT-P13 [14]. Moreover, registry-based evidence from DANBIO, which included patients with axSpA among other inflammatory arthritides, found no negative impact on disease activity after a nationwide switch, although treatment retention appeared slightly lower compared with a historic originator cohort [9, 15]. This study's observed retention and the timing of discontinuations, predominantly early after switching, fit the pattern described in real-world studies, where early stops may cluster around the switch period [15].

A notable observation in the current cohort was the modest but statistically significant improvement in BASDAI and BASFI at month 6, despite stable ASDAS and inflammatory markers. This discrepancy highlights the well-recognized divergence between patient-reported outcomes and objective measures of inflammation. While BASDAI and BASFI primarily capture subjective domains such as pain, fatigue and functional limitation, ASDAS incorporates an objective inflammatory parameter (CRP) [16], providing a more inflammation-driven assessment of disease activity. In this context, the observed improvements in patient-reported outcomes may reflect factors beyond true biological changes in inflammation, including

variability in symptom perception and expectancy-related effects. Although the nocebo effect has been widely discussed in the setting of biosimilar switching, a converse placebo or positive expectancy effect may also occur, particularly when patients perceive the switch as clinically acceptable or beneficial [17,18]. Such effects may preferentially influence subjective outcomes, including symptom perception and functional status, without corresponding changes in objective inflammatory markers [19]. Therefore, the observed improvements in BASDAI and BASFI should be interpreted with caution and may not necessarily reflect a true biological improvement in disease activity. Although BASFI showed a statistically significant improvement over time, the median values remained unchanged between baseline and month 6. This apparent discrepancy may be explained by the distribution of individual patient changes, where small but consistent improvements across a subset of patients can lead to statistical significance without a shift in the median value [20].

From a safety standpoint, adverse events were infrequent in the present cohort. In contrast, the French nationwide ReFLECT cohort reported at least one adverse event in more than half of patients, while serious adverse events occurred in approximately 10–14% across rheumatic indications, including axSpA [21]. Similarly, in a prospective cohort of patients with IBD undergoing a non-medical switch to the INF biosimilar GP-1111, allergic and paradoxical reactions were observed and led to treatment discontinuation in a subset of patients, although no new or unexpected safety signals were identified [22]. Differences in adverse event frequency across studies are likely attributable to variations in sample size, underlying disease populations and duration of follow up rather than to biosimilar specific safety concerns. Consistent with these observations, a narrative review by Abidin et al. summarizing randomized and observational studies on switching from reference INF to biosimilars across multiple inflammatory diseases reported maintained disease control and an acceptable safety profile without new safety concerns [23].

Although statistically significant changes were observed in AST and platelet levels over time, these variations remained within normal laboratory reference ranges and were not accompanied by clinical symptoms or other laboratory abnormalities suggestive of hepatotoxicity or hematological dysfunction. Therefore, these findings were considered unlikely to be clinically meaningful. However, it should be acknowledged that subtle trends, even within the normal range, may become more relevant over longer follow-up periods [24]. Accordingly, these parameters may warrant closer monitoring in future studies with extended observation periods [25].

When the situation in Türkiye is considered, real-world data on biologic switching and the use of INF biosimilars in axSpA have increasingly become available. Data from the TURKBIO registry have shown that the INF biosimilar CT-P13 is associated with acceptable long-term effectiveness, treatment retention and a favorable safety profile in axSpA [26]. In addition, national real-world analyses from Türkiye have evaluated treatment patterns with CT-P13, a descriptive study based on Turkish Ministry of Health claims reported higher discontinuation and switching rates among patients initiating CT-P13 compared with those starting on reference INF, suggesting differences in real-world utilization patterns between the biosimilar and the originator [13].

This study has limitations. The observational single-center design and the absence of a control group preclude causal inference and do not allow clear attribution of the observed outcomes to the switching strategy. The apparent stability in disease activity may partly reflect the natural course of the disease or regression to the mean, rather than a true effect of switching. Therefore, the findings should be interpreted with caution and considered descriptive rather than confirmatory. Follow-up was limited to 6 months, which may be insufficient to fully capture long-term treatment effectiveness, safety outcomes and durability of response in a chronic disease. In particular, this relatively short observation period may not adequately reflect the impact of immunogenicity, including the development of anti-drug antibodies (ADAs), which can occur over time. Additionally, certain adverse events, especially those related to cumulative exposure or delayed immunological mechanisms, may not be fully captured within this timeframe. Therefore, the present findings should be interpreted as reflecting short-term clinical stability and long-term outcomes after switching remain to be confirmed.

Additional important limitation is the lack of immunogenicity assessment, including INF trough levels and ADA measurements. This is particularly relevant given that treatment discontinuation in this cohort was exclusively attributed to loss of efficacy. In the absence of pharmacokinetic and immunogenicity data, it is not possible to distinguish between true pharmacodynamic failure and secondary loss of response. The development of ADAs has been associated with reduced drug levels and diminished clinical response in patients. This limitation is especially important for INF, as immunogenicity is known to play a central role in treatment response and persistence. Therefore, the lack of these data limits the interpretation of treatment discontinuation and prevents a more precise understanding of the underlying mechanisms.

Although this study provides real-world evidence on switching from originator INF, it was not designed or powered to formally assess non-inferiority. The relatively modest sample size and the absence of a parallel control group limit the ability to detect small differences in clinical outcomes or safety signals. The findings should be interpreted as descriptive and hypothesis-generating rather than confirmatory. In addition, treatment discontinuation due to loss of efficacy was not based on predefined standardized criteria but rather on physician judgment supported by clinical and laboratory parameters, which may introduce variability in outcome assessment. Future adequately powered, controlled studies with integrated immunogenicity monitoring are needed to assess non-inferiority between originator and biosimilar INF in axSpA, as well as to better define predictors of treatment failure following switching. The exclusion of patients with incomplete follow-up or those who discontinued treatment immediately after switching may introduce selection bias. This approach may have led to an overestimation of treatment retention rates and a potential underestimation of early adverse outcomes, particularly those occurring shortly after the switch.

Despite these limitations, current data contribute real-world evidence on switching from originator INF to Ixifi in axSpA which is a setting where molecule specific experience is still scarce. Taken together with prior randomized and registry data on INF switching, this study's findings may estimate that switching to Ixifi can be performed with maintained short term clinical stability, a favorable safety profile, and acceptable treatment persistence. Larger multicenter studies with longer follow up and immunogenicity monitoring are warranted to further clarify predictors of discontinuation and long-term outcomes after switching to Ixifi in axSpA.

5. Conclusions

In this cohort of patients with axSpA, switching from originator INF to the biosimilar Ixifi was associated with maintained short term clinical stability, acceptable treatment retention and a favorable safety profile. No clinically meaningful deterioration in disease activity or new safety concerns were observed over 6 months of follow up. These findings suggest that non-medical switching to Ixifi may be feasible in axSpA in the short term, however, larger studies with longer follow up are required to better define long term outcomes.

Declarations

Author Contributions

Conceptualization: D.B.G. and R.M.; Methodology: D.B.G and R.M.; Formal analysis: D.B.G.; Investigation: D.B.G.; Writing – original draft: D.B.G.; Writing – review & editing: all authors.

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Institutional Review Board Statement

The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of [Tekirdag Namik Kemal University] (approval number:2025.184.10.19, approval date: 30 October 2025)

Informed Consent Statement

Due to the retrospective observational design of the study, the use of anonymized data and the absence of any direct patient intervention, the requirement for written informed consent was waived by the local ethics committee.

Data Availability Statement

The data presented in this study are available on reasonable request from the corresponding author.

Conflicts of Interest

The authors declare no conflict of interest.

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Клинични резултати след преминаване от оригинален инфликсимаб към биоподобен Ixifi при пациенти с аксиален спондилоартрит: едноцентрово проучване от Турция

Резюме

Въведение: Биоподобните агенти инфликсимаб се използват все по-често при лечението на аксиален спондилоартрит (axSpA), главно поради съображения за цена. Въпреки че са докладвани клинични резултати след преминаване от оригинален инфликсимаб (INF) към няколко биоподобни лекарства, данните от реалния свят относно преминаването към Ixifi остават ограничени. Цели: Целта е да се оценят клиничните резултати, задържането на лечението и безопасността след немедицинско преминаване от оригинален INF към биоподобен Ixifi при пациенти с axSpA. Методи: Това едноцентрово обсервационно кохортно проучване включва възрастни пациенти с axSpA, които са преминали от оригинален INF към Ixifi по немедицински причини. Клиничните оценки и лабораторните параметри са записани в началото и на 3 и 6 месеца след преминаването. Активността на заболяването е оценена с помощта на ASDAS, BASDAI и BASFI. Резултатите от безопасността и прекратяването на лечението са систематично записани. Резултати: Включени са 72 пациенти. Възпалителните маркери, включително С-реактивен протеин и скорост на утаяване на еритроцитите, останаха стабилни в продължение на 6 месеца ($p>0,05$ за всички), както и ASDAS резултатите ($p>0,05$). За разлика от тях, BASDAI и BASFI показаха умерени, но статистически значими подобрения на 6-ия месец (съответно $p=0,008$ и $p=0,002$). Наблюдавани са 2 сериозни инфекции (2,8%) и 2 инфузионни реакции (2,8%). Прекратяване на лечението е наблюдавано при 13,9% от пациентите, изключително поради загуба на ефикасност. Очакваният 6-месечен процент на задържане на лечението е 86,1%. Заключение: В тази реална кохорта, немедикаментозното преминаване от оригинален инфликсимаб към Ixifi при axSpA е свързано с поддържана краткосрочна клинична стабилност, приемливо задържане на лечението и благоприятен профил на безопасност. Липсата на контролна група обаче ограничава причинно-следствената интерпретация на тези резултати. Необходими са по-големи проучвания с по-дълго проследяване, за да се потвърдят дългосрочните резултати.

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Review

IgG4-related Disease: Current Principles and Approaches in Diagnosis and Treatment

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Running title: IgG4-RD: Diagnosis and Management

Abstract

IgG4-related disease (IgG4-RD) has evolved from a series of organ-specific clusters into a recognized systemic fibroinflammatory disorder defined by a unique B-T cell axis. This review provides a comprehensive analysis of current diagnostic and therapeutic paradigms, emphasizing the pathogenic roles of CD4+ cytotoxic T lymphocytes and follicular helper T cells in driving storiform fibrosis. Despite the utility of the 2019 ACR/EULAR classification criteria, diagnostic challenges persist; notably, serum IgG4 remains a fallible biomarker, with a significant amount of patients maintaining normal concentrations during active disease. While glucocorticoids are the traditional first-line treatment, their long-term toxicity and high relapse rates have catalyzed a shift toward targeted B-cell depletion. Emerging evidence suggests that early intervention with biological agents can arrest and even reverse established fibrotic lesions, highlighting the dynamic nature of the immune-fibroblast interface. However, the current reliance on

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retrospective data and the lack of sensitive biomarkers for diagnosis and monito ring disease activity remain significant hurdles. This review underscores the necessity for precision-driven management and large-scale randomized trials to optimize long-term outcomes and minimize organ damage in this complex multi-organ condition.

Keywords: IgG4-related Disease, retroperitoneal fibrosis, biomarker, DMARDs

1. Introduction

Immunoglobulin G4-related disease (IgG4-RD) is a recently recognized, immune-mediated fibroinflammatory condition that can involve nearly any organ system, often presenting as tumefactive lesions that mimic malignancies [1,2]. Although some manifestations were described earlier, the disease was only recognized as a unified systemic entity in 2003, following the identification of extrapancreatic involvement in patients with autoimmune pancreatitis [1,3,4]. The condition is characterized by a distinct histopathological triad: a dense lymphoplasmacytic infiltrate rich in IgG4-positive plasma cells, storiform fibrosis, and obliterative phlebitis [5]. While elevated serum IgG4 concentrations are common - observed in approximately 50% to 90% of patients during the acute phase - they are not universal, and the diagnosis relies heavily on the correlation of clinical, radiological, and pathological findings [2,6].

Demographic data indicate that IgG4-RD predominantly affects middle-aged and elderly individuals, with a noted predilection for males [1,2]. However, the sex distribution can vary depending on the specific organ involved; for instance, certain head and neck manifestations such as Mikulicz syndrome show a more even distribution or even a slight female predominance [7]. Because IgG4-RD is a relatively new clinical entity, comprehensive epidemiological data regarding its global prevalence and incidence remain limited and are currently an area of active investigation [8].

The diagnostic process is frequently complicated by the "protean" nature of the disease, which serves as a major mimicker of infections, sarcoidosis, and various cancers [3]. A significant challenge for clinicians is the lack of a single, highly specific biomarker, as elevated serum IgG4 levels can be found in other inflammatory and neoplastic conditions [6,8]. From a therapeutic perspective, while most patients show a prompt initial response to glucocorticoids, the disease is often characterized by a relapsing and

remitting course. Furthermore, the degree of tissue fibrosis at the time of diagnosis is a critical determinant of treatment efficacy, as advanced storiform fibrosis may be irreversible and lead to permanent organ dysfunction or failure [2].

The aim of this review is to elucidate the complex pathophysiological mechanisms underlying the B-T cell axis and fibrotic pathways in IgG4-RD. Furthermore, we present current approaches in diagnosis and treatment, while clarifying the specific challenges and "red flags" that rheumatologists and other specialists face when managing these patients. Finally, this manuscript seeks to underline existing knowledge gaps and offer future perspectives on personalized therapeutic strategies, including the role of B-cell depletion and other targeted biologic interventions.

2. Materials and Methods

In accordance with the principles of high-quality narrative reviews outlined by Gasparyan et al. [9], we conducted a structured and comprehensive literature search to synthesize current evidence on the pathophysiology, diagnostic frameworks, and evolving therapeutic strategies for IgG4-RD.

2.1. Databases and Sources Consulted

To ensure a multi-disciplinary perspective (encompassing rheumatology, gastroenterology, pathology, and radiology), we systematically searched the following electronic databases: PubMed/MEDLINE, Scopus, and Web of Science. These platforms were selected to capture high-impact clinical trials, observational cohorts, and consensus statements. Additionally, Google Scholar was utilized to identify grey literature, conference proceedings from major international symposia on IgG4-RD, and recent preprints. The reference lists of key studies and previous systematic reviews were manually screened to ensure no seminal works were omitted.

2.2. Search Terms and Boolean Strategy

The search strategy utilized a combination of Medical Subject Headings (MeSH) terms and free-text keywords. The Boolean logic was tailored to each database's syntax to maximize sensitivity and specificity. The primary string used was: ("IgG4-related disease" OR "IgG4-RD" OR "immunoglobulin G4-related disease" OR "systemic IgG4-related plasmacytic syndrome") AND ("diagnosis" OR "diagnostic criteria" OR "classification criteria" OR "biomarkers" OR "pathology" OR "histopathology" OR "imaging") AND ("treatment" OR "management" OR "glucocorticoids" OR "rituximab" OR "B-cell depletion" OR "targeted therapy"). The search was iterative, allowing

for the inclusion of specific organ-related manifestations (e.g., "autoimmune pancreatitis", "Mikulicz's disease", "Reidels's thyroiditis") when relevant to the systemic overview.

2.3. Inclusion and Exclusion Criteria

Articles were considered eligible if they addressed the clinical spectrum, diagnostic challenges, or therapeutic outcomes of IgG4-RD. We prioritized: original research articles (prospective and retrospective), international consensus guidelines, diagnostic and classification criteria, high-quality reviews and meta-analyses, case series providing novel insights into rare manifestations or refractory cases. We excluded studies focusing on isolated IgG4-elevation without clinical features of the disease, technical laboratory reports without clinical validation, editorials, letters, and abstracts lacking sufficient methodology, articles published in languages other than English (to ensure consistency in terminology and peer-review standards).

2.4. Study Selection Flow

To capture the most contemporary advancements, particularly the shift toward steroid-sparing agents and biological therapies, we focused the search on publications from January 2010 to April 2026. This timeframe aligns with the modern recognition of IgG4-RD as a unified systemic entity. Findings were summarized thematically.

