REVIEW

Paraprotein deposits in the skin

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Cutaneous manifestations secondary to paraprotein deposits in the skin include a group of different disorders that although rare, may be the first clinical manifestation of the underlying hematologic dyscrasia. In this article we review the clinical manifestations and histopathologic findings of the processes that result from specific deposition of the paraprotein in different structures of the skin. Paraneoplastic processes frequently associated with hematologic malignancies will not be covered in this review. Some of the disorders included here result from deposition of the intact paraprotein in the skin, whereas in other cases the lesions are due to deposition of modified paraproteins in the form of amyloid substance, cryoglobulins, or crystalglobulins. Cutaneous amyloidoma refers to nodular dermal deposits of amyloid derived from immunoglobulin light chains produced by local plasma cells in the absence of systemic amyloidosis. Dermatologists and dermatopathologists should be aware of the clinical and histopathologic features of these rare disorders because sometimes the cutaneous lesions are the first sign of an underlying silent hematologic malignancy with paraproteinemia. (J Am Acad Dermatol http://dx.doi.org/10.1016/j.jaad.2017.07.039.)

Key words: amyloidosis; angioendotheliomatosis; cryoglobulins; crystalglobulins; heavy chains; immunoglobulin; light chains; macroglobulinosis; paraprotein.

A monoclonal gammopathy results from a clonal proliferation of lymphoplasmacytic cells producing a monoclonal immunoglobulin or paraprotein.[1] Paraproteins are associated with a wide variety of skin disorders.[2] In this review, we focus on the cutaneous manifestations associated with deposits of paraprotein or its fragments in different skin structures (Fig 1).

Abbreviations used:

AL:	amyloid light chain
CG:	cryoglobulinemia
CS:	cryokeratotic spicules
CSH:	crystal-storing histiocytosis
HCDD:	heavy chain deposition disease
LCDD:	light chain deposition disease
MM:	multiple myeloma
NM:	nodular macroglobulinosis
PAS:	periodic acid–Schiff
RAE:	reactive angioendotheliomatosis
WM:	Waldenström macroglobulinemia

CUTANEOUS DEPOSITION OF PARAPROTEINS WITH ASSOCIATED PARAPROTEINEMIA

This section includes conditions with cutaneous deposits of the same monoclonal immunoglobulin that the patient has in the peripheral blood (paraproteinemia).

Deposits of the intact protein

An immunoglobulin that does not undergo major biochemical, ultrastructural, or 3-dimensional changes, such as crystallization, cryoprecipitation, or β-folding, is called *intact immunoglobulin*. Once deposited in the skin, the immunoglobulin may either show the whole structure with 4 polypeptide chains (2 identical heavy chains and 2 identical nonglycosylate light chains) or be found as a partial structure in which light or heavy chains are deposited independently.

Deposits of the entire protein. Macroglobulinosis cutis. IgM is a polymer characterized by multiple immunoglobulins linked together by strong covalent bonds, giving rise to pentamers. The combination of increased vascular permeability, high serum concentration, and presence of specific antigens in the skin may result in its deposition within

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the dermis, a condition known as cutaneous macroglobulinosis. Depending on the site of deposition, namely, within the dermis or along the dermoepidermal junction, the process is called *nodular macroglobulinosis* (NM) (IgM storage papules) or *bullous macroglobulinosis*.

