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CASE REPORTS

Waldenström Macroglobulinemia Associated With Cutaneous Lesions and Type I Cryoglobulinemia

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Abstract. Waldenström macroglobulinemia is a blood dyscrasia characterized by monoclonal proliferation of B cells in the bone marrow, lymph nodes, and spleen. Patients with this disease show elevated serum levels and tissue deposition of monoclonal immunoglobulin (Ig) M produced by these aberrant cells. We present the case of a patient with Waldenström macroglobulinemia who suffered cutaneous lesions resulting from deposition of #k light chains of IgM and clinical manifestations secondary to associated type I cryoglobulinemia. We discuss the different pathological cutaneous processes caused by IgM in Waldenström macroglobulinemia.

Key words: Waldenström macroglobulinemia, IgM antibodies.

MACROGLOBULINEMIA DE WALDENSTRÖM ASOCIADA A LESIONES CUTÁNEAS Y CRIOGLOBULINEMIA TIPO IA

Resumen. La macroglobulinemia de Waldenström (MW) es una discrasia sanguínea caracterizada por la proliferación monoclonal de células linfoplasmocitarias en la médula ósea, ganglios linfáticos y bazo. Estos pacientes tienen niveles elevados en suero y depósito en tejidos de la inmunoglobulina (Ig) M, de tipo monoclonal, producida por estas células aberrantes. Presentamos el caso de un paciente afecto de MW, con lesiones cutáneas debidas al depósito de cadenas ligeras Kappa de IgM y con manifestaciones clínicas secundarias a la crioglobulinemia tipo I que el paciente tenía asociada. Discutimos los distintos proceso patológicos cutáneos provocados por la IgM en la MW.

Palabras clave: macroglobulinemia de Waldenström, anticuerpos IgM.

Introduction

Waldenström macroglobulinemia (WM) is a blood dyscrasia caused by monoclonal proliferation of B cells in the bone marrow, lymph nodes, and spleen.[1] It typically produces elevated serum levels and tissue deposition of monoclonal immunoglobulin (Ig) M.

Cutaneous lesions associated with this disease are rare and appear in only approximately 5% of patients. These lesions may be caused by several factors: infiltration of neoplastic cells in the skin, tissue deposition of IgM, abnormalities secondary to the presence of cryoglobulinemia, or blood hyperviscosity syndrome.[2-6] A group of miscellaneous entities may also appear (Table 1).

We present the case of a patient with WM who suffered cutaneous lesions secondary to deposition of IgM light chains and other clinical manifestations secondary to type I cryoglobulinemia. We discuss the possible cutaneous manifestations of this disease and their pathogenesis within the mechanism responsible for the lymphoreticular disease.

Case Description

A 72-year-old man visited our clinic with hyperkeratosis and ulceration on the sides of both feet that had appeared 2 years previously. These lesions were accompanied by dysesthesia in the feet and a burning sensation, which made walking difficult. The patient also reported a sensation of blockage of the left nostril and buzzing in the ears. Brownish-red raised lesions on the knees and buttocks had also appeared several months previously. He reported no other symptoms that suggested a systemic disease.

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Physical examination revealed brownish-red papules on the knees (Figure 1A), buttocks, and perianal region (Figure 1B). The sides of the feet had areas of hyperkeratosis with ulceration and an erythematous base that showed a livedoid pattern (Figures 1C and 1D). We performed 2 skin biopsies—1 of the lesions on the knees and 1 of the sides of the feet. The most significant finding in the knee lesions was the presence of eosinophilic hyaline material located in the dermis and subcutaneous cellular tissue (Figure 2A), and in the lumen of the blood vessels in sufficient quantity to cause obstruction. This material showed strong staining with periodic acid-Schiff (PAS) diastase (Figure 2B). Congo red staining was negative. Immunohistochemical staining with immunoperoxidase showed that the hyalin deposits were positive for κ light chains (DAKO, polyclonal antibodies; dilution, 1/100 000; Envision amplification method) (Figure 3A), but not for #l light chains (Figure 3C). Immunohistochemical staining for light chains and PAS stain were also positive in the intercellular space of the epidermis and the basement membrane. A biopsy of the lesions on the feet revealed a moderate, predominately neutrophilic, inflammatory infiltrate with evidence of leukocytoclastic vasculitis and damage to the endothelium. Direct immunofluorescence of the lesions showed a linear deposit of IgM (+++) on the basement membrane of the epidermis (Figure 3B) and discontinuous deposits of C3 (+). Indirect

