Localized Papular Mucinosis With IgA Nephropathy

A Case Report

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Background: Papular mucinosis is an idiopathic cutaneous mucinosis. It includes 3 clinicopathologic subtypes according to the recent Rongioletti classification: a generalized papular form, a localized form, and atypical forms. The localized form is subdivided into 5 subtypes. The atypical form does not meet the criteria for either the generalized papular form or the localized forms and includes localized forms with monoclonal gammopathy and/or systemic symptoms.

Observations: We describe a 37-year-old man who had multiple small, waxy papular lesions on the neck for 4 years. One year after the lesions first appeared, he developed IgA nephropathy. No paraproteinemia or thyroid dysfunction was observed. Histologic examination of the skin lesions showed mucin deposits in the upper dermis. Alcian blue–positive mucin was also found in the renal interstitium and around some vessels and capillary loops. A diagnosis of localized papular mucinosis with IgA nephropathy (atypical form) was made after the biopsy.

Conclusions: The patient showed an unusual manifestation of localized papular mucinosis with the lesions confined to the neck and IgA nephropathy. Alcian blue staining is a useful way to determine kidney involvement of papular mucinosis.

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PAPULAR MUCINOSIS (PM) (aka, lichen myxedematosus) is a disorder characterized by lichenoid papules, nodules, and/or plaques due to mucin dermal deposition. In 1953, Montgomery and Underwood1 established a clinical classification of PM with 4 subtypes: (1) generalized lichenoid papular eruptions; (2) discrete papular form; (3) localized or generalized lichenoid plaque form; and (4) urticarial plaques and nodular eruptions. The updated Rongioletti classification2 includes 3 clinicopathologic subsets: (1) generalized PM (scleromyxedema) with systemic manifestations; (2) localized PM without sclerotic features, paraproteinemia, or systemic involvement; and (3) atypical forms, not meeting the criteria for either scleromyxedema or the localized form, including localized forms with paraproteinemia and/or systemic symptoms. The localized form is subdivided into 5 sub-subtypes: (1) discrete PM; (2) acral persistent PM (APPM); (3) self-healing PM (SHPM); (4) PM of infancy; and (5) nodular PM. In this study, we describe a man with PM confined to the neck who later developed IgA nephropathy. The case represents a novel form of localized PM, a "confined" form with renal involvement.

REPORT OF A CASE

A 37-year-old Chinese man presented with multiple small, asymptomatic, waxy papular lesions on the neck for 4 years. Over the years, he had continued to develop new lesions, while the preexisting lesions coalesced into plaques. However, the lesions remained confined to the neck and did not spread to other parts of the body. His family history was negative. A review of systems revealed that 1 year after the lesions' first appearance, he had developed symptoms of flank pain, increased nocturia, hematuria, and albuminuria. There was no hypertension, edema, or other symptoms of chronic kidney disease. Through renal biopsy, he had been diagnosed as having IgA nephropathy (grade II). There was no other systemic involvement. Prednisone was given but was unsatisfactory in controlling both the skin and the renal symptoms. His renal function remained normal during these years.

Skin examination revealed multiple firm, waxy, opalescent, flat-topped, 2- to
4-mm papules. The coalesced papules formed a 12 × 6-cm linear plaque.

METHODS

Routine urinalysis revealed macroalbuminuria and hematuria; the 24-hour urinary protein level was 2.14 g. Routine blood test results, thyroid function, and liver and renal function were all normal. Levels of serum IgG, IgA, IgM, IgE, C4, circulating immune complexes, anti–double-stranded DNA, antinuclear antibody, anti-Sm, anti-Ro (SSA), anti-La (SSB), and Scl-70 antibodies were within normal limits. The patient tested negative for human immunodeficiency virus.

Color Doppler ultrasonographic examination of the thyroid gland showed no abnormalities.