3. Pathophysiological Insights: The B-T Cell Axis and Fibrotic Pathways

CD4+ cytotoxic T lymphocytes (CTLs) have emerged as a dominant and pathogenic immune cell population in the tissue infiltrates of IgG4-RD [10]. These cells are characterized by an effector memory phenotype and the expression of cytotoxic molecules such as granzyme A, perforin, and RNA-binding protein (TIA1) [11]. Phenotypically, they are often identified by the surface marker SLAMF7 and frequently lack the costimulatory molecule CD28, a feature common in chronic antigen-driven T-cell responses [12].

The pathogenic role of CD4+ CTLs extends beyond direct cytotoxicity; they are major producers of pro-fibrotic and pro-inflammatory cytokines, including transforming growth factor-beta 1 (TGF-β1), interleukin-1 beta (IL-1β), and interferon-gamma (IFN-γ) [10,13]. Evidence suggests that these CTLs are reactivated within affected tissues by B cells and plasmablasts acting as antigen-presenting cells [14,15]. This interaction is

supported by the clinical observation that B-cell depletion therapy leads to a significant decline in circulating CD4+ CTL counts [10,12]. Furthermore, these cells may contribute to organ dysfunction by inducing the apoptotic death of host cells, such as ductal epithelial cells, which present the same antigenic peptides [14].

The dynamics between B cells and specialized T-cell subsets are central to the production of IgG4 and the formation of inflammatory lesions. A hallmark of the disease is the oligoclonal expansion of circulating plasmablasts (CD19+CD20-CD27+CD38bright), which serves as a more reliable biomarker for disease activity than serum IgG4 levels [12,16]. In the tissues, B cells often aggregate into tertiary lymphoid structures (TLS), where they undergo differentiation and somatic hypermutation [17,18].

T follicular helper (Tfh) cells, specifically the Tfh2 subset, are critical drivers of this process. Activated Tfh2 cells are significantly increased in the peripheral blood and tissues of IgG4-RD patients, and they produce IL-4 and IL-10, cytokines essential for B-cell class-switching to IgG4 [17,19]. Recent studies have also highlighted the role of peripheral helper T (Tph) cells (PD-1hiCXCR5-). Tph cells produce high levels of CXCL13, which facilitates the recruitment of both B cells and Tfh cells to extranodal sites, thereby promoting the formation of ectopic germinal centers and persistent fibroinflammation [18,19]. Beyond antibody production, B cells contribute directly to tissue remodeling by secreting pro-fibrotic factors such as platelet-derived growth factor B (PDGF-B) and lysyl oxidase-like 2 (LOXL2) [20].

Storiform fibrosis is a distinctive histopathological feature of IgG4-RD, characterized by a radial, "woven mat" or cartwheel-like arrangement of collagen fibers and spindle-shaped myofibroblasts [21,22]. This fibrotic process is driven by a complex interplay between innate and adaptive immune cells. TGF-β1, primarily secreted by CD4+ CTLs and alternatively activated (M2) macrophages, is considered the master regulator of fibroblast-to-myofibroblast differentiation [10,20]. M2 macrophages are found in high concentrations in lesions and further promote fibrosis through the production of CCL18 and IL-33 [19].

Innate immune triggers are also implicated in initiating the fibrotic cascade. In murine models, the process begins with the activation of conventional dendritic cells (cDCs) via Toll-like receptor 3, which recruit CXCR3+ T cells. These T cells then facilitate the migration of plasmacytoid dendritic cells

(pDCs) that produce high levels of IFN-α and IL-33, establishing a positive feedback loop of chronic inflammation and fibrosis [13,23]. Unlike the fibrosis seen in conditions like systemic sclerosis, the fibrotic lesions in IgG4-RD are remarkably reversible upon treatment with glucocorticoids or B-cell depletion, highlighting the dynamic nature of the immune-fibroblast axis in this disease [10].

While these studies provide strong insights, a major limitation is the absence of a natural IgG4 equivalent in murine models, which makes it difficult to definitively determine whether the IgG4 molecule itself has a pathogenic or protective role [11,24]. Many current hypotheses regarding cytokine pathways are derived from observational human studies, necessitating further mechanistic validation [15]. Figure 1 summarizes the complex pathophysiological mechanisms in IgG4-RD.

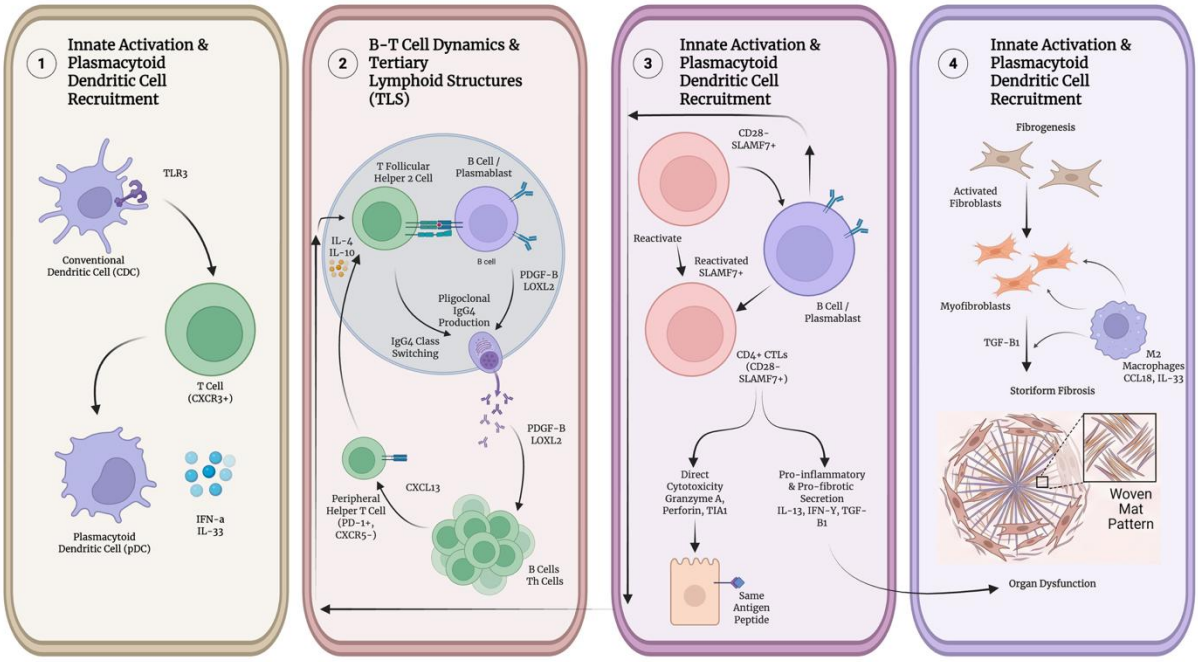


Figure 1. Multi-faceted Pathophysiology of IgG4-Related Disease.

4. Diagnostic Challenges: Integrating Clinical, Histopathological and Imaging Features

Diagnosis of IgG4-RD is challenging due to heterogeneous organ involvement and overlap with malignancy or other inflammatory disorders. A multimodal approach integrating clinical assessment, laboratory testing, imaging, and histopathology is essential for disease assessment and diagnosis.

4.1 Diagnostic Mimics: The "Great Mimicker"

IgG4-RD is frequently referred to as a "great mimicker" due to its ability to involve nearly any organ and its clinical overlap with a wide array of neoplastic, infectious, and other immune-mediated conditions [8,25]. The disease presents with remarkable clinical heterogeneity, which has been categorized into four distinct phenotypes: pancreato-hepato-biliary disease, retroperitoneal fibrosis and/or aortitis, head and neck-limited disease, and classic Mikulicz syndrome with systemic involvement [25,26]. This diversity necessitates a broad differential diagnosis; for instance, the pancreato-biliary phenotype must be distinguished from malignancies and type 2 autoimmune pancreatitis, while head and neck manifestations often overlap with Sjögren's syndrome and granulomatosis with polyangiitis [27].

A critical diagnostic challenge is the lack of a single, highly sensitive or specific biomarker. Serum IgG4 levels are elevated in 55-97% of patients but are normal in up to 40% of biopsy-proven cases and can be raised in healthy individuals or those with unrelated conditions like allergies and malignancies [8,25,28]. To address these challenges, the 2019 ACR/EULAR classification criteria utilize a three-step process that includes rigorous exclusion criteria - such as the presence of fever, specific autoantibodies (e.g., ANCA), or rapid radiological progression - to prevent misdiagnosis of mimickers [28,29]. While these criteria provide a robust framework for research, their complexity reflects the persistent challenge of diagnosing a condition that currently relies heavily on the exclusion of other diseases [8].

4.2 Histopathological Hallmarks and Limitations

Histopathology remains the cornerstone of IgG4-RD diagnosis, characterized by a "cardinal triad": a dense lymphoplasmacytic infiltrate, storiform fibrosis, and obliterative phlebitis. The 2020 Revised Comprehensive Diagnostic (RCD) criteria and the 2012 international consensus statement emphasize that a confident diagnosis typically requires at least two of these major features in addition to an increased number of IgG4+ plasma cells (typically >10 cells/hpf) and an IgG4+/IgG+ ratio exceeding 40% [5,30].

However, histopathological diagnosis faces significant limitations. There is considerable organ-specific variability; for example, storiform fibrosis and obliterative phlebitis are frequently inconspicuous or entirely absent in the lymph nodes, minor salivary glands, and lacrimal glands, complicating the pathological confirmation in these sites [5,31]. Furthermore, the increasing reliance on small needle biopsies rather than surgical resections often

results in insufficient tissue to identify the characteristic architectural features, leading to sampling errors [29,31]. Pathologists must also be cautious as IgG4+ plasma cell infiltration is not pathognomonic and can be observed in various inflammatory and neoplastic conditions, making strict adherence to morphological criteria essential.

4.3 Role of Imaging in Disease Diagnosis and Assessment

Imaging plays a strategic role in the initial identification of "tumefactive" or mass-forming lesions and is vital for staging the disease by identifying clinically silent organ involvement [27]. While most radiological findings are non-specific, certain features are highly suggestive, such as the "sausage-shaped" pancreas with a surrounding edematous halo in autoimmune pancreatitis or the periaortitis typically affecting the infrarenal aorta [25,29].

Functional imaging, particularly 18F-FDG PET/CT, has emerged as a valuable tool for assessing disease activity and predicting outcomes, especially in retroperitoneal fibrosis [32,33]. Studies have shown that persistent FDG uptake during follow-up is a strong predictor of clinical relapse, allowing for better risk stratification and potentially guiding the duration of maintenance therapy. Additionally, advanced MRI techniques, such as Diffusion-Weighted Imaging (DWI), offer a radiation-free method to differentiate active, cellular fibroinflammation from inactive, treated fibrosis, as evidenced by significantly higher signal intensities in untreated patients [34]. Despite these strengths, the lack of standardization in PET analysis and the non-specificity of FDG uptake—which can occur in both inflammation and malignancy - remain significant limitations that necessitate correlation with clinical and pathological data [25,32].

While the 2019 ACR/EULAR and 2020 RCD criteria have significantly improved diagnostic consistency, they remain "classification" rather than "diagnostic" tools, and their application in routine clinical practice is sometimes limited by the difficulty of obtaining representative biopsies in deep-seated organs [29,30]. The diagnosis of IgG4-RD continues to be an iterative process of clinicopathological correlation where no single finding is definitive.

5. The Biomarker Challenge: Beyond Serum IgG4 Levels

5.1 Limitations of Serum IgG4

Serum IgG4 is the most commonly utilized biomarker in IgG4-RD, reflecting the proliferation of IgG4-secreting plasmablasts and plasma cells [35,36].

Nevertheless, although it has historically aided in disease identification, serum IgG4 is now recognized as neither a dependable standalone diagnostic marker nor a consistent measure of disease activity [37].

Elevated serum IgG4 levels (>135 mg/dL) are seen in a substantial proportion of patients and can aid diagnosis when interpreted within the appropriate clinical context [38]. However, its diagnostic utility is limited by suboptimal sensitivity and specificity. Notably, around 30–40% of patients with biopsy-confirmed IgG4-RD have normal serum IgG4 levels [39], representing a significant seronegative subgroup for whom reliance on this marker may result in underdiagnosis. Conversely, elevated IgG4 levels are not specific to IgG4-RD and can be seen in a range of other conditions, including malignancies (such as pancreatic cancer and lymphoma), chronic infections, and other autoimmune disorders [40]. This limits its specificity and underscores the importance of interpreting IgG4 levels within a comprehensive clinical and histopathological context.

From a prognostic standpoint, serum IgG4 concentrations exhibit significant limitations, as approximately 10% to 48% of patients maintain normal levels despite biopsy-proven active disease [41]. Although markedly elevated baseline levels often correlate with multi-organ involvement and a higher risk of relapse [40], serum IgG4 fails to reliably reflect disease activity in patients with normal baseline values, showing no significant correlation with the IgG4-RD Responder Index in this subgroup [41]. Furthermore, clinical flares can occur in roughly 10% of patients even when serum IgG4 concentrations remain low or stable, underscoring that normal laboratory findings do not definitively preclude disease progression or the need for therapeutic adjustment [40].

Clinically, serum IgG4 retains value as a supportive diagnostic marker within composite criteria [29], as a baseline measure during initial evaluation, and as a non-specific adjunct in longitudinal monitoring. However, serum IgG4 cannot be used in isolation for diagnosis, disease stratification, or therapeutic decision-making. The high prevalence of seronegative disease and its frequent discordance with disease activity underscore the need for more reliable biomarkers [42].

5.2 Novel and Emerging Biomarkers

Owing to the recognized limitations of serum IgG4 as a standalone biomarker, contemporary research has increasingly pivoted toward parameters that may more precisely reflect the underlying immunopathology of IgG4-RD [43].

Circulating plasmablasts represent a notable candidate for clinical monitoring; preliminary evidence suggests that their concentrations may correlate more closely with disease activity than serum IgG4, particularly in patients with multi-organ involvement [44]. Their rapid decline following effective immunosuppression, especially B-cell depletion therapy, underscores their potential utility in both diagnostic adjudication and longitudinal surveillance [45]. Specific T-cell subsets, particularly Tfh2 and Tph cells, further delineate the pivotal role of the B–T cell axis in the pathogenesis of IgG4-RD [46]. The expansion of these populations appears to parallel IgG4 class switching and plasmablast differentiation, positioning them as mechanistic indicators of the inflammatory cascade rather than purely descriptive markers.

Furthermore, soluble markers of immune activation, including the soluble interleukin-2 receptor (sIL-2R) and cytokines such as IL-4 and IL-21, offer supplementary insights into systemic T-cell activation [47]. While these markers may assist in identifying patients at an increased risk of relapse, their clinical specificity and predictive value require further validation. In addition to inflammatory parameters, markers associated with fibrogenesis - such as CCL18, periostin, and various indicators of extracellular matrix turnover - may facilitate the differentiation between active inflammatory and established fibrotic stages [48,49]. Identifying these signatures is critical for recognizing patients at risk of irreversible organ dysfunction.

Despite the diagnostic potential of these emerging parameters, several challenges remain. The majority of these biomarkers are currently restricted to the investigational domain, characterized by a lack of standardized assays and insufficient validation within large-scale, prospective cohorts. Consequently, they do not yet possess the clinical robustness required to replace serum IgG4 in routine practice, serving instead as complementary tools in a multi-modal diagnostic approach.

6. Evolution of Treatment: Moving Toward Steroid-Sparing Strategies

6.1 Glucocorticoid Protocols and Relapse

Glucocorticoids remain the cornerstone of initial therapy for IgG4-related disease (IgG4-RD), inducing rapid clinical and radiologic remission in most patients [50]. Standard induction regimens typically use moderate-to-high doses, followed by gradual tapering over several months [51]. Despite high initial response rates, relapse is common, affecting approximately 40–60%

of patients, particularly during dose tapering or after treatment discontinuation [52]. Risk factors for relapse include multi-organ involvement, high baseline disease activity, and delayed initiation of therapy [53].

Long-term glucocorticoid use is associated with significant morbidity, including osteoporosis, diabetes mellitus, hypertension, weight gain, and an increased risk of infection [54]. These limitations highlight the need for steroid-sparing strategies and more targeted therapeutic approaches.

6.2 The Role of Conventional DMARDs

Conventional disease-modifying antirheumatic drugs (DMARDs), including azathioprine, mycophenolate mofetil, and methotrexate, are commonly used in clinical practice as maintenance therapy or steroid-sparing agents [55–57]. These agents are intended to reduce relapse risk and limit glucocorticoid exposure. However, the evidence supporting their use is largely observational, with limited data from randomized controlled trials. Reported efficacy is variable, and there is no consensus on the optimal choice of agent, dosing strategy, or duration of therapy.

