Clinical and laboratory studies

Drug-induced linear IgA bullous dermatosis: Report of six cases and review of the literature

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Background: Linear IgA bullous dermatosis (LABD) is an autoimmune subepidermal blistering disease that may be associated with drug exposure.

Objective: Our purpose was to compare the clinical, pathologic, and immunofluorescence findings in drug-induced LABD with those in the idiopathic type.

Methods: Six patients with an acute drug eruption were identified who had linear IgA deposition at the basement membrane zone (BMZ). Lesional tissue was examined by brightfield microscopy, and perilesional tissue was examined by direct immunofluorescence (DIF). The presence of circulating BMZ antibody was assayed by indirect immunofluorescence (IIF) on monkey esophagus (ME) and salt-split human skin (SS).

Results: Histopathologic examination showed subepidermal bullae with varying numbers of inflammatory cells. DIF showed linear IgA at the BMZ; three of the patients also had weak deposition of C3 at the BMZ. Serum from five patients was studied by IIF. One patient had circulating IgA BMZ antibodies in a titer of 1:80 on ME, localized to the dermal side on SS. All patients were free of lesions within 5 weeks after discontinuation of the drug.

Conclusion: Drug-induced LABD is a self-limited eruption characterized by linear deposition of IgA without IgG at the BMZ. Most patients lack circulating antibodies. The distribution of lesions and the course of the disease differ from those of idiopathic LABD.

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Linear IgA bullous dermatosis (LABD) is a subepidermal bullous disease characterized by linear deposition of IgA along the basement membrane zone (BMZ). A spectrum of clinical features has been described; some patients have lesions resembling dermatitis herpetiformis (DH) or bullous pemphigoid (BP). Although the clinical and histopathologic features of BP, DH, and LABD overlap, LABD may be differentiated from the other conditions by its characteristic immunofluorescence pattern. Pemphigoid and, particularly, pemphigus can be induced by drugs, but an association between LABD and drug exposure is less well characterized.

We report six cases of drug-induced LABD and review previously reported cases.

CASE REPORTS

Case 1. A 73-year-old white woman with a history of granular cell carcinoma of the ovary and hairy cell leukemia had a pleural effusion. Three weeks earlier, she had undergone splenectomy, and a pancreatic-pleural fistula was found. Administration of somatostatin, 150 μg three times daily, was begun to reduce pancreatic output. She had also been taking ampicillin/sulbactam, morphine sulfate, ranitidine, and triazolam. Four days after somatostatin therapy began, an erythematous, papular, nonpruritic eruption was noted on the trunk and proximal extremities. A biopsy specimen revealed neutrophilic infiltration at the dermoepidermal junction and in the papillary dermis. Direct immunofluorescence (DIF) revealed IgA deposition in a linear pattern at the BMZ and weak segmental linear deposition of C3, consistent with LABD. Somatostatin administration was discontinued, and the eruption resolved in 10 days without specific therapy.

Case 2. A 69-year-old white man underwent coronary artery bypass surgery. A draining sinus tract developed in the chest wall and became infected with methicillin-resistant Staphylococcus aureus. He was treated with vancomycin and rifampin. After 2 weeks of treatment, a generalized bullous eruption developed and antibiotic therapy was discontinued. A biopsy specimen revealed a
Case 3. A 74-year-old white man had coronary artery bypass surgery. Five days later, vancomycin was begun for a sternal wound infection. Other medications were morphine sulfate, digoxin, furosemide, diltiazem, cefazolin, and captopril; captopril was discontinued 1 day before the onset of his eruption. Nine days after administration of vancomycin began, targetoid papules developed on his palms (Fig. 1) and tense bullae developed on his fingers. Numerous erythematous urticarial plaques were noted on his trunk. A biopsy specimen from the palm revealed a subepidermal bulla with neutrophils (Fig. 2). DIF revealed linear deposition of IgA along the BMZ and weak, stippled deposition of C3; there was no deposition of IgG. Serum for indirect immunofluorescence (IIF) showed IgA deposition localized to the dermal side of split human skin (Fig. 3) and IgA BMZ antibodies in a titer of 1:80 on monkey esophagus (Fig. 4). No IgA endomysial antibodies, IgG BMZ antibodies, or IgG cell-surface antibodies were detected. The eruption resolved 1 week after vancomycin therapy was discontinued and has not recurred. Serum was restudied 2 years after the patient's eruption resolved. No circulating IgG or IgA antibodies were found with use of monkey esophagus and human split-skin substrates.

