AUTOIMMUNE BULLOUS DISEASES

The Relationship between Autoimmune Bullous Disease and Systemic Disorders

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The mystery of the association of skin disease with systemic disease has been a matter of fascination to dermatologists for hundreds of years. There are a myriad of articles and case reports linking various cutaneous findings to internal disease. The implication has always been that some soluble or cellular factor is being produced that results in a cutaneous disease. Immunobullous disease associates a particular antibody with a cutaneous disease and so the responsible factor for associating an immunobullous disease with a systemic disease is production of an antibody. We will review the milestones in immunobullous disease that have refined our understanding of these associations and consider possible pathogenic mechanisms.

Dermatitis herpetiformis (DH) is a papulovesicular skin disease with gluten-sensitive enteropathy (celiac disease, CD) and a unique HLA type (HLADQ2 and DQ8) associated in virtually all cases. Granular deposition of IgA is the immunopathological hallmark. Marks *et al*. (1966) are generally credited with describing the association of CD with DH. Marks, Fry, and others established that the skin disease with its IgA deposition as well as the intestinal disorder responded to gluten restriction and recurred with the reinstitution of a gluten-containing diet culminating in a landmark paper on gluten challenge in 1983 (Leonard *et al*., 1983). Katz and Strober (1978) clarified the association of HLA B8/DR3 with the entire spectrum of CD with DH. Kumar *et al*. (1987) established the presence of IgA endomysial antibodies in DH and CD patients. The endomysial antigen was found to be tissue transglutaminase, and now testing for IgA tissue transglutaminase antibody has become the standard for the serological diagnosis of CD. The link between the intestine and the skin in genetically predisposed individuals is twofold. First, Hall *et al*. (2007) have established that cytokines elaborated at the site of intestinal inflammation are likely critical to the inflammatory process in the skin. Second, Sardy *et al*. (2002) have shown that epidermal transglutaminase is the antigen bound to the IgA stimulated by the intestinal inflammatory process.

The association between DH and thyroid disease is even more intricate. In 1983, Cunningham and Zone (Cunningham and Zone, 1985) closely evaluated 50 DH patients, and showed that these patients had a high incidence of thyroid autoantibodies as well as hyperthyroidism, hypothyroidism, and thyroid enlargement. Gaspari *et al*., 1990. showed that this association was not related to the underlying HLA B8/DR3 genotype but was likely related to a high prevalence of Hashimoto's thyroiditis manifested by thyroid autoantibodies and was independently associated with DH. Whether or not the intestinal inflammation in DH patients is responsible for stimulating the thyroid autoimmune process by a cellular or humoral mechanism remains to be determined (Gaspari *et al*., 1990).

Since the 1980s, several immunobullous disorders have been linked to inflammatory bowel disease including bullous pemphigoid, epidermolysis bullosa acquisita (EBA), and linear IgA bullous disease in case reports and case series. Of these, EBA appears to have the strongest association with inflammatory bowel disease. EBA, an immunobullous disorder is characterized by autoantibodies to type VII collagen, the major structural protein of anchoring fibrils, and clinical presentations resembling bullous pemphigoid, cicatricial pemphigoid, or epidermolysis bullosa. EBA has been described in patients with both Crohn's disease and UC, with Crohn's disease being the predominant association. In a study of 51 EBA patients, Chen *et al*. (2002) found that 25% (13 of 51) had inflammatory bowel disease: 12 had Crohn's disease and 1 had UC. They also demonstrated full-length (290 kDa) type VII collagen in normal colonic extracts from four patients and type VII collagen immunoreactivity in the colonic basement membrane. Of 19 patients, 13 patients with Crohn's disease and 4 of 31 patients with UC were found to have elevated levels of circulating antibodies to the immunodominant NC1 domain of type VII collagen by ELISA. Despite these findings, there is no evidence linking an autoantibody to the pathogenesis of inflammatory bowel disease. The presence of type VII collagen antibodies is thought to represent epitope spreading, resulting from exposure of type VII collagen epitopes due to damage to the overlying colonic mucosa.