Histologic examination of the skin lesions showed loosely separated collagen fibers in the upper dermis, suggesting mucin deposition, and some dermal mesenchymal cells within and surrounding the mucinous stroma (Figure 2A). The mucinous stroma stained positively with Alcian blue (pH, 2.5) (Figure 2B) but not with toluidine blue (pH, 7.0). Immunohistochemically, the mesenchymal cells tested strongly vimentin positive (Dako, Carpinteria, California), and some of them were also positive for either CD34 (Dako) or factor XIIIa (Biovacell Ltd, Poole, England) (Figure 2C and D). The CD34+ cells were found mainly within the mucinous stroma and in the deeper part of the dermis (Figure 2C). Factor XIIIa-positive cells were predominant in the periphery of the mucinous stroma (Figure 2D). The mesenchymal cells tested negative for desmin (Dako) and S-100. (Maixin-Bio, Fuzhou, China).

Histologic examination of the renal tissue showed focal mesangial proliferation, sclerosis, and adhesion of the glomeruli; a moderate fibrous crescent formation could also been seen in the glomeruli. The glomerular capsules showed thickening and layering in the corticomedullary junction, and 10% of the renal tubules were atrophic. There was proliferation of the renal interstitium around the atropic tubules and in the corticomedullary junction (Figure 3). Immunofluorescence analysis showed deposits of IgA, mainly in the mesangium (++; Figure 3A), and segmental or focal deposits of IgG in glomeruli (+++); IgM, C3, C4, C1q, and fibronectin findings were negative.

After processing renal tissue with Alcian blue, we also found positively stained mucin deposits in the renal interstitium around some arterioles, venules, renal tubules, and capillary loops, part of them even projecting into the glomerular capsule, and we found some mucin deposits in the mesangium (Figure 4A and B). These mucinous depositions were shown again through staining with Alcian blue/periodic acid–Schiff (Figure 4C and D). To show the correspondence, we also stained with hematoxylin-eosin (HE). The Alcian blue–positive mucinous depositions corresponded to the HE stain of loosely separated collagen fibers and pale-staining areas. Increased numbers of vimentin-positive spindle-shaped cells were found in the mucinous deposition areas. These cells were negative for CD34 and factor XIIIa.

We proposed vaporizing the lesions with a carbon dioxide laser, but the patient declined the treatment because he had no cosmetic concerns.

COMMENT

Though Rongioletti and Rebora2 made significant contributions to the clinical classification of PM, there re-
main many cases that are not well characterized. Borradori et al. report a case of APPM with IgA monoclonal gammopathy that challenges the view that absence of paraproteinemia is a peculiar characteristic of APPM. Chen et al. report congenital cutaneous mucinosis with spontaneous regression. And our case also presents such an example. Because the lesions were confined to the neck, we believe it should belong to the localized form, but it cannot be categorized into any of the 5 localized subtypes, especially considering the renal association. Discrete PM is inappropriate because it is characterized by isolated papules, which present in a symmetric disposition, mainly on the trunk and extremities. The manifestation of this form is clearly different from our case. It is also necessary to differentiate our patient’s condition from mucinous nevus and SHPM. Mucinous nevus presents as asymmetric and localized papules at birth or shortly after birth, and SHPM spontaneously resolves within a few weeks or not more than 2 years after onset.

The histopathologic findings of PM are similar. Alcian blue–positive mucin is often deposited in the upper and mid dermis, and the number of dermal mesenchymal cells is increased. Immunohistochemical analyses in some cases of PM have detected CD34+ or factor XIIIa–positive dermal dendritic cells (DDCs) within and surrounding the mucin deposition, suggesting that they might have participated in the dermal deposition of mucin. Because vimentin is a general mesenchymal marker and DDCs have been characterized immunohistochemically by the presence of factor XIIIa or CD34, we also tested for these immunohistochemical markers. The findings in our case showed that vimentin-positive dermal mesenchymal cells were strongly expressed within and surrounding the mucinous stroma. The CD34+ DDCs were found mainly within the mucinous stroma and in the deeper part of the dermis. Factor XIIIa–positive DDCs were located predominantly in the periphery of the mucinous stroma. These cells tested negative for desmin and S-100. Thus, we concluded that CD34+ DDCs within the mucinous stroma, in combination with factor XIIIa–positive DDCs in the perilesional area, may have participated in the dermal deposition of mucin.