In addition, DMARDs appear less effective than targeted B-cell therapies in preventing relapse, especially in patients with severe or multi-organ disease. As a result, their role is being reconsidered in the era of precision immunotherapy [27]. Conventional disease-modifying antirheumatic drugs (DMARDs) are increasingly being repositioned as third-line or adjunctive therapies in the biologic era of IgG4-RD management, given their comparatively limited efficacy in relapse prevention when contrasted with B-cell–targeted agents such as rituximab and inebilizumab [55,56].

6.3 Novel and Emerging Targeted Therapies (B-cell Depletion and Intracellular Signaling Inhibitors)

B-cell–targeted therapy has emerged as a highly effective treatment strategy, reflecting the central role of the B–T cell axis in IgG4-RD pathogenesis [58,59] (Table 1). Rituximab, an anti-CD20 monoclonal antibody, has shown high efficacy in inducing remission and lowering relapse rates, including in patients who are refractory to glucocorticoids [60]. Clinical responses are frequently accompanied by rapid depletion of circulating plasmablasts and improvement in organ involvement. Inebilizumab, an anti-CD19 monoclonal antibody, has demonstrated promising results in the MITIGATE trial, significantly reducing relapse rates in both inflammatory and fibrotic disease manifestations [61]. Unlike rituximab, CD19-targeted therapy may affect a broader spectrum of B-

lineage cells, including plasmablasts [62]. Other B-cell–targeted agents, including obexelimab, are currently under investigation and may further expand therapeutic options [63].

Advances in understanding cytokine signaling pathways have further prompted the exploration of targeted immunomodulatory therapies [58]. IL-4 and IL-13 blockade (e.g., dupilumab) targets Th2-driven immune responses and IgG4 class switching [64]. Early data indicate potential glucocorticoid-sparing benefits, particularly in patients with pronounced allergic or Th2-dominant features [59]. Janus kinase (JAK) inhibitors represent a promising therapeutic class, targeting intracellular signaling pathways involved in cytokine-mediated inflammation [65]. Preliminary studies suggest potential efficacy, although robust clinical trial data are currently limited and their use is considered still experimental.

Table 1. Emerging and Targeted Therapies in IgG4-Related Disease.

Therapy	Target/Mechanism of Action	Key Clinical Role in IgG4-RD	Evidence/Notes	References
Rituximab	Anti-CD20 monoclonal antibody → B-cell depletion	Induction of remission; effective in glucocorticoid-refractory and relapsing disease	Rapid reduction in plasmablasts; strong real-world and observational evidence; current standard biologic therapy	[60]
Inebilizumab	Anti-CD19 monoclonal antibody → broader B-lineage depletion (including plasmablasts)	Reduction of relapse risk in inflammatory and fibrotic disease	Demonstrated efficacy in MITIGATE trial; potentially broader depletion than CD20 targeting	[61]
Obexelimab	CD19-directed B-cell modulation (FcγRIIB-mediated inhibitory signaling)	Investigational therapy aiming to suppress B-cell activation without full depletion	Early-phase evidence; potential for immune modulation with reduced immunosuppression	[62,63]
Dupilumab	Blockade of IL-4 and IL-13 signaling; targets Th2-driven	Potential glucocorticoid-sparing	Early-phase data suggest clinical benefit through	[59,64]

	immune responses and inhibits IgG4 class switching	maintenance therapy, particularly for patients with allergic or Th2-dominant clinical features	targeted immunomodulation of the Th2 pathway	
JAK inhibitors	Inhibition of JAK-STAT intracellular cytokine signaling	Experimental option for refractory disease or associated fibrosis	Limited early clinical data; potential broad anti-inflammatory effects but still investigational	[65]

CD, cluster of differentiation; FcγRIIB, Fc gamma receptor IIB; IgG4, immunoglobulin G4; IgG4-RD, immunoglobulin G4-related disease; IL, interleukin; JAK, Janus kinase; MITIGATE, Monoclonal Antibody against CD19 for the Treatment of IgG4-Related Disease; RI, responder index; STAT, signal transducer and activator of transcription; Th2, T helper type 2.

7. Strengths and Limitations

This review offers a multi-dimensional synthesis of IgG4-related disease, bridging the gap between molecular pathophysiology - specifically the B-T cell axis and the mechanisms of storiform fibrosis - and the practical challenges of clinical diagnosis and long-term therapeutic management. A primary strength of this work is the application of a structured, iterative search methodology, covering a 16-year period (2010–2026) that encompasses the most transformative era in the recognition and classification of this entity. By integrating the latest ACR/EULAR classification criteria and evaluating emerging steroid-sparing biological agents, this review provides a contemporary framework for clinicians navigating the complexities of multi-organ involvement. Furthermore, the detailed analysis of the CD4+ CTL and Tfh2 dynamics provides a robust immunobiological context for understanding why B-cell depletion has emerged as a cornerstone of modern therapy.

Despite these strengths, several methodological and inherent limitations must be acknowledged. First, a significant limitation of our methodology is the restriction of the search to English-language publications. Given that a substantial body of seminal work and large-scale cohort data on IgG4-RD originates from Japan and other East Asian countries, the exclusion of non-English literature may introduce a geographic and publication bias, potentially omitting localized clinical insights or alternative management

protocols. Secondly, although the search was systematic in its execution, this remains a narrative review. The inherent heterogeneity of the available literature - which consists predominantly of retrospective cohort studies, case series, and expert consensus rather than large-scale randomized controlled trials (RCTs) - precluded the performance of a formal meta-analysis or a universal quality appraisal of all cited sources.

The clinical evidence is further constrained by the relative rarity and phenotypic diversity of IgG4-RD. Many diagnostic and prognostic conclusions are drawn from small patient populations, which may limit their generalizability across different ethnic groups and environmental exposures. This is particularly relevant given that certain manifestations, such as IgG4-related dacryoadenitis and sialadenitis, may follow different clinical trajectories compared to retroperitoneal fibrosis or autoimmune pancreatitis. Additionally, as noted in our pathophysiological discussion, the current lack of a natural murine model for IgG4 remains a fundamental barrier to definitively establishing the pathogenic versus protective role of the IgG4 molecule itself. Finally, most data are derived from tertiary referral centers, which inherently introduces a selection bias toward more severe, symptomatic, or refractory cases, potentially overestimating the frequency of complications and the necessity for aggressive initial immunosuppression.

8. Conclusions

IgG4-related disease has evolved from a collection of isolated organ-specific conditions into a well-defined systemic entity with a unique immunopathological signature. The transition in our understanding of its pathophysiology - shifting from a purely IgG4-centric view to the recognition of the pathogenic B-T cell axis - has been transformative. The identification of CD4+ cytotoxic T lymphocytes and Tfh2 cells as central drivers of both inflammation and storiform fibrosis not only explains the disease's multi-organ nature but also provides a robust rationale for the clinical success of B-cell depletion therapies.

From a diagnostic perspective, the 2019 ACR/EULAR classification criteria represent a major milestone, emphasizing that while serum IgG4 remains a valuable clinical clue, it is neither a standalone diagnostic tool nor a flawless marker of disease activity. The fact that significant clinical relapses can occur despite normal IgG4 levels underscores the urgent need for more sensitive and specific biomarkers, such as circulating plasmablasts or specific cytokine profiles, to guide long-term monitoring.

Looking forward, the management of IgG4-RD is entering an era of precision medicine. While glucocorticoids remain the effective first-line response, their substantial toxicity profile necessitates the early integration of steroid-sparing strategies. The remarkable reversibility of even advanced fibrotic lesions upon B-cell depletion offers hope for preventing permanent organ damage. However, addressing the current evidence gaps - specifically the lack of large-scale randomized controlled trials and the limited understanding of the long-term outcomes in diverse ethnic cohorts - remains essential. Ultimately, a multi-disciplinary approach remains the cornerstone of achieving sustained remission and improving the quality of life for patients with this complex fibroinflammatory disorder.

Declarations

Author Contributions

Conceptualization: S.D & V.T; Methodology: S.D.; Formal analysis: S.D, V.T., G.K., M.I. & Z.K; Investigation: S.D & V.T; Writing—original draft: S.D, V.T., G.K., M.I. & Z.K; Writing—review & editing: S.D, V.T., G.K., M.I. & Z.K

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Institutional Review Board Statement

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Data Availability Statement

The data presented in this study are available on reasonable request from the corresponding author.

Conflicts of Interest

The authors declare no conflict of interest.

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IgG4-свързана болест: Съвременни принципи и подходи в диагностиката и лечението

Резюме

IgG4-свързаната болест (IgG4-RD) еволюира от поредица от органно-специфични състояния в признато системно фиброинфламаторно заболяване, дефинирано от уникална B-T клетъчна ос. Настоящият обзор предоставя всеобхватен анализ на съвременните диагностични и терапевтични парадигми, като акцентира върху патогенетичната роля на CD4+ цитотоксичните Т-лимфоцити и фоликуларните хелперни Т-клетки при индуцирането на сториформна фиброза. Въпреки приложимостта на класификационните критерии на ACR/EULAR от 2019 г., диагностичните предизвикателства персистират; по-специално, серумният IgG4 остава ненадежден биомаркер, тъй като значителна част от пациентите поддържат нормални концентрации по време на активно заболяване. Макар глюкокортикоидите да са традиционното лечение на първа линия, тяхната дългосрочна токсичност и високата честота на рецидивите катализираха прехода към таргетна В-клетъчна деплеция. Новите доказателства сочат, че ранната интервенция с биологични средства може да спре и дори да доведе до обратимост на вече установените фиброзни лезии, подчертавайки динамичния характер на имунно-фибробластното взаимодействие. Въпреки това, настоящото разчитане на ретроспективни данни и липсата на чувствителни биомаркери за диагностика и проследяване на активността на заболяването остават значителни препятствия. Този обзор подчертава необходимостта от прецизно управление и мащабни рандомизирани проучвания за оптимизиране на дългосрочните резултати и минимизиране на органните увреждания при това комплексно мултиорганно състояние.

Ключови думи: IgG4-свързана болест, ретроперитонеална фиброза, биомаркер, БПАРС

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Review

Genetic and Molecular Insights Linking Mood Disorders and Pain

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Abstract

Pain has been a constant companion of humankind since the dawn of time. As a sensory perception, it is a complex, multidimensional phenomenon and an integral part of human life. It is always a personal experience influenced by numerous endogenous and exogenous factors. Since pain is an unpleasant sensation, it is always associated with an emotional component. In addition to being personal, it is also a multifaceted experience, and its perception and awareness change throughout a person's life. Pain can lead to impulsive behavior, affecting decision-making and self-control.

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As a universal and complex phenomenon in the animal world, it has fascinated scientists, clinicians, and philosophers for centuries. It goes beyond simple sensory perception and encompasses a multidimensional experience that includes not only the recognition of harmful stimuli but also cognitive and behavioural responses. This multifaceted nature of pain makes it a subject of great interest and research in various fields, including neurology, psychology, and clinical medicine.

Keywords: pain, mood disorders, arthritis, biomarkers

1. Introduction

Pain and mood disorders frequently share common biological pathways, and an increasing body of evidence points to specific genetic factors and biomarkers that may underlie this overlap. In clinical practice and research, significant efforts are directed toward identifying specific determinants that link these two conditions, as their elucidation could open new avenues for therapeutic development [1].

Advances in genetics have revealed that subtle variations in genes encoding receptors and signaling molecules may partially explain interindividual variability in pain sensitivity, perception, and expression [2]. These variations may, in turn, influence how pain is treated and managed [3]. Several genetic markers and potential epitopes have been identified as critical contributors to both pain dysregulation and mood disorders.

2. Materials and Methods

In accordance with the principles of high-quality narrative reviews [4], we conducted a structured and comprehensive literature search to synthesize current available data on genetic and epigenetic insights that are linked in pain and mood disorders.

2.1 Databases and sources

To ensure a multi-disciplinary perspective (encompassing rheumatology, gastroenterology, pathology, and radiology), we systematically searched the following electronic databases: PubMed/MEDLINE, Web of Science, DynaMed, and Scopus. These platforms were selected to capture high-impact articles, reviews and meta-analyses and recent preprints. The reference lists of key articles and previous systematic reviews were manually screened to ensure no seminal works were omitted.

2.2 Search Terms and strategy

The search strategy utilized a combination of Medical Subject Headings (MeSH) terms and free-text keywords. The Boolean logic was tailored to each database's syntax to maximize sensitivity and specificity. The primary string used was: ("pain" OR "pain syndromes in rheumatology" OR "rheumatic pain") AND ("mood disorders" OR "depression and anxiety" AND ("genetic" OR "epigenetic" OR "mechanism" OR "insights"). The search was iterative, allowing for the inclusion of specific cytokines and gene epitopes which are relevant to the systemic overview.

2.3 Criteria

Articles were considered eligible if they addressed the link between the two topics. We prioritized: high-quality reviews and meta-analyses, case series providing novel insights into rare manifestations or refractory cases, original prospective and retrospective research articles. We excluded studies focusing on isolated disease, technical laboratory reports without clinical validation, editorials, letters, and abstracts lacking sufficient methodology, articles published in languages other than English (to ensure consistency in terminology and peer-review standards).

To capture the most contemporary advancements, we focused the search on publications from 1995 to 2025. This timeframe aligns with the modern recognition of the link of the topics. Findings were summarized thematically.

3. Genetic and epigenetic markers linked to pain and mood disorders

3.1 Brain-Derived Neurotrophic Factor

Brain-derived neurotrophic factor (BDNF) is a member of the neurotrophin family, which also includes nerve growth factor (NGF), neurotrophin-3 (NT-3), and neurotrophin-4/5 (NT-4/5). Early research on neuronal synthesis, secretion, and release of BDNF, as well as its interaction with the high-affinity receptor tropomyosin receptor kinase B (TrkB), was primarily conducted in the hippocampus, neocortex, and basal forebrain - regions essential for higher cognitive functions. However, neurotrophin synthesis and processing follow similar pathways in both central and peripheral neurons involved in nociceptive processing.

BDNF is present in human blood, although it is more highly concentrated in brain tissue. It has been suggested that BDNF can cross the blood–brain

barrier (Pan et al., 1998), and that its levels in the brain and serum undergo similar changes during maturation and aging. This suggests that serum BDNF levels may reflect central nervous system concentrations.

BDNF plays a crucial role in neuronal growth and survival and is implicated in both mood disorders (e.g., depression) and pain modulation [5, 6, 7]. It is increasingly recognized as a key regulator of synaptic plasticity, functioning both as a neurotransmitter and neuromodulator [8]. Furthermore, BDNF is a central molecule in neuroscience and neurobiology, contributing to neuronal differentiation, development, maintenance, and neuroprotection, as well as neurodegeneration and mood regulation [9, 10].

Genetic variability in BDNF is of particular importance [11, 12, 13]. The Val66Met polymorphism is among the most extensively studied variants; the Met allele has been associated with increased risk of depression and altered pain perception, particularly in chronic pain conditions. Additionally, the BDNF 196G/A polymorphism has been associated with geriatric depression in Chinese populations [14] and with Alzheimer's disease-related depression in Italian populations [15]. Licinio et al. reported that six single nucleotide polymorphisms (SNPs) in the BDNF gene (rs12273539, rs11030103, rs6265, rs28722151, rs41282918, rs11030101) are associated with mood disorders, with two haplotypes showing significant associations with depression [16]. Notably, a polymorphism in the 5′ untranslated region (rs61888800) has been linked to treatment response.

Alterations in BDNF levels have been observed in individuals with both chronic pain [17] and mood disorders [18], suggesting a shared pathophysiological mechanism. Reduced BDNF levels are consistently reported in patients with depression and are negatively correlated with disease severity [19]. Moreover, stress has been shown to decrease BDNF expression, implicating it in the pathophysiology of anxiety disorders as well [20].

Under physiological conditions, BDNF is synthesized by various neuronal and glial cell types within pain pathways. Noxious stimuli can induce its production and release, contributing to synaptic plasticity and increased responsiveness of peripheral nociceptors. This sensitization may occur at both peripheral and central levels. Inflammatory processes are often associated with increased BDNF release as part of complex signaling cascades, exerting both neuroprotective and detrimental effects depending on the context [21]. Similarly, peripheral nerve injury leading to neuropathic pain is associated with upregulation of BDNF.