Table 1. Cutaneous Manifestations Associated With Waldenström Macroglobulinemia

1. Specific cutaneous infiltrate in WM
   Specific infiltration of the skin in WM (cutaneous WM)
2. Nonneoplastic cutaneous manifestations associated with WM
   a) Secondary to paraproteinemia
      Associated with hyperviscosity syndrome
         Acral purpura
         Bleeding mucosa
         Peripheral edema
      Associated with cryoglobulinemia
         Cold urticaria
         Purpura
         Acral cyanosis
         Raynaud phenomenon
         Hypersensitivity to cold
         Cutaneous ulceration
         Livedo reticularis
         Leukocytoclastic vasculitis
      Cutaneous disease derived from the autoimmune phenomenon due to specific paraproteins:
         Bullous dermatosis
         Nonbullous dermatosis
            Cutaneous macroglobulinemia or IgM storage papules
            Erythematous papules associated with WM
            Mixed: combining characteristics of the previous 2 groups
   b) Miscellaneous
      Schnitzler syndrome
      Disseminated xanthoma
      Purpuric papules
      Amyloidosis
      Paraneoplastic pemphigus
      Urticaria

Abbreviations: IgM, immunoglobulin M; WM, Waldenström macroglobulinemia.

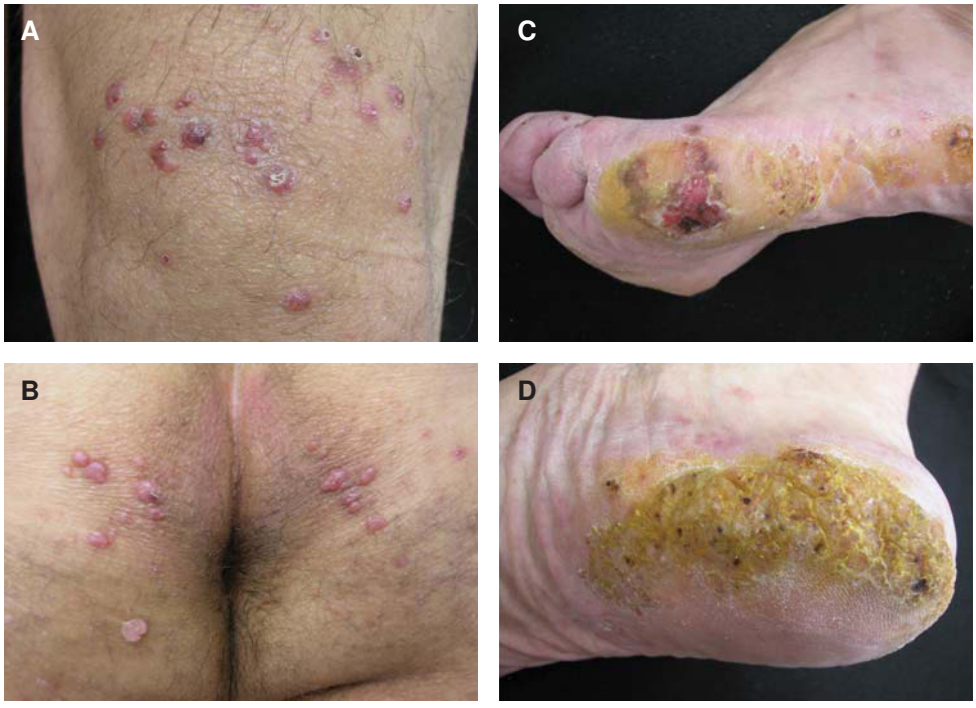

Figure 1. Translucent symmetrical roseate papules on the knees (A) and in the perianal region (B). Ulcerated lesions on the sides of the feet (C), with erythematous areas showing a livedoid pattern and hyperkeratotic areas on the heels (D).

