

Cutaneous Macroglobulinosis

A Report of 2 Cases

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Background: Specific cutaneous lesions of Waldenström macroglobulinemia are rare and include neoplastic cell infiltrates, IgM bullous disease, and so-called IgM-storage papules, which characterize cutaneous macroglobulinosis (CM).

Observations: We report 2 patients with CM. In patient 1, CM started as small papules, as reported in most of the previously published case studies of CM. In patient 2, lesion evolution was remarkable by its severity, with large ulcerated nodules, and the disease progressed rapidly. As mentioned for half the previously described patients, peripheral neuropathy was suspected in patient 2 and demonstrated in patient 1,

with production of antibodies to myelin-associated glycoprotein.

Conclusions: To the best of our knowledge, rituximab treatment of Waldenström macroglobulinemia associated with CM has not been described previously. Rituximab caused complete remission of the lesions in patient 1, whereas disease rapidly progressed in patient 2, and the patient died. These observations suggest that evolution of the cutaneous IgM-storage lesions reflects that of the underlying Waldenström macroglobulinemia, and CM is not a prognostic marker.

Arch Dermatol. 2010;146(2):165-169

WALDENSTRÖM MACROGLOBULINEMIA (WM) is a chronic lymphoproliferative disorder usually beginning in the fifth or sixth decade of life that is characterized by a monoclonal IgM secreted by malignant B cells that proliferate in the bone marrow, lymph nodes, and spleen. The clinical manifestations of WM reflect neoplastic B-cell infiltration (lymph node enlargement, splenomegaly, and bone marrow involvement with cytopenia) and the properties of circulating IgM, dependent on the biochemical characteristics of their fragment-crystallizable region (hyperviscosity symptoms, cryoprecipitation in the case of cryoglobulinemia, and tissue deposition) or their fragment antigen-binding region specificity (neurologic manifestations, hemolytic anemia, and Schnitzler syndrome). Cutaneous manifestations of WM are rare¹ and can be divided into specific and nonspecific findings. Specific manifestations include neoplastic B-cell infiltrates and monoclonal IgM deposition, which can cause either cutaneous macroglobulinosis (CM) or so-called IgM bullous disease. We describe 2 patients with WM who developed

associated CM and review 6 similar, previously published case reports.²⁻⁷

REPORT OF CASES

CASE 1

A 71-year-old man sought care March 15, 2006, for a 1-year history of peripheral distal and symmetric neuropathy of all 4 limbs, with sensory and motor deficits with electromyographic demyelination and axonal dysfunction. His medical history included hypertension, diabetes mellitus, and excision of an epidermoid carcinoma of the left ear. He was diagnosed as having WM on the basis of the results of a bone marrow biopsy, a monoclonal IgM protein level of 18.50 mg/dL (to convert to milligrams per liter, multiply by 10; reference range, 40-220 mg/dL) on serum electrophoresis, and positivity for anti-myelin-associated glycoprotein (MAG) antibodies. At the time of diagnosis, no adenopathy, hepatosplenomegaly, or hyperviscosity symptoms were present. The first cutaneous lesions appeared on both knees, resembling asymptomatic hyperkeratotic flesh-colored papules, some-

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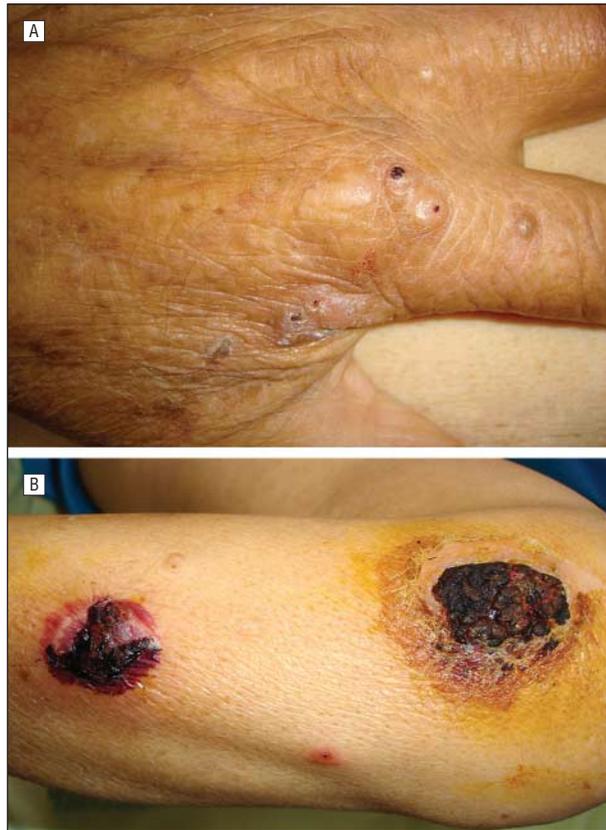