Understanding the role of BDNF holds significant promise for improving diagnosis and treatment of both pain and mood disorders. In nociception, it may inform novel strategies for chronic pain management. Three main therapeutic approaches targeting BDNF/TrkB signaling have emerged from preclinical studies: BDNF sequestration, blockade of the extracellular TrkB domain, and inhibition of the intracellular kinase domain. Although promising, these approaches are not yet ready for clinical application.

BDNF is also deeply involved in glutamatergic neurotransmission [22], which itself plays a critical role in mood disorders. Therefore, investigating correlations between BDNF (or proBDNF) and glutamate-related compounds may yield valuable biomarkers and therapeutic targets.

3.2. COMT – Catechol-O-methyltransferase

The metabolism of catecholamines is regulated by several enzymes, among which catechol-O-methyltransferase (COMT) plays a central role. In humans, COMT is encoded by the *COMT* gene and, together with voltage-gated sodium channels, contributes significantly to pain perception and processing [23, 24]. The gene is located on chromosome 22q11.2 and contains a well-characterized G-to-A missense single nucleotide polymorphism (SNP), resulting in the substitution of valine (Val) with methionine (Met) at codon 158 [25, 26].

COMT exists in two primary isoforms: membrane-bound (MB-COMT) and soluble (S-COMT) [25]. Functionally, COMT is primarily involved in the degradation of catecholamines such as dopamine and norepinephrine, thereby playing a crucial regulatory role in both mood regulation and pain processing.

Several genetic variations influence COMT enzymatic activity, among which the Val158Met polymorphism (rs4680) is particularly significant. This nonsynonymous SNP leads to a Val→Met substitution, resulting in a three- to fourfold reduction in enzymatic activity [27]. Consequently, this polymorphism directly modulates dopamine metabolism. Reduced COMT activity alters dopaminergic neurotransmission, leading to decreased endogenous enkephalin levels and increased pain sensitivity. Simultaneously, altered dopamine levels are associated with an increased risk of mood disorders, including depression. COMT is especially critical in the prefrontal cortex, where it accounts for approximately 60% of dopamine catabolism [28].

Notably, the Met allele exhibits approximately 40% lower enzymatic activity compared to the Val allele, which influences synaptic dopamine

availability [29]. COMT effects are predominantly cortical, particularly within the prefrontal cortex [30], but also extend to other brain regions such as the striatum and its functional interaction with the prefrontal cortex [31]. Furthermore, COMT modulates orbitofrontal–amygdala connectivity in response to negative emotional stimuli [32]. Sex differences have also been reported, with higher COMT activity observed in females, potentially due to estrogen-mediated transcriptional regulation [33].

Overall, evidence suggests that different COMT alleles are associated with distinct clinical phenotypes. The Val allele has been linked to certain mood-related traits and may contribute to increased pain sensitivity, highlighting the gene's role in the shared neurobiology of pain and affective disorders [34].

3.3. OPRM1 – μ-Opioid Receptor Gene

The endogenous opioid system plays a fundamental role in pain modulation, emotional regulation, reward processing, and substance use disorders. The *OPRM1* gene encodes the μ-opioid receptor (MOR), a key mediator of analgesia and affective processing. MORs are widely distributed throughout the brain, with particularly high expression in the thalamus, limbic system (including the amygdala), nucleus accumbens, and anterior cingulate cortex [35]. Genetic variation within *OPRM1* significantly influences receptor function.

A well-studied functional SNP, A118G (rs1799971), results in an amino acid substitution (Asn40Asp) within exon 1, affecting receptor glycosylation and function [36]. Carriers of the G allele exhibit reduced baseline μ-opioid receptor availability in brain regions associated with pain and emotional regulation. This polymorphism has been linked to altered pain perception, increased pain sensitivity, and heightened vulnerability to depression and anxiety [37]. G allele carriers not only experience pain more intensely but also rate it as more severe.

The opioid system also plays a role in sleep regulation. Opioid activity can reduce adenosine levels in the pontine reticular formation via μ1-opioid receptor activation, leading to dose-dependent sleep disturbances [38]. Variations in *OPRM1* may therefore contribute to individual differences in both analgesic response and sleep-related side effects [39].

In summary, individuals carrying the G allele may be more susceptible to both pain and mood disturbances due to altered opioid system functioning.

3.4. TNF-α – Tumor Necrosis Factor Alpha

Tumor necrosis factor alpha (TNF-α) is a pro-inflammatory cytokine that plays a critical role in the inflammatory response. Inflammation has been strongly implicated in both chronic pain and mood disorders, particularly depression.

Elevated levels of TNF-α have been consistently observed in individuals with chronic pain and depressive disorders. Initial reports linking increased TNF-α levels to depression date back to 2000 [40]. Subsequent studies have demonstrated correlations between circulating TNF-α levels and the severity of depressive symptoms, as well as normalization following antidepressant treatment [41]. Pro-inflammatory cytokines are also associated with increased pain sensitivity [42]. For example, patients with neuropathic pain exhibit elevated mRNA levels of TNF-α and IL-2, alongside reduced levels of the anti-inflammatory cytokine IL-10 [43].

The TNF-α gene contains a functional polymorphism at position -308 (G→A), which affects gene transcription. The A allele is associated with increased TNF-α production [44], contributing to an enhanced inflammatory response [45]. Importantly, this polymorphism has been linked to depression. Individuals carrying the A allele show a higher prevalence of depressive disorders, including early-onset depression [46].

These findings suggest that inflammation may represent a shared biological mechanism underlying both pain and mood dysregulation.

3.5 HTTLPR – Serotonin Transporter-Linked Polymorphic Region

Serotonin (5-hydroxytryptamine, 5-HT) is a monoamine neurotransmitter involved in regulating sleep, appetite, vascular tone, platelet function, motor activity, and pain [47, 48]. However, it is most widely recognized for its role in mood and behavior regulation [49, 50].

The serotonin transporter (5-HTT), encoded by the *SLC6A4* gene, is responsible for the reuptake of serotonin from the synaptic cleft, thereby terminating serotonergic signaling [51]. A polymorphism in the promoter region of this gene, known as 5-HTTLPR, results in two main alleles: short (S) and long (L). The S allele is associated with reduced transcriptional efficiency, leading to decreased transporter expression and impaired serotonin reuptake [52]. This results in altered serotonergic signaling. The S allele has been consistently associated with increased vulnerability to depression, anxiety, and pain-related conditions such as fibromyalgia and

tension-type headaches [53]. Additionally, S allele carriers exhibit higher levels of neuroticism, a personality trait linked to emotional instability [54].

Neuroimaging studies show that S allele carriers exhibit heightened amygdala reactivity to emotional stimuli, suggesting increased emotional sensitivity [55]. This may result from altered top-down regulation from the prefrontal cortex, affecting emotional processing circuits [56, 57]. Furthermore, the 5-HTTLPR polymorphism influences treatment response. Individuals homozygous for the L allele tend to respond better to selective serotonin reuptake inhibitors (SSRIs) compared to S allele carriers [58, 59].

Overall, this polymorphism plays a crucial role in both emotional regulation and pain modulation, supporting its relevance in the comorbidity of pain and mood disorders [60, 61, 63-65].

3.6. CACNA1C – Voltage-Gated Calcium Channel Subunit Alpha-1C

The *CACNA1C* gene encodes the α1C subunit of the Cav1.2 L-type voltage-gated calcium channel, which is essential for neuronal excitability, neurotransmitter release, and synaptic plasticity [66].

Cav1.2 channels are widely expressed in the brain and are involved in linking membrane depolarization to intracellular calcium signaling [67]. This process influences gene transcription, neuronal survival, dendritic development, learning, and memory [68, 69]. Genetic variations in *CACNA1C* have been associated with psychiatric disorders, including bipolar disorder, major depressive disorder, and anxiety [70, 71]. These variations have also been linked to pain conditions such as chronic pain and fibromyalgia [72, 73]. The overlap in genetic susceptibility suggests a shared mechanism involving calcium signaling dysregulation and neuronal hyperexcitability [74-77].

3.7. SCN9A – Voltage-Gated Sodium Channel

The *SCN9A* gene encodes the Nav1.7 sodium channel, which plays a crucial role in pain signal transmission [78]. These channels are expressed in sensory neurons, particularly in dorsal root ganglia [79]. Mutations in *SCN9A* can result in either loss or gain of function. Loss-of-function mutations lead to congenital insensitivity to pain, whereas gain-of-function mutations are associated with severe pain disorders such as erythromelalgia and small fiber neuropathy [80, 81].

Polymorphisms such as rs6746030 have been linked to increased pain sensitivity and chronic pain severity [82-84]. Altered sodium channel

function may also contribute to mood dysregulation through its effects on neural signaling.

3.8. HPA Axis and Glucocorticoid Receptor (NR3C1)

The hypothalamic–pituitary–adrenal (HPA) axis regulates the stress response, and its dysregulation is strongly associated with both mood disorders and chronic pain. The *NR3C1* gene encodes the glucocorticoid receptor (GR), which mediates the effects of cortisol [85]. Alterations in GR function can disrupt HPA axis feedback mechanisms, leading to abnormal stress responses. Patients with mood disorders often exhibit HPA axis hyperactivity, including elevated cortisol levels and impaired dexamethasone suppression [86, 87]. Chronic stress induces structural and functional brain changes, including reduced neurogenesis and altered serotonin metabolism [88].

Variations in *NR3C1* may influence receptor sensitivity and stress reactivity, contributing to both emotional dysregulation and pain hypersensitivity [89].

The intricate relationships between the various genes and epitopes described above are illustrated in Figure 1, highlighting their intersection across both clinical domains.

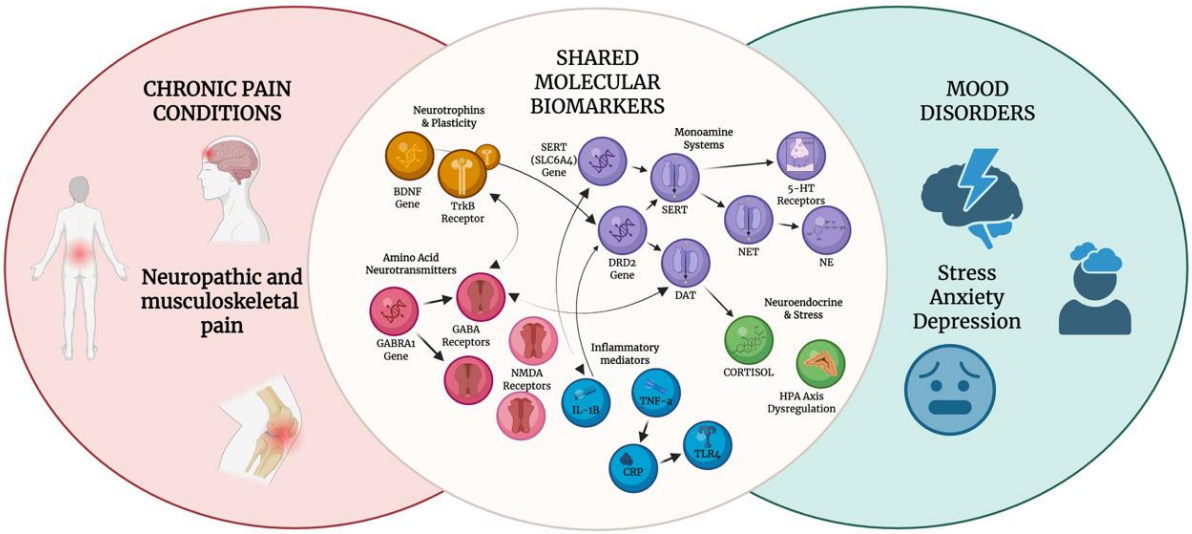


Figure 1. Shared Molecular Pathways and Biomarkers in Chronic Pain and Mood Disorders.

Abbreviations: BDNF, Brain-derived neurotrophic factor; TrkB, Tropomyosin receptor kinase B; SERT, Serotonin transporter; SLC6A4, Serotonin transporter gene; 5-HT, 5-hydroxytryptamine (Serotonin); DRD2, Dopamine receptor D2; DAT, Dopamine transporter; NET, Norepinephrine transporter; NE, Norepinephrine; GABRA1, Gamma-aminobutyric acid type A receptor alpha 1 subunit gene; GABA, Gamma-aminobutyric acid; NMDA, N-methyl-D-aspartate; IL-1B, Interleukin-1 beta; TNF-α, Tumor necrosis factor alpha; CRP, C-reactive protein; TLR4, Toll-like receptor 4; HPA, Hypothalamic–pituitary–adrenal.

4. Discussion

The present synthesis highlights that the comorbidity between chronic pain and mood disorders is best conceptualized as a shared neurobiological continuum rather than a co-occurrence of distinct clinical entities. Across genetic, epigenetic, and molecular levels, converging evidence supports the involvement of partially overlapping pathways regulating neuroplasticity, monoaminergic transmission, immune activation, and stress responsivity. However, the overall picture remains complex, with substantial heterogeneity in findings and limited translational consistency.

Among the most consistently implicated mechanisms is dysregulation of neuroplasticity-related signaling, particularly involving *BDNF*. Reduced BDNF expression has been associated with both depressive symptom severity and enhanced central sensitization in chronic pain states, supporting the hypothesis that impaired synaptic plasticity represents a shared biological substrate [17-20]. This aligns with the neurotrophic hypothesis of depression and extends its relevance to nociceptive processing. Similarly, alterations in HPA axis regulation, particularly via *NR3C1*-mediated glucocorticoid signaling, suggest that chronic stress exposure may act as a common upstream driver linking affective dysregulation and pain amplification [85].

Genetic variation in *COMT*, *SLC6A4* (5-HTTLPR), and *OPRM1* further reinforces the role of monoaminergic and opioid systems in the dual modulation of pain and mood [29,37,58]. However, a critical issue is the low replicability and small effect sizes of many candidate gene associations. For example, while *COMT Val158Met* has been widely studied, meta-analyses have demonstrated inconsistent associations across populations, suggesting that its functional relevance is likely context-dependent rather than deterministic [34]. This limitation reflects a broader methodological weakness in candidate gene research, particularly susceptibility to population stratification and publication bias.

Inflammatory signaling, particularly via TNF-α and related cytokine pathways, provides a more mechanistically robust link between pain and mood disorders [40-42]. Elevated pro-inflammatory cytokines have been observed in both conditions and are capable of inducing neurobehavioral changes through multiple pathways, including microglial activation, reduced monoamine availability, and altered glutamatergic transmission [90]. Importantly, inflammation may represent not only a consequence but also a causal amplifier of central sensitization and affective dysregulation, positioning it as a key therapeutic target. Nevertheless, heterogeneity in cytokine profiles across patient subgroups indicates that inflammation is unlikely to be a universal mechanism.

Variants in genes such as *CACNA1C* and *SCN9A* extend the discussion toward neuronal excitability and pain signal propagation. These genes underscore the importance of calcium and sodium channel regulation in shaping both sensory and affective processing networks [70-72, 80]. However, while their role in rare monogenic pain disorders is well established, their contribution to complex psychiatric and chronic pain phenotypes remains less clearly defined, with most evidence derived from association studies rather than functional validation.

A central limitation emerging from the literature is the dominance of the candidate gene approach, which has failed to fully capture the polygenic architecture of both pain and mood disorders. Many reported associations lack replication in genome-wide studies, reflecting the so-called “replication crisis” in psychiatric genetics [91]. In contrast, GWAS findings suggest highly polygenic risk profiles with individually small effect sizes distributed across hundreds of loci [92]. This discrepancy highlights a critical gap between early hypothesis-driven genetics and current systems-level genomic understanding.

An additional limitation of the current evidence base is the relatively superficial integration of epigenetic regulation and gene–environment interactions. Environmental stressors, early-life adversity, and chronic inflammation are increasingly recognized as key modulators of gene expression through DNA methylation, histone modification, and non-coding RNA activity [93]. These mechanisms may partially explain phenotypic divergence among individuals with similar genetic backgrounds. However, epigenetic studies in this field remain fragmented and lack longitudinal validation.

