

# Disseminated cutaneous immunoglobulin M macroglobulinosis associated with cryoglobulinemia and minimal residual disease of Waldenström macroglobulinemia



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**Key words:** cryoglobulinemia; cutaneous macroglobulinosis; IgM; Waldenström macroglobulinemia.

## INTRODUCTION

The dermatologic manifestations of Waldenström macroglobulinemia (WM) are typically categorized as disease specific or non-disease specific.<sup>1</sup> Non-disease-specific findings are related to hyperviscosity or cryoglobulinemia, including mucosal bleeding, purpura, livedo reticularis, and Raynaud phenomenon. Two rare types of specific skin findings have been identified: cutaneous infiltrates of mature B-cell neoplasms, specifically heavy-chain or malignant immunoproliferative diseases, and deposits of monoclonal immunoglobulin (Ig) M, referred to as *cutaneous macroglobulinosis* (CM).

Although classically described in patients with WM, cutaneous deposition could develop in any condition associated with IgM paraproteinemia. First documented in 1978 by Tichenor et al,<sup>2</sup> CM is remarkable for its association with underlying plasma cell dyscrasias and its ability to mimic other depositional disorders. Here, we report a patient initially diagnosed with lymphoplasmacytic lymphoma (LPL) whose subsequent development of neuropathy and hyperviscosity syndrome due to elevated serum IgM led to a diagnosis of WM. The patient then developed a disseminated cutaneous presentation of CM, with minimal residual WM disease and cryoglobulinemia.

### Abbreviations used:

BMB:	bone marrow biopsy
CM:	cutaneous macroglobulinosis
Ig:	immunoglobulin
LPL:	lymphoplasmacytic lymphoma
PAS:	periodic acid Schiff
R-CHOP:	rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone
WM:	Waldenström macroglobulinemia

## CASE REPORT

A 56-year-old woman initially presented with 1 month of severe fatigue and anemia. Workup was consistent with stage IV *MYD88*<sup>+</sup> *CD5*<sup>-</sup>/*CD10*<sup>-</sup>/*CD20*<sup>+</sup> LPL. Bone marrow biopsy (BMB) showed nearly 100% cellularity and diffuse infiltration of lymphoid aggregates. No skin findings were present. R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) was initiated, and the woman developed hyperviscosity syndrome, requiring plasmapheresis, and significant neuropathy from vinblastine. R-CHOP was discontinued after 4 cycles because of rising IgM, which reached 280 200 g/dL (normal range, 40-345 g/dL). A second BMB identified 50% LPL cells, with persistence of large B cells. IgM levels were 1500 to 6000 g/dL.

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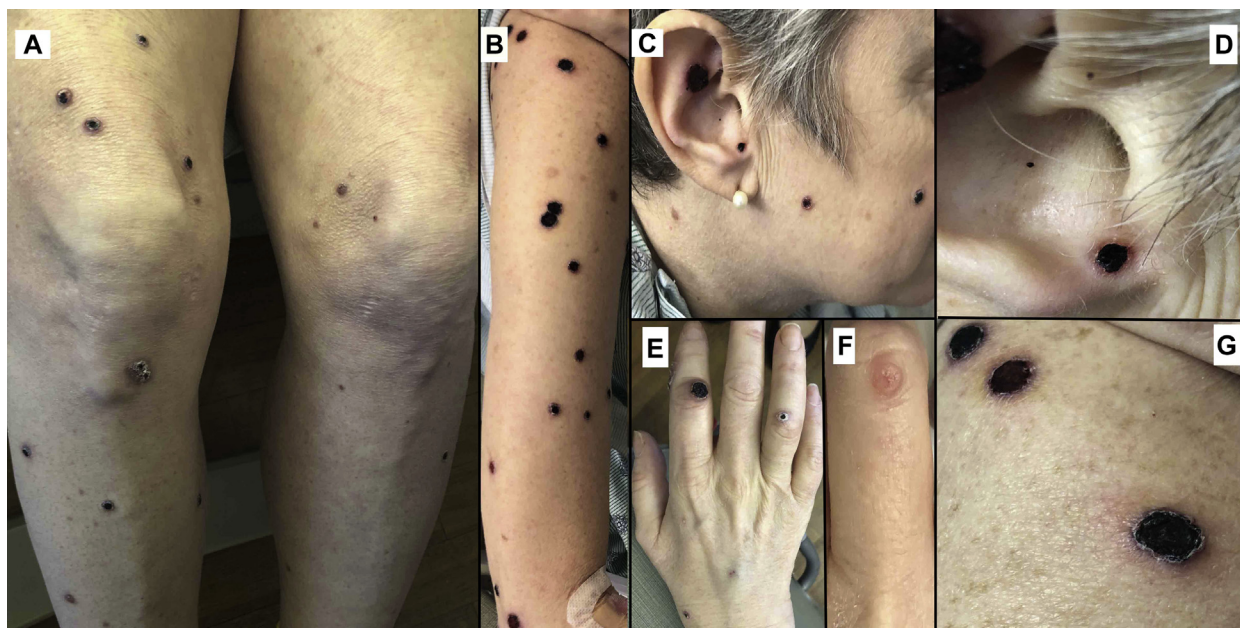
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**Fig 1. A-G,** Cutaneous macroglobulinosis presenting clinically with disseminated black eschars at various stages from skin-colored papule (finger) to large ulcerated black eschars across the patient's body, including the face and fingers.

