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Cutaneous Humoral Immunity: Vasculitis and Autoimmune Bullous Dermatoses

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Abstract

This mini-review regroups the distinct cutaneous lesions observed in the context of humoral immunity. The specific cutaneous immune responses can be divided in two main groups of diseases: A first group that is in relation with the production of circulating immune complexes and a second group corresponding to the auto-immune diseases that are provoked by the production of autoantibodies directed against specific proper molecules of the patients. Histologically, the first group is dominated by lesions of cutaneous leukocytoclastic vasculitis. The second group is dominated by the Autoimmune Bullous Dermatoses. Nevertheless, there are bridges between the 2 groups of diseases. Both can affect the same patient and provoke distinct lesions in a single skin sample.

Keywords Humoral immunity; Auto immune disease; Leukocytoclasic vasculitis; Urticarial; Levers faciale granuloma; Erythema elevatum diutinum; Autoimmune Bullous Dermatosis (AIBD); Pemphigoid; Epidermolysa bullous acquisita; Pemphigus; Linear IgA dermatosis; Herpetiform dermatitis

Introduction

Humoral immunity regroups specific immune responses produced by B-lymphocytes and directed by particular antigens present in the blood and/or in the organs. Schematically, in the skin, it is possible to classify the causal antigens in 2 groups, exogenous and endogenous antigens. The first group is dominated by cutaneous vasculitis with deposits of immune complexes. The second group is formed by the Autoimmune Bullous Dermatoses (AIBD).

Literature Review

Cutaneous vasculitis with immune complexes

In this group of diseases, immune complexes circulate in the blood as soluble form. They cross through the vascular wall and locally trigger an inflammatory reaction by binding the complement, particularly the C3 fraction. The complement attracts polymorphous leukocytes and trigger lesions of vasculitis.

Acute leukocytoclastic vasculitis: The skin is a privileged organ in setting of vasculitis because it harbors a micro-vascularization where the bloodstream slowdowns. Furthermore, a venous stasis is often observed in the lower limbs, a preferential site of vasculitis. The extravasation of red blood cells is responsible for purpura, the major clinical sign of vasculitis. The term leukocytoclastic vasculitis refers to a common form of small vessel vasculitis [1]. The histologic aspect of early cutaneous lesions combines fibrinoid deposits and leukocytoclasia and necrotic alterations of endothelial cells. In the aging lesions, the vascular walls become fibrous, lymphocytes and macrophages with hemosiderin deposits progressively replace neutrophils. Lymphocytic vasculitis may correspond to an evolutionary stage of leukocytoclastic vasculitis, marking the transition from an acute to a subacute stage. However, some lesions of vasculitis can be primarily lymphocytic [2]. True lymphocytic vasculitis must be differentiated from perivascular lymphocytic infiltrates without fibrinoid necrosis of the vessel wall. In the acute phase of the eruption, the cutaneous Direct Immuno Fluorescence (DIF) shows immunoglobulin deposits in the vessel walls. Deposits of immunoglobulin IgM and complement fraction C3 are the commonest. They don't suggest a particular cause. In contrast, deposits of IgA are in favor of IgA vasculitis that is present in the Henoch-Schonlein purpura. Thus, the DIF is a useful help in favor of leukocytoclastic vasculitis. Nevertheless, the immunoglobulin deposits may disappear in a lesion of more than 72 hours old and the DIF may only show C3 deposits in the vessels wall. Cutaneous lesions have a major interest for the diagnosis of vasculitis but they do not allow etiological diagnosis. The lesions of vasculitis are either skin-limited or associated with deeper medium/ large-sized vessels lesions like in PAN, ANCA associated vasculitides [3]. Furthermore, cutaneous vasculitis may be observed in numerous systemic diseases: Lupus erythematosus, Churg and Strauss disease, inflammatory rheumatologic diseases, cryoglobulinemia, Chrohn's disease, hypersensitivity syndromes, bacterial and viral infections, drug eruptions, malignancies [4-7]. When the cutaneous lesions are inaugural, they may help the etiologic investigation, but the nature of the immune complexes responsible for the immune response is often unknown.

Besides the lesions of acute cutaneous vasculitis, entities can be classified as chronic localized cutaneous vasculitis: 1. Lever's facial granuloma 2. Erythema Elevatum Diutinum (EED). They are both skin limited but they are distinctly located on the body.

Lever's facial granuloma: The Lever's facial granuloma is a rare and chronic form of cutaneous vasculitis that results in one or more facial yellowish papules or nodules. The biopsy shows an inflammatory infiltrate of medium dermal seat, rather well limited, respecting as a rule the epidermis from which it is separated by a grenz-zone. The pores of the hair follicles are dilated contrasting to the inter-follicular site of the inflammation. This inter-follicular

location of the inflammation is helpful for the differential diagnosis from common inflammatory facial lesions. In early lesions, the infiltrate is polymorphous and rich in picnotic leukocytes that are eosinophils and neutrophils. In later stage lamellar fibrosis containing debris of nuclei and foamy macrophages are predominant.

