Blistering lesions associated with Waldenström macroglobulinemia: new insights into pathogenesis

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A 69-years old woman showed recurrent vesicles on both dorsal feet and hands (Fig. 1A, B). The lesions have been developed over the years. A monoclonal IgM component (3350 mg/dL) and lambda light chain with no evidence of Bence-Jones proteinuria were detected. The diagnosis of Waldenström Macroglobulinemia (WM) was confirmed by a radiologic evidence of mediastinal lymphadenopathy and a bone marrow biopsy. A skin punch biopsy showed a dermo-epidermal split (Fig. 1F). The direct immunofluorescence (DIF) on perilesional skin showed a linear deposition of IgM at the dermo-epidermal junction (DEJ) (Fig. 1C). A strong intercellular IgM deposition was detected (Fig. 1D). The indirect immunofluorescence showed a deposition of IgM at the DEJ, and on the dermal side of salt-split skin (SSS) (Fig. 1E). To identify a possible autoantigen on the dermal side of the SSS, immunoblotting (IB) on keratinocyte extracts and supernatant, dermal extracts, affinity purified laminin 332 and a modified commercial ELISA to detect type VII collagen (coll VII) (MBL) IgM were performed. Although no band was detected by IB, a significant reactivity of circulating IgM to coll VII was detected by ELISA (Fig. 1G). We have also analysed the IgM binding with normal sera (Fig. 1F) and on other skin autoantigens (BP180 and BP230) by modified ELISA and no reactivity was found (data not shown). ELISA is often more sensitive than IB and this could be due to the loss of native epitopes present in coated protein (ELISA) and absent in the denatured one (IB)[1]. Modified ELISA is based on (i) coll VII coated on commercially available wells (MBL) and (ii) a secondary antibody goat anti-human IgM mu chain HRP conjugated (ab97205, Abcam Inc, Toronto, ON, Canada) used to detect human IgM autoantibodies bond to coll VII.

WM belongs to non-Hodgkin's B-cell lymphoma [2,3]. It is characterized by IgM paraproteinemia and lymphoplasmacytoid infiltration in the lymph nodes, spleen, and bone marrow [2,3]. Cutaneous manifestations of WM can be classified in non-specific and specific. The specific manifestations are associated with lymphocytic infiltration or skin deposition of IgM antibodies [2,4]. Non-specific cutaneous lesions of WM include leucocytoclastic vasculitis and Raynaud's phenomenon, while specific cutaneous lesions include papules and blisters [5]. The presence of isolated IgM deposits in

the skin is defined as cutaneous macroglobulinosis (CM)[2,5]. CM usually presents with pruritic, papules or plaques. Subepidermal blistering lesions are rare, specific manifestations of CM [5].

Some immunological features detected in our patient, such as IgM deposition at the DEJ, IgM staining of dermal side of SSS, and intercellular IgM deposition, were previously described [2–4,6,7]. However, with the exception of West et al., who detected an IgM reactivity to a 290 kDa antigen by IB [6], no other Author identified the antigen targeted by the patient's IgM[3,4,6,8,9] . In this context, we demonstrated a reactivity to coll VII by ELISA and not by IB, suggesting that IgM reacted with an epitope exclusively presents on the native protein. However, when patient serum was diluted to normalize IgM levels to those found in normal human serum, we obtained a negative result by coll VII ELISA (data not shown), suggesting that IgM could have low affinity for coll VII and/or this reactivity is due to a cross-reaction. These findings highlight that anti-coll VII IgM autoantibodies could represent the trigger for the blister formation, while the intercellular deposition of IgM could represent an epitope spreading phenomenon. Because of the high serum concentration of IgM, an unspecific result by ELISA cannot be excluded. However, it is possible that a huge concentration of IgM reacting or cross-reacting with an hemidesmosomal and/or desmosomal antigen leads to skin lesions.

