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SHORT COMMUNICATION

Hyaluronidase in the treatment of papular dermal mucinosis: First case reported in North America

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Abstract: Papular mucinosis is an uncommon, idiopathic disorder characterized by dermal mucin deposition and increased collagen in the skin and internal organs. Its clinical presentation is characterized by dome-shaped, flesh colored papules that are closely spaced or linearly arranged. Papular mucinosis has been individually associated with several entities that include discoid lupus erythematosus, systemic lupus erythematosus and monoclonal gammopathy of undetermined significance. We encountered a 60-year-old woman with papular mucinosis in the setting of three concurrent disorders: discoid lupus erythematous, systemic lupus erythematosus and IgG paraproteinemia. Furthermore, we have reported the first case in North America of papular mucinosis being successfully treated with intralesional hyaluronidase.

Keywords: papular mucinosis; discoid lupus erythematosus; systemic lupus erythematosus; monoclonal gammopathy; paraproteinemia; hyaluronidase

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Introduction

Papular mucinosis is a relatively uncommon disease characterized by diffuse papular eruption due to mucin deposition in the skin[1–6]. This disease most commonly affects middle-aged adults and has been associated with monoclonal gammopathy, systemic lupus erythematosus and discoid lupus, independently[2–14]. The report presents the first case of papular mucinosis in the setting of three concurrent disorders: IgG paraproteinemia, systemic lupus erythematosus and discoid lupus erythematosus. Additionally, we also report the first case in North America of papular mucinosis being successfully treated with intralesional hyaluronidase.

Case presentation

A 60-year-old woman was evaluated in the clinic for a five-month history of pruritic, eruptive lesions on the chest, back, and legs. She also reported a several-year history of localized hair loss on the scalp, which had not been previously evaluated. Physical exam revealed multiple smooth, dome-shaped and flesh-colored 2–3 mm papules on the chest, back, upper arms, abdomen, bilateral lower extremities and feet (**Figures 1** and **2**). Additionally, a 4-cm pink, painful plaque with overlying crust was noted on the right parietal scalp (**Figure 3**). Differential diagnosis for these findings included lichen myxedematosus, eruptive seborrheic keratoses and discoid lupus of the scalp.

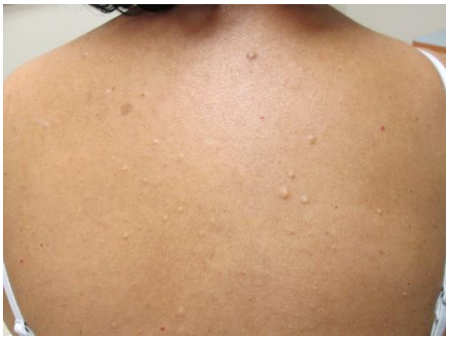

Figure 1. Multiple, smooth, flesh-colored papules on back

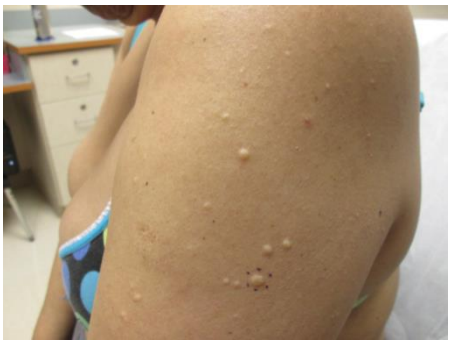

Figure 2. Multiple, smooth, flesh-colored papules on left arm

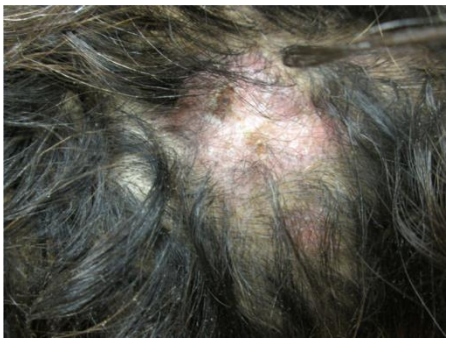

Figure 3. Erythematous plaque with overlying crust on right parietal scalp

Biopsy of a dome-shaped papule on the left forearm revealed focal deposition of mucin within the reticular dermis, consistent with focal cutaneous mucinosis. Biopsy of the plaque from right parietal scalp revealed vacuolar interface changes at the dermal-epidermal junction, with focal thickening of the basement membrane, as well as a superficial and deep perivascular infiltrate of lymphocytes with increased mucin within the dermis. Direct immunofluorescence revealed granular staining along the dermal-epidermal junction with the use of IgG, IgM, and complement 3 (C3). These findings were consistent with discoid lupus.

