Cutaneous macroglobulinosis with Waldenström macroglobulinemia

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INTRODUCTION

Waldenström macroglobulinemia (WM) is a rare subtype of lymphoplasmacytic lymphoma of B lymphocytes. It is characterized by monoclonal proliferation of lymphoplasmacytes in the bone marrow, lymph nodes, and spleen. Increased levels of circulating IgM monoclonal antibodies lead to their deposition in the skin and other organs.1

Cutaneous manifestations of WM are rare and can be classified into specific and nonspecific findings. Nonspecific findings are attributed to hyperviscosity or cryoglobulinemia, whereas specific manifestations are related to neoplastic B-cell infiltrates and monoclonal IgM deposition in the skin, which is referred to as cutaneous macroglobulinosis (CM).1

We report a case of a 50-year-old woman whose clinical, laboratory, and pathologic findings are consistent with the diagnosis of CM that developed after WM. To our knowledge, only 9 cases of CM in patients with an established diagnosis of WM have been previously reported (Table I).1-9

CASE REPORT

A 50-year-old diabetic woman presented to our department with itchy skin lesions affecting the face and both upper limbs of 2 months duration.

One year ago, she complained of chronic anemia and peripheral sensory neuropathy of both upper and lower limbs that was diagnosed at that time as chronic inflammatory polyradiculopathy. The patient was treated with iron and vitamin B complex supplements without significant improvement. After 6 months, a bone marrow biopsy found marked reduction in hematopoietic stem cells, CD20+ lymphoplasmacytic infiltrate and markedly elevated IgM assay. The diagnosis of WM was proposed, and few months later, skin lesions appeared.

Abbreviations used:
CM: cutaneous macroglobulinosis
WM: Waldenström macroglobulinemia
| Study            | Year | Age  | Sex | Duration of WM (yrs) | Clinical presentation                                                                 | Sites affected                                                                 | IgM level         | Lymph nodes/HisM | History of neuropathy                        | Special stains | Treatment                                                                 | Outcome of treatment                                                                 |
|-----------------|------|------|-----|---------------------|--------------------------------------------------------------------------------------|-------------------------------------------------------------------------------|------------------|-----------------|-----------------------------------------------|----------------|--------------------------------------------------------------------------|----------------------------------------------------------------------------------------|
| Mascaro et al   | 1982 | 48/M | 4   | 4                   | Asymptomatic, discrete, smooth, pink, translucent, pearly and shiny papules, each 1-5 mm in diameter. Some of them show central crust and erosion. | Buttocks, thighs and legs                                                     | 3400 mg/dL       | Bilateral cervical lymphadenopathy            | NM               | + by DIF                                                    | Chlorambucil and prednisone (before onset of skin lesions)                               |
| Cobb et al      | 1992 | 59/M | 4   | 4                   | Widespread eruption of 2-4 mm succulent erythematous excoriated papules, with confluence to plaques | Trunk, arms and legs                                                           | 1520 mg/dL       | None            | NM               | + by DIF                                                    | Erythromycin and dapsone Daily prednisone PUVA                                      | Ineffective The eruptions improved. The eruptions completely cleared.                   |
| Gressier et al  | 2010 | 71/M | NM  | NM                  | Asymptomatic hyperkeratotic flesh-colored papules, some with central crust          | Both knees                                                                     | 18.50 mg/dL      | None            | Peripheral neuropathy of all 4 limbs          | + by DIF                                                    | Rituximab and chlorambucil                                                                 | Clearance of cutaneous lesions                                                            |
| Marchand et al  | 2011 | 67/M | NM  | NM                  | Multiple erythematous, nonpruriginous, 1-2 mm papules                               | Anterior face of the knees and calves                                        | NM               | NM             | NM               | + by DIF                                                    | Bortezomib and rituximab                                                                | The skin lesions remained unchanged.                                                      |
| Camp and Magro  | 2012 | 80/M | NM  | NM                  | Painful erythematous papules and nodules with central ulceration                   | Bilateral lower extremities and back of right hand                            | 3016 mg/dL       | NM             | NM               | + by DIF                                                    | Patient received 2 doses of rituximab prior to the onset of the skin eruption.          | NM                                                                                      |
| D’Acunto et al  | 2014 | 70/M | 15  | 15                  | Nodules covered by a thick hyperkeratotic layer. The lesions were extremely painful to pressure. | Soles of the feet                                                             | 2290 mg/dL       | NM             | + by IHC                                                   | + by DIF                                                    | Intravenous immunoglobulin therapy Rituximab                                            | Ineffective                                                                 |
| Oshio-Yoshii et al | 2017 | 63/M | 1   | 1                   | Small reddish papules, some of which developed into discrete blister-like nodules | On and around the right medial malleol                                        | NM               | NM             | + by IHC                                                   | + by IHC                                                    | Intravenous immunoglobulin therapy Rituximab                                            | Clearance of the skin lesions leaving pigmented macules, but lesions recurred after 6 months |
and prednisone) chemotherapy. Unfortunately, she died after rapid deterioration of her general condition.