Second-line treatment with bendamustine-rituximab was initiated but discontinued after 1 cycle because of development of severe neutropenia. Third-line treatment with ibrutinib was started, at which time IgM was 4096 g/dL.

After 1 month of taking ibrutinib, the woman presented to an outside institution with skin lesions on the face, chest, and abdomen, which were reported to show ulcerated hyaline deposits in the upper dermis that stained positive with periodic acid–Schiff (PAS) and were considered to be cutaneous IgM deposits in this clinical setting. Three months later, she showed a partial response to ibrutinib, with IgM levels at 2242.28 g/dL. BMB showed a hypercellular marrow with 65% plasma cells, which stained CD19<sup>+</sup>/CD20<sup>+</sup> with kappa light-chain restriction. Laboratory evaluation showed no immunity to hepatitis B or C and showed cryoglobulins; the patient was determined to have type 1 cryoglobulinemia. She was never noted to be hypothermic, and no association between temperature and disease course was observed.

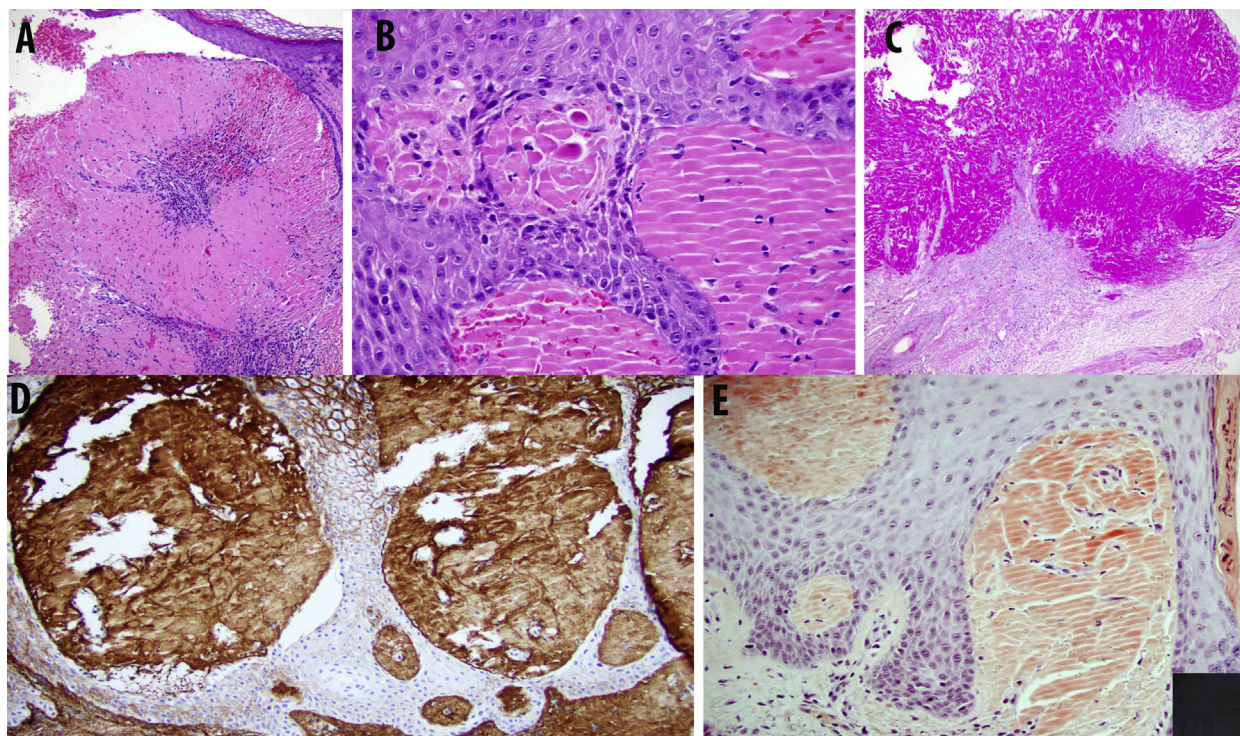
Physical examination at that time showed numerous crusted papules and nodules with eschars disseminated across her body, including the face and fingers (Fig 1, A-G). Skin biopsy showed large amorphous PAS<sup>+</sup> and IgM<sup>+</sup> deposits in the papillary and upper dermis that were weakly positive on Congo red staining but negative for birefringence under polarizing light (Fig 2, A-E). A majority of mild lymphocytic infiltrates in the dermis were CD20<sup>+</sup> B

