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Concurrent Dermatomyositis, Celiac Disease, and Dermatitis Herpetiformis in a Patient with a History of Morphea

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INTRODUCTION

Dermatomyositis is a type of idiopathic inflammatory myopathy (IIM), characterized by an autoimmune response primarily against skin and muscle tissues.[1,2] A variety of cutaneous manifestations can be seen in dermatomyositis, although Gottron's papules, Gottron's sign, and a heliotrope rash are considered pathognomonic.[1,3] Gottron's papules are flat-topped, red-to-purple papules and plaques involving the skin, metacarpophalangeal, and interphalangeal joints of the dorsal aspect of both hands. These lesions resolve, leaving areas of dyspigmentation, atrophy, and scarring. Gottron's papules should be differentiated from similar lesions, such as verruca vulgaris, lichen planus, knuckle pads, sarcoidosis, and erythema elevatum diutinum.[1,3] If a clinician initially suspects a Gottron's mimicker and treats with the standard treatment for that diagnosis (i.e., verruca without resolution), a biopsy should be considered.

Morphea, dermatomyositis, celiac disease, and dermatitis herpetiformis are autoimmune disorders that share similar pathogenesis and triggers. The diagnosis of multiple autoimmune syndrome (MAS) is given to patients with at least three autoimmune disorders with involvement of one or more autoimmune endocrine disorders.[4] We present a case describing a patient with morphea, dermatomyositis, and celiac disease/dermatitis herpetiformis, suggesting a constellation of autoimmune disorders not subclassified by the MAS classification and not reported in the literature.

CASE REPORT

A 40-year-old male with fibromyalgia was seen with a three-month history of "warts" on his right knuckles. The patient was treated initially with cryotherapy, but the lesions did not resolve. Upon evaluation, the clinician had an index of suspicion that the warts had a unique distribution and surprisingly had not responded to therapy.

Upon additional questioning, his past medical history was significant for a 10-year history of multifocal morphea. No additional information was known about his morphea history. He did not take any medications, and his family history was unremarkable for autoimmune conditions.

On physical exam, multiple inconspicuous areas of hyperkeratotic, lichenified, violaceous plaques were seen on the dorsal surface of the metacarpophalangeal and distal interphalangeal joints. There was a small, flat-topped, scaly papule with central atrophy located on his right 2nd metacarpophalangeal joint (Figure 1a). Nailbed findings were significant for dystrophic growth with "ragged" cuticles (Figure 1b). Of note, areas of hyper- and hypo-pigmented indurated plaques were noted on the trunk and upper extremities, consistent with morphea (Figure 1c).

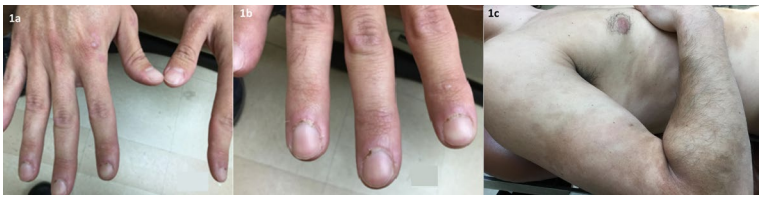

Figure 1. (a and b) Gottron's papules and dystrophic "ragged" cuticles of dermatomyositis. (c) Morphea: Hyper- and hypo-pigmented indurated plaques were noted on the trunk and upper extremities.

Due to the lack of resolution and the clinical appearance/distribution of the lesions, a scoop shave biopsy was performed. Histopathologic findings included acanthosis, basal layer vacuolization, and perivascular lymphocytic infiltrates with increased mucin deposition in the dermis. The biopsy was consistent with features of a connective tissue disease, and in this case, Gottron's papule. The patient was diagnosed with amyopathic dermatomyositis with mild myopathy initially thought to be secondary to his history of fibromyalgia. Creatine kinase and aldolase were normal; however, there was a mild elevation of AST, which can be seen in myopathy or myositis. Complete blood count and the rest of the comprehensive metabolic panel were within normal limits. Antinuclear antibodies were positive and extractable nuclear antigens were remarkable for antibodies against nuclear matrix protein 2 (NXP2).