Routine laboratory investigations were noted for pancytopenia with white blood cell count of 4.5×10^9/L, hemoglobin of 11.9 gm/dL, and platelet count of 130×10^9/L. Urinalysis was unremarkable. Serum protein electrophoresis revealed a distinct M-band (1.5 g/dL) in the gamma region, and urine protein electrophoresis was unremarkable. Levels of serum immunoglobulins were elevated with IgG of 1746 mg/dL, IgA of 581 mg/dL, kappa light chain of 7.00 mg/dL, and lambda light chain of 4.26 mg/dL. Bone marrow biopsy was also performed and revealed 10% polyclonal plasma cells. These findings were interpreted as monoclonal gammopathy of undetermined significance (MGUS). In addition to the above, further follow-up confirmed the diagnosis of systemic lupus erythematosus. Positive anti-nuclear antibody titer was observed at 1:2560 in a speckled pattern, as well as positive anti-smooth muscle antibody, positive anti-ribonucleoprotein antibody and a slightly decreased complement/C3 level of 80 mg/dL.

Based on clinical examination, histopathology, serum protein electrophoresis, bone marrow biopsy findings and antibody titers, a final diagnosis of concomitant papular mucinosis associated with (MGUS), discoid lupus and systemic lupus erythematosus was performed. Hydroxychloroquine was initiated at a dose of 200 mg via oral administration twice daily, and topical clobetasol ointment was prescribed for the papular eruption and the affected scalp for management of both papular mucinosis and discoid lupus erythematosus. The patient reported no significant improvement of papular mucinosis lesions with this regimen. In the follow up session, selected lesions of papular mucinosis were treated with 0.35 mL of intralesional hyaluronidase (Hylenex®). The patient was observed to have visible improvement in papular lesions within 48 h after the injection. Unfortunately, she declined to do repeated biopsies and follow-up was not done.

Discussion

Papular mucinosis is an uncommon, idiopathic disorder characterized by dermal mucin deposition with increased collagen in the skin and internal organs[1–6]. Also known as discrete papular lichen myxedematosus, there are four subtypes of this entity that include discrete papular mucinosis, acral mucinosis, cutaneous mucinosis of infancy, and nodular mucinosis. Our patient presented with the discrete papular form of mucinosis. This rare condition predominantly affects middle-aged adults between 30–80 years old with no predilection for race or gender[1,2]. Significant morbidity and mortality may be seen with ex-

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tracutaneous manifestations involving the cardiac, gastrointestinal, pulmonary and central nervous systems[1].

Clinical presentation is characterized by widespread dome-shaped, flesh colored papules that are closely spaced or linearly arranged. Classically, papules are small, waxy and symmetric in shape with lesions, most commonly affecting the face, neck, distal forearms and hands. Lichenification may be noted as well[1,2]. Although affected areas are not pruritic, koebnerization in areas of excoriation is widely reported[2]. In some cases, skin may appear shiny as in scleroderma; however, the lack of telangiectasia and cutaneous calcinosis preclude this diagnosis. Diffuse involvement of the face may also produce characteristic leonine facies[1]. Definitive diagnosis of papular mucinosis is largely based on histopathologic findings, as clinical presentation may be non-specific. Biopsy results show diffuse deposition of mucin in the upper and mid-reticular dermis, increased collagen deposition, and marked proliferation of irregularly arranged fibroblasts. A perivascular lymphoplasmacytic infiltrate may be noted, as well[1,10,13].

The etiology of papular mucinosis is unknown. It is theorized to be primarily due to immunologic dysregulation, in which cytokines and immunoglobulins lead to an increase in glycosaminoglycan synthesis by fibroblasts. In fact, it has been shown that dermal fibroblasts in patients with papular mucinosis produce a higher amount of hyaluronic acid, a glycosaminoglycan found in mucin, as compared with regular fibroblasts[1]. Serum from patients with papular mucinosis has been found to stimulate *in vitro* fibroblast proliferation. In contrast, purified immunoglobulin from paraprotein-containing serum does not contribute to fibroblast proliferation. Therefore, it is likely that non-paraprotein factors contribute to the pathogenesis of papular mucinosis, causing increased fibroblast production and subsequent hyaluronic acid production[1]. Furthermore, the association between papular mucinosis and other immunologic disorders such as rheumatoid arthritis, hashimoto thyroiditis, HIV and acquired immunodeficiency syndrome suggests that aberrancy in immune regulation may indeed play a key role in the pathogenesis[15-21].

