Mixed Connective Tissue Disease Presenting as Diabetic Ulcer in a 52 Year Old Female Patient: A Case Report

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ABSTRACT
Mixed connective tissue disease (MCTD) is a rare and complex autoimmune condition characterized by overlapping features of systemic lupus erythematosus (SLE), systemic sclerosis, polymyositis/dermatomyositis, and rheumatoid arthritis. Due to the varied clinical presentation and the absence of validated classification criteria, early diagnosis can be challenging, often leading to misclassification or delayed recognition. Here, we report a case of a 52-year-old female with MCTD and vasculitis, underscoring the importance of considering uncommon autoimmune etiologies in patients with non-healing ulcers. The patient presented with skin tightening, Raynaud's phenomenon, and chronic non-healing ulcers, initially attributed to diabetic complications. Diagnostic evaluation revealed high-titre anti-U1-RNP antibodies, confirming MCTD. Treatment with oral steroids, cyclophosphamide, and sildenafil led to significant clinical improvement, particularly in ulcer resolution. This case emphasizes the critical need for early intervention and a multidisciplinary approach in managing autoimmune vasculitis associated with MCTD to prevent progression and optimize patient outcomes.

1. Introduction

Mixed connective tissue disease (MCTD) is a rare autoimmune disorder characterized by overlapping features of systemic lupus erythematosus, systemic sclerosis, polymyositis/dermatomyositis, and rheumatoid arthritis. The presence of high-titer anti-U1-ribonucleoprotein (anti-U1-RNP) antibodies is a hallmark of MCTD, aiding in its diagnosis. Despite this serological marker, the clinical presentation can be highly variable, often mimicking other connective tissue diseases, which complicates early diagnosis.

MCTD predominantly affects women, with the peak incidence between 20 and 40 years of age. Vasculitis, while rare, is a serious complication occurring in approximately 10% of cases, leading to vascular manifestations such as Raynaud's phenomenon and digital ulcers. These symptoms can easily be misattributed to more common conditions like diabetes mellitus, contributing to diagnostic delays. Early recognition and intervention are essential to prevent severe complications such as ischemic ulcers and gangrene.

This case report presents a 52-year-old female with long-standing type 2 diabetes mellitus and non-healing ulcers, highlighting the diagnostic challenges in distinguishing diabetic complications from autoimmune vasculitis in MCTD. The case emphasizes the importance of clinical vigilance and a multidisciplinary approach to treatment.

2. Case Presentation

A 52-year-old female, with a known history of type 2 diabetes mellitus for four years, presented to the rheumatology outpatient department with complaints of progressive skin tightening over her face and right lower limb. She reported a three-month history of blackening and pain in the second and fifth toes of her left foot, without any associated fever, trauma, or discharge. Despite being under consistent treatment for diabetes, these non-healing ulcers were initially suspected to be a complication of her diabetic status.

On clinical examination, the patient was alert, oriented, and hemodynamically stable. Cardiovascular examination revealed normal heart sounds, with no murmurs detected. Respiratory examination was unremarkable, with normal vesicular breath sounds bilaterally. The abdomen was soft and non-tender, with no palpable organomegaly. Neurological examination showed no focal deficits.

Closer inspection revealed skin tightening in the infraorbital region, and an ulcer measuring 6 × 4 cm over the

left foot, filled with granulation tissue. Raynaud's phenomenon was clinically evident, with color changes in her fingers upon exposure to cold temperatures. No other cutaneous or musculoskeletal abnormalities were noted on initial assessment.

Given her diabetic background, a comprehensive evaluation of the ulcers was undertaken. Blood investigations revealed a hemoglobin level of 11.6 g/dL, an elevated erythrocyte sedimentation rate (ESR) of 199 mm/hour, and a C-reactive protein (CRP) of 4.8 mg/L. Renal function tests were within normal limits, with a creatinine level of 0.6 mg/dL. Liver function tests were normal, and serological markers for infectious etiologies, including HIV, HCV, and HBsAg, were negative. Creatine phosphokinase (CPK) was mildly elevated at 351 IU/L, raising suspicion for possible myositis or muscle inflammation.

