Epidermolysis bullosa acquisita and Crohn's disease

Jihad T. Al-Ratrout, MBBS, KFU(Derm),
Naseem A. Ansari, MBBS, MRCPath.

Epidermolysis bullosa acquisita (EBA) is an uncommon acquired subepidermal blistering disease associated with autoimmunity to type-VII collagen within anchoring fibrils, leading to formation of bullae at the dermoepidermal junction. There are a few well-defined clinical presentations of EBA including the classical variant and also variants which resemble other blistering disorders, such as the cicatricial pemphigoid-like variant of EBA. Epidermolysis bullosa acquisita is distinguished from the other forms of epidermolysis bullosa by its nonhereditary pattern and its association with other disorders including amyloidosis, diabetes mellitus (DM), and Addison's disease. Particularly interesting is the fact that EBA has an especially strong association with inflammatory bowel disease. Here we present one such case of a young adult male with Crohn's disease who developed EBA.

Our patient, a 22-year-old male, complained of epigastric pain, diarrhea with occasional blood in the stool, and weight loss for more than one year. Upper gastrointestinal endoscopy revealed an unremarkable esophagus and superficial erosions in the gastric pylorus and duodenal bulb. Colonoscopy showed aphthous ulcers in the ascending colon and 2 irregular ulcers in the ileocecal area with narrowing of the lumen. Apart from mild congestion of the rectal mucosa, the remaining colon was essentially normal. Biopsies from the duodenum showed mild duodenitis. Ileal biopsies showed moderate architectural distortion, focal edema and a moderate mixed inflammatory infiltrate. Scattered multinucleate giant cells and one granuloma were identified, the latter being well clear of crypt epithelium. Inflammatory granulation tissue indicative of ulcer was readily identified. A diagnosis of ileocecal Crohn's disease was made with possible involvement of the duodenum. Treatment with prednisolone 35mg/day and mesalazine 800mg 3 times per day improved the bowel symptoms, but after 5 months of tapering the dose, he started to complain of recurring non itchy bullous eruptions on the hands, elbows, knees and feet, which were induced by slight trauma and usually resolved in 2 weeks leaving hyperpigmentation, atrophic scars and milia. These eruptions were not related to sun exposure. The family history was negative for similar illness and the patient was otherwise in good health. Cutaneous examination (**Figure 1**) showed multiple tense bullae and vesicles 2mm-2cm on non-erythematous skin; the bullae contained clear fluid. There were also crusted erosions on the dorsum of the hands, fingers, elbows, feet and knees as well as hyperpigmented atrophic scars with numerous milia. The nails were not affected and neither oral nor dental lesions were noted. A biopsy was taken from lesional and perilesional skin and showed focal parakeratosis and irregular acanthosis. There was a subepidermal blister (**Figure 2**) free of inflammatory cells but rich in hemorrhage and fibrin. There was mild dermal fibrosis but no festooning of the dermal papillae. Direct immunofluorescence revealed strong immunoglobulin G (IgG) and C3 deposition in the dermo-epidermal junction, while immunoglobulin M (IgM) and immunoglobulin A (IgA) were negative. There were no immune deposits around dermal blood vessels. Full blood

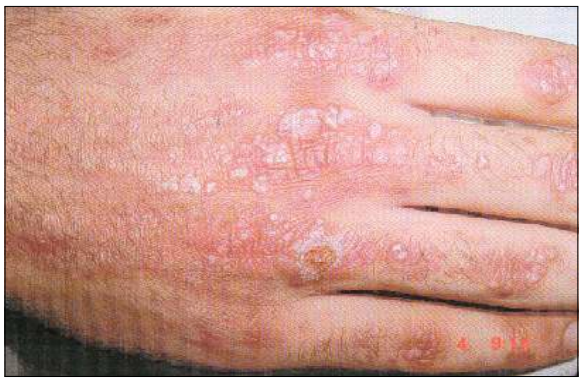

Figure 1 - Multiple small residual vesicles are seen on the dorsum of the hand with scarring. A single crusted erosion 1cm in diameter is also present.