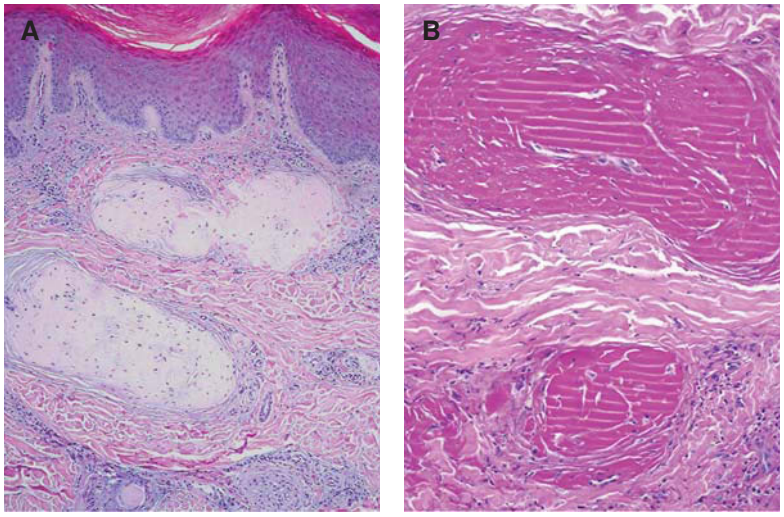

Figure 2. A, Hematoxylin–eosin stain showing a deposit of amorphous eosinophilic material occluding part of the vascular lumen. The deposit is also present in the extravascular areas of the papillary and reticular dermis (original magnification, ×40). B, This amorphous material was labeled strongly with periodic acid-Schiff stain (original magnification, ×100).

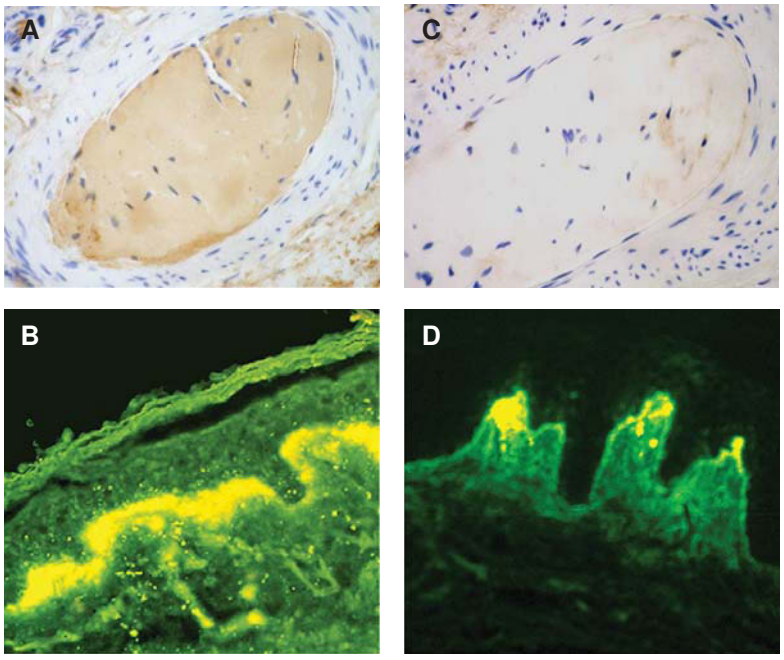

Figure 3. Immunoperoxidase staining showing positive labeling of the amorphous material with k light chain antibodies (A) but not with λ light chain antibodies (C). Direct immunofluorescence for IgM, showing a marked linear deposit in the dermal-epidermal junction of the lesional skin (B) and a discontinuous deposit in the perilesional skin (D) (original magnification ×40). IgM indicates immunoglobulin M.

immunofluorescence showed discontinuous staining for IgM in the perilesional skin (Figure 3D). Direct immunofluorescence was negative in the nonlesional skin. Indirect immunofluorescence using the salt-split skin technique (1 mM NaCl) revealed no appreciable abnormalities. We performed immunoblotting using an extract of the epidermis, an extract of the dermis, and a keratinocyte culture; all were negative for IgG.