Specific investigations were initiated to explore the possibility of autoimmune involvement. Antinuclear antibody (ANA) testing using immunofluorescence revealed a speckled pattern (4+) at a dilution of 1:320. Further immunoblot analysis confirmed the presence of U1-RNP antibodies with a strong positive result (3+), suggestive of mixed connective tissue disease (MCTD). Antineutrophil cytoplasmic antibodies (ANCA) were negative. Histopathological examination of biopsied tissue from the ulcer revealed chronic inflammatory changes consistent with vasculitis. Additionally, arterial Doppler ultrasonography of the right lower limb showed atheromatous plaques in the superficial femoral artery, causing approximately 60% stenosis.

The clinical picture, together with the serological findings, confirmed a diagnosis of MCTD complicated by autoimmune vasculitis. This diagnosis was established based on the Alarcón-Segovia criteria, which includes the presence of high-titer anti-U1-RNP antibodies and at least three clinical features, such as Raynaud's phenomenon, myositis, and synovitis. The presentation of vasculitis, although less common in MCTD, further complicated the clinical course and warranted aggressive immunosuppressive therapy.

The patient was promptly started on oral corticosteroids (prednisolone 30 mg daily) to control the underlying autoimmune inflammation. Sildenafil (50 mg three times daily) was introduced to manage Raynaud's phenomenon and promote vasodilation. Monthly intravenous pulse therapy with cyclophosphamide was initiated to target the vasculitic process. Over the subsequent months, the patient showed notable improvement. The ulcers on her toes regressed, and the severity of the skin tightening reduced significantly. Raynaud's symptoms also improved with the vasodilator therapy, and no new ischemic events were reported.

The patient continues to be managed with a multidisciplinary approach, involving regular follow-up with rheumatology, dermatology, and vascular surgery teams. Following six months of cyclophosphamide therapy, she was transitioned to maintenance therapy with mycophenolate mofetil (500 mg twice daily). Preventive strategies for digital ulcers, including lifestyle modifications and the avoidance of cold exposure, were emphasized as part of her ongoing care plan.

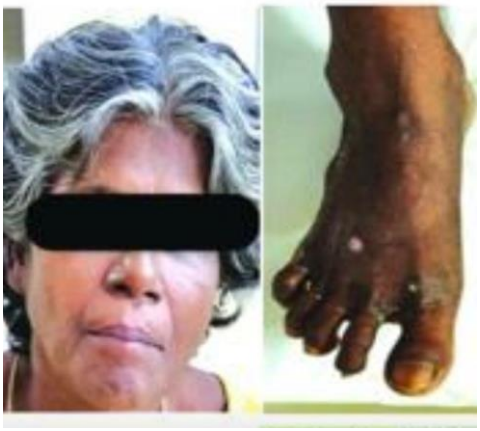

Figure 1 and 2: Clinical Findings

Figure 1 illustrates visible skin tightening in the right infraorbital region, a common feature of mixed connective tissue disease (MCTD), typically associated with systemic sclerosis-like manifestations. The patient demonstrates facial skin involvement, contributing to the clinical suspicion of MCTD with associated sclerodermatous features.

Figure 2 shows blackening of the second and fifth toes, along with skin tightening over the foot. These findings

are consistent with digital ischemia, likely secondary to vasculitis associated with MCTD. The blackened toes suggest advanced ischemic changes, indicative of compromised blood flow, further supporting the diagnosis of autoimmune vasculitis. The skin changes over the foot underscore the presence of systemic involvement, aligning with the patient's overall presentation of MCTD.

3. Discussion

Mixed connective tissue disease (MCTD) is a rare autoimmune disorder characterized by overlapping features of systemic lupus erythematosus (SLE), systemic sclerosis (SSc), polymyositis/dermatomyositis (PM/DM), and rheumatoid arthritis (RA). The presence of high-titer anti-U1-ribonucleoprotein (anti-U1-RNP) antibodies is a hallmark of MCTD, providing crucial serological evidence for its diagnosis (Ferrara et al., 2023) . However, the clinical variability and overlap with other connective tissue diseases (CTDs) complicate early identification, often leading to delays in diagnosis and treatment, as seen in this case.

This patient presented with non-healing ulcers initially attributed to her long-standing diabetes mellitus. However, further investigation revealed a positive anti-U1-RNP antibody test, confirming the diagnosis of MCTD. Non-healing ulcers in patients with diabetes are frequently attributed to peripheral arterial disease (PAD) or diabetic neuropathy, leading to potential misclassification (Pepmueller, 2016) . The challenge in this case lay in distinguishing diabetic ulcers from autoimmune vasculitis-related ulcers. Vasculitis, while rare in MCTD, is a significant complication, occurring in about 10% of cases. It can affect vessels of any size but predominantly targets small to medium vessels, leading to tissue ischemia, ulceration, and, if untreated, gangrene (Choi & Henkin, 2021) .