Tichenor et al[3] first reported a patient with Waldenström macroglobulinemia (WM), with asymptomatic, pearly flesh-colored papules located on the knees. Histopathology showed hyaline deposits of IgM in the dermis. NM should not be confused with specific cutaneous involvement by neoplastic cells of WM.[4-8] Macroglobulinosis cutis consists of deposits of macroglobulins without associated amyloid or cellular infiltration. Seventeen cases of authentic NM have been published.[3,9-21] NM is slightly more frequent in male[3,9,10,13,15-17,20] than in female patients[11,12,14,18,21]; it may appear after,[3,10,13,17,18,20,21] simultaneously,[11,13,15] or even before[9,12,16,18,19] the diagnosis of WM and is usually characterized by the presence of pearly, flesh-colored, excoriated papules on the extensor aspect of the extremities[3,9,10,13,17,18,21] (Fig 2). Cutaneous lesions are asymptomatic and may be hemorrhagic,[13] umbilicated,[11] or crusted.[9,10] Histopathology reveals an eosinophilic, amorphous, homogenous, periodic acid–Schiff–positive (PAS^+), and IgM^+ material involving the upper dermis and mid dermis (Fig 2). Ultrastructurally, this material has a nonfibrillary, amorphous, or granular appearance. These nodular deposits of macroglobulin do not seem to have prognostic significance.[12-15,18]

Published cases of WM-induced immunobullous disease are difficult to interpret, either because of the lack of precise data[22-25] or because nonspecific immunobullous diseases due to paraneoplastic phenomena[26,27] were included. Only 6 published cases meet the specific criteria for WM-induced immunobullous disease.[28-33] Clinically, blisters,[31,33] scars,[31] erosions,[29,32] excoriations,[31] or papules,[28-30] especially on the dorsum of the hands,[29,31,32] have been described. Usually although not always,[28,30,31] there is a subepidermal blister[29,32,33] with linear deposits of IgM along the basement membrane zone that is located on the dermal side after 1 mol/L NaCl split.[30,33] In 2 cases,[30,31] immunoblotting revealed 2 bands, at the 82 kD[30] and the 290 kD[31] areas, respectively. The pathogenetic mechanism is unknown, although it may be similar to that of acquired epidermolysis bullosa. The culprit antigen could be a major structural component of anchoring fibrils,[31] although the variability of clinical findings in this rare condition may be due to lack of specificity of the IgM autoantibodies against the skin antigens.[33]

CAPSULE SUMMARY

- Cutaneous manifestations secondary to paraprotein deposition in the skin are rare but very characteristic.
- These disorders may be due to deposition of intact paraprotein (nodular and bullous macroglobulinosis, light chain disease, and heavy chain disease) or to deposit of modified paraprotein (amyloid, cryoglobulins, and crystalglobulins).
- Skin changes may be the first sign of a silent hematologic malignancy with paraproteinemia.

Cutaneous light chain deposition disease. Light chain deposition disease (LCDD) is characterized by visceral deposits of an amorphous material that is different from amyloid and contains the determinants of a monoclonal immunoglobulin light chain. This condition, which was first described by Randall et al in 1976,[34] is characterized by severe nephropathy. Other organs frequently involved include the liver, heart, lungs, and peripheral nerves.[35] Only a few cases of cutaneous LCDD have been described (Fig 3).[34,36-39] Specific cutaneous manifestations of this rare entity are similar to those of systemic amyloidosis; the histopathologic differences between these 2 conditions are summarized in Table I (Fig 3). Hydrophobic residues at unusual positions or the appearance of abnormal N-glycosylations in the variable domains that may modify the equilibrium of light chains in solution and promote their precipitation and tissue deposition have been proposed as the most plausible etiopathogenic mechanisms.[40]

Cutaneous HCDD. Heavy chain deposition disease (HCDD) is a form of plasma cell dyscrasia characterized by uncontrolled production and tissue deposition of abnormal immunoglobulin heavy chains without light chain deposition.[41] The truncated heavy chains in this disorder typically share deletions in the heavy chain constant domain 1. Heavy chains lacking the heavy chain constant domain 1 are unable to bind to chaperone proteins, which are responsible for keeping the heavy chains within the endoplasmic reticulum of the plasma cell for binding them to light chains.[42] Tissue deposition results not from antigen-specific binding but from altered chemical properties of the mutated heavy chain that govern its solubility, glycosylation, and charge.[43] The main involved organs are the kidneys and heart. In our review, we have found only 4 reported cases of cutaneous involvement in HCDD