Erythema Elevatum Diutinum (EED): The EED and the Lever's facial granuloma are similar, but the location of the cutaneous lesions is distinct. The usual presentation of EED consists of multiple nodules on the limbs. Its evolution is more chronic than Lever's facial granuloma's one. Neutrophils are more numerous than eosinophils in the early stages of the lesions. In both entities, the chronic stage is characterized by a lamellar and angiocentric fibrosis which contains nuclear debris of leukocytes. In spite of the presence of IgG4+ plasma cells in the infiltrates of EED and Lever's facial granuloma, both entities did not meet the consensus immunohistochemical diagnostic criteria for IgG4 related diseases [8]. Contrary to the Lever's facial granuloma, the EED may occur in the course of systemic pathologies like hemopathy, lymphoma, and chronic enteropathy.

Autoimmune Bullous Dermatoses (AIBD): This group of diseases is related to autoimmune blistering diseases [9]. The lesions are usually localized in the skin or mucosae homing the target antigens that are bound *in situ* to autoantibodies. The pathophysiology responsible of autoimmunity is discussed [10]. The origin may be either a disruption of the patient's immune system or an immune response to altered tissue proteins or both. The consequence is that the patient abnormally produces antibodies directed against his own proteins that constitute the target antigens. Skin and/or mucosal blisters are common clinical features that may lead to significant cutaneous damage with vast erosions. The lesions are usually limited to the skin and/or the mucous membranes. The target antigen is specific for the disease and the molecular weight of the target antigens leads to a detailed classification of the AIBD. The location and the type of immunoglobulins (IgG, IgA, IgM) are specified by the DIF. The location of the blister depends on the location of the target antigens intra-epidermal or Dermal Epidermal Junction. The AIBD comprise heterogeneous disorders including the intra-epidermal pemphigus group, namely pemphigus vulgaris and foliaceus, and the subepidermal pemphigoid group, namely pemphigoid, Epidermolysis Bullosa Acquisita (EBA), linear IgA disease, and Dermatitis Herpetiformis (DH).

Intra-epidermal group of aibd

Pemphigus is a group of skin and mucous-bubbling diseases [11]. All pemphigus are due to the production of specific antibodies directed against inter-keratinocytic adhesion molecules, named desmosomes. Five main types of pemphigus are described: *P. vulgaris*, *P. foliaceus*, IgA pemphigus, drug-induced pemphigus and paraneoplasic pemphigus.

Pemphigus vulgaris: The pemphigus vulgaris is the most common. Mucosal lesions are almost constant and sometimes inaugural, including oral erosions. There is skin fragility. Detachments are caused by a simple friction of the skin (sign of Nicholsky). The biopsy of a bulla shows a supra-basal acantholytic cleavage and reactive superficial infiltrates with eosinophils. An aspect of eosinophilic spongiosis may be the only lesion present in recent non-bullous lesion or at the periphery of a bubble. In the bullae and erosions, acantholytic cells are evidenced on smears. The DIF of a cutaneous or mucosal lesion shows fluorescent filet-like IgG and C3 deposits in the epithelium. The DIF is necessary to rule out the non-immunologic acantholytic diseases like Hailey-Haileys, Grovers, Dariers disease in which the DIF is negative.

Pemphigus foliaceus: The bullae are due to a superficial intra-epidermal cleavage. Commonly, there is no mucosal lesion. The target antigen is DSG-1. It is less present than DSG-3 in mucosae. That is an explanation why the mucosae are usually normal in this type of pemphigus.

IgA pemphigus: Clinically IgA pemphigus is characterized by pruritic vesiculopustular eruptions. Histopathology is useful in differentiating the two major subtypes of IgA pemphigus [12]. In the Subcorneal Pustular Dermatosis (SPD) subtype, there is an increased intensity of IgA autoantibodies in the upper surface of the epidermis. In contrast, in the Intra Epidermal Neutrophilic (IEN) type, the IgA antibodies are located either in the entire or in the lower part of the epidermis. The target antigen type of the SPD subtype is desmocollin-1, which is important for the differential diagnosis with Sneddon-Wilkinson sub-corneal pustulosis in which the DIF is negative. The IEN type involves IgA antibodies directed against desmogleins 1 and 3. IgA pemphigus has been associated with monoclonal IgA gammopathy and multiple myeloma. Other associated diseases include human Immunodeficiency Virus (HIV) infection, Sjogren disease, rheumatoid arthritis, and Crohn's disease.

