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Primary Raynaud's Syndrome: An Intrinsic Autoimmune Disease that Is Amenable to Mycophenolate Mofetil

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Abstract

Raynaud's syndrome (RS) is a vasospastic disorder with potential hereditary predisposition and multiple triggering factors. After the exclusion of external stimuli and local disorders, autoimmunity presents a potential intrinsic trigger even in idiopathic RS. We present a 47-year-old woman with severe and progressive RS in both hands and toes for 2 years. She did not have: a) clinical and laboratory evidence of systemic autoimmune diseases; b) prior drug exposure; c) local digits disease. She could not tolerate vasodilators. Since she had elevated C-reactive protein, she received MMF as immunosuppressive therapy. Within 2 weeks, her symptoms improved, and she remained disease-free for 2 years. In conclusion, blocking intrinsic autoimmune triggers with MMF is a safe, practical, and effective short- and long-term treatment for refractory primary RS.

Keywords

Raynaud's Syndrome, Mycophenolate Mofetil, Treatment, Autoimmune, Idiopathic

1. Introduction

Raynaud's syndrome (RS) is caused by arteriolar spasms of the digits, leading to the following triad: a) decreased supply leading to white discoloration followed by b) deoxygenation that manifests as blue discoloration then c) relief of the spasms leading to blood return with reddish discoloration [1]. The episodes typically last minutes but can last several hours. The condition was first described by Auguste Raynaud in 1862 [2]. The majority of cases (80% - 90%) are primary (idiopathic),

while a secondary form has been described in patients with connective tissue diseases, viz. systemic lupus erythematosus, Sjogren disease, and scleroderma [1]. Its estimated prevalence is 4%, with the onset of primary one between 15 - 30 years with more frequency in females, while secondary one affects older patients [3]. Both forms are more common in cold climates. Idiopathic RS has been attributed to an "allergy" to cold in hereditary predisposed individuals, with 50% having a family history of RS [4]. In the present case report, we present a patient with an idiopathic form of RS in whom treatment with Mycophenolate mofetil (MMF) abolished her disorder, indicating intrinsic autoimmune triggers in its development and opening the stage for new management.

2. The Case

A 47-year-old woman presented with a 2-year history of recurrent fingers and toes numbness followed by pain and skin changes. The latter include pallor followed by dusky discoloration and then redness. The frequency of the attacks and their duration have increased with time despite the avoidance of cold exposure and the warming of hands and feet with gloves and stockings. She could not tolerate Calcium channel blockers for hypotension, and Hydroxychloroquine was ineffective after 2 months of use. The patient did not have other systemic complaints, significant medical illness, surgery, allergy, chronic intake of medications, alcohol, caffeine, and cigarette smoking. There was no family history of autoimmune diseases. On her initial physical examination, she was in pain and distress in her fingers and toes, which showed typical triple changes (**Figure 1**). Her body weight was 73 kg, her blood pressure was 110/70 mm Hg, and she was afebrile. Systemic examination did not show abnormality. Moreover, her extremities did not show ulcerations or permeant skin changes. She had normal peripheral leucocytic and platelet counts. Hemoglobin was normal. Serum sugar, urea, creatinine, electrolytes, and liver functions were normal. Lipid profile, TSH and arterial blood gas were normal. Urine routine and microscopy were normal. Normal albumin/creatinine ratio. Autoimmune testing showed: a) C-reactive protein was 40 (normal < 5), b) negative anti-CCP, c) negative ANCA, d) normal serum protein electrophoresis, e) negative ANA, anti-dsDNA, nRNP/Sm, Sm, SS-A, Ro-52, SS-B, Scl-70, PM-Scl 100, Jo-1, Centrosome B, Nucleosomes, Histones, Ribosomal protein, AMA-M2, and DSF70, f) normal serum complements 3 and 4, g) negative hepatitis B surface antigen and anti-hepatitis C antibodies, and h) negative anticardiolipin and anti-b2-glycoprotein antibodies and lupus anticoagulant. Ultrasound of the abdomen and pelvis did not show abnormality. Doppler ultrasound of limb arteries was normal. ECG was normal. Echocardiogram did not show valvular or myocardial abnormality. Moreover, microscopic nail fold capillary examination or "capillaroscopy" did not show abnormality. Hence, a diagnosis of persistent and recurrent idiopathic Raynaud's was established [5]. She was started on MMF at a dose of 1 g twice daily. Within 2 weeks, the attacks were abolished. Over 2 years of follow up, she did not have: a) relapse of RS, b) evolution of clinical, laboratory and serological manifestations of autoimmune disease, and c) abnormal CRP.