Association with these immunologic conditions further highlights the relationship between papular mucinosis and immune dysregulation. There are several reports of papular mucinosis in the setting of monoclonal gammopathy with paraproteinemia, as in our patient, most commonly of IgG with lambda light chains[3,14]. Paraproteinemia is present in up to 83% of these patients. Our patient's MGUS was confirmed via serum protein electrophoresis and bone marrow biopsy. Other paraproteinemias include IgM or IgA levels and, occasionally, kappa light chains[2]. Interestingly, paraprotein levels do not correlate with disease severity and patients rarely progress to develop multiple myeloma[2,3]. However, Waldenstrom's Macroglobulinemia, Hodgkin's and non-Hodgkin's lymphomas have all been associated with the disease[1].

Papular mucinosis also has a well-known association with discoid lupus erythematosus (DLE) and systemic lupus erythematosus (SLE)[4–13]. Up to 80% of cases of papular mucinosis may be associated with SLE. Further, papular mucinosis has been reported as the first clinical clue in some cases of SLE[4,5]. Gold *et al.* was the first to describe two patients with an unusual papular eruption associated with lupus erythematosus. In this report, histopathologic evaluation of suspicious lesions showed diffuse deposits of dermal mucin with scant perivascular lymphocytic infiltrate, which is characteristic of papular mucinosis[10]. The epidermal changes that are seen in SLE or DLE were lacking[10]. Similarly, though our patient had SLE and DLE in association with papular mucinosis, histopathologic findings of papular lesions failed to show epidermal or inflammatory infiltrate suggestive of SLE or DLE.

Treatment options for papular mucinosis are varied and primarily anecdotal. Melphalan, antimalarials, systemic steroids, intravenous immunoglobulins and plasmapheresis have all been reported used. While this disease is chronic and slowly progressive, spontaneous resolution has been reported as well[1,2]. Perhaps most notable in the case presented here was our patient's rapid response to treatment with intralesional hyaluronidase. Hyaluronidase is a naturally occurring enzyme that hydrolyzes hyaluronic acid, a glycosaminoglycan present in mucin. It is most commonly used as an adjunct therapy to facilitate absorption of other injectable drugs by increasing tissue permeability[22]. Our patient was specifically treated with a purified preparation of hyaluronidase derived from recombinant human deoxyribonucleic acid (DNA) called Hylenex®. The method of action of intralesional hyaluronidase in these cases deserves further investigation, though it has been used as a successful adjuvant therapy in the treatment of various epithelial and mesenchymal cell-driven processes including dermatofibrosarcoma protuberans prior to excision, bladder cancer, breast cancer and Kaposi's sarcoma[23–26]. Our success in this case further suggests a role for hyaluronidase in the treatment of papular mucinosis.

Two other reports of successful treatment of papular mucinosis with intralesional hyaluronidase have been described[9]. While its use for papular mucinosis has

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not been reported since 1995, more recent success is well-documented in the treatment of scleroderma and pretibial myxedema. Adverse effects of intralesional hyaluronidase are uncommon, and intralesional injections can take effect immediately for up to 48 hours, as seen in our case[22]. Given the chronic nature of papular mucinosis, intralesional hyaluronidase may have a therapeutic role in the treatment and prevention of the progressive disease and deserves further investigation.

Conclusion

We presented a unique case of papular mucinosis diagnosed concomitantly with three other entities: monoclonal gammopathy, discoid lupus and systemic lupus erythematosus. The patient's condition proved refractory to conventional treatment methods, including oral hydroxychloroquine and topical clobetasol, but her lesions improved dramatically with the use of intralesional hyaluronidase. This may support the role of hyaluronidase in the treatment of papular mucinosis and should be investigated further.

Conflict of interest

The authors declared no potential conflict of interest with respect to the research, authorship, and/or publication of this article.

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