IgA Autoimmune Disorders: Development of a Passive Transfer Mouse Model

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IgA is present in the skin in several dermatoses, including dermatitis herpetiformis, linear IgA bullous dermatosis, and Henoch-Schoenlein purpura. The neutrophilic infiltration in the area of the IgA deposition suggests that IgA is responsible for the associated inflammatory events. The mechanism for this process is unproven, but is likely to involve IgA-mediated neutrophil chemotaxis with inhibition of chemotaxis by dapsone. Elucidation of the mechanism of IgA-mediated inflammation will require an animal model. We have established a model for linear IgA bullous dermatosis as a prototype disease to be studied. IgA mouse monoclonal antibodies against a linear IgA bullous dermatosis antigen have been passively transferred to SCID mice with human skin grafts. This has produced neutrophil infiltration and basement membrane vesiculation in 4 of 12 mice tested. We conclude that an animal model for the pathogenesis of IgA dermatoses with IgA deposition and inflammation can be produced by passive transfer of mouse IgA antibodies against a linear IgA antigen. ***Keywords:* *J Investig Dermatol Symp Proc 9:47–51, 2004***

IGA IN AUTOIMMUNE DISORDERS OF THE SKIN

The hallmark of IgA autoimmune disorders of the skin is the deposition of IgA in tissue at the site of the inflammatory process. In these disorders, IgA is the only or the predominant immunoglobulin detected in the skin. Next there is infiltration of neutrophils into the skin and compromise of the function of structural proteins. This produces vesiculation or blood vessel destruction that is clinically evident as vesicles, bullae, and purpura. Dapsone usually inhibits the inflammatory process, but it does not inhibit the deposition of IgA in the skin.

Tissue-specific IgA antibodies in the serum may be identified. This is the case in linear IgA bullous dermatosis (LABD) and IgA pemphigus. In dermatitis herpetiformis (DH), IgA vasculitis, and bullous lupus erythematosus, however, no tissue-specific antibodies have been identified in the circulation. The IgA dermatoses are listed in **Table 1**.

Table 1. IgA Dermatoses

Dermatitis herpetiformis
Linear IgA bullous dermatosis
Chronic bullous disease of childhood
Linear IgA/IgG bullous dermatosis
Ocular cicatricial pemphigoid
IgA pemphigus (intraepidermal type)
IgA pemphigus (subcorneal pustular dermatosis type)
IgA vasculitis (Henoch-Schoenlein purpura)
Bullous lupus erythematosus

CONTRAST WITH IGG DERMATOSES

Many of the IgA dermatoses have IgG-associated counterparts. The contrast between the IgA dermatoses and the analogous IgG dermatoses also provides insight into pathogenic factors related to antibody class specificity.

Pemphigus vulgaris (PV) and pemphigus foliaceus (PF) demonstrate cell surface deposition of IgG on epithelial cells. These antibodies bind the cadherins desmoglein 3 and desmoglein 1, respectively (Emery *et al*, 1995; Harman *et al*, 2000). The acantholytic process seems to be one of direct destruction of the cadherins, which maintain epithelial cell adherence, or possibly an antibody-stimulated proteolytic process that destroys the adherence proteins. Fixation of complement and infiltration of inflammatory cells is not essential to the acantholytic process. IgA pemphigus foliaceus (referred to as the subcorneal pustular variant of IgA pemphigus) and IgA PV (referred to as the intraepidermal variant of IgA pemphigus) demonstrate cell surface deposition of IgA on epithelial cells. IgA pemphigus antibodies only bind infrequently to desmogleins, however, but more often bind to another class of cadherins termed desmocollins (Hashimoto *et al*, 2001). They do not seem to stimulate acantholysis by their physical presence, but require the infiltration of neutrophils for acantholysis and vesiculation. The pathogenic process is clearly different for IgG and IgA dermatoses. Autoantigen stimulation of the IgA immune system produces a response to a neighboring autoantigen. The amino acid sequence of the alpha chain of IgA somehow initiates an entirely different process than that of the gamma chain.

