

Anifrolumab as a therapeutic option in mixed connective tissue disease with autoimmune cytopenia: a case report and narrative review of the literature

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Abstract

Mixed connective tissue disease (MCTD) represents a complex autoimmune condition characterized by vasculopathy, fibrosis, and immune dysregulation. Autoimmune cytopenias are rare but clinically significant complications that increase morbidity and complicate management of these diseases. Current therapies, including glucocorticoids and conventional immunosuppressants, may be limited by intolerance or inadequate hematologic response. Type I interferon (IFN) signaling has emerged as a key pathogenic pathway, and its blockade represents a novel therapeutic approach. We describe a 39-year-old woman with MCTD and clinical features of systemic sclerosis, presenting with Raynaud's phenomenon, digital ischemic ulcers, esophageal involvement, and pulmonary arterial hypertension. Her disease course was complicated by progressive cytopenia, including leukopenia, severe lymphopenia, mild anemia, and thrombocytopenia. Azathioprine therapy led to worsening pancytopenia, necessitating discontinuation, while glucocorticoids provided only partial hematologic recovery. Subsequent treatment with mycophenolate was ineffective. Introduction of anifrolumab (300 mg IV every 4 weeks) resulted in hematologic improvement, with normalization of hemoglobin and stabilization of leukocyte and platelet counts, without infusion-related adverse events. The findings support type I IFN blockade as a promising therapeutic avenue in refractory hematologic manifestations of connective tissue disease, warranting further investigation in larger studies.

Key words: anifrolumab, systemic sclerosis, autoimmune cytopenias, mixed connective tissue disease.

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Introduction

Systemic connective tissue diseases encompass a spectrum of autoimmune conditions characterized by multi-organ involvement and immune-mediated inflammation and damage. Among them, systemic sclerosis (SSc) and mixed connective tissue disease (MCTD) represent clinically complex entities with overlapping features, yet distinct pathogenic and phenotypic patterns (1). SSc is classically defined by vasculopathy, immune dysregulation, and progressive fibrosis of the skin and internal organs (2). In contrast, MCTD, first described by Sharp *et al.* in 1972, is defined by high titers of anti-U1 ribonucleoprotein antibodies and mixed clinical manifestations resembling systemic lupus erythematosus (SLE), SSc, and polymyositis (2). Debate persists as to whether MCTD is a distinct disease entity or a subtype of SSc. Recent consensus criteria emphasize the coexistence of overlapping features with immunological specificity, reinforcing its relevance in clinical practice (3). Patients with MCTD having component of SSc often exhibit limited cutaneous disease, Raynaud's phenomenon, pulmonary arterial hypertension (PAH), and esophageal dysfunction (4). Importantly, hematologic abnormalities, particularly cytopenias, can complicate the disease course. Blood count abnormalities in connective tissue diseases (CTDs) are variable, ranging from

mild lymphopenia to severe immune-mediated thrombocytopenia. While mild cytopenias are common in SLE and MCTD, severe thrombocytopenia, though rare, carries significant prognostic implications, increasing morbidity and mortality due to bleeding risk (5). Pathogenesis is often linked to autoantibody-mediated peripheral destruction of blood elements, immune complex deposition, and bone marrow suppression from both the disease and its treatment (2). Thus, cytopenias represent both a diagnostic challenge and a therapeutic priority in MCTD/SSc.