Despite these limitations, the convergence of multiple biological systems provides a rationale for mechanism-based stratification of patients rather

than symptom-based classification alone. Biomarkers derived from neurotrophic, inflammatory, and neuroendocrine pathways may ultimately enable more precise phenotyping of patients with overlapping pain and mood disorders [94]. Moreover, the partial efficacy of existing therapies targeting serotonergic, opioid, or inflammatory systems supports the notion of shared downstream pathways, even if upstream genetic drivers remain heterogeneous.

Future research should prioritize integrative multi-omics approaches, combining genomic, epigenomic, transcriptomic, and proteomic data within longitudinal clinical cohorts. Such strategies are essential to move beyond association-based frameworks toward predictive and mechanistic models. In parallel, standardized phenotyping of pain–mood comorbidity and harmonization of outcome measures will be necessary to improve reproducibility across studies. Ultimately, a shift toward systems biology and network-based psychiatry is required to fully elucidate the shared architecture of these conditions.

5. Strengths and limitations of the review

This review provides a timely and mechanistically oriented synthesis of genetic and epigenetic factors implicated in the shared pathophysiology of pain and mood disorders. Its principal strength lies in the integrative framework across molecular, neurobiological, and immunological domains, linking candidate gene variation (e.g., BDNF, COMT, OPRM1) with inflammatory signalling, ion channel dysfunction, and HPA axis dysregulation. By moving beyond single-pathway explanations, the manuscript appropriately reflects the current conceptual shift toward network-based and systems-level models of neuropsychiatric and pain comorbidity.

A further strength is the broad temporal scope of the literature base (1995–2025), which enables contextualization of early candidate gene findings alongside more recent mechanistic advances. The structured organization of genetic markers according to functional biological systems enhances conceptual clarity and supports translational interpretation. Importantly, the review also highlights clinically relevant convergence points, particularly neuroplasticity, immune signalling, and monoaminergic regulation, which are central to emerging precision medicine approaches.

However, several limitations constrain the interpretative strength and translational weight of the findings. First, despite the structured search strategy, the work remains a narrative synthesis without systematic

methodology, lacking formal study selection transparency, risk-of-bias assessment, and reproducibility of inclusion decisions. This inherently increases susceptibility to selection bias and author-dependent interpretation, particularly in a field characterized by heterogeneous and sometimes contradictory evidence.

Second, the review is largely anchored in the candidate gene paradigm, which has substantial limitations in the context of complex polygenic traits. Many highlighted associations (e.g., COMT Val158Met, 5-HTTLPR) have shown inconsistent replication across ethnic groups and study designs, reflecting well-documented issues of low effect sizes, population stratification, and publication bias in candidate gene research. Consequently, several mechanistic inferences should be interpreted as hypothesis-generating rather than confirmatory.

Third, there is limited integration of genome-wide association studies (GWAS), epigenome-wide data, and multi-omics approaches, which currently represent the most robust frameworks for understanding complex neuropsychiatric–pain overlap. The absence of these datasets partially restricts the manuscript's alignment with the most recent advances in psychiatric genetics and pain genomics. Finally, although the review acknowledges biological convergence, it underrepresents the critical role of gene–environment interactions, developmental influences, and psychosocial determinants, which are increasingly recognized as essential modifiers of both pain perception and affective vulnerability. This omission may overemphasize biological determinism in a clinically heterogeneous spectrum of disorders. In summary, while this review provides a coherent mechanistic synthesis of overlapping genetic pathways in pain and mood disorders, its conclusions should be interpreted within the constraints of narrative methodology and the inherent limitations of candidate gene evidence. Future high-impact research will require integration of multi-omics data, longitudinal cohort designs, and environment-stratified analyses to move from associative findings toward predictive and clinically actionable models.

6. Conclusions

Accumulating evidence supports a substantial biological convergence between chronic pain and mood disorders, underpinned by overlapping genetic, epigenetic, and neurobiological mechanisms. Rather than being independent clinical entities, these conditions increasingly appear to represent interconnected phenotypes within a shared dysregulated system,

involving neurotransmitter signaling, immune activation, synaptic plasticity, and stress-response pathways.

Key candidate genes, including *BDNF*, *COMT*, *OPRM1*, *TNF-α*, *SLC6A4*, *CACNA1C*, *SCN9A*, and components of the HPA axis, collectively highlight the multisystem nature of vulnerability, where modest genetic effects converge on common downstream pathways such as altered monoaminergic transmission, neuroinflammation, and impaired neuroplasticity. Among these, the most consistently supported mechanisms involve dysregulation of neurotrophic signaling, particularly BDNF-mediated synaptic plasticity, and persistent low-grade inflammatory activation, which together may facilitate both central sensitization in pain and affective instability.

Importantly, current evidence indicates that the clinical overlap between pain and mood disorders cannot be sufficiently explained by single-gene effects. Instead, it reflects a polygenic and context-dependent architecture, in which genetic susceptibility interacts with environmental exposures, stress load, and developmental factors. This complexity is further compounded by inconsistent replication of candidate gene associations and the limited predictive value of individual polymorphisms across diverse populations. From a translational perspective, these insights reinforce the need to move beyond reductionist models toward integrated systems biology frameworks. Such approaches should incorporate genome-wide data, epigenetic regulation, transcriptomic signatures, and longitudinal clinical phenotyping to better capture disease heterogeneity and temporal dynamics. In parallel, identifying biologically meaningful endophenotypes - such as altered stress responsivity, neuroinflammatory profiles, or pain sensitization patterns - may provide more robust targets for stratified intervention.

Finally, the shared molecular pathways identified in this review provide a rationale for mechanism-based therapeutic strategies that simultaneously address affective and nociceptive dysregulation. However, the current evidence base remains largely associative, and significant gaps persist in establishing causality, clinical utility, and treatment predictability.

In conclusion, while substantial progress has been made in delineating the biological interface between pain and mood disorders, the field remains in a transitional phase. Future advances will depend on the integration of multi-omics approaches, well-characterized longitudinal cohorts, and gene–environment interaction models, ultimately enabling a shift from descriptive associations toward clinically actionable precision medicine frameworks.

Declarations

Author Contributions

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Conflicts of Interest

The authors declare no conflict of interest.

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Генетични и молекулярни прозрения, свързващи афективните разстройства и болката

Резюме

Болката е постоянен спътник на човечеството от зората на времето. Като сетивно възприятие, тя представлява комплексен, многоизмерен феномен и неделима част от човешкия живот. Тя винаги е субективно преживяване, повлияно от множество ендогенни и екзогенни фактори. Тъй като болката е неприятно усещане, тя неизменно е свързана с емоционален компонент. Освен че е личен опит, тя е и многостранно преживяване, като нейното възприемане и осъзнаване се променят в хода на целия човешки живот. Болката може да доведе до импулсивно поведение, засягайки процесите на вземане на решения и самоконтрола. Като универсално и сложно явление в животинския свят, тя е обект на интерес за учени, клиницисти и философи в продължение на векове. Тя надхвърля рамките на обикновеното сетивно възприятие и обхваща многоизмерен опит, който включва не само разпознаването на вредни стимули, но и когнитивни и поведенчески реакции. Този многостранен характер на болката я превръща в обект на задълбочени изследвания в различни научни области, включително неврология, психология и клинична медицина.

Ключови думи: болка, афективни разстройства, артрит, биомаркери

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Case report

Eosinophilic Fasciitis Following SARS-CoV-2 Infection: A Case Report and Review of Temporal Associations

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Running title: Eosinophilic Fasciitis after COVID-19 Infection

Abstract

Background: Eosinophilic fasciitis is a rare scleroderma-like disorder characterized by inflammation and thickening of the fascia, typically presenting with skin induration, peripheral eosinophilia, and absence of systemic organ involvement. Its etiology remains unclear, although immune-mediated mechanisms and various triggers have been proposed. Case presentation: We report a case of a 49-year-old woman who developed progressive pain, stiffness, and skin induration of the upper extremities shortly after COVID-19 infection. Laboratory evaluation revealed eosinophilia, acute phase reactants and negative autoimmune serology. Magnetic resonance imaging demonstrated fascial involvement without muscle pathology. Histopathological examination confirmed eosinophilic fasciitis, showing inflammatory infiltrates and fibrosis within the fascia. The

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patient was treated with high-dose glucocorticoids and steroid-sparing agent – methotrexate, with subsequent clinical and laboratory improvement. At follow-up, complete resolution of symptoms was observed, reaching drug-free remission after approximately 18 months. Conclusion: This case highlights eosinophilic fasciitis as a potential post-infectious immune-mediated condition following COVID-19. Early recognition, appropriate imaging, and confirmatory biopsy are essential for timely diagnosis, appropriate treatment and favorable outcomes.

Keywords: Eosinophilic fasciitis; COVID-19; post-infectious immune-mediated disease; case report

1. Introduction

Eosinophilic fasciitis (EF) is a rare scleroderma-like disorder involving inflammation and thickening of the fascia, often accompanied by eosinophilia and hypergammaglobulinemia. It was first described by Shulman in 1974 [1], and after the first big clinical cohort was reported in 1988 [2], EF was largely accepted as a separate entity. Unlike systemic sclerosis, it typically spares the face and internal organs and is not associated with Raynaud's phenomenon or specific autoantibodies. It presents clinically with rapidly progressive skin induration and limb stiffness, sometimes leading to contractures. Diagnosis is based on histological evidence of fascial inflammation and thickening [3].

The exact etiology of eosinophilic fasciitis remains uncertain, although an immune-mediated mechanism is strongly suspected. This assumption is supported by the frequent presence of hypergammaglobulinemia, occasional detection of autoantibodies, and the generally favorable response to corticosteroid therapy [4,5]. Various predisposing factors have been described, including local tissue injury, exposure to certain medications, infectious agents, especially viruses, underlying hematological or solid malignancies, and coexisting autoimmune disorders.

We present a case of eosinophilic fasciitis following COVID-19 infection, emphasizing the potential role of viral-triggered immune dysregulation in disease pathogenesis.

2. Case Presentation

A 49-year-old woman presented with progressive pain and stiffness of the shoulder girdle, upper limbs, abdominal muscles, and hips, beginning in

January 2024 2 weeks after COVID-19 infection. Symptoms initially involved painful, restricted shoulder movement, later extending to the arms and forearms. Within a week, she developed right arm swelling with forearm and lateral elbow skin induration, followed by milder similar changes on the left. Her past medical history was unremarkable.



Figure 1. Clinical photograph of the right forearm demonstrating localized skin induration and hyperpigmentation along the ulnar aspect, corresponding to the area of maximal involvement. The skin appears thickened and firmly attached to the underlying tissues, also demonstrating the "groove sign" —a longitudinal depression of the skin along blood vessels. A biopsy was obtained from this region for histopathological confirmation.

On admission, the patient was afebrile and in good general condition. Examination revealed painful restriction of both active and passive shoulder movements and painful active movement of the right wrist. Firm induration was present along the ulnar aspect of the right forearm and right lateral epicondyle, with milder involvement of the left forearm. No peripheral joint swelling was observed. During follow-up, induration extended to right forearm and elbow with hyperpigmentation and induration.

Laboratory evaluation revealed inflammatory activity and eosinophilia: ESR 50 mm/h (normal <20), CRP 38.1 mg/L (normal <5), leukocytes 13.73 $\times 10^9$/L (normal 4–10), platelets 540 $\times 10^9$/L (normal 150–400), eosinophils 10% (normal <5), and elevated LDH (491 U/L), while creatine kinase remained within the normal range. Liver and renal function were normal. ANA was positive at low titer (1:80, granular), while extended autoantibody

panel was negative. Complement and immunoglobulin levels were within normal ranges. Infectious screening (HBV, HCV, QuantiFERON-TB) was negative, and no hematologic malignancy was identified.

MRI of the right forearm demonstrated increased T2 signal intensity along the fascial planes, with contrast enhancement following administration of contrast medium. No fluid collections were observed. The adjacent muscle groups showed preserved signal intensity, without evidence of myositis. These findings were consistent with isolated fascial inflammation and supported the diagnosis of eosinophilic fasciitis (Figure 2).

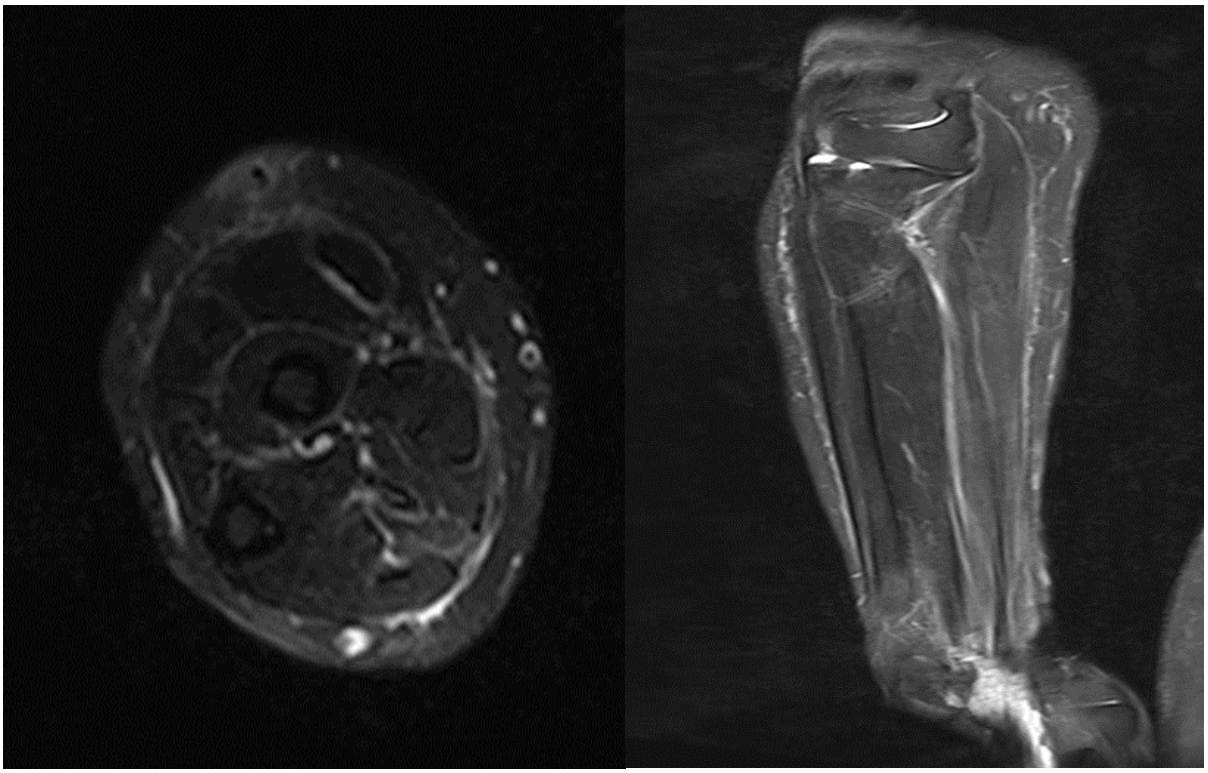


Figure 2. Axial T2-weighted fat-suppressed magnetic resonance imaging (MRI) of the right forearm demonstrating increased signal intensity and thickening along the fascial planes, consistent with inflammatory involvement of the fascia. The adjacent muscle groups show preserved signal intensity, without evidence of myositis or fluid collections. These findings are in keeping with eosinophilic fasciitis.

An incisional biopsy of skin, subcutis, and fascia from the right arm (12 April 2024) showed fibrotic changes with sparse lymphocytic infiltrates in the dermis and subcutis, and mixed inflammatory infiltrates in the fascia (lymphocytes, plasma cells, neutrophils, eosinophils) with focal necrosis and fibrosis, consistent with eosinophilic fasciitis.

The diagnosis of diffuse eosinophilic fasciitis was established based on the clinical presentation, peripheral eosinophilia, negative autoimmune serology, MRI evidence of fascial involvement, and confirmatory histology. Systemic sclerosis and inflammatory myopathy were excluded due to absence of Raynaud's phenomenon, sclerodactyly, internal organ involvement, and normal muscle enzymes.

Treatment was initiated with intravenous methylprednisolone at approximately 1.5 mg/kg/day, resulting in rapid clinical improvement. The patient was subsequently discharged on oral methylprednisolone 64 mg/day with gradual tapering. Methotrexate (15 mg/week) was introduced early as a steroid-sparing agent, together with folic acid supplementation. By October 2024, inflammatory markers and eosinophil count had normalized, with partial functional recovery under tapering glucocorticoids. Subsequent follow-up showed continued improvement, allowing discontinuation of glucocorticoids and gradual methotrexate taper.