cells. Immunoglobulin light-chain in situ hybridization showed slight kappa-dominant expression over lambda. Immunostaining results for collagen IV and elastic stain were negative, excluding lipoid proteinosis and colloid milium, respectively.

Treatment was escalated from ibrutinib monotherapy to rituximab, ifosfamide, carboplatin and etoposide with concurrent ibrutinib, which was complicated by pancytopenia and septic shock. The refractory nature of the woman's disease raised suspicion for leukemic phase transformation to diffuse large B-cell lymphoma. Currently, she is pending approval for chimeric antigen receptor T-cell therapy using Kymirah (Novartis, Basel, Switzerland) with 1 cycle of chemotherapy to achieve lymphoid depletion before infusion. If her disease remains refractory, she will be recommended for allogeneic stem cell transplant.

## DISCUSSION

WM is a form of LPL with high serum IgM.<sup>3</sup> CM refers to isolated deposition of IgM in the dermis, which can be confirmed by immunofluorescence and immunohistochemistry on tissue biopsy. More than 90% of patients with WM, including ours, have mutated MYD88 proteins, with downstream pro-oncogenic effects on the nuclear factor  $\kappa$ B pathway via alteration of toll-like receptor 4 and interleukin 1 and 2 receptors.<sup>3</sup> The temporal relationship between CM and WM varies because patients can develop CM



**Fig 2.** **A** and **B**, Cutaneous macroglobulinosis with histologic findings of amorphous, eosinophilic deposits in the papillary and upper dermis. Deposits were positive for **(C)** PAS and **(D)** IgM, and **(E)** weakly positive for Congo red, with negative birefringence (**E**, inset). **A**, H&E; original magnification,  $\times 100$ . **B**, H&E, original magnification,  $\times 400$ . **C**, PAS stain; original magnification,  $\times 100$ . **D**, IgM immunostain; original magnification,  $\times 200$ . **E**, Congo red stain without birefringence (inset); original magnification,  $\times 100$ .

before, concurrent with, or—as in our case—after diagnosis of the underlying plasma cell dyscrasia. Hence, diagnosis of CM can permit the diagnosis of a latent plasma cell dyscrasia before any other indicative information becomes available.

There are only 8 previously reported cases of CM in a patient with a history of WM (Table I).<sup>1,4-10</sup> These show a predilection for middle-aged men and lesions that appear as skin-colored, pink, or red papules and nodules on the trunk, extremities, and soles of the feet. Serum IgM levels ranged from 0.019 g/dL to 3.40 g/dL (converted from original reports in g/L and mg/dL). Our case involves a woman with remarkably high serum IgM levels (highest documented was 280,200 g/dL) and a disseminated cutaneous manifestation of black eschars of varying sizes and stages.