Current treatment strategies for autoimmune cytopenias in CTDs primarily rely on immunosuppression. Glucocorticoids (GC) remain the first-line therapy, offering rapid but transient benefit and carrying long-term toxicity risks (2). Conventional immunosuppressants such as azathioprine and mycophenolate mofetil (MMF) are commonly used as steroid-sparing agents. Azathioprine has broad use across autoimmune diseases which is frequently limited by intolerance and cytopenia exacerbation. MMF has shown efficacy in SSc-associated interstitial lung disease and is increasingly employed in hematologic manifestations due to a more favorable safety profile (6). Despite these therapies, many patients develop refractory or relapsing cytopenias, necessitating exploration of novel treatment targets. In this context, type I interferon (IFN) signaling has emerged as a central pathogenic

pathway in autoimmune rheumatic diseases. Aberrant activation of IFN-regulated genes has been consistently demonstrated in SLE and, more recently, in SSc and MCTD (6). Type I IFNs contribute to autoantibody production, endothelial damage, and fibroblast activation, thereby bridging immune dysregulation with vasculopathy and fibrosis. Therapeutic blockade of IFN signaling has therefore become an area of active investigation. Anifrolumab, a monoclonal antibody targeting the type I IFN receptor (IFNAR1), has shown efficacy in SLE by reducing disease activity, sparing glucocorticoid use, and improving hematologic manifestations (7). Early-phase studies suggest potential benefits in SSc as well, particularly through attenuation of profibrotic signaling (6).

We report a case of MCTD with prevalent features of limited cutaneous SSc (lcSSc) with autoimmune cytopenia, characterized by intolerance to azathioprine, partial response to GC, and MMF. Ultimately, the patient was switched to anifrolumab with evidence of hematologic improvement. To our knowledge, this represents one of the first documented cases of IFNAR blockade in MCTD having features of SSc complicated by cytopenia. This case underscores the potential role of IFN-targeting therapy in rare, treatment-refractory hematologic manifestations of CTD.

Case Report

We report a case of a 39-year-old woman diagnosed with MCTD with prevalent features of lcSSc. She tested positive for anti-centromere antibodies, anti-Ro antibodies (119 UA/mL), anti-La antibodies, anti-RNP antibodies (77 UA/mL). Symptoms began in 2017 at the age of 31 with the onset of Raynaud's phenomenon, later complicated by digital ischemic ulcers, sclerodermic

esophageal involvement, and PAH. For the latter, she was started on macitentan and tadalafil. Concomitant therapy included pantoprazole (20 mg daily), hydroxychloroquine (200 mg daily), prednisone 5 mg daily and aspirin (100 mg daily).

Between September 2022 and March 2023, the patient developed progressive cytopenia, mainly characterized by leukopenia with severe lymphopenia, mild anemia, and thrombocytopenia. Complement analysis also revealed reduced C3 levels. During this period, hemoglobin (Hb) fluctuated between 10 and 11.9 g/dL, white blood cell (WBC) counts remained below 3000/ μ L, and platelets (PLT) ranged between 116 and 155 $\times 10^3$ / μ L. Coombs test was negative. Given the persistence of cytopenia, azathioprine (100 mg/day) was introduced in April 2023 as a steroid-sparing, immunosuppressive strategy. However, this therapy was associated with a further decline of Hb (falling below 10 g/dL) and lymphocytes (Lym) ($0.23 \times 10^3/\mu$ L). Within weeks, worsening cytopenia and lymphocytopenia ($0.19 \times 10^3/\mu$ L) prompted discontinuation of azathioprine. Following withdrawal of azathioprine, the patient restarted GC at a higher dose (prednisone equivalent, initial dose ~ 0.5 mg/kg/day with gradual tapering). This intervention led to partial hematologic recovery: WBC increased to $3.7 \times 10^3/\mu$ L and PLT improved to $177\text{--}195 \times 10^3/\text{mm}^3$, although Hb remained around 10–10.8 g/dL. In May 2024, MMF was introduced as an alternative immunosuppressant for the long-term control of autoimmune cytopenia. Over subsequent months, blood counts remained relatively stable.