Raynaud's phenomenon (RP), which was positive in this patient, is a common early vascular manifestation in MCTD, appearing in up to 90% of patients (Sato et al., 2023) . RP often precedes other clinical features and serves as an early indicator of underlying connective tissue disease. Vasculopathy associated with RP in MCTD can lead to digital ulcers, ischemic complications, and potentially irreversible vascular damage if left untreated (Reiseter et al., 2017). Therefore, the presence of RP in patients with unexplained ulcers should raise suspicion for underlying autoimmune pathology, especially in those with additional systemic features like skin tightening or myositis.

The pathogenesis of vasculitis in MCTD is multifactorial, involving immune complex deposition, complement activation, and subsequent inflammation of the vessel walls. These immune-mediated processes result in damage to endothelial cells and increased vascular permeability, culminating in tissue ischemia and ulceration (Didier et al., 2018). Histopathological findings in this patient revealed chronic inflammatory changes consistent with vasculitis, further supporting the diagnosis.

Early diagnosis and prompt intervention are critical to prevent severe complications in MCTD-associated vasculitis. This patient's treatment regimen of corticosteroids and immunosuppressive therapy with cyclophosphamide led to significant clinical improvement. Steroids are the mainstay of treatment for controlling inflammation and autoimmune activity, while cyclophosphamide is often used in severe or refractory cases of vasculitis due to its potent immunosuppressive effects (Tikoo & Deshpande, 2022). Additionally, the use of vasodilators such as sildenafil in managing RP contributed to the resolution of digital ulcers by improving blood flow and preventing further ischemic injury (Hettema et al., 2007) .

While this case demonstrates a favorable outcome with timely treatment, the long-term management of MCTD requires a multidisciplinary approach. Autoimmune diseases like MCTD often involve multiple organ systems, necessitating collaboration between rheumatologists, dermatologists, and vascular surgeons. Close monitoring for disease progression and treatment-related complications, such as steroid-induced diabetes or cyclophosphamide-related toxicity, is crucial for optimizing patient outcomes (Tanaka et al., 2021) .

MCTD remains a diagnostic and therapeutic challenge due to its rarity and the overlap of its clinical features with other CTDs. The presence of anti-U1-RNP antibodies is essential for diagnosis, but clinicians should maintain a high index of suspicion for MCTD in patients presenting with RP, non-healing ulcers, and multisystem involvement (Ungprasert et al., 2016) . Furthermore, this case highlights the importance of differentiating between diabetic ulcers and vasculitis-related ulcers in patients with concurrent diabetes mellitus, emphasizing the need for comprehensive evaluation in complex cases.

This case report underscores the complexity of diagnosing MCTD, especially in patients with comorbidities like diabetes mellitus. It highlights the importance of recognizing autoimmune vasculitis as a potential cause of non-

healing ulcers, which can be misattributed to diabetic complications. Early diagnosis and aggressive immunosuppressive therapy can prevent severe complications, such as ischemic ulcers and gangrene, and improve outcomes (Sapkota & Al Khalili, 2024). Clinicians should maintain vigilance in considering a broad differential diagnosis when presented with atypical ulcerative lesions and systemic autoimmune symptoms. Multidisciplinary care is essential in managing MCTD's multisystem involvement and ensuring optimal long-term outcomes.

4. Conclusion

This case demonstrates the diagnostic challenges posed by overlapping comorbidities in MCTD, particularly diabetes. The patient's non-healing ulcers were initially misdiagnosed as diabetic in origin, delaying the recognition of vasculitis. Diagnosis was eventually confirmed through clinical, serological, and histopathological evaluations, emphasizing the need for comprehensive approaches in similar cases.

The patient's positive response to corticosteroids and cyclophosphamide underscores the value of early intervention in preventing vascular complications. This case reinforces the need for heightened suspicion in patients presenting with atypical ulcers, especially when systemic features like Raynaud's phenomenon or skin tightening are evident. MCTD remains challenging due to its varied manifestations and multisystem involvement. Early recognition and treatment are critical to improving outcomes. Continued multidisciplinary care and monitoring are vital for managing long-term complications, particularly vasculitis, and ensuring timely and effective treatment, even in patients with common comorbidities like diabetes.

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