Immunobullous diseases have also been linked to malignancies. The quintessential disorder is paraneoplastic pemphigus (PNP), described by Anhalt *et al*. (1990). PNP is characterized by painful mucosal erosions and polymorphous

skin lesions that may resemble pemphigus vulgaris, bullous pemphigoid, erythema multiforme, graft vs host or lichenoid eruptions and a mortality rate approaching 90% (Nousari *et al.*, 1999). More recently, it has been recognized as a multisystem disease involving lung, kidney, and muscles, in addition to skin and mucosa. In the landmark paper by Anhalt, all the five patients had a related disease: four malignancies (chronic lymphocytic leukemia, one; non-Hodgkin's lymphoma, two; poorly differentiated sarcoma, two) and one benign thymoma. At present, PNP is largely seen in conjunction with lymphoproliferative neoplasms including non-Hodgkin's lymphoma and chronic lymphocytic leukemia (two of three cases), Castleman's disease, benign and malignant thymomas, sarcomas, and Waldenström's macroglobulinemia. PNP in association with solid tumors such as lung, breast, and colon cancer has also been reported.

Anhalt *et al.* (1990) initially described four autoantigens with molecular weights of 250, 230, 210, and 190 kDa, which are now recognized as desmoplakin I, BPAg1, envoplakin, and periplakin, respectively. Since then, other autoantigens have been identified including desmoglein-1 and -3, plectin, and desmoplakin II. The polymorphous nature of the skin and mucosal lesions can be attributed to this potpourri of autoantigens. Cytotoxic T cells, natural killer cells, and macrophages have been identified in involved tissue, suggesting a function for cell-mediated immunity in the pathogenesis of PNP.

Anti-epiligrin cicatricial pemphigoid is an autoimmune blistering disease with autoantibodies against the basement membrane protein, laminin 5. Egan *et al.* (2001) described an increased risk of malignancy in patients with anti-epiligrin cicatricial pemphigoid. A total of 35 patients met the case definition for anti-epiligrin cicatricial pemphigoid: presence of erosive or blistering lesions of the mucous membranes with or without cutaneous involvement; deposition of IgG in the epidermal or mucosal basement membrane and/or circulating IgG autoantibodies that bound to the dermal side of 1 M NaCl split human skin; and circulating IgG that immunoprecipitated laminin 5 from extracts or conditioned media from cultured human keratinocytes. A total of 10 patients (28.6%) developed a solid cancer (lung, three; gastric, three; colon, two; endometrial, two). Of these ten cancers, 9 were adenocarcinomas. Nine patients developed cancer ±14 months from the onset of blistering. Eight cancers occurred after onset of blistering, the majority (six of eight) within the first year. The median observation period was 2.67 years. In the general population, 1.48 cancers would be expected to occur in this time frame, yielding a relative risk of cancer of 6.8 in these patients with anti-epiligrin cicatricial pemphigoid. This cancer risk is similar to that of patients with dermatomyositis. Two patients' clinical disease improved with resection of the primary tumor.

Systemic lupus erythematosus exhibits a panoply of deranged immunologic processes. The association of systemic lupus with bullous lupus erythematosus is just another manifestation of this immune regulation gone awry. Bullous lupus erythematosus is a widespread inflammatory subepidermal vesiculobullous eruption that is associated with systemic lupus erythematosus. It may occur with or without an exacerbation of the systemic lupus. Gammon and Briggaman (1993) defined an immunopathologic process in a portion of the patients when they found that many cases of bullous lupus have circulating antibodies that bind to type VII collagen, as is characteristic of EBA. However, the association with the wide range of immunologic abnormalities seen in bullous lupus erythematosus is absent in EBA.

Immunopathologically, some cases of bullous lupus may be indistinguishable from dermatitis herpetiformis although other Igs in combination with IgA are usually seen in the basement membrane zone. In addition, no association with gluten-sensitive enteropathy in patients with bullous lupus has been described. In a landmark study, Hall *et al.* (1982) reported rapid and complete response of patients to dapsone.

In conclusion, our understanding of the relationship between immunobullous disease and systemic disorders has expanded dramatically over the past 30 years. We have summarized the milestones that have paved the way to our current insights.

CONFLICT OF INTEREST

The authors state no conflict of interest.

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