Drug-induced pemphigus: The lesions are polymorphous in this type of pemphigus. Clinically and histologically, they may be lichenoid or erythema multiforme. The etiologic investigation may find that some cases are drug-Induced. Because of the atypical presentation of the lesions, it may be very difficult to establish the diagnosis of pemphigus. If firstly negative, the DIF must be repeated.

Para Neoplastic Pemphigus: Para Neoplastic Pemphigus (PNP) is a rare muco-cutaneous autoimmune disease associated with neoplasm. Blisters and interface dermatitis sometimes co-appear in the same lesion. In DIF of the muco-cutaneous lesions, IgG autoantibodies and/or complement deposition is observed in the epidermal intercellular spaces and/or along the basement membrane zone. Immunoblot analysis using epidermal extracts has been used to detect 210 kDa envoplakin and 190 kDa periplakin, which are highly sensitive and specific for PNP Cutaneous and/or mucosal erosions may be the inaugural sign of a malignant condition like hemopathy / lymphoma or solid cancer.

Sub-epidermal group of AIBD

Pemphigoid: Pemphigoid is the most frequent of AIBD [13]. The cutaneous biopsy of a bullous lesion shows polymorphic perivascular infiltrates rich in eosinophilic polynuclear associated with smaller lymphocytes in the superficial dermis. There is no vasculitis. Cutaneous DIF test made on the non-bullous erythematous zone confirms the diagnosis by showing a linear deposition of IgG and C3 complement fraction in Dermal-Epidermal Junction (DEJ). The pemphigoid target antigens are BP180 (BPAG2) or BP230 (BPAG1) proteins located in lamina lucida.

The Mucus Membrane Pemphigoid (MMP): MMP is characterized by predominant mucous membranes erosions. The distinction from EBA may be difficult. Some authors have proposed as a diagnostic tool the detection of IgG and IgA antibodies in both serum and saliva of patients [14].

Epidermolysis Bullosa Acquisita (EBA): EBA is a bullous dermatosis of the Dermal-Epidermal Junction (DEJ), but the cleavage

is deeper than that of pemphigoid. Clinically, bubbles occur in middle-aged adults, in areas exposed to trauma (feet, hands, buttocks) and in the mucous membranes. The DIF shows a linear IgG deposit at the DEJ. The autoantibody targets the NC1 domain of collagen VII.

Linear IgA disease: In adults, lesions are easily annular or in cockroaches, the newer bubbles have a circinate arrangement around the older lesions [15]. Some forms can manifest as detachments simulating toxic epidermal necrolysis or Lyell syndrome, with mucosal lesions. The differential diagnosis is all the more difficult as drugs are incriminated in linear IgA dermatosis, especially vancomycin. Histologically, a sub-epidermal bulla with an intact roof is observed. The superficial dermis contains numerous neutrophils. The DIF shows a linear IgA deposit at the DEJ.

Dermatitis Herpetiformis (DH): DH preferentially affects young adults and children. DH is associated to coeliac disease in 15%-25% of the patients [16]. Clinically the lesions are herpetic-like small grouped vesicles that are symmetrically arranged. The lesions are preferentially located on the trunk and the bottom. The histological lesions are intra-papillary micro-abscesses located in some dermal papillae. Discrete lesions of leucocytoclastic vasculitis may occur. The DIF shows IgA granular and/or fibrillar IgA and C3 deposits in the dermal papillae, and inconstant IgA deposits in vessels. In the blood, circulating immune complexes may be present.

Associations of humoral immune pathologies

Schematically, the dermatoses related to humoral immunity can be divided into 2 groups of pathologies: Those due to vascular deposits of circulating immune complexes and those due to autoimmune antibodies. In the first group, the main lesions are cutaneous vasculitis. The second group is dominated by Autoimmune Bullous Dermatoses. Nevertheless both types of humoral immunity may be combined, especially in systemic diseases.

Discussion and Conclusion

For instance, patients with lupus erythematosus may have lesions of vasculitis and lesions of AIBD, like linear IgA bullous dermatosis or acquisita bullous epidermolysa. Regarding their cause, infectious and non-infectious agents, environmental agents and drugs, may be invoked as a possible cause of vasculitis as well as autoimmune diseases. For instance, pemphigoid can be observed after scabiosis, vancomycin is a possible cause of linear IgA bullous dermatosis; D-penicillamine can induce lesions of drug-induced pemphigus. Both circulating immune complexes and autoimmune antibodies are possibly found in the same disease: For instance, patients with Dermatitis Herpetiformis may have in the same cutaneous sample granular deposits in the capillaries and fibrillar anti-fibronectin antibodies in the dermal papillae.

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