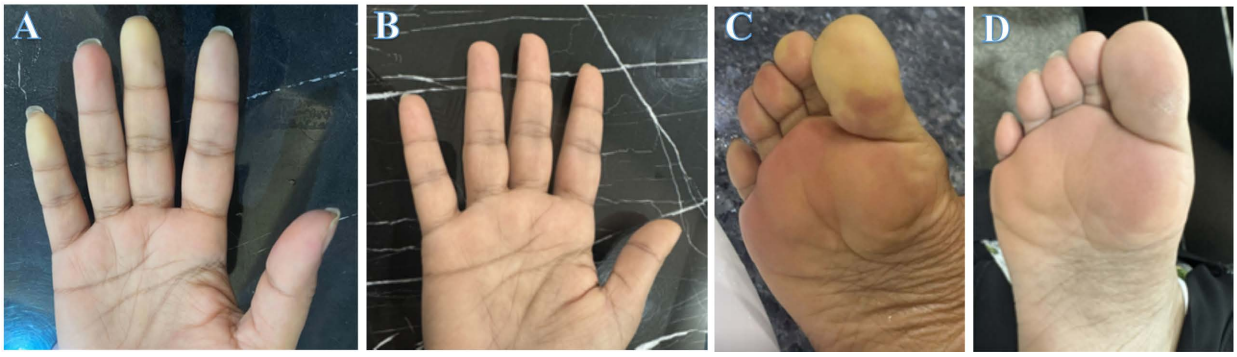

Figure 1. Photograph of the digital vascular compromise due to Raynaud's phenomenon in right hand (A) and toes in (C) with respective return to normal in (B) and (D) after MMF treatment.

3. Discussion

RS is a "two-hit phenomenon". It develops when triggers expose the hereditary predisposition and polymorphism in the *NOS*1 gene [4] [6]. The latter is evident from presentation in selected patients with a) autoimmune diseases, b) external factors and medication exposure, and c) familial prevalence in familial idiopathic RS. Triggers include a) cold and vibration exposure, b) digit injury, c) smoking, d) certain medications, viz. beta blockers, birth control pills, and brain-stimulants (caffeine, nicotine, and amphetamines), e) anxiety, and f) systemic autoimmune diseases [7]. In our patient, such triggers were not operative. Since she had high CRP, intrinsic autoimmunity was considered a potential trigger. Her disease was severe, frequently relapsing and progressive. Hence, we elected to treat her with MMF as a potent immunosuppressive agent. Fortunately, she responded within weeks and long-term prevention was evident up to 2 years. Irrespective of the underlying cause, RP has a significant negative impact on individuals' quality of life and can result in persistent digital ischemia, including ulceration and gangrene [8]. The current management of RS include a) prevention with avoidance of cold exposure, smoking and certain medications, b) treatment with calcium channel blockers, angiotensin-converting enzyme inhibitors, angiotensin II receptor antagonists, and selective serotonin receptor antagonists, phosphodiesterase-type 5 inhibitors (Sildenafil), prostanoids (Iloprost or Epoprostenol), and endothelin-receptor antagonist (Bosentan), and c) Botulinum toxin injections or endoscopic thoracic sympathectomy [9]. In our patient, intrinsic autoimmune was the etiology of her primary RS and our innovative management improved her disabling disorder.

4. Conclusion

Intrinsic autoimmune trigger/s should be considered in primary RS, and MMF is a safe, practical, and effective short- and long-term treatment.

Statement of Ethics

There was no harmful investigation or unethical new treatment conducted on this

patient that needed the approval of an Ethical Committee. It was a report on an approved drug for refractory and disabling disorder in a patient. Moreover, the patient accepted, in writing, investigations, and treatment of his disease as well as publication of the details of her medical case, including censored pictures of her phenomenon.

Authors' Contributions

Prof. Kamel El-Reshaid planned therapy with MMF. Moreover, he identified the case as primary and not secondary. He planned the investigations and management. He wrote the draft of the article and added the input of the second co-author. He is also the corresponding author of this article to the journal. Dr. Shaima Al-Bader is the dermatologist responsible for the patient and her follow-up. She was the one who consulted Prof. Kamel El-Reshaid about the new phenomenon. All the authors satisfied the ICMJE criteria for the author's contributions as they: 1) had substantial contributions to the conception, analysis, and interpretation of data. 2) Dr. Shaima provided data from patient follow-ups. 3) The 2 authors approve the final version to be published. 4) The 2 authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Availability of Data and Material The data and images of this study are openly available to Prof. Kamel El-Reshaid (corresponding author), and further enquiries can be directed to him.

Conflicts of Interest

The authors have no conflicts of interest to declare.

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