In a similar manner, basement membrane antibody–related diseases differ in their antigenic specificity and presumed pathogenesis. Bullous pemphigoid (BP) and the lamina lucida type of LABD both demonstrate lamina lucida deposition of immunoglobulin and are associated with BMZ vesiculation. The antigenic specificity differs, however. Pathogenic epitopes for the IgG immune response are believed to be in the MCW-1 region of the

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Abbreviations: AB, antibody; BMZ, basement membrane zone; BP, bullous pemphigoid; DH, dermatitis herpetiformis; EBA, epidermolysis bullosa acquisita; LABD, linear IgA bullous dermatosis; Mab, monoclonal antibody; PF, pemphigus foliacious; PV, pemphigus vulgarous;

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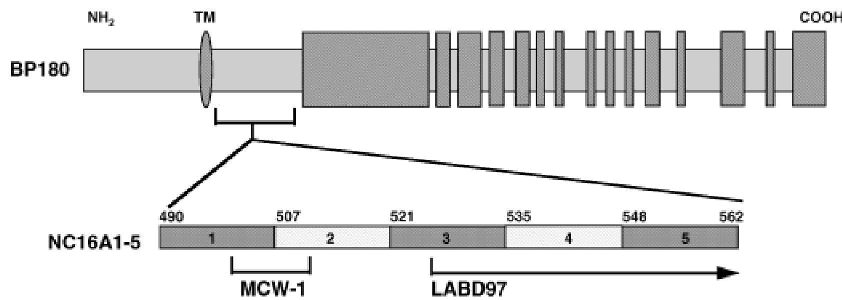

Figure 1. Diagrammatic representation of the transmembrane hemidesmosomal protein BP180 (BPAg2). The primary site of antigenic reactivity for bullous pemphigoid (MCW1) is different from that for linear IgA bullous dermatosis (LABD97).

NC16 domain of BP Ag2 (BP180), whereas the epitopes that have stimulated an IgA immune response are toward the carboxy terminus of the same molecule (**Fig 1**) (Giudice *et al*, 1993; Zone *et al*, 1998). Epitopes in LABD appear to become antigenic only when the molecule has been proteolytically cleaved. The typical inflammatory cell in BP is the eosinophil with an admixture of neutrophils and mononuclear cells. There is also a "cell-poor" histologic variant of pemphigoid. In contrast, LABD is invariably associated with the intense infiltration of neutrophils at the BMZ and in dermal papillae identical to that of DH. No cell-poor variant has been described. Epidermolysis bullosa acquisita (EBA) and the sublamina densa type of LABD are analogous in that antibody deposition is in the sublamina densa area in both conditions. In EBA the antigenic specificity for IgG antibodies has been identified as type VII collagen (Lapiere *et al*, 1993). In the sublamina densa variant of LABD, some cases have been reported in which patient serum IgA antibodies bind to type VII collagen (Zambruno *et al*, 1994). We had the opportunity to test 11 sera with antibodies binding to the dermal side of BMZ split skin, however, and only 1 of those sera was found to bind to type VII collagen on immunoblot. It seems likely that other antigens may be involved in these dermal LABD patients. We were not able to establish any other antigenic specificity on immunoblot. Classically, both EBA and sublamina densa LABD have an intense infiltration of neutrophils. Why the nature of the inflammatory infiltrate should vary from BP to EBA is likewise unclear.

LINEAR IGA/IGG DERMATOSES

Frequently, patients with linear deposition of immunoglobulin along the BMZ demonstrate both IgG and IgA deposition. The exact terminology to describe these cases is difficult. Convention has dictated that these diseases be described as BP if IgG is the predominant immunoglobulin, or as LABD if IgA is the predominant immunoglobulin. It has been our belief, however, that these represent diseases different from true BP or true LABD. If, indeed, the antibody deposition at the BMZ is responsible for the pathogenesis of the disease, it makes sense that a combination of two immunoglobulin classes would produce a different pathogenesis than a single antibody class. We investigated the antigenic specificity in these disorders and found that for these basement membrane antibodies it is mixed (Zone *et al*, 1994). Studying the pathogenesis of disorders such as these will be accomplished only when multiple specific antibodies are available for passive transfer experiments. In the meantime, it is our opinion that these diseases should be called linear IgA/IgG bullous dermatosis (LAGBD), rather than be named on the basis of the predominant immunoglobulin.

