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Authors
Garber, Caren
Rosmarin, David
Nguyen, Bichchau
et al.

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Cutaneous mucinosis in a patient taking ustekinumab for palmoplantar psoriasis

Caren Garber BA,[1,2] David Rosmarin MD,[1] Bichchau Nguyen MD MPH,[1] Mahmoud Goodarzi MD,[3,4] Shweta Shinagare MD,[4] Chad Jessup MD,[1] Abdulaziz Madani MD,[1] Shiu-Chung Au MD,[1] and Afnan Hasanain MD[1]

Affiliations: [1]Department of Dermatology, Tufts Medical Center, Boston, MA. [2]Tufts University School of Medicine, Boston, MA. [3]Miraca Life Sciences, Newton, MA. [4]Department of Pathology, Tufts Medical Center, Boston, MA

*Corresponding Author: Caren Garber, B.A. Department of Dermatology, Tufts Medical Center. E*mail: caren.garber@tufts.edu

Abstract

Discrete papular lichen myxedematosus (DPLM), a subset of localized lichen myxedematosus, is a rare cutaneous mucinosis of unknown etiology. We report a case of a 57-year-old woman with palmoplantar psoriasis who developed DPLM 8 weeks after adding ustekinumab to a long-term course of methotrexate. The patient had previously failed 2 prior tumor necrosis factor (TNF) inhibitors, adalimumab and etanercept. This case demonstrates an association between TNF inhibitor and ustekinumab use in a psoriasis patient and localized lichen myxedematosus for the second time in the literature. The presented case is of interest because of the rare diagnosis of DPLM, especially in association with the start of the anti-IL 12/23 agent ustekinumab. The appearance of DPLM in this setting suggests a possible etiology for the disease.

Keywords: Cutaneous mucinosis, lichen myxedematosus, ustekinumab, psoriasis, TNF inhibitor, biologic

Introduction

Lichen myxedematosus (LM, often referred to as papular mucinosis) is a cutaneous mucinosis of unknown etiology [1]. According to an updated classification scheme summarized in **Table 1**, LM is divided into three clinicopathologic subsets: (1) a generalized form (scleromyxedema) with a progressive, sometimes lethal, systemic course, (2) a localized form limited to the skin, and (3) an atypical form for those cases not meeting the criteria for the systemic or localized forms [2].

Localized LM presents as firm, waxy, often asymptomatic flesh-colored or erythematous papules, nodules, or plaques localized to few anatomical locations often in a symmetrical distribution [1]. Histological examination of localized LM characteristically reveals dermal mucin deposition with fibroblast proliferation but without fibrosis. Patients lack signs of a monoclonal gammopathy or thyroid disease [1].

Localized LM is further subdivided into 4 categories: (1) discrete papular LM (DPLM) occurring anywhere on the body, (2) acral persistent papular mucinosis (APPM) occurring only on acral surfaces, (3) papular mucinosis of infancy, the pediatric form of DPLM or APPM, and (4) a nodular form [2]. DPLM is rare with only 10 cases in the English literature reported prior to 2005, two of which have occurred in patients with a history of plaque psoriasis [3]. We present a unique case of a 57-year-old woman with psoriasis who developed DPLM in association with systemic immunotherapy for palmoplantar psoriasis (PPP).

Case Synopsis

A 57-year-old woman with PPP presented with flesh colored, non-pruritic, non-tender, dome-shaped papules on the upper cutaneous lip that appeared 8 weeks after adding ustekinumab (45mg every 12 weeks, later transitioned to 90mg every 12 weeks) to a long-term course of methotrexate (MTX, 20mg weekly). Subsequent visits were notable for multiple additional similar 2-13mm papules on the upper lip and superior aspect of the left external auditory canal (**Figure 1**).