Figure 1. Cutaneous lesions in patient 2. At relapse, the patient had cutaneous macroglobulinosis lesions associated with small flesh-colored papules, some of which had a small central crust (A), and large ulcerated and necrotic nodules and plaques (B).

times with a small central crust. A skin biopsy specimen of 1 of those papules showed CM in the form of nodular eosinophilic periodic acid–Schiff (PAS)–positive deposits, which were positive for IgM with immunofluorescence labeling but negative for amyloid-specific stains. A mild lymphocytic infiltrate without plasma cells was seen.

The patient first received 4 perfusions of rituximab (375 mg/m²) and, because the serum IgM protein level did not decrease, chlorambucil was added. His IgM level and neuropathy stabilized and the cutaneous lesions disappeared. No relapse occurred after 18 months of follow-up, and chlorambucil therapy was discontinued when the monoclonal IgM level decreased to 550 mg/dL and anti-MAG antibody levels returned to normal (<1000 BTU).

CASE 2

A 65-year-old man was referred to our hospital February 1, 2005, for the spread of red-pink papular lesions on his buttocks, leukopenia, and a circulating monoclonal IgM protein. His medical history included leukocytoclastic vasculitis of the lower limbs in 1986 that led to the discovery of a monoclonal IgM κ protein level of 200 mg/dL (reference range, 40–220 mg/dL) with a normal bone marrow biopsy result. Skin lesions disappeared spontaneously. Of note, at the time of admission, the patient reported lower limb paresthesia.

Physical examination revealed small papules over the buttocks with no objective evidence of neurologic involvement, adenopathy, or splenomegaly. Blood cell count revealed that the patient had lymphopenia (white blood cells, 600/ μ L; to convert to $\times 10^9$ /L, multiply by 0.001) and normochromic anemia (hemoglobin, 8.8 g/dL; to convert to grams per liter, multiply by 10); his monoclonal IgM level was 1500 mg/dL. A new bone marrow biopsy led to the diagnosis of WM, with a κ light chain restriction. The skin biopsy specimen showed IgM-storage papules, in the form of dermal eosinophilic deposits, strongly PAS-reaction positive and negative for amyloid-specific stains, without neoplastic B-cell infiltration. Electromyography results were normal, and the search for anti-MAG antibodies was negative. The patient was diagnosed as having WM with CM, oral chlorambucil therapy was initiated, an initial regression of skin lesions was obtained, and the monoclonal IgM level decreased to 500 mg/dL.

The patient had a relapse August 1, 2007, with weakness and weight loss. Physical examination found numerous cutaneous lesions, splenomegaly, and hyperviscosity symptoms (epistaxis and purpura). Cutaneous lesions included multiple papules, sometimes with a central crust (**Figure 1A**), and necrotic and ulcerated nodules and plaques (**Figure 1B**) on the hands, elbows, ankles, buttocks, and lower limbs. Blood tests revealed severe pancytopenia (hemoglobin, 4.4 g/dL; white blood cells, 600/ μ L; and platelets, 26 000/ μ L; to convert to $\times 10^9$ /L, multiply by 1.0) and a monoclonal IgM flare to 2400 mg/dL associated with a monoclonal IgM κ in the urinary protein immunoelectrophoresis. The results of cryoglobulinemia tests and bacteriologic and parasitologic examinations were negative. A new skin biopsy specimen that resembled the first found CM deposits in the dermis (**Figure 2A**), with evidence of transepidermal elimination (**Figure 2B**). Immunohistochemical labeling of the deposits was positive for IgM and κ light chains (**Figure 2C**). Total-body computed tomography did not find any adenopathies, but splenomegaly was confirmed. Chlorambucil therapy was stopped because of severe pancytopenia, and 5 perfusions of rituximab (375 mg/m²) were administered. The first rituximab perfusion achieved an initial attenuation of skin lesions, reduction of splenomegaly, stabilization of blood cell counts, and a decrease in IgM protein level to 1900 mg/dL. Fludarabine was then added to the next 4 rituximab perfusions. Unfortunately, complete and durable remission was not obtained; systemic and skin involvement worsened, and the patient died of disease progression.