DERMATITIS HERPETIFORMIS

Dermatitus herpetiformis (DH) has no real analogy in any of the IgG bullous dermatoses. Virtually all patients with DH have granular IgA deposition along the basement membrane or in dermal papillary tips. Because the inflammatory infiltrate is predominantly neutrophilic, the connection between IgA deposition and neutrophil infiltration is again demonstrated. Likewise, responsiveness to dapsone is one of the hallmarks of DH and emphasizes the unique nature of IgA dermatoses.

DH patients have a unique HLA type (HLA DQ2 A1*501B1*201). This is present in greater than 90% of patients and appears to be central to the antigen recognition process in which gliadin initiates a systemic immune response. This antigen recognition is essential in the pathogenesis of both DH and celiac disease which shares DH's immunogenetic predisposition. Virtually all patients with DH have some degree of celiac disease. This covers the histologic spectrum of jejunal mucosal inflammation and ranges from minimal intraepithelial lymphocyte infiltration with normal villi to an entirely flat intestinal mucosa. As such, DH can be considered an extraintestinal manifestation of celiac disease (Zone, 1991).

Until recently, no consistent serologic difference could be established that differentiated DH from celiac disease, and thus there was no serologic explanation for the deposition of IgA in dermal papillae. There was also no evidence of an antigen associated with the deposition of granular IgA. Recently, Sardy and colleagues found that IgA antibodies to epidermal transglutaminase are higher in patients with DH whereas IgA antibodies to tissue transglutaminase are higher in celiac disease. Both groups, however, may have some amount of antibody to each transglutaminase antigen. The researchers also demonstrated that DH skin contains epidermal transglutaminase in dermal papillae that colocalizes with IgA (Sardy *et al*, 2002). Tissue transglutaminase was not found in association with the IgA in dermal papillae. Patients with LABD were not found to have transglutaminase in dermal papillae or at the BMZ, indicating that the distribution was specific for DH and did not colocalize or cross-react with all cutaneous IgA. These findings speak strongly for epidermal transglutaminase as an antigen in DH. Although this work has been a landmark of progress in understanding DH, the exact method by which the antigen/antibody complex reaches the tissue has not yet been established and there is no animal model for DH that has yet been developed as a result of this work.

The responsiveness of DH to dapsone Responsiveness to dapsone was once considered a diagnostic criterion for DH. A number of other dermatoses clearly respond to dapsone, however and the list of dapsone-responsive dermatoses includes all of those listed in **Table 1**. One would think that dapsone's mechanism of action would be specifically related to IgA antibody and possibly related to neutrophil chemotaxis, but the exact mechanism by which dapsone is effective in these dermatoses has not been established. It is known that dapsone has no effect on antibody or complement deposition. Dapsone does inhibit neutrophil lysosomal activity and has been shown to inhibit myeloperoxidase-mediated iodination. Dapsone has also been shown to inhibit F-met-leu-phe-derived chemotaxis, but not to inhibit chemotaxis to C5a. We evaluated the role of dapsone in the neutrophil attachment assay and found that it inhibits the adherence of neutrophils to basement membrane

zone antibody in a dose-dependent manner that covers the pharmacologic range of serum dapsone levels (Thuong-Nguyen *et al*, 1993). Nevertheless, this still does not explain how dapsone inhibits chemotaxis of neutrophils into sites of IgA deposition.

AN ANIMAL MODEL OF IgA DERMOTOSES

Perhaps the biggest differentiation between IgG and IgA dermatoses is the fact that IgG autoantibodies have been proven to be pathogenic to skin in an animal model. In 1982 Anhalt and colleagues published their landmark work demonstrating that human pemphigus antibody passively transferred to neonatal mice produces acantholytic changes in mouse epithelium similar to those found in human pemphigus (Anhalt *et al*, 1982). Similar experiments with human BP antibodies were, however, unsuccessful (Anhalt and Diaz, 1987). It was subsequently shown that the epitopes to which IgG BMZ antibodies to BPAg2 reacted were not present in mouse skin. Liu and colleagues demonstrated that rabbit IgG antibodies directed against mouse BPAg2 epitopes are pathogenic when passively transferred to neonatal mice (Liu *et al*, 1993).