In the classification system of Montgomery and Underwood, the discrete papular form and localized form are 2 different subtypes. The localized form, in the Rongioletti classification, does not run a disabling course. In fact, as localized literally means confined or restricted to a particular location, the Rongioletti system likely caused misunderstandings by assigning too many additional definitions to the localized form. We propose adding the localized lichenoid plaque form as a new subtype of the localized papular form described by Rongioletti and Rebora, defined as lichenoid plaque eruptions confined or restricted to a particular location, which would describe the lesions in our case. When it has an internal association, as in our case, we classify it as an atypical form.

Although scleromyxedema is associated most frequently with monoclonal gammopathy and various systemic disorders, there have been cases of localized PM showing systemic involvement. They are classified as atypical forms. However, kidney involvement is seldom reported in either the generalized (scleromyxedema) or localized forms (atypical type). In 2007, Peeters et al. reported a patient with scleromyxedema and chronic kidney disease. Biopsy specimen analysis revealed that renal failure was due to accumulation of Alcian blue–positive mucin deposits in the wall of the arterioles, which caused concentric narrowing of the renal arteries and severe glomerular ischemia.

We think that our patient’s history of localized PM was involved with his development of his IgA nephropathy. We tested renal tissue with Alcian blue and found Alcian blue–positive mucin deposition in the renal interstitium and capillary loops. Part of the mucin even projected into the glomerular capsules and was deposited in the mesangium. We also found that the number of vimentin-positive spindle-shaped cells was increased in the mucinous deposition areas. These cells tested negative for CD34 and factor XIIIa, which suggests that they were fibroblasts. The proliferation of fibroblasts can cause mucin deposition in the skin, which may also cause mucin deposition in the kidney. As Peeters et al. reported, mucin deposition around vessels can cause narrowing of renal vessels and glomerular ischemia. It is possible that in our case, the proliferation of fibroblasts in combination with mucin deposition in the renal interstitium and glomeruli caused glomerular sclerosis, interstitial fibrosis, atrophic renal tubules, mesangial proliferation, and crescent formation. The pathologic mechanism that
caused the underlying defective fibroblasts that produced mucin may also have caused IgA deposition in the mesangium.

Immunoglobulin A nephropathy, a mesangial proliferative glomerulonephritis characterized by deposition of IgA in the glomerular mesangium, is the most common glomerulonephritis throughout the world. The exact pathogenesis of it remains unclear. Various systemic diseases are associated with IgA nephropathy, such as liver failure, rheumatoid arthritis, and Reiter disease. The role of IgA in IgA nephropathy is uncertain. Waldo believes that IgA deposition alone is inadequate to explain the pathogenesis of IgA nephropathy because IgG deposition occurs at the site of complement activation and fixation. The IgA in the aggregate actually inhibits complement activation and prevents effective immune complex clearance. Oortwijn et al hold the opposite view, that IgA deposition may be one of the initiators of local complement activation in the kidney. We believe that the main cause of nephropathy in our patient was the proliferation of fibroblasts and mucin deposition in the renal interstitium and glomeruli. The IgA deposition in the mesangium may have aggravated it. Because the renal function of our patient was normal, we can easily rule out scleromyxedema-like diseases, such as nephrogenic fibrosing dermopathy or nephrogenic systemic fibrosis, which have been described in patients with stage 4 or 5 chronic kidney disease.

Treatment of PM is empirical and usually unsatisfactory. Tacrolimus ointment can be used in topical therapy, and carbon dioxide laser can also be used to clear mild lesions. In this case, prednison was used to control nephropathy, but it appeared ineffective in controlling either the lesions or the nephropathy. We proposed vaporizing the lesions with a carbon dioxide laser, but the patient declined the treatment because he did not have any cosmetic concerns. The particular eruption pattern of the lesions and kidney involvement are the main points of interest in this case.

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REFERENCES