Case 4. A 67-year-old white man had coronary artery bypass surgery. A sternal wound infection developed, and vancomycin therapy was started 16 days after operation. Other medications were digoxin, levethoxazine, meperidine, promethazine, triazolam, quinidine, and isosorbide dinitrate. Two weeks after vancomycin therapy began, erythematous papules, plaques, and excoriations developed on both legs. Quinidine administration was discontinued because of persistent atrial flutter. Five days later, new pruritic vesicles were observed on his abdomen, axillae (Fig. 5), knees, and feet. Histologic examination revealed a subepidermal bulla and mixed inflammatory cell infiltration with eosinophils. DIF revealed linear deposition of IgA as well as C3 along the BMZ. IIF with the patient's serum was negative on monkey esophagus substrate for anti-IgG and anti-IgA. Administration of vancomycin was discontinued, and no new lesions developed. The patient was treated with dapsone for 3 weeks. Evaluation 7 months later revealed no recurrence.

Case 5. A 67-year-old white man was hospitalized for Haemophilus influenzae pneumonia and congestive heart failure. Medications included captopril, isosorbide dinitrate, and cefuroxime. At discharge he was receiving trimethoprim-sulfamethoxazole, captopril, and isosorbide dinitrate. Ten days later, an erythematous papular eruption developed, extending from the trunk to the proximal extremities, with clear blisters arising on an erythematous base. Histologic examination revealed a subepidermal bulla with neutrophils and eosinophils. DIF of perilesional skin revealed linear deposition of IgA along the BMZ. IIF studies of serum on monkey esophagus substrate were negative. Trimethoprim-sulfamethoxazole and captopril...
were discontinued. Oral prednisone 30 mg/day was given that was tapered over 3 weeks. There was complete resolution of the eruption with no recurrence.

Case 6. A 70-year-old white man began taking phenytoin for a seizure disorder. One week later, erythematous plaques and urticarial lesions developed on his trunk. Histologic examination of lesional tissue showed a subepidermal bulla with neutrophils. DIF showed linear IgA and C3 deposition along the BMZ. The eruption resolved 1 week after phenytoin therapy was discontinued.

MATERIAL AND METHODS

Biopsy specimens were taken from lesional and perilesional tissue. The lesional tissue was processed for histologic bright field microscopic study; the perilesional tissue was prepared for DIF. Perilesional skin specimens were examined for immunoglobulins, complement, and fibrinogen with fluorescein-conjugated, heavy-chain specific antibodies directed against human IgG, IgM, IgA, C3, and fibrinogen.

Circulating BMZ antibody in the serum of patients 2, 3, 4, and 5 was assayed by IIF on monkey esophagus substrate with antibodies to IgG and IgA. Serum from patient 3 was also tested on 1 mol/L salt-split human skin with antibodies to both IgG and IgA.

RESULTS

The clinical, histologic, and immunofluorescence findings are summarized in Table I. Cutaneous lesions appeared within 4 to 14 days after administration of the implicated drug. Patients 1, 3, 4, and 5 initially had a papular eruption; targetoid papules resembling erythema multiforme developed in patient 3, and patients 4 and 5 later had bullae resembling BP. Patient 2 had a generalized bullous eruption resembling BP. An urticarial eruption developed in patient 6. Although the lesions varied clinically, DIF testing of perilesional skin showed linear IgA deposition in each. Patients 3, 4, and 5 had weak C3 deposition, but no patients had IgG deposition. Only patient 3 had circulating IgA anti-BMZ antibodies. None of the patients had circulating IgG anti-BMZ antibodies. All patients had clinical resolution after discontinuing treatment with the suspected drug. Patients 1, 2, 3, and 6 required no therapy; patient 4 was treated with dapsone for 3 weeks, and patient 5 received prednisone for 3 weeks.

Patient 3 did not demonstrate circulating IgA anti-BMZ antibodies when the eruption had cleared. None of the patients had repeat biopsies for DIF studies after their eruptions cleared.

DISCUSSION

LABD is defined by the linear deposition of IgA at the BMZ. No histologic features differentiate LABD from BP or DH. Several cases of drug-induced LABD have been reported, including a recent series of three patients with LABD induced by vancomycin (Table I). Other drugs implicated in LABD are lithium, cefamandole, captopril, and diclofenac.

Both idiopathic LABD and drug-induced LABD are heterogeneous in clinical presentation. Cases of drug-induced LABD have shown erythema multiforme-type lesions, BP-like lesions, or DH-like lesions. However, drug-induced LABD appears to differ from idiopathic LABD in several respects. In our patients and previously reported patients with drug-induced LABD, mucosal or conjunctival lesions were lacking, spontaneous remission occurred
once the offending agent was withdrawn, and immune deposits disappeared from the skin once the lesions had resolved. 