In the aforementioned cases and our case, histology of CM was characterized by pink, eosinophilic, amorphous deposits in the papillary and reticular dermis. The PAS staining result was positive and the Congo red result was negative in all cases reviewed. However, Congo red can variably be without

birefringence, as in our case. Detection of IgM by immunohistochemistry and/or direct immunofluorescence is diagnostic (Table I).

Skin involvement in WM is more often secondary to features of systemic disease, such as hyperviscosity or, as in our case, cryoglobulinemia, which occurs when monoclonal IgM precipitates upon cooling.<sup>3</sup> Clinical evidence of cryoglobulinemia can be noted by findings such as Raynaud phenomenon or skin ulcers.

Treatment for WM is symptom directed. Patients whose disease follows an indolent course, like those with other low-grade lymphoproliferative disorders, may have regular monitoring and often die of unrelated conditions rather than the disease itself.<sup>3</sup> There are no trials assessing a primary outcome of improvement in cutaneous involvement. For patients with symptomatic disease, including cutaneous involvement, several treatments, including monoclonal antibody therapy, alkylating chemotherapeutic agents, and others, have been studied with varying success, but available data are limited and are based on outcomes for those with systemic disease.<sup>3</sup> This

**Table I.** Summary of published cases of cutaneous macroglobulinosis in patients with a history of Waldenström macroglobulinemia

Case	Age, y	Sex	History of WM, y	IgM, g/dL	Physical examination	PAS	Congo red	DIF	IHC	Treatment and response
Gressier et al <sup>1</sup>	71	M	NR	0.019	Asymptomatic hyperkeratotic flesh-colored papules, some with small central crusts, on the bilateral knees	NR	NR	IgM <sup>+</sup>	NR	Rituximab + chlorambucil Complete response
Roupie et al <sup>4</sup>	56	M	3	NR	Papules covered by a thick hyperkeratotic layer on the soles of the feet	+	-	NR	IgM heavy- and lambda light-chain deposition	Rituximab + cyclophosphamide + corticosteroids Cutaneous response Partial hematologic response
Mascaro et al <sup>5</sup>	48	M	4	3.4	Smooth, pink, translucent, pearly, shiny papules on the buttocks, thighs, and legs	+	NR	Anti-IgM antibody <sup>+</sup>	NR	NR
Oshio-Yoshii et al <sup>6</sup>	63	M	1	NR	Small reddish papules on the right medial malleolus, some developing into blister-like nodules	+	-	IgM <sup>+</sup>	NR	Rituximab Complete response
Marchand et al <sup>7</sup>	67	M	NR	NR	Multiple erythematous, nonpruriginous 1- to 2-mm papules on the anterior knees and calves	+	-	IgM <sup>+</sup>	NR	Bortezomib + rituximab No cutaneous response Partial hematologic response
D'Acunto et al <sup>8</sup>	70	M	15	2.29	Thick hyperkeratotic layer on the soles of the feet	+	-	NR	IgM <sup>+</sup>	NR

Continued

Table 1. Cont'd

Case	Age, y	Sex	History of WM, y	IgM, g/dL	Physical examination	PAS	Congo red	DIF	IHC	Treatment and response
Cobb et al <sup>9</sup>	58	M	4	1.52	Widespread eruption of 2- to 4-mm erythematous papules, some with confluence into plaques on the trunk, arms, legs, and back	NR	NR	IgM <sup>+</sup>	NR	Erythromycin + dapson No response Systemic corticosteroids Partial cutaneous response Ultraviolet light Cutaneous response
Camp et al <sup>10</sup>	80	M	NR	0.003	Painful erythematous papules and nodules with central ulceration on the lower portion of the bilateral extremities and right hand	NR	NR	NR	IgM <sup>+</sup>	NR

DIF, Direct immunofluorescence; Ig, immunoglobulin; IHC, immunohistochemistry; M, male; NR, not reported; PAS, periodic acid–Schiff; WM, Waldenström macroglobulinemia.

case describes a patient with a 6-month history of WM for whom treatment with R-CHOP, rituximab-bendamustine, and ibrutinib failed and who developed disseminated CM.

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