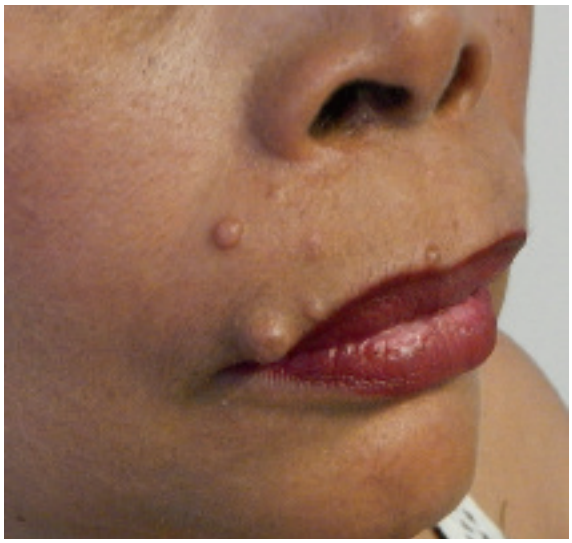

Figure 1. *DPLM on upper cutaneous lip*

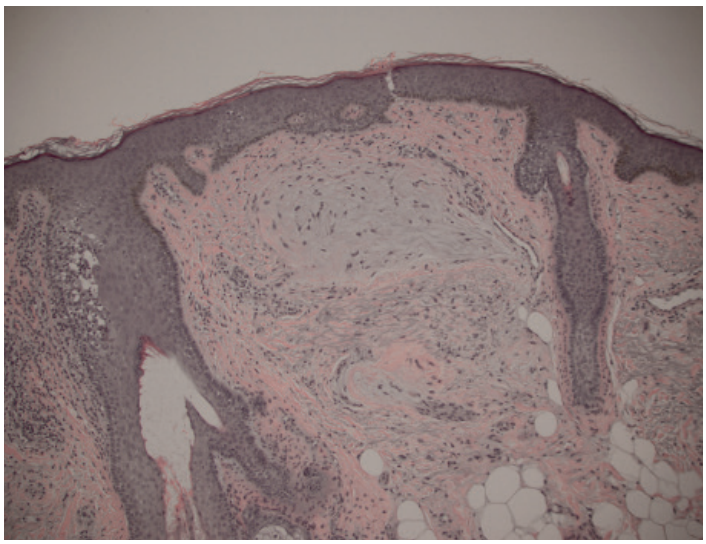

Figure 2. *Hematoxylin and Eosin Stain 10x*

The patient had previously failed a 4-month trial of adalimumab and a 1.5-year trial of etanercept with MTX, owing to lack of efficacy and loss of efficacy, respectively. She had discontinued etanercept 4 weeks prior to starting ustekinumab but had continued MTX in the interim. The patient's medical history was significant for major depressive disorder, hypertension, hyperlipidemia, diabetes, asthma, and PPP. She had no history of thyroid disease.

The liver function tests, basic metabolic panel, thyroid stimulating hormone, 1,25-dihydroxyvitamin D, human immunodeficiency virus, rapid plasma reagin, hepatitis B, hepatitis C, and antinuclear antibody were negative or within normal limits. Serum protein electrophoresis revealed mild increase in serum betaglobulin (1.12 g/dL, upper limit of normal was 1.10 g/dL) but immunofixation identified no abnormal bands or evidence of monoclonality of immunoglobulins. Urine protein electrophoresis was unremarkable. Her erythrocyte sedimentation rate was elevated at 81mm/hr. Despite her normal liver function tests, the patient's hepatologist recommended a right upper quadrant ultrasound given that her cumulative dose of MTX was >3 grams.

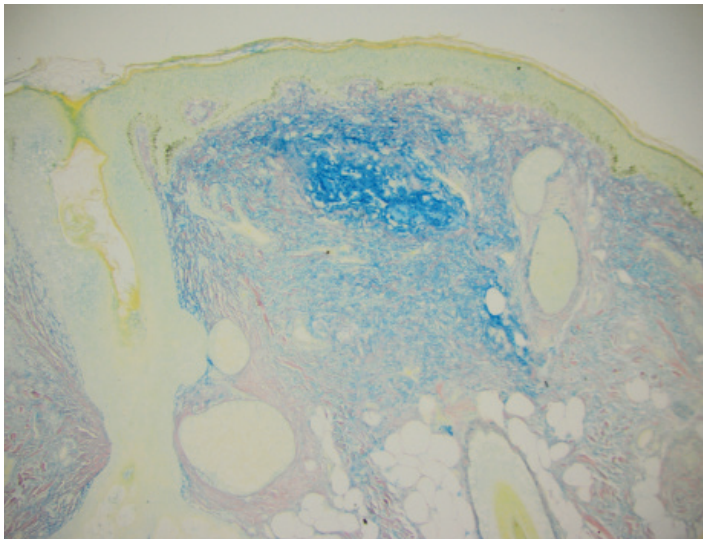

Figure 3. *Colloidal Iron Stain 10x*

The ultrasound revealed fatty infiltration of the liver, which was confirmed on a subsequent liver biopsy.

A total of nine biopsies of the patient's lesions each showed increased dermal mucin (confirmed by Alcian blue stain) with stellate fibroblasts and increased ectatic vessels (Figures 2 and 3). Objectively, angiomyxoma was favored on histology. However, given the clinical history of multiple lesions

Table 1. *Criteria for Diagnosing Lichen Myxedematosus*

Scleromyxedema	Localized Lichen Myxedematosus
Widespread papular/sclerodermoid outbreak	Localized papular/nodular outbreak
Mucin deposition, fibroblast proliferation, fibrosis	Mucin deposition, fibroblast proliferation
Monoclonal gammopathy	No monoclonal gammopathy
No thyroid disorder	No thyroid disorder

in the absence of Carney complex, the lack of well-defined multinodularity, and a weak CD34 staining, a clinicopathologic diagnosis of DPLM was made.

Based on reports [4] of topical tacrolimus 0.1% success in mucinosis, this medication was tried without success on our patient. The larger lesions were excised without complications or recurrence. Ustekinumab was continued, despite its possible relation to the DPLM, as the patient felt its benefit outweighed the risk of developing additional DPLM lesions. Just prior to publication, approximately 2 years after starting ustekinumab, the patient was diagnosed with metastatic cancer with unknown primary. She was placed on hospice care and the decision was made to discontinue ustekinumab given its potential to make the cancer more aggressive.