Analyses showed serum levels of IgM of 3950 mg/dL (normal range, 70-150 mg/dL) and immunoelectrophoresis showed that the IgM was monoclonal. Levels of IgG, IgA, and IgD were within the normal range. The patient was also diagnosed with type I cryoglobulinemia and serum viscosity was 3.4 centipoise (normal range, 1.6-1.95 centipoise). All other test results were normal: complete blood count, general biochemistry, hematocrit, antinuclear antibodies, anti-DNA and extractable nuclear antibodies, and Bence-Jones protein in urine.

Bone marrow biopsy revealed a proliferation of lymphoplasmacytoid cells characteristic of WM. Other radiologic examinations such as chest x-ray, abdominal ultrasound, and computed tomography of the chest and

abdomen were normal. A neurophysiological examination was also performed, revealing sensorimotor polyneuropathy in the legs.

The patient began treatment with plasmapheresis; clinical signs improved after 4 months and this improvement is sustained at present.

Discussion

Libow et al[7] classified the cutaneous lesions of WM in 2 categories: neoplastic (cutaneous WM) and nonneoplastic. The latter may be associated with hyperviscosity syndrome, cryoglobulinemia, IgM deposition in the skin, or a group of miscellaneous diseases (Table 1).

Neoplastic skin lesions are the least frequent manifestations in WM. These cutaneous lesions are secondary to infiltration of the skin by neoplastic lymphoid cells. The lesions manifest as brownish-red infiltrated plaques. This type of lesion, which was not present in our patient, tends to manifest later in the course of the disease, though it may, occasionally, be the initial presentation.[2,5,7-15]

Nonneoplastic cutaneous manifestations of WM are more varied and appear more frequently.[15-25] Most are secondary to hyperviscosity syndrome and cryoglobulinemia (Table 1). Hyperviscosity syndrome tends to manifest clinically as heart failure, headache, tinnitus, visual disturbances, and hemorrhage; hemorrhage is due to entrapment of coagulation factors by IgM.[2] The clinical manifestations of cryoglobulinemia are also varied and include glomerulopathies, neuropathies, Raynaud phenomenon, livedo reticularis, and cutaneous ulceration (Table 1). Our patient presented type I cryoglobulinemia associated with WM, with purpuric lesions showing a livedoid pattern on the feet and leukocytoclastic vasculitis lesions, which probably caused the ulceration on the feet and the peripheral neuropathy—as described in the literature.[2-4]

Nonneoplastic cutaneous manifestations of WM may also be secondary to the deposition of IgM in the skin (Table 2); there are 4 different clinical forms. Some patients with WM present pruriginous papules associated with the deposition of IgM in the basement membrane zone (BMZ).[25] Histologic findings in these patients show only a nonneoplastic perivascular lymphocytic infiltrate. These patients may present associated circulating IgM antibodies against the BMZ.

In other cases, the cutaneous lesions are associated with a linear deposition of IgM throughout the BMZ and in lesional and perilesional skin with subepidermal bullous dermatosis (Table 2).[16-19] In these cases, indirect immunofluorescence using the salt-split skin technique is positive for IgM on both the dermal and epidermal side of the BMZ or only on the dermal side. Some authors have suggested that these patients would present bullous pemphigoid or acquired bullous epidermolysis associated with WM. In these cases, either the immunoblotting studies were not all carried out or the results were negative. These patients may be producing monoclonal IgM antibodies that cause an autoimmune bullous disease and are aimed at as yet unidentified antigens in the basement membrane.