DISCUSSION

Waldenström macroglobulinemia is a lymphoplasmytic lymphoma associated with monoclonal IgM gammopathy. It represents approximately 2% of all hematologic malignancies. It is more common in men, with a median age of 60 to 70 years. The disease is characterized by an indolent course in most patients, with a median survival of about 5 years. IgM paraprotein can cause various symptoms resulting from systemic amyloidosis, paraprotein depositions in the organs, cryoglobulinemia, peripheral neuropathy, and hyperviscosity syndrome.10

Tichenor et al first described cutaneous macroglobulinemia in 1978 as macroglobulinemia cutis. Most reported presentations are skin-colored and pink papules, sometimes with central crust, on the knees, buttocks, and extensor aspects of the extremities. Uncommon clinical presentations of nodules, plaques, or ulcerated lesions along with involvement of the trunk, face, neck, and scalp were occasionally reported.2

Patients can develop CM before, concurrent with, or—as in our reported case—after diagnosis of the underlying lymphoplasmacytic lymphoma. Hence, CM can predict a latent plasma cell dyscrasia before any other clinical or pathologic evidence.3

Nine previous case reports exist of CM that developed in patients after WM was diagnosed (Table I).1-9 Of these 9 cases, only one female case was reported, and this makes our case the second reported female case of CM in a patient with a history of WM.3 Our case had peripheral neuropathy, which is also a rare association with CM.1 The development of neuropathy is thought to be related to the accumulation of IgM in myelin sheaths.2 A unique clinical finding in our case is the involvement of the eyelids, which, to our knowledge, has not been previously reported in any case of CM.

Finding dermal deposits of eosinophilic amorphous material is the pathologic hallmark of CM. The deposited material is usually positive for PAS, but negative for Congo red stain. Only 1 report showed weak positive staining for Congo red.3

The most relevant diagnostic test is the detection of IgM by immunohistochemistry and/or direct immunofluorescence (Table I). Immunoelectron microscopy was found to clearly demonstrate the presence of large amounts of IgM in the dermis, which were found in the lesions of CM and in normal skin. These results suggest that the IgM storage papules result from
a greater density of deposits rather than a site-specific accumulation.11 Treatment for WM is symptom directed. There are neither guidelines for initial therapy nor trials assessing a primary outcome of improvement in cutaneous involvement. Therefore, alkylator-based therapy, purine nucleoside analogue agents, and rituximab may all be considered for initial therapy for newly diagnosed patients.2

We present a new rare case of CM associated with WM. The clinical features of this case are interesting, as it affected a female patient with involvement of eyelids and associated with peripheral neuropathy. IgM deposits are a characteristic histologic feature that helps pathologists differentiate CM from other PAS-positive depositional disorders such as lipoid proteinosis. In clinical practice, knowledge of different clinical
manifestations related to IgM can be useful for early diagnosis of lymphoid hemopathies associated with it.

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