In contrast, 26% to 80% of patients with idiopathic LABD have mucosal lesions, and 10% to 50% have spontaneous resolution of disease, with persistence of immune deposits in the skin after lesions have resolved in some to most cases. Two other bullous diseases occur with drug exposure—pemphigus and pemphigoid. Although lesions resolve in most patients with drug-induced pemphigus or pemphigoid when treatment with the implicated drug is discontinued, lesions progress or persist in a subset of patients despite removal of the presumed offending agent.

Wojnarowska et al. reported that 38% of children and 26% of adults had an infection, such as a viral respiratory illness, typhoid, brucellosis, tetanus, or streptococcal pharyngitis, preceding the onset of LABD. Janniger et al. reported a case of LABD that developed 2 weeks after an increase in phenytoin dosage; the patient had been receiving a lower dose of phenytoin and phenobarbital for 8 years previously. Four of our patients had infection, three had recent cardiac bypass surgery, and one was taking phenytoin. Furthermore, all our patients were receiving multiple drugs. These reports suggest that multiple precipitating factors may induce LABD. The patients in the report by Wojnarowska et al. were treated with dapsone or sulfonamide. Remission, defined as absence of cutaneous lesions or mucous membrane symptoms, occurred in 52%. None of the patients was left untreated for observation after a presumed precipitating event.

Godfrey et al. reviewed 70 patients with linear IgA bullous dermatosis. Three had malignant lymphoma of B-cell origin. Nine had a nonlymphoid malignant disease. Our patient 1 had both ovarian carcinoma and hairy cell leukemia. The association of LABD with both lymphoid and nonlymphoid malignant disease, however, adds additional evidence for an association between LABD and a precipitating immunologic event. Because the eruption in patient 1 resolved in 10 days after somatostatin was discontinued, we believe that the eruption is attributable to the medication. Finally, lesions in all the patients cleared within 5 weeks of removal of the suspected drug (four of the six patients did not require systemic treatment), a strong implication that the drug helped induce the reaction.

Immunoelectron microscopic examination of immune deposits in drug-induced LABD showed localization in the lamina lucida and sublamina densa from one patient and the lamina densa and sublamina densa from another. Localization at these sites has also been observed in spontaneous LABD. The dermal pattern of IgA BMZ antibody deposition on split-skin substrate in one of our patients is consistent with localization at the lamina densa and sublamina densa regions. Similar findings have been reported with IIF of sera in idiopathic LABD. Both dermal and epidermal patterns have also been reported.

Two unrelated antigens have been found in LABD: a 285 kd antigen in the lamina densa and sublamina densa regions and a 97 kd antigen in the upper lamina lucida. The 285 kd antigen differs

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*We have since learned of a patient with vancomycin-induced LABD who had oral ulcerations (Antoinette F. Hood, M.D., personal communication, December 1992).
from the epidermolysis bullosa acquisita antigen (type VII collagen)\(^6\); no reports characterizing the 97 kd antigen appear in the literature. The dermal staining pattern seen on human split-skin substrate in our patient with circulating IgA BMZ antibodies and the dermal IgA on autologous split-skin substrate reported by Carpenter et al.\(^1\) suggest that these patients are forming antibodies to the 285 kd lamina densa and sublamina densa antigen.

Circulating IgA BMZ antibodies are detectable on monkey esophagus substrate in approximately 20% of patients with adult idiopathic LABD and 70% of patients with chronic bullous disease of childhood.\(^1\) The percentages increase to approximately 50% and 90% in LABD and chronic bullous disease of childhood, respectively, when split human skin is used as the substrate.\(^1\) IIF was performed in 10 of the 15 cases of drug-induced LABD (five of nine cases in the literature combined with five of six current cases). Two of the 10 sera had IgA BMZ antibodies. In the three patients re-

