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INVITED REVIEW ARTICLE

A widening perspective regarding the relationship between anti-epiligrin cicatricial pemphigoid and cancer

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Summary Anti-epiligrin cicatricial pemphigoid (AECP) is a chronic, autoimmune, subepidermal blistering disease characterized by circulating anti-basement membrane autoantibodies to laminin 5. Recent studies have shown that patients with this form of cicatricial pemphigoid have an increased relative risk for malignant solid tumors. The mechanism underlying this association of AECP and cancer is unknown, but there is accumulating evidence that laminin 5 plays a central role. In this article we report a patient with AECP and co-associated cutaneous T cell lymphoma and summarize all to date reported cases of AECP associated with malignancies. In addition we provide a review of the biology of laminin 5 and its potential role in cancer development.

Contents

Over the past 15 years it has become apparent that a subset of cicatricial pemphigoid (CP) patients has circulating autoantibodies directed against the basement membrane (BM) protein laminin 5 (laminin 332). Since initial studies showed that this ''autoantigen'' is present in the extracellular

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matrix of cultured human keratinocytes and was specifically reactive with a monoclonal antibody directed to a protein called at that time "epiligrin", this disorder was termed anti-epiligrin cicatricial pemphigoid (AECP) [1]. Anti-laminin 5 autoantibodies are specific to patients with AECP and are not seen in patients with other autoimmune blistering diseases or normal volunteers. Recent studies showed that patients with AECP have an increased relative risk (RR) of solid cancer. This association underscores the importance of defining AECP as a specific disease subtype within the spectrum of CP [2].

Herein we describe a patient with AECP and co-associated cutaneous T cell lymphoma (CTCL). This case (and others) broadens the association of this subtype of CP with cancer. A summary overview of all AECP cases associated with cancer along with a review of the biology of laminin 5 and its potential role in cancer development is provided.

1. Case report

A 46-year-old Caucasian female presented with a 12-year history of mildly pruritic, persistent dermatitis. The skin showed thin plaques of 2—5 cm^2 with secondary erythema and scale mainly on the lower trunk, groin, and thighs (Fig. 1A). Light microscopy studies of lesional skin revealed an infiltration of atypical lymphocytes in the upper dermis with extensive overlying epidermotropism, characteristic of CTCL (i.e., mycosis fungoides). There was no lymphadenopathy, hepatosplenomegaly, generalized pruritus, fever, or weight loss on initial or subsequent follow-up exams. Lesions were controlled (i.e., thinned, rendered asymptomatic) by daily applications of triamcinolone acetonide 0.1% or clobetasol proprionate 0.05% ointment.

Shortly, after the diagnosis of CTCL was established, the patient developed oral and nasal erosions. Direct immunofluorescence microscopy of perilesional skin demonstrated linear deposits of IgG and C3 in epidermal BM. Indirect immunofluorescence microscopy studies showed that the patient's serum contained circulating IgG autoantibodies that bound the dermal side of 1 M NaCl split human skin (titer, 5). Subsequent immunoblot and immunoprecipitation studies (Fig. 1B) demonstrated that the patient's serum contained IgG reactive with the α subunit of laminin 5 (200 and 165 kDa unprocessed and processed forms, respectively), leading to the diagnosis of AECP.

Mucosal involvement (i.e., oral and nasal erosions) has been generally controlled with low doses of daily (5—20 mg) or alternate day (10—20 mg) systemic corticosteroids in conjunction with daily topical glucocorticosteroids (triamcinolone acetonide 0.1% or clobetasol proprionate 0.05% ointment). To date, no cutaneous, laryngeal, or anogenital lesions have developed. Besides mild scarring of the conjunctiva and lower eyelid of the right eye (along with focal loss of eyelashes), the overall course of this patient's AECP has been without further complications. Overall, both AECP and CTCL in this patient are stable, of low-grade activity, and well controlled by low dose systemic and/or topical glucocorticosteroids.

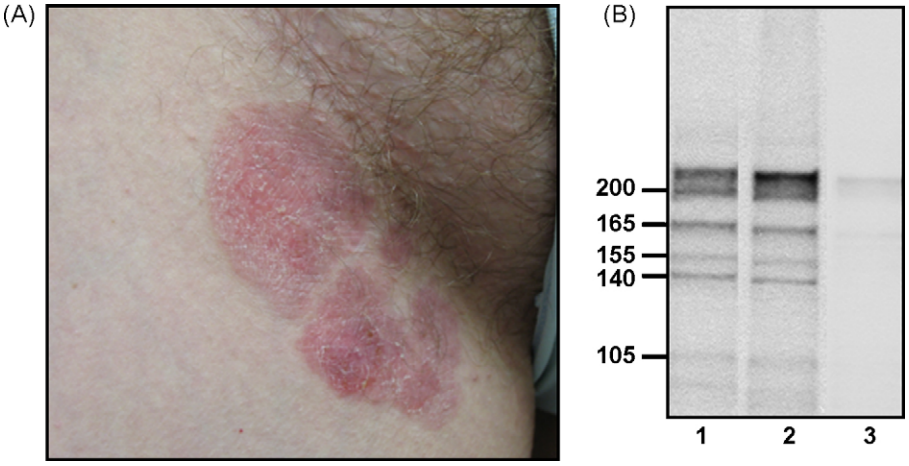

Fig. 1 (A) CTCL presented with scaly pink patches and plaques in the right groin. (B) Immunoprecipitation studies of biosynthetically radiolabeled human keratinocytes extracts showed that the patient's serum (lane 1) recognized the same set of polypeptides as the reference laminin 5 antiserum (lane 2). None of these polypeptides were immunoprecipitated by normal human serum (lane 3). The markers in the left margin denote molecular weights (kDa) of the unprocessed and processed subunits of laminin 5.