At the latest follow-up (March 2026), complete clinical remission was achieved, with full recovery of range of motion, resolution of skin induration, normal laboratory parameters, and no evidence of relapse off therapy (Figure 3).

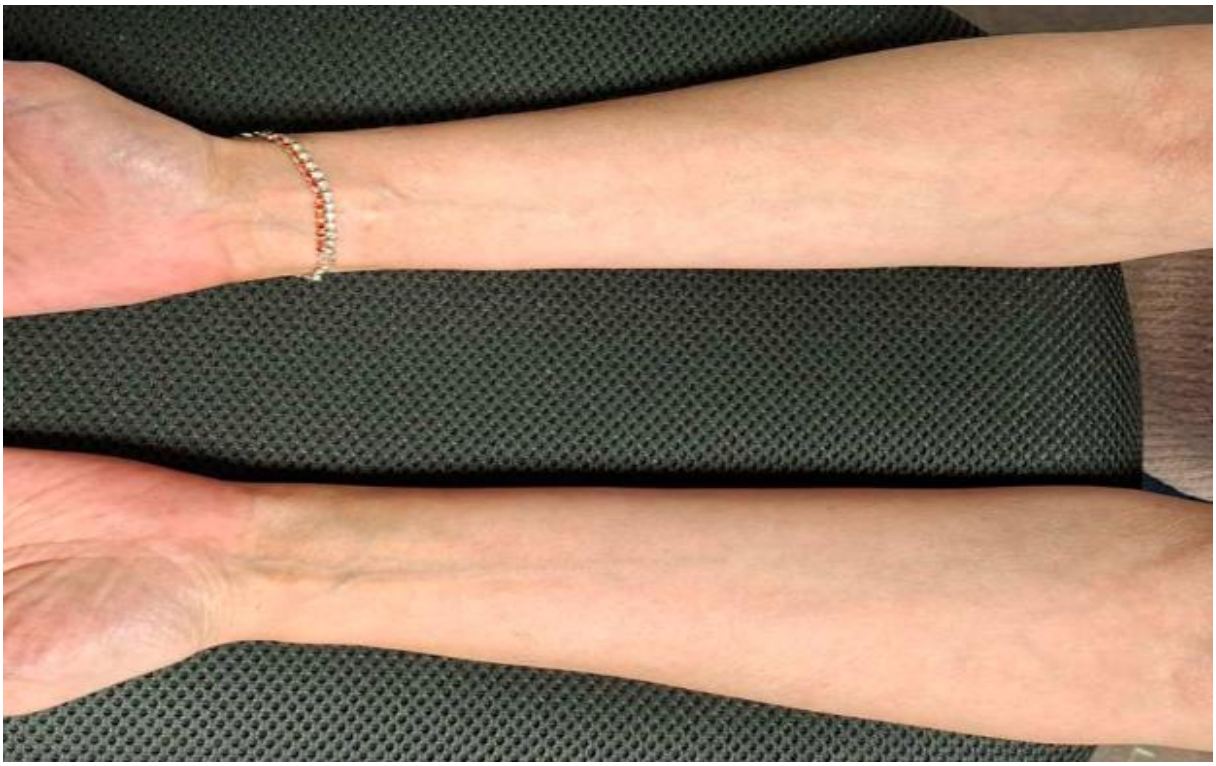


Figure 3: Clinical appearance of both forearms at follow-up showing complete resolution of previous skin induration. The skin is soft, with normal contour and mobility, without residual thickening, hyperpigmentation, or contractures, indicating full clinical remission

Given the close temporal relationship between symptom onset and recent COVID-19 infection, together with the absence of other evident causes, COVID-19 was considered a possible triggering factor.

3. Discussion

Although no universally accepted diagnostic criteria for eosinophilic fasciitis exist, several classification approaches have been proposed, including those by Bennett et al., Endo et al., Pinal-Fernandez et al., and Jinnin et al. [5,8-10] Despite some differences in structure, these frameworks consistently emphasize a characteristic pattern of limb or truncal induration, exclusion of systemic sclerosis, peripheral eosinophilia or inflammatory abnormalities, imaging evidence of fascial involvement, and histopathological confirmation by full-thickness biopsy. Our patient fulfilled these core diagnostic elements. Given the rarity of the disease, none of the sets was validated in larger cohorts.

Since the first described patients in the late 1970s, temporal associations with possible etiological/triggering implications were reported for many factors (Table 1).

Table 1. Reported precipitating and associated factors in eosinophilic fasciitis, with the typical level of supporting evidence and representative key references.

Factor	Typical supporting evidence	Key references
Vigorous physical exercise	Repeatedly reported across reviews, cohorts, and case reports; often temporally linked by days to weeks	[2], [11], [12], [13]
Trauma or mechanical stress	Recurrent association in reviews and clinical summaries; evidence is observational rather than controlled.	[11], [13]
Hematologic malignancy	Systematic review identified 104 malignancies among 1,703 EF patients, with many hematologic cancers; multiple case reports support temporal linkage.	[15], [16]
Solid tumors	Included in malignancy systematic review, but less frequent than hematologic cancers.	[15], [16]
Specific autoimmune comorbidities	Co-reported conditions include lupus , primary biliary cirrhosis, and thyroid autoimmunity, mostly from case-based literature.	[17], [18], [19]
Immune checkpoint inhibitors	PD-1/PD-L1 blockade – nivolumab, pembrolizumab	[20], [21], [22]

Other medications	Reported drugs include statins, heparin, phenytoin, carbidopa, anti-TNF agents – certolizumab [12]; mostly case reports or small clusters.	[23]
Borrelia burgdorferi / Lyme disease	Reported in some reviews and case reports, but causal inference is limited and may vary by endemic area.	[24]
Radiation therapy	Reported in review summaries and isolated case-based literature.	[25]
Burns / local tissue damage	Based mainly on isolated reports and review mentions.	[26]
Graft-versus-host disease / post-transplant state	Reported in small numbers; difficult to separate from sclerodermoid GVHD or malignancy-related disease.	[27]
COVID-19 infection	Case-report and case-series	[7], [28], [32]
EBV infection	Case report	[29]
Idiopathic	Modern reviews and series still note that many patients have no clear precipitating factor.	[2], [11]

EF: Eosinophilic Fasciitis, PD-1: Programmed cell death protein 1, PD-L1: Programmed death-ligand 1, anti-TNF: Anti-tumor necrosis factor, GVHD: Graft-versus-host disease, COVID-19: Coronavirus disease 2019, EBV: Epstein-Barr virus.

A consistent body of evidence indicates that eosinophilic fasciitis is frequently preceded by mechanical triggers, particularly strenuous physical exertion or localized trauma. These observations suggest that repetitive fascial microinjury may initiate an aberrant immune response characterized by eosinophil recruitment and subsequent fibrotic remodeling of the fascia.

Other triggers, described in the scientific literature, are malignancies, autoimmune conditions, drug-induced cases, with evidence supporting strongly association with immune check-point inhibitors, specifically PD-1 and PD-L1 blockers, and radiation therapy. Given the known association between eosinophilic fasciitis and malignancy, hematologic evaluation was performed and did not reveal evidence of a hematologic disorder. In addition, the patient had no B symptoms, no hepatosplenomegaly, and no suspicious findings on chest radiography or abdominal ultrasonography. Therefore, no further oncological work-up was considered clinically indicated at that stage.

Viral infections have been increasingly implicated as potential triggers of eosinophilic fasciitis, particularly in the context of SARS-CoV-2. Reviews and case-reports implicate also boreliosis and EBV-infection but the data is scarce and causal relationship cannot be estimated.

Accumulating epidemiological evidence supports a potential association between SARS-CoV-2 infection and the subsequent development of autoimmune and autoinflammatory diseases [30, 31].

From a clinical care perspective, our case highlights a potential pitfall in the evaluation of patients after COVID-19. Early symptoms such as pain, stiffness, and fatigue are frequently attributed to post-viral or nonspecific inflammatory syndromes, which may lead to diagnostic delay. In contrast, the presence of progressive skin induration, symmetrical limb involvement, and eosinophilia should be considered red flags prompting targeted investigation. In this setting, MRI is particularly valuable for identifying fascial inflammation and guiding biopsy, especially when clinical findings are subtle or evolving.

Moreover, available evidence indicates that prognosis in eosinophilic fasciitis is primarily determined by disease stage at presentation and timeliness of treatment initiation. Multiple cohort studies have consistently identified diagnostic delay as one of the strongest predictors of poor outcome, reflecting progression from an early inflammatory phase to irreversible fibrosis [33, 34]. Additional adverse prognostic factors include truncal involvement [9], coexistence of morphea-like lesions [9], elevated inflammatory markers, and histological evidence of dermal fibrosis [9]. Recent multicenter analyses further suggest that a fibrotic disease phenotype and persistent eosinophilia are associated with relapse and long-term sequelae, whereas patients presenting in an early edematous stage have a more favorable course [35].

Consistent with these findings, our patient, who received an early diagnosis, demonstrated a sustained and complete response to systemic glucocorticoids followed by methotrexate, with full clinical remission at long-term follow-up.

4. Conclusions

Eosinophilic fasciitis is a rare immune-mediated condition that may occur following SARS-CoV-2 infection. This case highlights the importance of considering eosinophilic fasciitis in patients presenting with compatible

clinical features after COVID-19, even in the absence of classical triggers. Early recognition based on clinical findings, supported by imaging and histopathology, is essential for prompt initiation of immunosuppressive therapy and favorable outcomes.

Declarations

Author Contributions

Conceptualization: M.K.; Methodology: M.K., M.M.; Formal analysis: M.K., M.D.; Investigation: M.M., M.K.; Writing: original draft preparation: M.M., M.K.; Writing: review and editing: M.D., M.M., M.K., V.V.

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Declaration

The case report was conducted in accordance with the Declaration of Helsinki.

Informed Consent Statement

Informed consent was obtained from all subjects involved in the study.

Data Availability Statement

The data presented in this study are available on reasonable request from the corresponding author.

Conflicts of Interest

The authors declare no conflict of interest.

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Еозинофилен фасциит след инфекция със SARS-CoV-2: клиничен случай и обзор на времевите асоциации

Резюме

Въведение: Еозинофилният фасциит е рядко заболяване от групата на склеродермоподобните състояния, характеризиращо се с възпаление и задебеляване на фасцията, клинично проявяващо се с кожна индурация и периферна еозинофилия. Етиологията му остава неясна, като се предполага имунно-медииран механизъм и участие на различни отключващи фактори. Клиничен случай: Представяме случай на 49-годишна жена с прогресираща болка, скованост и кожна индурация на горните крайници, възникнали скоро след преболедуване от COVID-19. Лабораторните изследвания установиха еозинофилия и повишени възпалителни маркери при отрицателен автоимунен профил. Магнитнорезонансната томография демонстрира засягане на фасцията без ангажиране на мускулатурата. Хистологичното изследване потвърди диагнозата еозинофилен фасциит. Проведено бе лечение с високи дози глюкокортикостероиди и метотрексат като стероид-спестяващ агент, с последващо клинично и лабораторно подобрение. При проследяване се установи пълна клинична ремисия без поддържаща терапия. Заключение: Представеният случай подкрепя възможна връзка между еозинофилния фасциит и прекарана SARS-CoV-2 инфекция като потенциален отключващ фактор. Ранното разпознаване, образната диагностика и хистологичното потвърждение са от ключово значение за навременното лечение и благоприятния изход.

Ключови думи: еозинофилен фасциит; COVID-19; постинфекциозно имуномедиирано заболяване; клиничен случай

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Case report

Immune-mediated Arthritis after Treatment with Nivolumab in a Patient with Malignant Melanoma

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Running title: Immune-mediated Arthritis after Treatment with Nivolumab

Abstract

Malignant melanoma is an aggressive skin tumor that accounts for 1% of all skin tumors. Immunotherapy is a new therapeutic approach for the treatment of melanoma neoplasms. Nivolumab is an immunotherapeutic product that belongs to the so-called checkpoint inhibitors. Nivolumab therapy has demonstrated a good effect in terms of overall survival and progression-free survival in patients with malignant melanoma. Nivolumab treatment is used both for therapy in patients in the metastatic stage and in the adjuvant aspect in patients with a high risk of disease recurrence. The interaction between the ligand of the programmed cell death receptor (PD-L1) and the programmed cell death receptor (PD-1) leads to suppression of autoimmune manifestations. Blocking this interaction carries a risk of various autoimmune reactions, which are expressed to varying degrees, and can sometimes be life-threatening and require prolonged immunosuppression or discontinuation of treatment with checkpoint inhibitors. Immune-related adverse reactions of varying degrees and severity have been described with the use of anti-PD-1 antibodies, such as

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pneumonitis, hepatitis, endocrinopathies, immune-mediated colitis, dermatitis, etc. Rheumatic immune-mediated complications such as myositis, myalgia, arthritis, arthralgia, vasculitis, scleroderma are rare with Nivolumab treatment. Most often, patients report arthritis that starts after several cycles of Nivolumab administration. The mechanism of occurrence of immune-mediated arthritis has not yet been established. A clinical case of an 84-year-old patient who developed immune-related arthritis after treatment with Nivolumab is presented. After treatment with corticosteroids and immunosuppressants led to the control of the immune-related arthritis, reinitiation of immunotherapy is being evaluated for the management of the oncological disease.

Keywords: checkpoint inhibitors, immune-mediated arthritis, immunotherapy, malignant melanoma, Nivolumab

1. Introduction

Malignant melanoma is an aggressive skin tumor that accounts for 1% of all skin tumors. It is characterized by an aggressive course and a low 5-year survival rate [1]. Patients with melanoma and distant metastasis show a 5-year survival rate of 23%, making metastasis the leading cause of melanoma-related death [2]. Even after radical resection of patients with local disease, an increased risk of local recurrence and distant metastasis is observed [3].

Immunotherapy is a new approach for the treatment of malignant melanoma even in advanced disease [4-6]. The high immunogenicity of melanoma is the basis of the relationship between this neoplasm and the immune system, which is a prerequisite for the use of immunotherapy in a therapeutic aspect through the so-called checkpoint inhibitors [3, 7-12].

Nivolumab is a fully human IgG4 monoclonal antibody directed against the programmed cell death receptor 1 (PD-1). PD1 is expressed on the surface of T lymphocytes, while its ligand (PD-L1) is expressed on both immune and non-immune cells [13]. The interaction of PD-1 with PD-L1 results in reduced T-cell activity, promoting self-tolerance [14]. PD-L1 is overexpressed on a wide variety of tumors, including melanoma, leading to immune evasion by tumor cells. Inhibition of PD-1 restores standard immune recognition of malignant cells and subsequent immune-mediated tumor destruction [13]. Nivolumab inhibits the interaction between PD-1 and PD-L1 thereby allowing the immune system to recognize and attack tumor cells.

Approximately 50% of patients receiving immunotherapy experience immune-related adverse events, ranging from severe and potentially life-threatening pneumonitis and colitis to autoimmune thyroid disease, hypophysitis, and vitiligo. The incidence of events varies depending on the type of drug and tumor type, requiring prolonged immunosuppression or discontinuation of checkpoint inhibitor therapy [15,16].

Rheumatological immune-induced reactions occur in 5%–20% of cases [17-19]. Rheumatic and musculoskeletal immune-related adverse events are usually unrecognized. Rheumatic immune-mediated complications such as myositis, myalgia, arthritis, arthralgia, vasculitis, and scleroderma are rare with Nivolumab treatment. Most often, patients report arthritis that begins after several cycles of Nivolumab. The mechanism of the appearance of immune-mediated arthritis during treatment with checkpoint inhibitors is still unclear, but a number of authors have found an association between the expression of PD-1 in the synovial fluid and the development of arthritis of the autoimmune type [20].

Immune-related rheumatological events, due to their low frequency and insufficient research, represent a serious challenge and diagnostic difficulty among medical specialists. Recognition of rheumatological immune-related events following immunotherapy treatment, which resemble autoimmune diseases, is increasingly important for both oncologists and rheumatologists. A multidisciplinary approach allows for the management of these immune-related reactions and the continuation of antitumor therapy.