COMMENT

Specific skin manifestations in patients with WM are rare, and 2 main types are described: neoplastic plasma cell and lymphocyte infiltrates and monoclonal IgM deposits. Sixteen cases of such specific malignant infiltrates have been previously reported^{18–20} (eTable, <http://www.archdermatol.com>). The most common lesions were plaques and nodules, which involved the face and the trunk in 9 and 4 patients, respectively, and the in-

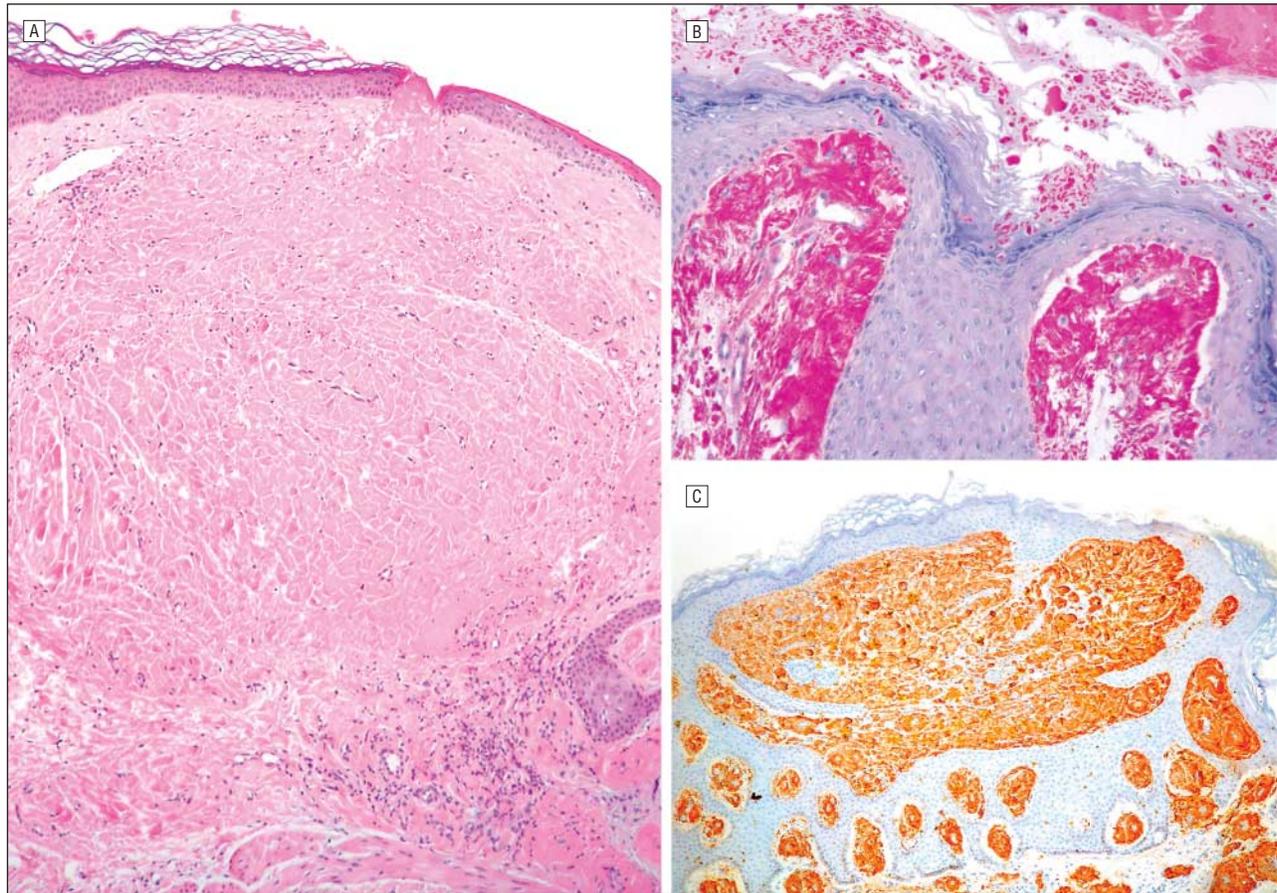


Figure 2. Histologic findings in patient 2. Lesions contained dermal accumulations of a dense eosinophilic material, with minimal infiltrate (A; hematoxylin-eosin; original magnification, $\times 10$), that was strongly positive for periodic acid–Schiff reaction with evidence of transepidermal elimination (B; original magnification, $\times 20$), together with IgM κ light chain restriction detected by immunohistochemical analysis (C; original magnification, $\times 10$).