The patient was referred for malignancy screening. Upon evaluation with esophagogastroduodenoscopy and small bowel follow-through, duodenal biopsy exhibited villous atrophy, crypt hyperplasia, and intraepithelial lymphocytic infiltrate. The diagnosis of celiac disease was confirmed after serologic studies were positive for tTG-IgA autoantibody. A gluten-free diet was recommended to the patient, and he was referred to a nutritionist. Dapsone therapy was discussed, but the patient preferred to try a gluten-free diet.

Five months later, he returned for evaluation of a new rash. The rash differed from the previous dermatoses in that the lesions were notably itchy. An erythematous papulovesicular eruption with excoriations on the knees, elbows, and buttock was observed (Figure 2). A 4-mm punch biopsy of the buttock was performed, which showed subepidermal vesicles and accumulation of neutrophils at the tips of dermal papillae with some features of folliculitis. Granular deposits of IgA within the dermal papillae and along the basement membrane were noted on direct immunofluorescence, consistent with dermatitis herpetiformis. The patient was not compliant with the gluten-free diet during that period. Treatment with dapsone was again offered but was declined by the patient. He preferred to recommit to the gluten-free diet and start topical clobetasol therapy and agreed for routine follow-up.

DISCUSSION

The diagnosis of Gottron's papules is important because it can assist in diagnosis of dermatomyositis and hasten a malignancy workup. The risk of malignancy in association with dermatomyositis is well known, with 20 - 25% of dermatomyositis cases having coexisting cancer, typically in an older population. Cancer of the breast, ovary, cervix, colon, stomach, and lung are common cancers associated with dermatomyositis.[3] As in our case, a diagnosis of Gottron's papules and subsequently

dermatomyositis led to a malignancy workup which resulted in the identification of celiac disease in the patient. Making the diagnosis of celiac disease was important to avoid its complications if untreated, including osteoporosis, enteropathy-associated intestinal T-cell lymphoma, collagenous sprue, ulcerative jejunoileitis, and non-Hodgkin lymphoma, among others.

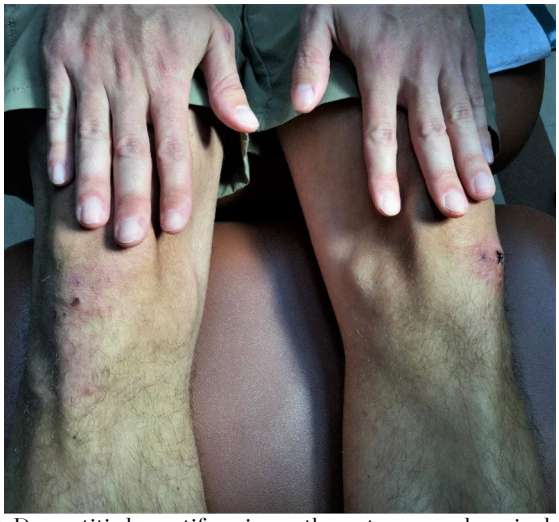

Figure 2. Dermatitis herpetiformis; erythematous papulovesicular eruption with excoriations predominantly on the knees.

The discovery of myositis-specific autoantibodies (MSA) has provided further stratification of dermatomyositis based on clinical findings and prognostic values. Autoantibodies associated with dermatomyositis include transcriptional intermediary factor 1γ (TIF-1γ), nucleosome-remodeling deacetylase complex (Mi-2), melanoma differentiation-associated gene 5 (MDA5), small ubiquitin-like modifier activating enzyme (SAE1/2), and NXP2.[1] Compared to adults, anti-NXP2 antibodies are seen more commonly in juvenile dermatomyositis.