Case Discussion

Dermal mucin is produced in small amounts by fibroblasts in normal situations and consists predominantly of the glycosaminoglycan hyaluronic acid (HA) [5]. Although the reason for mucin overproduction in DPLM is uncertain, immunoglobulins and cytokines, such as interleukin-1 (IL-1), tumor necrosis factors (TNF), transforming growth factor-β (TGF-β), or interferon-γ (IFN-γ) have been implicated in the stimulation of HA synthesis by dermal fibroblasts or dermal dendrocytes [6,7]. Psoriasis is characterized by an upregulation of similar proinflammatory cytokines that could theoretically stimulate dermal fibroblasts to produce excess HA, leading to DPLM, though this has not yet been validated in the literature [6].

Localized LM in association with systemic psoriasis therapy is especially rare (**Table 2**). To date, one study in the English literature reports the development of multiple focal cutaneous mucinosis, a term which generally corresponds to localized LM [1], after systemic immunotherapy for plaque psoriasis [6]. The patient's treatment course was remarkably similar to our patient's: she presented with the lesions after 8 weeks of treatment with ustekinumab and MTX and had previously failed multiple TNF inhibitors [6]. Given the brevity of her course of ustekinumab and MTX, the authors attributed the mucin deposition to the 1.5 years of exposure to TNF inhibitors [6]. An additional case in the French literature also suggests a possible role of TNF inhibitors in multiple lesions of focal cutaneous mucinosis [8].

It has been proposed that TNF inhibitors may indirectly activate fibroblastic mucin production by decreasing the amount of active TNF, which in turn allows skin dendritic cells to produce elevated amounts of IFN-α, which likely activates lymphocytes thereby stimulating fibroblasts to produce mucin [6]. Another theory is that with TNF inhibition, there is less of an inhibitory effect of TNF on dermal dendrocytes, which some postulate are a source of excess HA production [6,7].

Our patient's concomitant use of MTX may have contributed to the development of DPLM. One report describes the eruption of DPLM in a patient with a 12-year history of psoriatic erythroderma treated with oral steroids followed by MTX, then mercaptopurine [9]. However, the outbreak occurred while on mercaptopurine, not MTX [9].

Despite our inability to prove causation, the striking similarity between our case and that of Lesiak [6] leads us to question whether there is a possible role for ustekinumab in the formation of cutaneous mucinosis. To our knowledge, no additional cases have been reported linking ustekinumab

Table 2. *Patients with Localized LM Associated with Systemic Psoriasis Therapy*

Citation	Patient Age	Patient Sex	Type of Psoriasis	Treatment	Duration of Treatment Prior to Appearance of Lesions
Lesiak, et al. [6]	66	F	Plaque	Ustekinumab and MTX	8 weeks
Duparc, et al. [8]	44	M	Plaque	Etanercept and infliximab (separately)	Not documented; lesions appeared on etanercept and worsened with infliximab
Current Case	57	F	Palmo-plantar	Ustekinumab and MTX	8 weeks

Table 3. *Cancers Reportedly Associated with Localized LM*

Type of Cancer Reportedly Associated with Localized LM[a]
Breast adenocarcinoma [14]
Colon adenocarcinoma [14]
Extramedullary cutaneous plasmacytoma [15]
Gastric adenocarcinoma [16]
Lung adenocarcinoma [13]
Mucinous ovarian carcinoma [17]
Multiple myeloma [18]
Mycosis fungoides [19]
Nasopharyngeal carcinoma [20]
Nephroblastoma [21]
Pancreatic carcinoma [16]
Pseudomucinous cystadenoma of the ovary [22]
Squamous cell carcinoma [23]

[a]*We reviewed the English literature regarding reported cancers associated with localized LM. We excluded genodermatoses such as Birt-Hogg-Dubé from our search results as our patient was not suspected to have a genodermatosis.*

or the combination of ustekinumab and MTX to DPLM. Theoretically, the inhibition of IL12/23 by ustekinumab could, either directly or indirectly, trigger increased mucin production by dermal fibroblasts or dermal dendrocytes. The association between type 2 T-helper (Th2) cells, their downstream cytokines, and increased mucin production has been well documented, especially in upper airway pathology [10]. TNF inhibitors and anti-IL12/23 agents alter the Th1/Th2 balance [11]. Presumably, this could explain an increased mucin production and tendency towards cutaneous mucinosis with the use of these medications in psoriasis patients. This hypothesis warrants further investigation now that multiple cases have brought it into question.

As is summarized in **Table 3**, the association between focal cutaneous mucinosis and internal malignancies such as gastric, pancreatic, lung, and ovarian neoplasms has been reported in the past [12,13]. In our patient, it is unclear which process presented first. That is, it is possible that the tumor growth factors from her internal malignancy stimulated fibroblasts to produce mucin, resulting in cutaneous mucinosis [5]. However, it is also possible that the systemic immunosuppressants used to treat her PPP provided the stimulus for the cutaneous mucinosis and the neoplastic process. Regardless, this possible association and its prognostic implications further mandate that we define the relationship between TNF inhibitors, ustekinumab, and DPLM.

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