interval between WM diagnosis and the onset of the skin lesions varied, ranging up to 12 years. Histologically, specific neoplastic infiltrates consisted of perivascular, periaxonal, and interstitial lymphocytic infiltration into the dermis that extended into the subcutaneous fat and contained small lymphoplasmacytoid lymphocytes and mature plasma cells. The clonality of skin-infiltrating B cells can be confirmed by the demonstration of an immunoglobulin light chain restriction or heavy or light chain gene rearrangement. Deposits of IgM in 4 patients were detected by immunofluorescence.^{4,8,9,12} Cryoglobulins and subsequent autoimmune-related manifestations were reported for 1 patient.¹⁶

The presence of isolated IgM deposits in the skin is currently called cutaneous macroglobulinosis (CM), and a bullous disease form that results from immunoglobulin deposition on the basal membrane has been reported.^{21–25} Because only 6 previous cases have been published to date, CM is considered a rare clinical manifestation of WM (**Table**). Age and sex distribution of the patients, including our 2 patients, are within the normal range for WM, with a male predominance (75%) and a median age of 61.9 years (range, 48–73 years). The most frequently observed lesions were papules, sometimes associated with nodules and/or plaques. The evolution of disease in patient 2 was atypical, with progressive development of confluent, necrotic, and ulcerated plaques. A

neoplastic B-cell infiltrate and/or an infectious disease was evoked, but histologic analysis revealed massive IgM deposits with transepidermal elimination. Transepithelial elimination was previously described in 3 patients with CM, with lesions that presented as necrotic and crusted papules. In the setting of CM, skin lesions commonly appear on the knees, buttocks, and extensor surfaces of the lower and upper limbs, as in our 2 patients. Occasionally, lesions can be found on the trunk, face, neck, and scalp. Histologic examination of a skin biopsy specimen provides the diagnosis: a dense, eosinophilic, amorphous, strongly PAS-positive material fills the dermis. The search for amyloid deposits is negative (Congo red and thioflavine T stains; original magnification, $\times 10$ and $\times 20$, respectively). Deposits of IgM in the skin are demonstrated by immunofluorescence and immunohistochemical analysis.

Although CM has been rarely reported, we hypothesize that a peripheral neuropathy can be associated with this condition. Considering the 8 known patients with CM (including our 2 patients), 5 (62%) had symptoms of numbness and paresthesia of the legs, and anti-MAG antibodies were detected in our patient 1. Unfortunately, further investigations (eg, electromyography) were not performed (Table). Furthermore, among the 8 patients with CM, 2 had confirmed cutaneous leukoclastic vasculitis and another had immune

Table. Clinical and Pathologic Features of Patients With Cutaneous Macroglobulinosis

Age, y/ Sex	Time From CM Onset to Diagnosis, y	Skin Lesions and Distribution	Direct Immunofluorescence	IgM Level, g/L	Autoimmune Manifestations	Autoantibodies	Treatment/ Outcome	Evolution of Skin Lesions	Source ^e
72/M ^a	6, After	Papules on the knees	IgM	NR	Neuropathy suspected, vasculitis confirmed	NR	NR/NR	NR	2
54/M ^a	1, Before	Papules and nodules on the knees, elbows, neck, and periumbilical area	IgM κ	18	Neuropathy suspected	ANA	Chlorambucil/PR	PR	3
48/M ^a	4, After	Papules on the buttocks, thighs, and legs	IgM	34	None	NR	Chlorambucil and prednisone/NR	NR	4 (case 2)
73/F ^a	1, After	Nodules and plaques on the trunk, upper limbs, and face	IgM	4.8	Immune hemolytic anemia	anti-erythrocytes (Coombs+)	Chlorambucil, lomustine, vincristine sulfate, and prednisone/NR	PR	5 (case 4)
52/M ^b	Concurrent	Papules on the ear, trunk, scalp, and extensor surfaces of the arms	IgM κ	20	Neuropathy suspected	Cryoglobulin	Chlorambucil and prednisone/PR, relapse, DOD	CR, relapse	6
60/F ^c	1, Before	Papules on the upper limbs and trunk	IgM κ	11.9	None	NR	Chlorambucil/PR	CR, relapse	7
71/M ^b	Concurrent	Papules on the knees	NR	18.5	Neuropathy confirmed	Anti-MAG	Chlorambucil and rituximab/PR	CR	This study (case 1)
65/M ^d	Concurrent	Papules and necrotic nodules on the buttocks and limbs	IgM	15	Neuropathy suspected, vasculitis confirmed	None	Chlorambucil and rituximab/PR, relapse, DOD	CR, relapse	This study (case 2)

Abbreviations: ANA, antinuclear antibodies; anti-MAG, anti-myelin-associated glycoprotein antibodies; CR, complete remission; DOD, died of disease; NR, not reported; PR, partial remission.