NXP2 has been identified as an autoantibody target in a subset (1.6 - 30%) of adult dermatomyositis patients.[5-7] An association has been suggested between anti-NXP2 and an increased risk of malignancy.[8] However, a recent meta-analysis of 20 cohort studies found no association between anti-NXP2 and malignancy.[9] Autoantibodies against TIF-1γ are associated with cancer occurrence with a sensitivity of 78% and specificity of 89%.[8] The presence of anti-MDA5 autoantibodies is associated with a higher risk of developing interstitial lung disease,[10] and 50% of those with this autoantibody will die from respiratory failure in the first six months following diagnosis.[11] The presence of SAE1/2 autoantibodies is associated clinically with severe dysphagia.[12] Lastly, patients with anti-Mi-2 antibodies may have a better response to immunosuppressive treatment.[13]

Characteristic muscle biopsy findings in dermatomyositis are perivascular and perimysial infiltration of CD4 T-cells and B-cells, suggesting a production of autoantibodies involved in the pathogenesis. Dermatomyositis likely develops in patients who are predisposed genetically and commonly is triggered by factors such as infection, medication, radiation, or malignancy.[1,2]

Morphea is an autoimmune connective tissue disorder characterized by inflammation and fibrosis of the skin and soft tissues.[14,15] Patients with generalized morphea rarely may involve muscle and joints, causing myalgia and arthritis. The pathogenesis of morphea is unknown, but the combination of vascular dysfunction and autoimmunity may result in an abnormal recruitment of inflammatory cells and an increase production of collagen. Morphea, like dermatomyositis, commonly develops after an extrinsic insult such as infection, trauma, radiation, or medication.

Celiac disease is a multifactorial condition caused by an abnormal immune response to gluten at the level of the intestinal mucosa.[16] Celiac disease is associated with HLA-DQ2 and/or HLA-DQ8 though these allele associations alone are not sufficient for the diagnosis, given that 30% to 40% of the general population are carriers for at least one of these alleles. Exposure to gliadin in genetically predisposed individuals results in the production of IgA autoantibodies that target tissue transglutaminase 1(tTG).

Dermatitis herpetiformis is associated with celiac disease and is thought to be due to cross reaction of anti-tTG IgA against tissue transglutaminase 3 found in the dermis, resulting in the deposition of IgA in the dermal papilla and the accumulation of neutrophils and eosinophils.[17] Environmental factors play a major role in the development of celiac disease such as breastfeeding, gastrointestinal infections, antibiotics, and proton-pump inhibitors.

There were no known previously published reports of dermatomyositis, celiac disease, and dermatitis herpetiformis concurrently in a patient with a history of morphea. Celiac disease was associated with juvenile dermatomyositis and cases of celiac disease in adult-onset dermatomyositis have been emerging.[18-20] Similarly, a case report described a patient with morphea and celiac disease.[21] The common pathogenesis, triggering factors, and genetic background associated with morphea, dermatomyositis, celiac disease, and dermatitis herpetiformis may suggest a common etiology consisting of both genetic and autoimmune components.

Individuals with at least three autoimmune diseases fall under the diagnosis of multiple autoimmune syndrome.[4] MAS can be classified into three types determined by the cluster of autoimmune conditions most commonly seen together. This classification requires the involvement of at least one endocrine gland dysfunction. The autoimmune nature of the diseases in our case, the common triggers associated with disease onset, and the lack of glandular involvement in our patient may suggest an autoimmune syndrome that has not been reported.

CONCLUSIONS

In conclusion, this unique patient with multiple confirmed autoimmune diagnoses may suggest an autoimmune constellation not reported in the literature and not compliant with the MAS classification. Three major points of consideration in this case are: 1) a clinician should have a high index of suspicion to biopsy a lesion that does not respond to standard therapy or clinically fit the rendered diagnosis; 2) when evaluating a patient with an autoimmune disease, additional autoimmune diseases should be considered; and 3) while clusters of autoimmune disorders have been reported, the nature and variety of autoimmune conditions may lead to new associations and potential for therapeutic targets.

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