Translucent erythematous papules, also known as storage papules or IgM storage papules, or macroglobulinemia cutis, may occur in association with WM.[5,20-23] They tend to appear on the limbs, buttocks, and torso. Histologic studies of this disease reveal a homogeneous eosinophilic material in the dermis as a result of IgM deposition[23]; the material is positive for PAS and negative for Congo red staining. These findings show that extravasation of IgM light chains probably takes place; direct immunofluorescence reveals the presence of these deposits in the amorphous material of the dermis and in the intercellular spaces of the epidermis. Indirect immunofluorescence tends to be negative and patients do not usually present associated cryoglobulinemia (Table 2). In our patient, the cutaneous lesions were clinically, histologically, and immunohistochemically similar to the storage papules described in WM. However, direct immunofluorescence in our patient was only positive for the subepidermal side of the BMZ.

The case described by West et al[24] showed 3 relevant histologic anomalies: deposition of amorphous material in the dermis, around the blood vessels, and under the lamina densa of the basement membrane; subepidermal bullous dermatosis (Table 2); and linear deposition of IgM in the BMZ and, occasionally, around the blood vessels. Immunoblotting techniques with dermal extracts showed circulating IgM antibodies against a 290 kDa protein antigen, and it was suggested that these may be antibodies against type VII collagen, the antigen of acquired bullous epidermolysis. Indirect immunofluorescence is usually positive. Our patient presented an accumulation of amorphous material in the dermis and direct immunofluorescence was positive for IgM in the BMZ, though there were no signs of subepidermal bullous dermatosis.

Finally, WM may be associated with several diseases with cutaneous manifestations, such as Schnitzler syndrome,[26] urticarial dermatitis,[27] diseases due to amyloid deposits,[28] disseminated xanthoma,[29] and paraneoplastic pemphigus.[30]

In summary, in a small number of patients with WM, the sole manifestation will be cutaneous lesions associated with IgM deposits in the skin, in the form of subepidermal bullous dermatosis or as a deposit of amorphous material in the dermis, or both. In other cases, patients will present

Table 2. Pathological Processes Associated With IgM Antibodies That Affect the Skin in Waldenström Macroglobulinemia

References	*Clinical Findings*	*Cryoglobulinemia*	*Histologic Forms*	*DIF of Lesional and Perilesional Skin*	*DIF of Nonlesional Skin*	*IIF*	*Electron Microscopy*	*Immunoblotting*
Whittaker et al[16] Wuepper et al[17] Gompel et al[18] Morita et al[19]	Bullous dermatosis	Not performed, negative, or mixed IgM/polyclonal IgG	Subepidermal separation	Linear deposits of IgM throughout the BMZ	Linear deposits of IgM throughout the BMZ Weak deposit of I gM in the epidermis and in the vascular region of the superficial dermis	Anti-BMZ IgM antibodies Anti-BMZ IgM antibodies that react on both the epidermal and dermal sides of the BMZ using the salt-split skin technique	Not performed	Not performed or negative
Lipsker et al[20] Tichenor et al[21] Hanke et al[22] Mascaro et al[5] Lowe et al[23]	IgM storage papules (macroglobulinemia cutis)	Not performed or negative	Eosinophilic amorphous deposit in dermis	Intercellular IgM deposit in dermis Focal deposit of IgM in dermis	Not performed	Negative	Not performed	Not performed or negative
West et al[24]	Bullous dermatosis and IgM storage papules	Negative	Subepidermal separation and deposit of amorphous eosinophilic material in dermis	Linear deposit of IgM throughout the BMZ	Not performed	Anti-BMZ IgM antibodies	Deposits of amorphous material in the superficial dermis, just below the lamina densa	290 kDa band in dermal extract
Cobbs et al[25]	Erythematous papules	Negative	Superficial perivascular lymphocytic infiltrate	Linear deposit of IgM throughout the BMZ	Not performed	Anti-BMZ IgM k antibodies that react on both the epidermal and dermal sides of the BMZ using the salt-split skin technique	Not performed	Negative
Our case	IgM storage papules	Type I	Deposit of amorphous material in the dermis. Perivascular neutrophilic infiltrate	Linear deposit of IgM throughout the BMZ	Negative	Neither IgG nor IgM antibodies found using salt-split skin immunofluorescence technique	Not performed	Negative for IgM

Abbreviations: BMZ, basement membrane zone; DIF, direct immunofluorescence; Ig, immunoglobulin; IIF, indirect immunofluorescence.

clinical manifestations of both types (Figure 4). Furthermore, only a few patients will develop manifestations secondary to cryoglobulinemia or hyperviscosity syndrome.