^aPatient had elevated erythrocyte sedimentation rate or 1 or more cytopenias and weight loss, asthenia, lymphadenopathy, splenomegaly, night sweats, or pruritus.

^bPatient had no blood inflammatory involvement or cytopenia and no clinical symptoms.

^cPatient had weight loss, asthenia, lymphadenopathy, splenomegaly, night sweats, or pruritus and no blood inflammatory involvement or cytopenia.

^dPatient had no clinical symptoms and either an elevated erythrocyte sedimentation rate or 1 or more cytopenias.

^eFrom reference list.

hemolytic anemia during or before the CM diagnosis, whereas none of the 18 patients with tumor-specific infiltrates had either neuropathy or autoimmune hemolytic anemia (eTable).

It is known that during WM, symptoms reflect tumoral infiltration or the direct effect of the serum monoclonal protein.²⁶ The pathogenic role of monoclonal IgM in WM can be attributed to various mechanisms. First, circulating IgM, above a level depending on each patient,²⁷ can lead to serum hyperviscosity. Second, IgM deposition in various tissues can be directly responsible for amyloidosis or CM. Third, IgM can be type 1 or 2 cryoglobulins or induce various autoimmune manifestations, such as immune hemolytic anemia, Schnitzler syndrome, or peripheral neuropathy. Peripheral neuropathy occurs in nearly 20% of patients with WM.²⁸ Most of those WM-associated neuropathies correspond to amyloidosis, cryoglobulinemia, or anti-MAG antibodies, but some patients with anti-MAG antibodies have tested positive for deposits on nerve tissue biopsies,²⁹ which suggests that several pathogenic pathways may be working in tandem. In addition, such findings suggest the presence of extracutaneous symptomatic and/or asymptomatic IgM

deposits, but postmortem studies on patients with CM are lacking to verify this hypothesis.

We describe, to the best of our knowledge, the first 2 patients with CM to be treated with rituximab, which had previously been used to treat WM, as first-line therapy or after relapse.³⁰ The evolution of disease in patient 1 after rituximab administration was favorable, whereas the biologic was unable to stop the disease progression and death in patient 2. We hypothesize that the progression of CM lesions follows the evolution of the underlying disease, regardless of the treatment. The CM skin lesions followed a waxing-and-waning course, with new flares of papules and nodules appearing as the disease progressed. In agreement with this hypothesis, patient 1 experienced almost complete remission, including healing of skin lesions, without relapse. In contrast, in patient 2, disease relapsed and progressed, and he died of WM. In that case, skin lesions worsened and became confluent and necrotic as CM progressed. Therefore, it is possible that the progression of the cutaneous IgM-storage lesions follows the course of the underlying disease, independently of the treatment given. Thus, the severity of skin involvement in CM may reflect the circulating IgM

level, which, in turn, corresponds to disease activity. Nevertheless, the opposite outcomes of our patients 1 and 2 treated with rituximab suggest that CM is not a prognostic marker.

In conclusion, CM should be considered a possible manifestation of WM. Usually, CM manifests as small papules on the trunk or extremities but can sometimes be large necrotic plaques that resemble neoplastic infiltration or an infection. Finding CM should incite the search for peripheral neuropathy or an associated autoimmune process. The intensity of CM may reflect the circulating IgM level and disease severity, but further investigations are required to better understand the prognostic implication of CM in WM.

Accepted for Publication: August 14, 2009.

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Author Contributions: Dr Ortonne had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Drs Melica and Ortonne contributed equally as senior authors of this article. *Study concept and design:* Gressier, Hotz, Lelièvre, Melica, and Ortonne. *Acquisition of data:* Gressier and Hotz. *Analysis and interpretation of data:* Gressier, Hotz, Lelièvre, Melica, and Ortonne. *Drafting of the manuscript:* Gressier, Hotz, Melica, and Ortonne. *Critical revision of the manuscript for important intellectual content:* Gressier, Hotz, Lelièvre, Melica, and Ortonne. *Administrative, technical, or material support:* Carloti, Buffet, Wolkenstein, Bagot, and Ortonne. *Study supervision:* Melica and Ortonne.

Financial Disclosure: None reported.

Online-Only Material: The eTable is available at <http://www.archdermatol.com>.

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