Despite overall stabilization, blood count abnormalities persisted at suboptimal levels, with the occurrence of recurrent upper respiratory tract infection, leading to consideration of targeted therapy. On May 9, Hb declined modestly to 11.3 g/dL and PLT to $107 \times 10^3/\text{mm}^3$, WBC was $1.98 \times 10^3/\mu$ L (the absolute number of

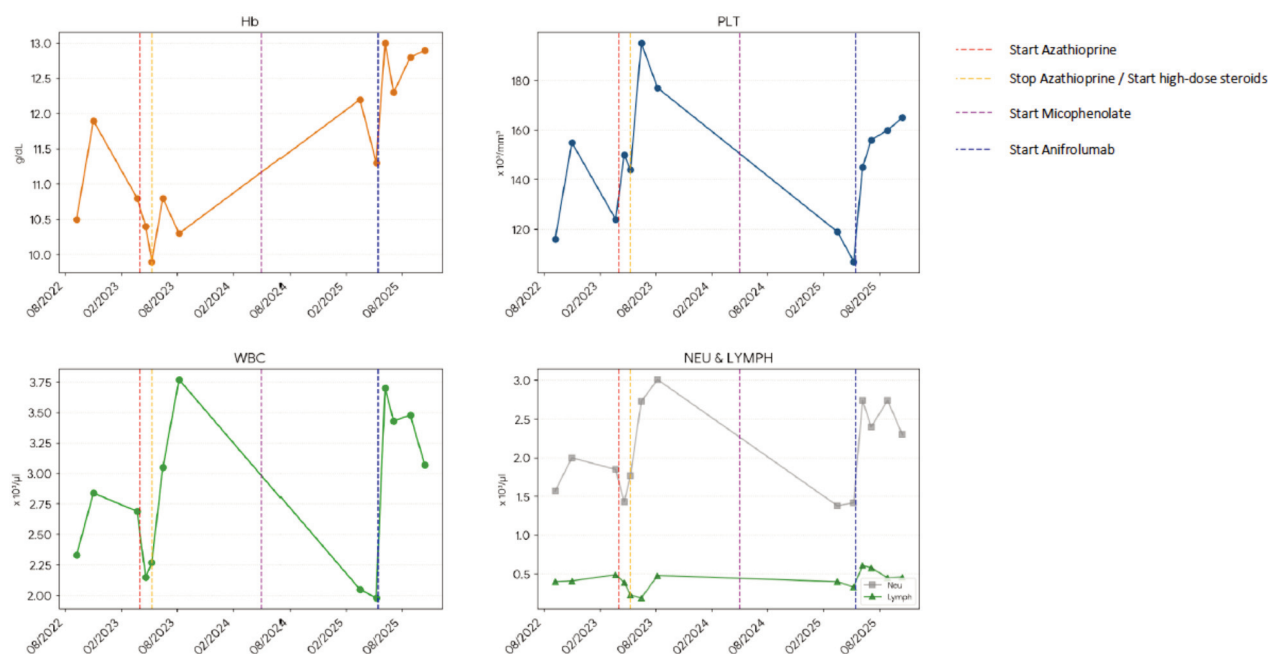


Figure 1. Trend of hemoglobin, white blood cells and platelets over time. Hb, hemoglobin; WBC, white blood cells; PLT, platelets; NEU, neutrophils; LYMPH, lymphocyte.

neutrophils was $1.42 \times 10^3/\mu\text{L}$, absolute Lym count was $0.33 \times 10^3/\mu\text{L}$. On May 15th, 2025, the patient started anifrolumab at a dose of 300 mg intravenously every 4 weeks, infused over 30 minutes in 100 mL of saline. By June 7, Hb rose to 13 g/dL, WBC to $3.7 \times 10^3/\mu\text{L}$, and PLT to $145 \times 10^3/\text{mm}^3$. Serial monitoring demonstrated fluctuating but progressively improving hematologic values (Figure 1). This course suggested a delayed but clinically meaningful hematologic stabilization under IFN blockade.

On October 15th, 2025, at the latest follow-up, the patient achieved partial hematologic recovery with Hb normalization (12.9 g/dL), leukocyte stabilization ($3.05 \times 10^3/\mu\text{L}$), and improved PLT count ($165 \times 10^3/\text{mm}^3$); systemic disease manifestations remained clinically stable, with no new vascular or gastrointestinal complications. Importantly, anifrolumab was well tolerated without infusion reactions or serious adverse events.