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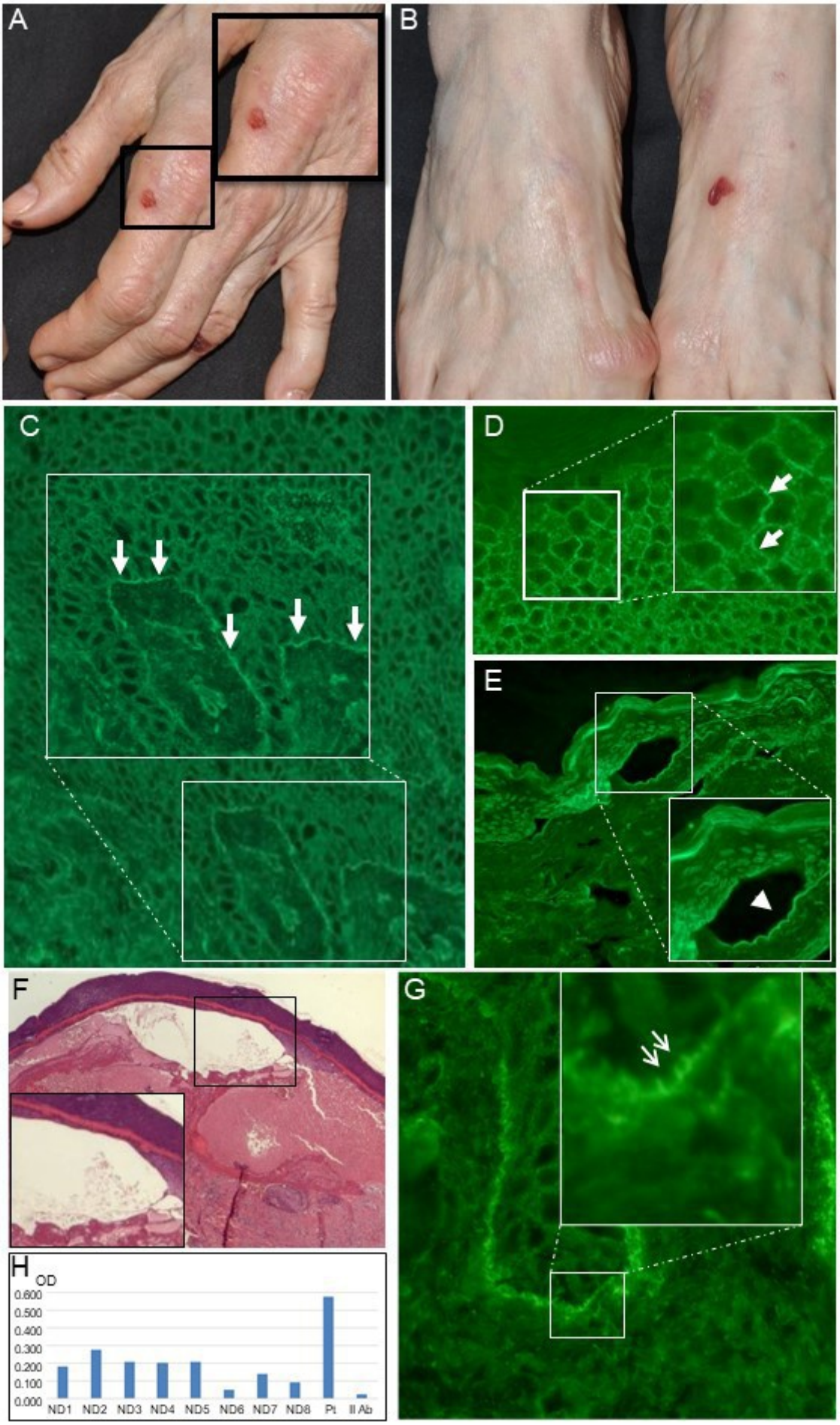
Figure legends:

Figure 1: Clinical and pathological manifestations of the patient A) Vesicular lesions on the dorsum of the hand; B) Vesicular lesions on the dorsal aspect of the foot; C) Direct immunofluorescence of perilesional skin showing deposits of IgM at the dermo-epidermal junction (DEJ) (arrows underline the linear staining at DEJ); D) Direct immunofluorescence of perilesional skin showing intercellular

deposition of IgM; E) Indirect immunofluorescence showing linear staining of IgM on the dermal-side (arrow head underlines the dermal staining) of salt-split skin; F) Histopathological examination shows a dermo-epidermal detachment; G) Modified ELISA for IgM shows a significant reactivity of patient serum (Pt) on recombinant collagen VII. Eight normal donors sera (ND1-ND8) and the anti-human IgM secondary antibody (II Ab) used show lower optical density (ODs) than Pt.

We obtain the consent of the patient for the publication of identifiable details, which can include photograph(s), case history and/or details within the text.



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