2. Case Presentation

We present a case of an 84-year-old female patient in good general health (ECOG PS 0) and physically active, with a history of nodular malignant melanoma of the left gluteal region diagnosed in 2022. Postoperatively, the patient was staged as T2N0M0. No lymphatic dissection was performed, and she remained under active surveillance. Her medical history included COPD, a 20-year history of well-controlled arterial hypertension, and a cholecystectomy in 2000. In 2024, restaging via PET-CT revealed disease progression, characterized by multiple inguinal lymph nodes and pulmonary metastases. Although the patient was referred for BRAF testing to evaluate eligibility for targeted therapy, no BRAF mutation was identified. Following a multidisciplinary team review, treatment with Nivolumab (240 mg i.v. every 14 days) was initiated in October 2024.

Evaluation after six cycles demonstrated a complete response of the lung metastases and a partial response of the lymph nodes.

In January 2025, the patient was admitted for another cycle of immunotherapy with complaints of persistent pain, difficulty moving the knee, ankle and wrist joints, especially pronounced soreness and stiffness of the interphalangeal joints (Figure 1). There was no swelling of the knee and ankle joints. Mild swelling, thickening of the palms, severe soreness and stiffness (Figure 2).



Figure 1. Swelling of the interphalangeal joints and palmar thickening with associated skin induration.



Figure 2. Diffuse palmar induration and mild soft-tissue edema of the digits.

The patient was assessed for manifestation of immune-mediated arthritis and was referred to a rheumatologist, who prescribed therapy with methylprednisolone 8 mg daily for 2 weeks. The Nivolumab treatment was temporarily discontinued. After the prescribed therapy with

methylprednisolone, the patient's condition improved, the pain and stiffness decreased and she decided to discontinue the methylprednisolone therapy by herself. She refused a new examination with a rheumatologist in order not to delay her oncological treatment.

After reducing the complaints, the patient decided to reinitiate therapy with Nivolumab. After 2 applications of the medication, a month after, the complaints worsened again - pain and stiffness in the knee and ankle joints, mild edema and slight redness of the ankle joints, persistent tightness of the palms and severe soreness in the interphalangeal joints.

The therapy was discontinued again and the patient was referred for hospitalization for diagnostic clarification at the Rheumatology Clinic. Musculoskeletal evaluation revealed arthritis in the wrist, knee and ankle joints. Laboratory tests revealed positive values for anti-MCV, RF IgM, elevated levels of C-reactive protein (CRP 112mg/L) and erythrocyte sedimentation rate (ESR 82 mm/h), thrombocytosis (578 x 10^9/L) (Table 1).

Table 1. Laboratory tests before starting Nivolumab treatment, at diagnosis of immune-mediated arthritis, and after treatment for arthritis

Laboratory tests	Reference range	10.10.2024	04.04.2025	08.12.2025
CRP (mg/L)	0–5	6	112	18
WBC (10^9/L)	3.50–10.50	5.10	10.40	5.70
Uric acid (μmol/L)	140–410	228	400	280
PLT (10^9/L)	130–360	278	578	326
ESR (mm/h)	<30*	21	82	25
Immunology				
Anti-CCP (IgG+IgA), U/mL	<20	Neg (-)	26	20
RF (IU/mL)	<30	<30	<30	<30
Anti-MCV, U/mL	<20	Neg (-)	65	18
RF IgM, U/mL	<20	Neg (-)	44	20

Abbreviations: Anti-CCP, anti-cyclic citrullinated peptide; Anti-MCV, anti-mutated citrullinated vimentin; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; Neg, negative; PLT, platelet count; RF, rheumatoid factor; RF IgM, rheumatoid factor immunoglobulin M; WBC, white blood cell count. Asterisk (*) denotes age-adjusted or laboratory-specific upper limit for ESR.

The performed knee radiography revealed cystic effusions in the distal part of the diaphysis of the right femur and osteophytes bilaterally. Less pronounced changes in the left knee joint.

An ultrasound examination of the right and left knee joint was performed with data on mild hydrops, synovial proliferation, degenerative changes in

the lateral and medial meniscus. After a multidisciplinary meeting, it was concluded that the patient had Grade 2 immune-mediated arthritis, probably as a result of the treatment with Nivolumab [21]. A follow-up PET-CT scan was performed to assess the current oncological status, demonstrating stable disease.

Treatment was initiated with methotrexate 10 mg weekly, methylprednisolone 4 mg daily with a gradual tapering to 2 mg daily and folic acid 1200 μg daily. Etodolac 400 mg daily for two weeks was prescribed to suppress the pain symptoms. At the eight-month follow-up, the patient showed no evidence of joint involvement and remained symptom-free. Baseline parameters before treatment, at diagnosis of arthritis and after treatment are presented in Table 1.

A multidisciplinary meeting is to be held to discuss the reintroduction of Nivolumab in dynamic follow-up by a rheumatologist.

3. Discussion

PD-1 expression on T-cells in synovial fluid is significantly increased in inflammatory joint disease. Higher levels of PD-1+ T-cells are often observed in active synovitis, reflecting the intensity of the local immune response. This increase reflects the body's desire to suppress autoimmune inflammation, although it is often not sufficient to completely control the synovitis. The PD-1/PD-L1 pathway functions as a negative regulator of the immune response, attempting to limit the autoaggression in the joint environment. Nivolumab blocks PD1, which activates inflammatory cytokines, disrupts autoimmunity and leads to immune-mediated toxicity. Immune-mediated arthritis is not yet well studied, but the idea of impaired immune tolerance and autoimmunity is supported. The PD1 axis is involved in the maintenance of peripheral tissue tolerance, and its dysregulation has been implicated in the development of autoimmune diseases. PD-1 expression has increased on synovial lymphocytes of patients with various types of autoimmune diseases. Although the exact mechanism of immune-related arthritis remains unclear, the checkpoint inhibitors block negative signals on activated T-cells, leading to increased autoreactive T-cells and inflammatory cytokines such as tumor necrosis factor-α (TNF-α), IL-6, and IL-17 [21-23] (Figure 3). This gives grounds for targeted inhibition of these cytokines for the treatment of rheumatic immune-related adverse events (irAEs) [24, 25]. Checkpoint inhibitors prevent B-cell apoptosis, allowing for longer cell survival and increased autoantibody burden [21].

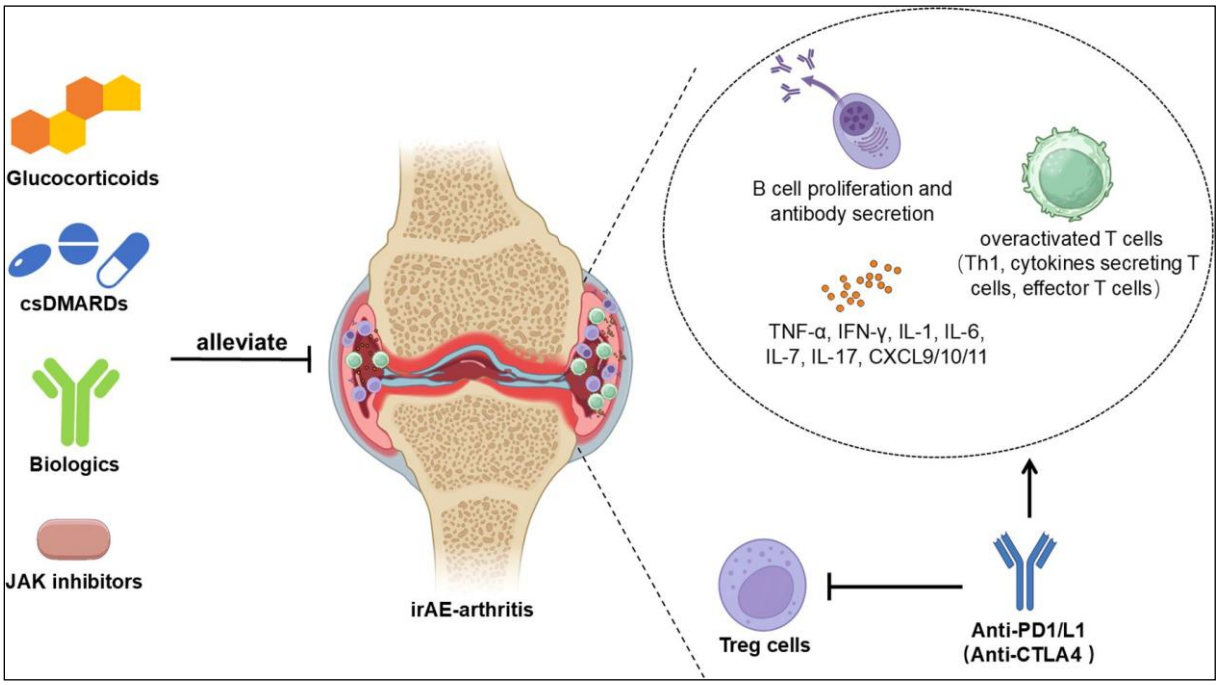


Figure 3. The pathogenesis of irAE-arthritis is characterized by the accumulation of overactivated T cells and inflammatory cytokines, coupled with B-cell proliferation and increased autoantibody secretion and current therapeutic strategies.

The presented clinical case is an example of de novo immune-mediated toxicity during treatment with a checkpoint inhibitor. Before starting therapy with Nivolumab, the patient had no history or laboratory evidence of arthritis. The coincidence of the complaints with the start of immunotherapy, as well as the effect of corticosteroid administration, support the diagnosis of immune-mediated arthritis due to Nivolumab administration.

The patient developed immune-mediated arthritis with persistent arthritis of the wrist, knee, and ankle joints, severe pain and stiffness of the interphalangeal joints, and palmar thickening, elevated markers of inflammatory activity - ESR, CRP, and the presence of RA-specific autoantibodies, anti-MCV, and RF IgM.

The management of immune-mediated arthritis is based on shared decision-making between the patient, treating oncologist, and rheumatologist [26]. The role of the rheumatologist is to support the oncologist and to alleviate the immune-mediated arthritis, allowing patients to maintain effective immunotherapy for their oncological disease. Currently, algorithms for the management of irAEs are based on the severity/grade of the irAE according to the Common Terminology Criteria for Adverse Events (CTCAE v5.0) [26]. Referral to a rheumatologist is

recommended before initiating treatment for immune-mediated arthritis. In the absence of contraindications, symptomatic treatment, including nonsteroidal anti-inflammatory drugs and/or analgesics, should be the initial treatment for mild to moderate rheumatic manifestations [26]. Intra-articular glucocorticoids should be considered in the context of monoarthritis or oligoarthritis, combined with synovial fluid analysis whenever possible. If symptomatic treatment is insufficient and tissue inflammation is still present, systemic glucocorticoids should be considered in immune-related arthritis. Because of the potential for corticosteroids to compromise the antitumor response, the use of pulse therapy with methylprednisolone or high-dose per os glucocorticoids is not recommended in the absence of life-threatening complications. In addition, gradual tapering of corticosteroids to the lowest effective dose over a period of weeks or as soon as improvement is achieved is recommended. The goal is to achieve a dose of less than or equal to 10 mg daily prednisone equivalent. The dosage regimen and route of administration should be determined according to the clinical form and activity [26].

Following the discontinuation of Nivolumab, the patient was started on immunosuppressive therapy with corticosteroids and methotrexate in accordance with EULAR recommendations. Based on the National Cancer Institute CTCAE v5.0 grading, clinical improvement was subsequently observed [27,28]. The treatment of this patient is undoubtedly a challenge for medical professionals, due to the need to control the immune-mediated arthritis on one hand, and the oncological disease on the other. Re-initiation of Nivolumab is supported by international and national guidelines [27], with clinical benefit from continuing therapy and managing complaints in immune-mediated arthritis, while assessing the risk of new manifestation of immune-mediated toxicity [29].

4. Conclusions

Metastatic melanoma is a malignant disease with a poor prognosis. The introduction of immunotherapy has significantly changed the approach to this tumor. Unfortunately, immunotherapy has a specific toxicity, characterized by adverse reactions, such as immune-mediated arthritis. In the case reported, the patient responded to corticosteroids and immunosuppressive therapy, suggesting that the PD1/PDL1 axis plays a role in the pathophysiology of arthritis. With coordinated collaboration between medical specialists - oncologists, immunologists and rheumatologists - and a multidisciplinary approach to the patient, irAEs can

be successfully controlled; patients can continue their treatment and maintain their quality of life.

Author Contributions

Conceptualization: I.I.; Methodology: I.I.; Formal analysis: I.I.; Investigation: I.I.; Writing—original draft: I.I.; Writing—review & editing: author.

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Declaration

The case report was conducted in accordance with the Declaration of Helsinki.

Informed Consent Statement

Informed consent was obtained from the patient involved in the study.

Data Availability Statement

The data presented in this study are available on reasonable request from the corresponding author.

Conflicts of Interest

The author declares no conflict of interest.

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Имуномедииран артрит след лечение с Nivolumab при пациент с малигнен меланом

Резюме

Малигненият меланом е агресивен кожен тумор, който представлява 1% от всички новообразувания на кожата. Имунотерапията е нов терапевтичен подход за лечение на меланомните неоплазии. Nivolumab е имунотерапевтичен продукт, който принадлежи към т.нар. чекпойнт инхибитори (контролни точки). Терапията с Nivolumab демонстрира добър ефект по отношение на общата преживяемост и преживяемостта без прогресия при пациенти с малигнен меланом. Лечението с Nivolumab се прилага както за терапия при пациенти в метастатичен стадий, така и в адювантен аспект при пациенти с висок риск от рецидив на заболяването. Взаимодействието между лиганда на рецептора за програмирана клетъчна смърт (PD-L1) и самия рецептор за програмирана клетъчна смърт (PD-1) води до потискане на автоимунните прояви. Блокирането на това взаимодействие крие риск от различни автоимунни реакции, които се изразяват в различна степен, а понякога могат да бъдат животозастрашаващи и да изискват продължителна имуносупресия или преустановяване на лечението с чекпойнт инхибитори. При употребата на анти-PD-1 антитела са описани имуносвързани нежелани реакции с различна тежест, като пневмонит, хепатит, ендокринопатии, имуномедииран колит, дерматит и др. Ревматичните имуномедиирани усложнения, като миозит, миалгия, артрит, артралгия, васкулит и склеродермия, се срещат рядко при лечение с Nivolumab. Най-често пациентите съобщават за артрит, който започва след няколко цикъла на приложение на Nivolumab. Механизмът на възникване на имуномедиирания артрит все още не е установен. Представен е клиничен случай на 84-годишен пациент, развил имуносвързан артрит след лечение с Nivolumab. След като лечението с кортикостероиди и имуносупресори довежда до контрол на имуномедиирания артрит, се прави оценка за повторно инициране на имунотерапията с цел овладяване на онкологичното заболяване.

Ключови думи: чекпойнт инхибитори, имуномедииран артрит, имунотерапия, малигнен меланом, Nivolumab

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Case report

Clinical Case of a Patient with Multiple Sclerosis, Polymyositis and Melanoma. Is There a Connection Between Them?

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Running title: Multiple Sclerosis, Polymyositis, and Melanoma Association

Abstract

Background: We present a case of a patient with the sequential development of clinical symptoms characteristic of multiple sclerosis, polymyositis, and malignant melanoma. Case presentation: Polymyositis occurred two years after the onset of multiple sclerosis. Clinical signs of melanoma were identified following the development of polymyositis. Treatment with corticosteroids and immunosuppressants positively affected the patient's clinical manifestations of multiple sclerosis. It remains unclear whether there was an insidious progression of melanoma without clinical manifestations and whether the myositis developed in parallel with this melanoma. It is possible that polymyositis developed independently or preceded the onset of melanoma with lymph node metastases. Conclusion: The patient's clinical history demonstrates an overlap of demyelinating, systemic, and malignant diseases. Integrated treatment is essential for achieving clinical improvement in these patients.

Keywords: multiple sclerosis, polymyositis, melanoma

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1. Introduction

Multiple sclerosis (MS), polymyositis (PM), and melanoma are interconnected primarily through the complex interplay between autoimmunity, immunosuppressive therapies, and oncological risk. While dermatomyositis exhibits a stronger association with cancer, polymyositis is recognized as a potential paraneoplastic syndrome that can manifest in conjunction with various malignancies, including melanoma. Studies have reported a higher standardized incidence ratio (SIR) for cancer in patients with PM; however, melanoma incidence is relatively rare compared to other types of malignancy, such as adenocarcinoma. While both conditions possess an autoimmune etiology and have been linked to melanoma, the simultaneous occurrence of all three pathologies is exceedingly rare and likely related to the immunomodulatory effects of the prescribed treatments.