Discussion and Conclusions

Cytopenias are recognized complications of autoimmune CTDs, though they are less frequently reported in SSc compared to SLE or MCTD. The patient developed anemia, leukopenia, and thrombocytopenia in the context of MCTD with prevalent features of lcSSc. This is consistent with previous reports (8), in which autoimmune cytopenias often result from autoantibody-mediated destruction and marrow suppression, and may mimic features seen in primary immunodeficiencies. Importantly, cytopenias may complicate the management of the underlying disease activity. Our patient's low complement levels further support an immune-mediated mechanism, consistent with the hypothesis that humoral dysregulation contributes to hematologic involvement.

Initial treatment with azathioprine worsened cytopenia, paralleling reports of severe azathioprine-induced myelotoxicity described by Panda *et al.* (9). This underscores the drug's narrow therapeutic window and potential for life-threatening pancytopenia, highlighting the need for close hematologic monitoring. In contrast, GC therapy in our case achieved partial hematologic recovery, mirroring Seidel's description of GC as rapid but temporary immunosuppressants (8). Transition to MMF provided disease stabilization, which is consistent with its growing use in autoimmune cytopenias and CTD-associated organ involvement (6). However, cytopenias persisted at suboptimal levels, suggesting that standard immunosuppression may be insufficient for certain immune-mediated hematologic manifestations.

The decision to initiate anifrolumab reflects a growing understanding of type I IFNs in SSc and MCTD pathogenesis. Ciechomska and Skalska demonstrated that type I IFNs drive vascular permeability, fibroblast activation, and autoantibody production in SSc (10). Similarly, Wu and Assassi described how IFN blockade attenuates pro-inflammatory and fibrotic pathways, including TGF- β regulated gene expression (6). The improvement in leukocyte and PLT counts observed in our patient after anifrolumab initiation mirrors findings from phase I trials in SSc (6). Although anifrolumab is currently approved for SLE, its application in SSc is being formally evaluated through the DAISY phase 3 trial (11). Our case provides preliminary, real-world evidence for its potential hematologic benefits, particularly in refractory autoimmune cytopenia. This expands the scope of anifrolumab beyond fibrotic or cutaneous outcomes into hematologic stabilization. Autoimmune thrombocytopenia, as modeled by Katsman (12), highlights the complexity of PLT destruction and compensatory thrombopoiesis, which may explain the fluctuating PLT

counts in our patient. Furthermore, Budhram *et al.* noted that pulmonary hypertension is a frequent complication in CTD, particularly SSc, supporting the relevance of macitentan and tadalafil in our patient's management (13). O'Reilly emphasized the heterogeneity of SSc pathogenesis, where subsets of patients may respond to targeted interventions such as JAK inhibitors or B cell therapies (14). Similarly, our case suggests that IFN blockade may benefit a distinct subgroup of MCTD patients with cytopenia.

The key strength of this report lies in its novelty: to our knowledge, this is the first published case of anifrolumab used for autoimmune cytopenia in MCTD with prevalent features of SSc. The progressive hematologic improvement provides a rationale for further study of IFN blockade in hematologic manifestations of CTDs.

In conclusion, this clinical case aligns with the growing body of reports on the efficacy of anifrolumab in cytopenias. Despite intolerance to azathioprine and partial benefit from GC and mycophenolate, hematologic recovery was only achieved after IFN blockade. The observed stabilization of leukocyte and PLT counts underscores the pathogenic role of type I IFNs in CTD-related cytopenias. While limited by its single-patient nature, this report highlights anifrolumab as a promising therapeutic option and supports further evaluation of IFN-targeted strategies in larger studies, even in the context of the broad spectrum of systemic manifestations of autoimmune disease (15).

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