Our long-term goal has been to develop a mouse model for the pathogenesis of IgA dermatoses. We initially attempted to passively transfer the immunoglobulin fraction (ammonium sulfate precipitation fraction) of DH serum to athymic mice that carried grafts of normal human skin. This approach did produce occasional aggregates of IgA in dermal papillae, but IgA deposition was not consistent and the pattern was not that of granular IgA seen in the dermal papillae in DH; neutrophil infiltration and vesiculation were only noted on rare occasions.

As no circulating antibody responsible for the IgA deposition in DH has been identified, we turned our attention to LABD. In LABD, circulating IgA antibodies directed against cutaneous basement membrane have been consistently identified by indirect immunoflourescence. Clinically, there are two types of LABD. In the first type, the disease is very similar to DH in its clinical appearance and is characterized by grouped or scattered papulovesicles and excoriations. In the second type, the disease is clinically similar to BP, in which there are larger bullae and excoriations in a more scattered distribution (Smith *et al*, 1995). These clinical types occur in both the lamina lucida and sublamina densa variants.

Ultrastructurally, there are also two subtypes of LABD: the lamina lucida type, in which IgA antibodies adhere to the epithelial side of BMZ split skin, and the sublamina densa type, in which IgA antibodies adhere to the dermal side of BMZ split skin. Our early studies showed that the lamina lucida type is much more common and that antibody was more likely to be identified in the serum of these patients; consequently, all of our subsequent studies focused on that LABD type.

In 1990, we reported the results of the immunoreactivity of LABD sera on immunoblot (Zone *et al*, 1990). It had been previously stated that antigens were consistently identified that reacted with sera from patients with BP: BP230 (subsequently termed BPAg1) and BP180 (subsequently termed BPAg2) (Stanley *et al*, 1981; Diaz *et al*, 1990). We assumed that the reactivity of IgA sera would be similar, but our studies identified predominant reactivity with a 97-kDa protein found in epidermal extract. We were not able to identify reactivity of LABD sera with BP180 or BP230. We then studied patients with chronic bullous disease of childhood and found that their IgA antibodies reacted in a similar manner (Zone *et al*, 1996). We concluded that the antigenic specificity for linear IgA disease antibody was different from that for BP antibody, but the nature of the 97-kDa protein was unknown.

Marinkovich and colleagues developed a monoclonal antibody that reacted with a 120-kDa antigen from keratinocyte culture and a 97-kDa antigen from human skin extracts, but not BP180. They noted that linear IgA disease antibodies reacted with this antigen (Marinkovich *et al*, 1996). Further work showed that patients with generalized atrophic benign epidermolysis bullosa, who were deficient in BP180, also failed to show reactivity to this linear IgA disease antigen (Marinkovich *et al*, 1997). This suggested that this antigen is the same as BP180; however, the lack of immunoreactivity of sera with the intact BP180 antigen on immunoblot was not yet understood.

We next prepared mouse monoclonal IgG1 antibodies to the LABD 97-kDa antigen. This was accomplished by using nitrocellulose strips containing the 97-kDa antigen as the immunogen implanted into mice. We were successful in using these mouse monoclonal antibodies on an immunoaffinity column to purify the 97-kDa antigen from epidermal extract. N-terminal amino acid sequencing was then used to identify the amino acid sequence of the 97-kDa antigen. It showed identity with BP180 (Zone *et al*, 1998). The amino terminal of the 97-kDa antigen, however, was within the extracellular portion of the molecule and did not contain the MCW-1 region of BP180, which is the antigenic epitope for BP patients. It is our conclusion from these studies that the 97-kDa antigen is an epitope contained within the 120-kDa protein identified by Marinkovich. We believe that this represents a proteolytic fragment of BP180 that does not become antigenic until proteolysis of the molecule occurs. This produces a fragment with an epitope that is distinct from the BP180 antigen recognized by BP sera (**Fig 1**).