The mechanisms involved in the deposition of IgM in the skin of some patients with WM are not understood; nor is it understood why this deposition occurs in the BMZ in some cases, causing subepidermal bullous dermatosis, and in the form of deposits of amorphous material in the dermis and blood vessels in others. Further studies with similar patients are needed to understand the pathophysiology of this surprising clinical manifestation of WM.

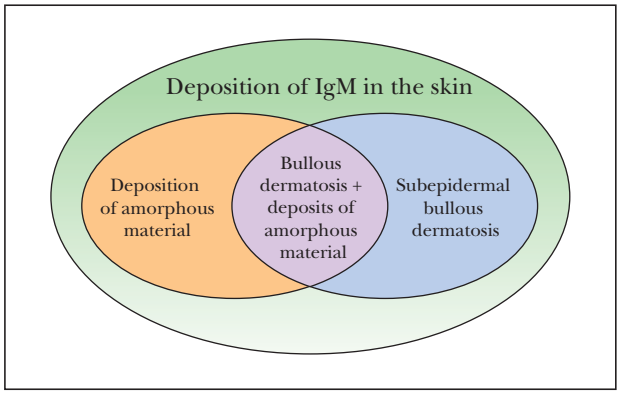

Figure 4. Patients with Waldenström macroglobulinemia who present nonneoplastic cutaneous lesions may have different types of manifestations secondary to deposition of IgM in the skin. Subepidermal bullous lesions may occur in some cases, a deposit of amorphous material in the dermis in other cases, and both types of manifestations may be present in other cases. IgM indicates immunoglobulin M.