2. Case presentation

We present the clinical case of a 54-year-old man presenting with neurological deficits characteristic of multiple sclerosis, polymyositis, and melanoma. The initial clinical symptoms began in October 2017, manifesting as acute paresthesia, stiffness, and fatigue in the right arm, alongside rapid fatigue during exertion and urinary dysfunction. Magnetic resonance imaging (MRI) of the brain and cervical spine confirmed a diagnosis of multiple sclerosis, specifically the cerebrospinal form with a relapsing-remitting disease course.

On January 4, 2018, the patient developed pain and stiffness in the cervical spine, accompanied by paresthesia of the left arm, as well as tingling, stiffness, and fatigue of the right arm, and gait-related fatigue. By October 1, 2018, he reported tingling, stiffness, and fatigue in all extremities. Between 2017 and 2019, the patient underwent annual neurological evaluations. Clinical examinations revealed that the cranial nerves were intact. Motor assessment confirmed a quadripyramidal syndrome with monoparesis of the right arm (resulting in a ”useless hand”). Neurological examination revealed proprioceptive hyperreflexia and pathological reflexes in the extremities. Coordination testing showed dynamic ataxia during the finger-to-nose test, while the Romberg test remained stable. Sensory examination revealed impaired two-dimensional spatial localization and joint-muscular sense in the right hand.

Magnetic resonance imaging (MRI) of the brain and cervical spine revealed supratentorial frontal white matter hyperintensities consistent with

vascular leukoencephalopathy, alongside zones of altered signal intensity. Within the cervical spinal cord from C2 to C5, areas of ill-defined signal changes were identified. The patient received a single pulse of 500 mg methylprednisolone, resulting in a favorable clinical response. This was followed by the chronic administration of dimethyl fumarate (240 mg, two tablets daily) to manage the relapsing-remitting course of multiple sclerosis.

Three months later, a follow-up neurological examination showed no significant changes in the patient's status. Motor assessment revealed a quadripyramidal syndrome with latent paraparesis in the lower extremities. Sensory evaluation demonstrated paresthesia in the upper extremities, tactile hypesthesia, and impaired two-dimensional spatial sense in the right hand. Coordination was characterized by static, dynamic, and locomotor ataxia, as well as altered two-dimensional spatial perception in the lower extremities. Follow-up MRI of the brain and cervical spine showed persistent T2-hyperintense lesions situated within the juxtacortical white matter (Figure 1).

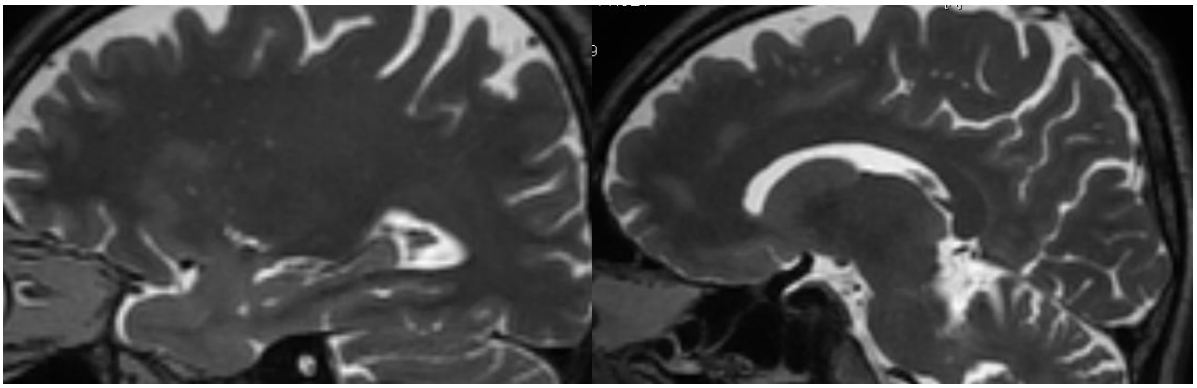


Figure 1. Magnetic resonance imaging (MRI) of brain and cervical spine from January 4, 2018.

This was followed by pulse therapy with 500 mg of methylprednisolone, which had a positive effect on the clinical symptoms. Differential diagnoses considered at this stage included other neurological disorders, such as neuropathies, polyneuritis, and multiple small ischemic zones; however, diagnostic criteria were insufficient to confirm these alternative diagnoses. Subsequent treatment with teriflunomide (14 mg daily) showed no effect on the neurological findings. On October 1, 2018, the patient underwent a third neurological examination, which revealed no significant changes in his neurological status. Motor assessment continued to show a quadripyramidal syndrome with latent paraparesis in the lower extremities. Sensory examination revealed persistent paresthesia in the

upper extremities, tactile hipesthesia, impaired two-dimensional spatial sense in the right hand, and neuropathic pain in the lower extremities. Coordination was characterized by dyscoordination with static, dynamic, and locomotor ataxia. Follow-up brain and cervical spine MRI demonstrated persistent T2 hyperintensities located juxtacortically within the white matter. The MRI also revealed a new subcortical lesion in the right hemisphere. Within the cervical spinal cord (C2–C5), areas of ill-defined signal intensity changes remained present, with the lesion at the C3-C4-C5 level increasing in longitudinal extent from 24 to 30 mm. These MRI findings indicated a progression of cerebrospinal multiple sclerosis (Figure 2).

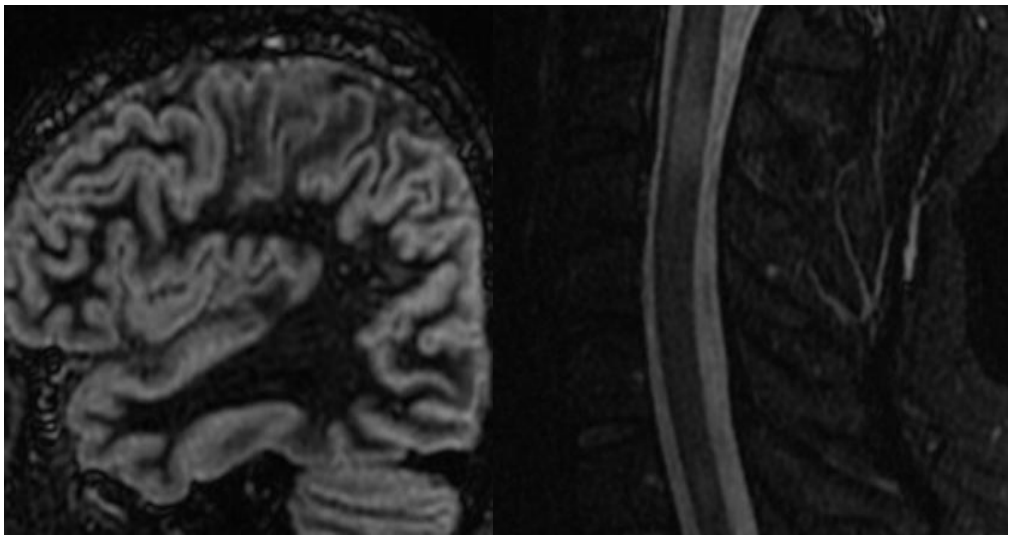


Figure 2. MRI of brain and cervical spine from October 1, 2018.

This was followed by a pulse of 1,000 mg methylprednisolone, which resulted in significant clinical improvement. Following neurological and laboratory investigations, the patient was found to have severely elevated creatine kinase (CK) levels (10,126 U/L). He reported significant proximal muscle weakness in the limbs, difficulty climbing stairs, myalgias, and malaise. Electromyography (EMG) of the upper and lower extremities showed an absence of spontaneous activity, while motor unit action potentials demonstrated decreased duration and an increased number of phases. These findings were consistent with myositis. Immunological testing revealed elevated antinuclear antibody (ANA) titers of 1:1280 (normal < 1:80), as well as myositis-specific antibodies: Anti-PM-Scl100 (8 U/mL) and Anti-TIF1-γ (11 U/mL; normal < 5 U/mL). Based on these results, a diagnosis of polymyositis was confirmed. Initial treatment consisted of 32 mg methylprednisolone (subsequently tapered to 8 mg) and 150 mg azathioprine daily, which led to a reduction in CK levels to 5,509

U/L, then 2,440 U/L, eventually reaching normal values. Dimethyl fumarate was discontinued. From September 25, 2019, to the present, the patient has not experienced any new neurological deficits, and the initial symptoms from 2017 have diminished. A follow-up neurological consultation did not confirm the previous diagnosis of multiple sclerosis. On May 20, 2022, the patient was diagnosed with a high-risk malignant melanoma of the right thigh (T3a) with inguinal lymph node metastases, for which he underwent surgical intervention.

Histological examination of a lymph node demonstrated sinus histiocytosis and a small subcapsular focus containing a cluster of cells with moderate atypia. Technetium-99m nanocolloid lymphoscintigraphy was performed, which revealed rapid lymphatic drainage from the tumor region to the left inguinal region, marked by an intense focus of radiotracer uptake. In August 2024, the patient underwent surgical dissection of the affected lymph node, confirming metastasis from malignant melanoma; this was followed by the initiation of immunotherapy using anti-PD-L1 immune checkpoint inhibitors.

3. Discussion

A review of the scientific literature reveals only sporadic reports of similar clinical cases. Integrated management of systemic, neurological, and malignant conditions is essential for achieving clinical improvement in these complex patients. Several key aspects of this case warrant further discussion. First, it is important to consider whether the combined administration of methylprednisolone and azathioprine contributed to the sustained reduction in clinical symptoms and the stabilization of MRI findings observed from September 2019 to the present. Furthermore, the potential role of dimethyl fumarate in the induction of polymyositis should be evaluated as a possible secondary complication. Finally, the presence of anti-TIF1-γ antibodies - which possess a reported 70% sensitivity and 89% specificity as paraneoplastic markers - may have served as a critical predictive factor for the underlying melanoma, potentially acting as a serological precursor to the oncological diagnosis.

MS is the most prevalent demyelinating disease, characterized by damage to the myelin sheaths of neurons within the central nervous system. Although the exact etiology remains elusive, the underlying pathophysiology is thought to involve either immune-mediated destruction or the failure of myelin-producing cells [1].

Etiological factors include genetic predisposition and environmental triggers, such as viral infections. During symptomatic exacerbations, the administration of high-dose intravenous corticosteroids, such as methylprednisolone, is the standard therapy; however, oral corticosteroids and azathioprine appear to demonstrate comparable efficacy and safety profiles [2]. A review of the literature reveals no existing publications established a connection between treatment with Tecfidera and the development of polymyositis. It remains possible that polymyositis developed independently or as a paraneoplastic phenomenon preceding the progression of melanoma with metastases. It is hypothesized that Anti-TIF1-γ antibodies may serve as a predictive marker for the onset of melanoma.

Analysis of four cohort studies involving 4,239 patients with polymyositis was conducted to assess the risk of malignancy. A total of 19 cases of melanoma were identified, although specific demographic data regarding the age and gender of these patients were not provided [3].

Targeting cancer screening protocols based on idiopathic inflammatory myositis (IIM) subtype, autoantibody profile, and age may help to maximize cancer detection while limiting false positives. In their study, Mecoli et al. analyzed 1,086 patients enrolled in the center's Myositis Research Registry from 2003 through 2020. The analysis included patients with diagnoses of dermatomyositis (DM), polymyositis (PM), immune-mediated necrotizing myopathy (IMNM), and antisynthetase syndrome (ASyS). The researchers also investigated myositis-specific autoantibodies (MSAs), including anti-TIF1γ, anti-Jo1, and anti-HMGCR. Patients were excluded from the analysis if they had a cancer diagnosis prior to the onset of their myositis. The findings demonstrated that computed tomography (CT) of the chest, abdomen, and pelvis had the highest diagnostic yield in patients with DM and those with DM-specific MSAs (anti-TIF1γ, anti–NXP-2, anti-SAE, and anti–Mi-2), while showing the lowest diagnostic yield in patients with ASyS and those with PM. These data provide evidence that may inform clinical decision-making to maximize cancer detection while minimizing the risks and costs of over-screening in this patient population [4].

Polymyositis is a systemic autoimmune disorder characterized by proximal muscle weakness, primarily involving the limbs, neck, and trunk. Interferon-alpha is an antiviral cytokine with well-established immunomodulatory and antiproliferative effects; however, its administration is frequently associated with various side effects, particularly autoimmune phenomena. Authors have reported cases of

polymyositis occurring during interferon-alpha therapy in patients diagnosed with malignant melanoma. Indirect evidence suggested that, in these instances, the myositis was not paraneoplastic, as the melanoma was confirmed to be in remission both at the initial diagnosis of the muscle disease and during a one-year follow-up period [5].

Originally utilized for the treatment of psoriasis, dimethyl fumarate (DMF) was approved for the management of multiple sclerosis in 2013. Although the exact mechanism of action of DMF in multiple sclerosis is not yet fully elucidated, it is considered an immunomodulatory therapy that reduces inflammatory T-cell activity by activating nuclear factor erythroid 2-related factor 2 (Nrf2) and modulating glutathione (GSH). These key cellular regulators of the antioxidant response exert potent anti-inflammatory and antioxidant effects. DMF was associated with a low incidence of malignancies in the DEFINE and CONFIRM clinical trials, accounting for less than 1% of all reported adverse events [6].

The primary role of the immune system is to protect the host from pathogenic pathogens and malignancies while maintaining tolerance to self-antigens. Malignant and autoimmune diseases, such as rheumatic disorders and multiple sclerosis, result from immune dysregulation. In multiple sclerosis, an aberrant immune response leads to the demyelination of the central nervous system. Malignant cells adapt to either evade standard immune surveillance mechanisms or directly influence an immune phenotype favorable to malignant proliferation, such as by recruiting and differentiating regulatory T cells (Tregs), regulatory B cells (Bregs), and CD5+ and CD19+ B cells within the tumor microenvironment [6].

A primary objective in the successful management of patients with multiple sclerosis is determining how to optimize the therapeutic manipulation of the immune system without increasing the risk of malignancy, as well as establishing protocols for patients with multiple sclerosis who develop a concomitant malignancy.

In the context of the presented case, it remains possible that polymyositis developed independently or as a paraneoplastic phenomenon preceding the progression of melanoma with lymph node metastases.

The patient's clinical history demonstrates an overlap between demyelinating, systemic, and malignant diseases. A multidisciplinary treatment approach is essential for achieving clinical improvement in these complex patients.

5. Conclusions

The management of central and peripheral nervous system symptoms, initially diagnosed as multiple sclerosis, was successfully stabilized through treatment with methylprednisolone and azathioprine. In our clinical case, the melanoma was detected three years after the diagnosis of polymyositis. This suggests that Anti-TIF1-γ antibodies may serve as a predictive paraneoplastic marker for melanoma.

Declarations

Author Contributions

Conceptualization: V.R.; Methodology: V.R.; Formal analysis: V.R.; Investigation: V.R.; Writing—original draft: V.R.; Writing—review & editing: V.R.

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The data presented in this study are available on reasonable request from the corresponding author.

Conflicts of Interest

The authors declare no conflict of interest.

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Клиничен случай на пациент с множествена склероза, полимиозит и меланом. Съществува ли връзка между тях?

Резюме

Въведение: Представяме случай на пациент с последователно развитие на клинична симптоматика за множествена склероза, полимиозит и малигнен меланом. Представяне на случая: Полимиозитът се проявява две години след началото на множествената склероза. Клиничните признаци на меланом са установени след развитието на полимиозита. Лечението с кортикостероиди и имуносупресори оказва благоприятно въздействие върху клиничните прояви на множествената склероза при пациента. Не е изяснено дали е налице латентно развитие на меланома без клинична изява и дали миозитът се развива паралелно с неопластичния процес. Възможно е полимиозитът да се развие напълно независимо или да предхожда появата на меланом с метастази в лимфните възли. Заключение: Анамнезата на пациента съчетава клиничните характеристики на демиелинизиращо, системно и малигнено заболяване. Прилагането на комбинирано лечение е от решаващо значение за клиничното подобрение при такива пациенти.

Ключови думи: множествена склероза, полимиозит, меланом

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