As this unique epitope on BP180 seemed to be a central part of the lamina lucida LABD, we decided to evaluate the reactivity of these monoclonal antibodies in a mouse model. As noted above, the 97-kDa antigen is not expressed in mouse skin but is expressed in human skin. In order to have a model in which the antigen is expressed, we transplanted human neonatal foreskin to adult athymic mice, allowing the grafts to mature for three to five weeks. Mouse IgG1 monoclonal antibodies, MAb 97–1 and MAb 97–2, were purified from ascites. Following delipification, the fluid was passed repeatedly over a protein G column and eluted with 0.1 M acetic acid and neutralized with Tris buffer. This yielded purified antibodies with titers $>$1:10 000. We evaluated the effect of using MAb 97–1 and MAb 97–2 alone or in combination. One mg of each purified monoclonal Ab was injected subcutaneously into the grafted athymic mice at 0 and 48 hours. The combination injection involved 1 mg of each antibody. All injections produced titers of 1:640 in the serum of the mice at 48 h, and titers could be maintained at $>$1:160 for 21 days. At 96 h, biopsies revealed intense deposition of IgG and complement at the BMZ and a basement membrane blister in some, but not all, animals. A control group received an irrelevant IgG1 mouse monoclonal antibody (RSLD09, ATCC number HB-8525, raised to prostate antigen) in an identical protocol. This group did not develop serum BMZ antibody titers. The results of these experiments are summarized in **Table 2**.

From this we concluded that: (1) both IgG MAb 97–1 and IgG MAb 97–2 are pathogenic; that is, they produce microvesicles at the BMZ in the skin grafts, indicating that the epitope recognized by these antibodies is pathogenic; (2) vesicle formation and eosinophil infiltration are increased when both antibodies are administered simultaneously; (3) there is unexplained variability in the production of microvesicles and inflammation within

Table 2. Passive transfer of IgG mouse monoclonal antibodies to the 97 kD LABD antigen to athymic mice with human skin transplants

Antibodies Administered	Number of mice	Grafts with BMZ split (%)	Grafts with eosinophils (%)
MAb 97-1 & MAb 97-2	15	12 (80%)	6 (40%)
MAb 97-1	5	2 (40%)	1 (20%)
MAb 97-2	5	3 (60%)	0 (0%)
Control	5	1 (20%)	0 (0%)

groups; (4) eosinophil numbers are variable in association with vesicles; the size of the biopsy specimens did not allow further processing for granule proteins; and (5) occasional control grafts develop basement membrane zone blisters.

The development of spontaneous basement membrane zone inflammation and vesiculation in the control animals was of great concern to us. Further evaluation of the human skin grafts revealed that up to one-quarter of the mice demonstrated spontaneous IgM deposition in the graft, indicating an immune response in some of the presumably immunodeficient nude mice. This greatly confused the passive transfer experiments, and we decided to turn to SCID mice as recipients for the human skin grafts in our later experiments with IgA monoclonal antibodies.

After evaluating the IgG hybridomas to the 97-kDa antigen, we isolated IgA switch variants after exposing the hybridomas to the mutagen acridine orange (ICR 191) (Paizi *et al*, 1995). IgA hybridoma cells were then isolated either by fluorescein-activated cell sorting (FACS) or by the ELISA spot assay (Spira and Scharff, 1992). Briefly, the IgG hybridomas were exposed to ICR 191 at the level of 1 μg/ml for 24 h to achieve a 30%–40% death rate. The surviving cells were then grown and subjected to either FACS using fluorescein-conjugated antimouse alpha chain or an ELISA that identifies positive clones in a 96-well plate using appropriate antibodies and an alkaline phosphatase detection system.