### Table I. Drug-induced linear IgA bullous dermatosis

<table>
<thead>
<tr>
<th>Authors</th>
<th>Sex/Age (yr)</th>
<th>Drug</th>
<th>Clinical features</th>
<th>Histopathology</th>
<th>DIF</th>
<th>HF</th>
<th>IEM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gabrielsen et al.(^5)</td>
<td>F/63</td>
<td>Diclophenac</td>
<td>BP, EM</td>
<td>SEB</td>
<td>Linear IgA</td>
<td>ME: neg</td>
<td>ND</td>
</tr>
<tr>
<td>Valsecchi et al.(^3)</td>
<td>M/21</td>
<td>Diclophenac</td>
<td>DH</td>
<td>DH</td>
<td>Linear IgA</td>
<td>ME: pos</td>
<td>ND</td>
</tr>
<tr>
<td>McWhirter et al.(^7)</td>
<td>M/26</td>
<td>Lithium</td>
<td>LABD</td>
<td>SEB</td>
<td>Linear IgA</td>
<td>ND</td>
<td>LL, SLD</td>
</tr>
<tr>
<td>Argenyi et al.(^8)</td>
<td>F/58</td>
<td>Cefamandole</td>
<td>EM</td>
<td>EM</td>
<td>Linear IgA, fibrinogen, cytoid IgM</td>
<td>ND</td>
<td>LD, SLD</td>
</tr>
<tr>
<td>Baden et al.(^9)</td>
<td>M/58</td>
<td>Vancomycin</td>
<td>BP, LABD</td>
<td>SEB</td>
<td>Linear IgA</td>
<td>ME: neg</td>
<td>ND</td>
</tr>
<tr>
<td>Klein et al.(^10)</td>
<td>M/58</td>
<td>Captopril</td>
<td>BP, EM</td>
<td>SEB</td>
<td>Linear IgA, IgG, fibrinogen</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Carpenter et al.(^11)</td>
<td>M/54</td>
<td>Vancomycin</td>
<td>BP</td>
<td>SEB</td>
<td>Linear IgA</td>
<td>ME: neg</td>
<td>SS: neg</td>
</tr>
<tr>
<td>F/72</td>
<td>Vancomycin, rifampin</td>
<td>EM, BP</td>
<td>SEB</td>
<td>Linear IgA</td>
<td>ME: neg</td>
<td>SS: neg</td>
<td></td>
</tr>
<tr>
<td>M/54</td>
<td>Vancomycin,</td>
<td>BP, EM</td>
<td>SEB</td>
<td>Linear IgA</td>
<td>ME: neg</td>
<td>SS: neg</td>
<td></td>
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<tr>
<td>Kuechle et al. (present study)</td>
<td>Patient 1</td>
<td>Somatostatin</td>
<td>BP</td>
<td>PMNs at DEJ</td>
<td>Linear IgA</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>F/73</td>
<td>Vancomycin, rifampin</td>
<td>BP,</td>
<td>SEB</td>
<td>Linear IgA</td>
<td>ME: neg</td>
<td>ND</td>
<td></td>
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<tr>
<td>Patient 2</td>
<td>M/69</td>
<td>Vancomycin</td>
<td>BP</td>
<td>SEB</td>
<td>Linear IgA</td>
<td>ME: neg</td>
<td>ND</td>
</tr>
<tr>
<td>Patient 3</td>
<td>M/74</td>
<td>Vancomycin</td>
<td>EM, BP</td>
<td>SEB</td>
<td>Linear IgA, weak C3</td>
<td>ME: pos</td>
<td>ND</td>
</tr>
<tr>
<td>Patient 4</td>
<td>M/67</td>
<td>Vancomycin</td>
<td>BP</td>
<td>SEB</td>
<td>Linear IgA, weak C3</td>
<td>ME: neg</td>
<td>ND</td>
</tr>
<tr>
<td>Patient 5</td>
<td>M/67</td>
<td>Captopril, trimethoprim-sulfamethoxazole</td>
<td>BP</td>
<td>SEB</td>
<td>Linear IgA, weak C3</td>
<td>ME: neg</td>
<td>ND</td>
</tr>
<tr>
<td>Patient 6</td>
<td>M/70</td>
<td>Phenytoin</td>
<td>BP</td>
<td>SEB</td>
<td>Linear IgA, weak C3</td>
<td>ND</td>
<td>ND</td>
</tr>
</tbody>
</table>

BP, Bullous pemphigoid; DEJ, dermoeipidermal junction; DH, dermatitis herpetiformis; DIF, direct immunofluorescence; DS, dermal staining; EM, erythema multiforme; IEM, immunoelectron microscopy; HF, indirect immunofluorescence; LABD, linear IgA bullous dermatosis; LD, lamina densa; LL, lamina lucida; ME, monkey esophagus substrate; ND, not done; neg, negative; PMN, polymorphonuclear neutrophils; pos, positive; SLD, sublamina densa; SS, human split-skin substrate.
ported by Carpenter et al., a dermal staining pattern of IgA was reported with serum on split autologous skin, whereas the IIF with serum in both monkey esophagus and nonautologous split human skin substrates was negative. A comparison of circulating IgA BMZ antibodies in drug-induced LABD with those in idiopathic LABD is difficult because of the small number of reported drug-induced LABD cases. However, the data suggest that fewer patients with drug-induced LABD than with idiopathic LABD have circulating antibodies.

Drug-induced LABD, despite varied clinical and histologic presentations, should be considered when a suspected drug eruption resembles erythema multiforme, DH, or BP. Biopsy specimens for DIF are required for the diagnosis. Histologically, drug-induced LABD and idiopathic LABD are similar. However, because areas of disease involvement and the clinical course differ, drug-induced and idiopathic LABD may be pathogenetically different; drug-induced LABD may be an immunologic response to a drug or infection.

REFERENCES