References

1. Deuel TF, Davis P, Avioli LV. Waldenström's macroglobulinemia. Arch Intern Med. 1983;143:2946-51.
2. Abdallah-Lotf M, Bourgeois-Droin C, Perronne V, Fouchard N, Michael S, Launay-Russ E, et al. Cutaneous manifestations as initial presentation of Waldenström's macroglobulinemia. Eur J Dermatol. 2003;13(1):90-2.
3. Dimopoulos MA, Alexanian R. Waldenström's macroglobulinemia. Blood. 1994;83:1452-9.
4. Daoud MS, Lust JA, Kyle RA, Pittelkow MR. Monoclonal gammopathies and associated skin disorders. J Am Acad Dermatol. 1999;40:507-35.
5. Mascaro JM, Monserrat E, Estrach T, Feliu E, Ferrando J, Castel T, et al. Specific cutaneous manifestations of Waldenström's macroglobulinemia: a report of two cases. Br J Dermatol. 1982;106:217-22.
6. Hanke CW, Steck WD, Bergfeld WF, Valenzuela R, Weick JK, Young JR, et al. Cutaneous macroglobulinosis. Arch Dermatol. 1980;116:575-7.
7. Libow LF, Mawhinney JP, Bassinger GT. Cutaneous Waldenström's macroglobulinemia: report of a case and overview of the spectrum of cutaneous disease. J Am Acad Dermatol. 2001;45 Suppl 6:S202-6.
8. Chan I, Calonje E, Whittaker J. Cutaneous Waldenström's macroglobulinemia. Clin Exp Dermatol. 2003;28:491-2.
9. Baudach W, Schulz K, Moldenhauer E, Tessmann K. Beitrag zur makroglobulinämie Waldenstöm mit kutaner tumormanifestation. Zschr Inn Med. 1970;25:604-8.
10. Green T. Cutaneous manifestations of Waldenström's macroglobulinemia. Br J Dermatol. 1989;121:55.
11. Bergrouth V, Reitamo S, Konttinen YT, Wegelius O. Skin lesions in Waldenström's macroglobulinemia: characterization of the cellular infiltrate. Acta Med Scan. 1981;209:129-31.
12. Orengo IF, Kettler AH, Bruce S, Levy ML, Rosen T, Tschen J. Cutaneous Waldenström's macroglobulinemia: a report of a case successfully treated with radiotherapy. Cancer. 1987; 60:1341-5.
13. Mozzanica N, Finzi AF, Faccetti G, Villa ML. Macular skin lesion and monoclonal lymphoplasmacytoid infiltrates: occurrence in primary Waldenström's macroglobulinemia. Arch Dermatol. 1984;120:778-1.
14. Meiers HG. Immunchemische untersuchung der paraproteinbildung im hauttumor. Dtsch Med Wochenschr. 1968;93:1795-800.
15. Appenzeller P, Leith CP, Foucar K, Scott AA, Bigler CF, Thompson CT, et al. Cutaneous Waldenström's macroglobulinaemia in transformation. Am J Dermatopathol. 1999;21:151-5.
16. Whitataker SJ, Bhogal BS, Black MM. Acquired immunobullous disease: A cutaneous manifestation of IgM macroglobulinemia. Br J Dermatol. 1998;135:283-6.
17. Wuepper KD, Key DJ, Kane PJ. Bullous pemphigoid due to a 19S monoclonal paraprotein in a patient with Waldenström's (abstract). Clin Res. 1978;26:579A.
18. Gompel A, Bletry O, de Prost Y, Wechsler J, Wechsler B, Lebon P, et al. Bullous dermatosis associated with dysglobulinemia (two cases): relationships with epidermolysis bullosa. Biomed Pharmacother. 1982;36:199-203.
19. Morita E, Horiuchi K, Yamamoto S, Hashimoto T. A case of acquired autoimmune bullous disease associated with IgM macroglobulinaemia. J Dermatol. 1999;26:671-6.
20. Lipsker D, Cribier B, Boehm N, Heid E, Grosshans E. Examination of cutaneous macroglobulinosis by immunoelectron microscopy. Br J Dermatol. 1996;135: 287-91.
21. Tichenor RE, Rau JM, Mantz FA. Macroglobulinemia cutis. Arch Dermatol. 1978;114:280-1.
22. Hanke W, Steck WD, Bergfeld WF, Valenzuela R, Weick JK, Young JR, et al. Cutaneous macroglobulinosis. Arch Dermatol. 1980;116:575-7.
23. Lowe L, Fitzpatrick JE, Huff JC, Stanley PF, Golitz LE. Cutaneous macroglobulinosis: a case report with unique ultrastructural findings. Arch Dermatol. 1992;128:377-80.
24. West NY, Fitzpatrick JE, David-Bajar KM, Bennion SD. Waldenström's macroglobulinemia-induced bullous dermatosis. Arch Dermatol. 1998;134:1127-31.
25. Cobb MW, Domloge-Hultsch N, Frame JN, Yancey KB. Waldenström's macroglobulinemia with an IgM-k antiepidermal membrane zone antibody. Arch Dermatol. 1992;128:372-6.

26. Welsh B, Tate B. Schnitzler's syndrome: report a case with progression to Waldenstrom's macroglobulinemia. Australas J Dermatol. 1999;40:201-3.
27. Pujol RM, Barnadas MA, Brunet S, de Moragas JM. Urticarial dermatosis associated with Waldenström's macroglobulinemia. J Am Acad Dermatol. 1989;20:855-7.
28. Baudach W, Schulz K, Moldenhauer E, Tessmann K. Beitrag zur makroglobulinämie Waldenström mit kutaner tumormanifestation. Zschr Inn Med. 1970;25:604-8.
29. Goodenberger M, Piette WW, Macfarlane DE, Argenyi ZB. Xanthoma disseminatum and Waldenström's macroglobulinemia. J Am Acad Dermatol. 1990;23:1015-8.
30. Perera GK, Devereux S, Mufti G, Salisbury J, Creamer D. PNP with Waldenström's macroglobulinemia. Clin Exp Dermatol. 2005;30:27-9.