The IgA hybridomas were grown in Freunds incomplete adjuvant primed Balb/c mice, and the resulting ascites fluid was administered subcutaneously to SCID mice bearing human skin grafts. Preliminary experiments indicated that a 14-day time course was optimal and that injection of 1 mg of ascites on days 1, 3, 7, and 10 was necessary to maintain serum antibody titers between 1:10 and 1:40. In the IgG experiments, we had noted that the administration of both antibodies simultaneously, 97–1 and 97–2, produced vesiculation more frequently than separate administration. Therefore, a combination of these antibodies was always used in our initial efforts to produce vesiculation with the IgA monoclonals. The conditions necessary to maintain serum titers for the IgA antibodies were different from those established for the IgG antibody. IgA antibodies were cleared from the circulation rapidly, so the animals required repeated dosing. The SCID mice were never able to maintain serum IgA BMZ antibody titers >1:40, as they could with the IgG BMZ antibodies. Preliminary experiments also indicated that there was no inflammation until after day 7, so we settled on a protocol involving a 4-mm punch biopsy taken on days 0 and 14. Direct immunofluorescence and routine histology with H&E staining of formalin-fixed sections were performed. In an additional set of animals. GMCSF (300 ng/mouse) was injected intradermally into the graft on day 13 to see if activation of neutrophils or accentuation of chemotaxis augmented the inflammatory response (Zygmunt *et al*, 1989; Metcalf *et al*, 1987).

The results of these experiments are shown in **Table 3**. It is important to realize that at no time in either the IgG or the IgA experiments were visible vesicles or inflammation identified. All results are histologic and immunopathologic, the result of 4-mm punch biopsies that were randomly obtained from grafts that were approximately 3 cm in diameter. All biopsies were reviewed without knowledge of the intervention used in that animal. At baseline, all 32 mice used in this study had negative BMZ immunofluorescence. This is important in view of the autoantibody formation that occurred using athymic mice. Grafts were allowed to mature for 3 to 5 weeks, so these baseline values represent the negative control of the expected outcome with no antibody administration. An IgA mouse monoclonal Ab is not available to use as a negative control, as was done with the IgG experiments (**Table 3**).

IgA deposition was evaluated by direct immunofluorescence (DIF) using FITC mouse antialpha chain. Following passive transfer of the IgA antibody, there was strong positivity in the graft in the 12 mice that received IgA alone and the in 7 mice that also received GMCSF. The mice receiving GMCSF alone did not show IgA deposition at the BMZ. No deposition of other immunoglobulin classes was ever seen in the grafted SCID mice. We concluded that our protocol produces consistent and significant IgA deposition at the BMZ.

Complement deposition was evaluated by DIF for mouse C3. Occasional deposition was noted spontaneously at baseline (2/36). Granular complement deposition was noted in 7 of 12 mice receiving IgA alone at day 14, with 3 of 12 demonstrated linear deposition. Of the 7 mice receiving GMCSF plus IgA, 3 also showed complement deposition, as noted in **Table 3**. GMCSF alone produced complement deposition in one animal. We concluded that complement deposition is irregularly present with an inconsistent pattern. It was not selectively present in biopsies where a vesicle was identified. For this reason it seems unlikely that complement plays a role in any inflammatory process in this model.

Minimal neutrophil infiltration was noted in 9 of 32 animals at baseline, but no animals demonstrated significant neutrophil infiltration, defined in **Table 3** as $2-3+0$. Following the administration of IgA alone, 6 of 12 animals demonstrated significant neutrophil infiltration, with infiltration of dermal papillae (**Fig 2**). Two of seven animals receiving IgA plus GMCSF demonstrated a similar significant infiltration, as well as 2 of 12 animals receiving GMCSF alone. From this, we conclude that the passive transfer of IgA antibodies does produce neutrophil infiltration in a significant number of animals and this infiltration occurs in dermal papillary tips. It does not seem to be accentuated by GMCSF, although GMCSF alone does produce some inflammation. Initial results reported in abstract form suggested that the process isaccentuated by GMCSF.

We next turned our attention to the presence of BMZ separation in these specimens. Minimal vacuolization was noted in a small number of animals, as reviewed in **Table 3**. Significant BMZ separation (**Fig 3**), however, was noted in test animals after administration of IgA or IgA plus GMCSF. A single animal receiving GMCSF alone did have significant vesiculation. It is not surprising that in some situations GMCSF could produce vesicles.

Table 3. Passive transfer of IgA mouse monoclonal antibodies to the 97 kD LABD antigen to SCID mice with human skin transplants

Evaluation Of Biopsy		Baseline	IgA alone	IgA + GMCSF	GMCSF alone
IgA	BMZ (−)	32/32	0/12	0/7	12/12
	BMZ (+)	0/32	12/12	7/7	0/12
Complement	Granular	2/36	7/12	2/7	1/12
	Linear	0/36	3/12	1/7	0/12
Neutrophils	1+	9/32	4/12	4/7	3/12
	2–3+	0/32	6/12	2/7	2/12
Vacuoles	Present	4/36	0/12	0/7	1/12
Blister	1+	1/36	1/12	3/7	3/12
	2–3+	0/36	4/12	1/7	1/12

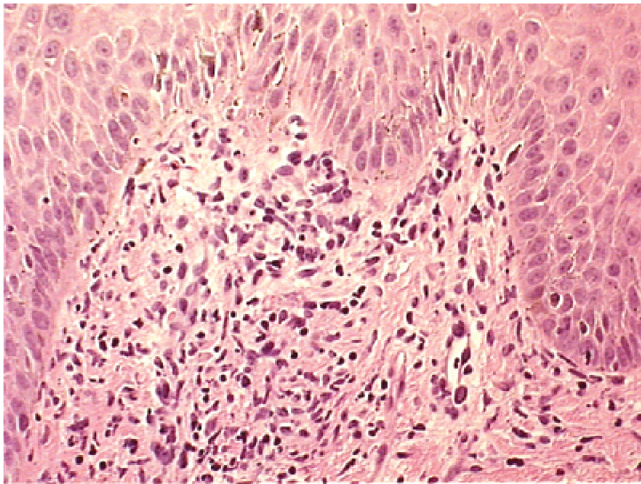

Figure 2. Infiltration of dermal papillae with neutrophils and mononuclear cells after administration of IgA BMZ antibodies (H&E 40 X).

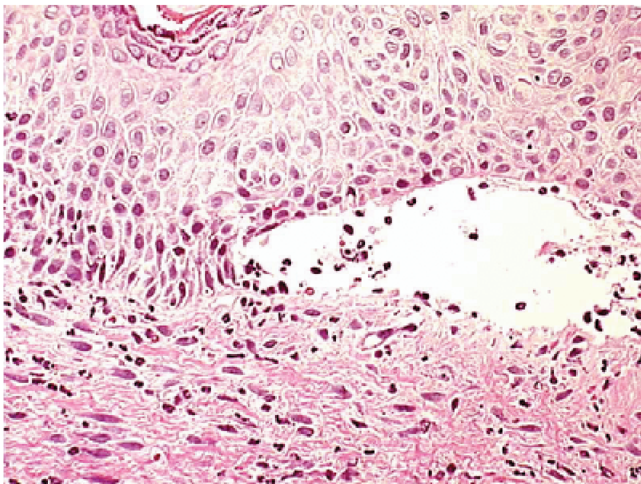

Figure 3. BMZ vesicle with neutrophil infiltration after administration of IgA BMZ antibodies (H&E 40X).

It is chemotactic for neutrophils, and BMZ separation is likely induced by neutrophil enzymes. We conclude that at least one-third of the animals receiving IgA alone tested in this manner developed significant BMZ vesiculation with significant neutrophil infiltration. This indicates that IgA is pathogenic in this model. The fact that positive findings were noted in only a minority of animals makes it difficult to study the mechanism of this process in detail. We suspect that two issues are important and need to be investigated. First, only a small portion of the graft was sampled. Sampling of the entire graft may identify inflammation and vesiculation in grafts that would otherwise be called negative. Second, the antibody titers in the IgA model are always much lower in the IgG model. We are currently exploring new experimental protocols that will raise the serum antibody levels to titers comparable to those in the IgG experiments.

SUMMARY

IgA is present in the skin of a number of dermatoses, suggesting that it is responsible for the associated inflammatory events. The mechanism for this process is unclear, but it is likely to involve IgA-mediated neutrophil infiltration. Elucidation of the mechanism will require a mouse model. We have established a model for LABD as a prototype disease to be studied. Our experiments to date indicate that this model is feasible and that IgA deposition and inflammation can be produced by passive transfer of mouse IgA antibodies against a linear IgA antigen.

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