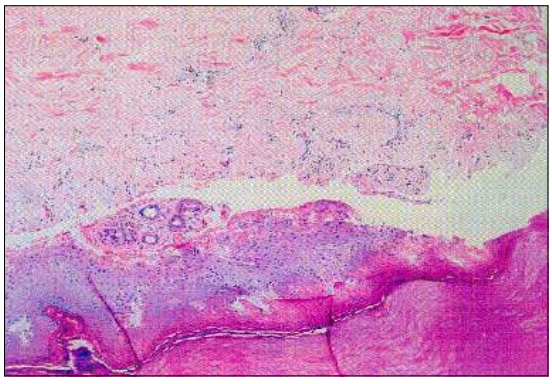

Figure 2 - Lesional skin demonstrating hyperkeratosis and a subepidermal cell-free blister (hematoxylin-eosin).

count showed hypochromic microcytic anemia, which was corrected with treatment. Other investigations including liver function tests, renal function tests, urine biochemistry, stool examination, and fasting blood sugar were normal. Hepatitis profile was non reactive and erythrocyte sedimentation was 55mm/hr. The 24-hour urinary uroporphyrin and coproporphyrin levels as well as the stool porphyrin levels were normal. Chest x-ray was normal. The reported case fulfilled the diagnostic criteria for EBA clinically, histologically and by immunofluorescence; other similar bullous disorders were excluded. The dose of prednisolone was increased to 40mg od, and azathioprine 50mg od was added together with vitamin E 400IU/day for 6 weeks. This resulted in subjective lessening of blister formation.

Epidermolysis bullosa acquisita is an acquired subepidermal blistering disease associated with autoimmunity to type-VII collagen within anchoring fibrils leading to formation of bullae at the dermoepidermal junction. Roenigk et al[1] have defined certain criteria for the diagnosis of EBA: 1. Acquired chronic bullae, usually trauma induced, which have an acral distribution and heal with scarring, milia and nail dystrophy, 2. Adult onset, 3. No family history of similar disease, 4. Exclusion of all other bullous disease such as porphyria cutanea tarda, pemphigoid, pemphigus, dermatitis herpetiformis, and bullous drug eruption on the basis of clinical and laboratory evidence, 5. IgG at the basement membrane zone (BMZ) by direct immunofluorescence of perilesional skin predominantly, but IgM can be detected, 6. The demonstration of blister formation beneath the basal lamina by electron microscopy, 7. Deposition of IgG beneath the basal lamina of the basement membrane zone by immunoelectron microscopy, which is the gold standard for the diagnosis and differentiates it from bullous pemphigoid and cicatricial pemphigoid (alternatively: indirect or direct salt-split skin immunofluorescence, western blotting, and enzyme-linked immunosorbent assay), 8. Circulating antibasement membrane zone antibodies in approximately half of the cases.

Epidermolysis bullosa acquisita is a rare disease with an incidence of 0.17-0.26 per million people in Western Europe. Although there is no racial or gender predilection, it has recently been suggested to have a higher incidence in the Korean population.[2] The clinical spectrum of EBA is still being defined, and it appears that there are at least 5 clinical presentations, classical presentation, bullous pemphigoid-like presentation, cicatricial pemphigoid-like presentation, linear IgA bullous dermatosis-like disease, and Brunsting-Perry pemphigoid-like presentation.

Epidermolysis bullosa acquisita is distinguished from the other forms of epidermolysis bullosa by its nonhereditary pattern and its association with other disorders including amyloidosis, multiple myeloma, DM, systemic lupus erythematosus and others. Of particular interest is the fact that EBA has an especially strong association with inflammatory bowel disease[3] and should be recognized as one of its extraintestinal manifestations. Several patients have had no associated disease. There is no entirely satisfactory explanation at the present time of the pathogenesis of EBA or the interrelationship between EBA and its associated systemic disorders. However, the demonstration of IgG and components of complement at the BMZ, the presence of circulating antibodies against the BMZ in at least some of the patients, and the association of a number of systemic diseases of autoimmune pathogenesis with EBA, strongly implicate an immune-mediated process. Furthermore, a high incidence of the HLA-DR2 phenotype has been reported in black patients with EBA in the South Eastern United States of America. It has been found that EBA antibodies bind to type-VII collagen within anchoring fibrils. Type-VII collagen normally binds to fibronectin in the papillary dermis thereby ensuring effective epidermal-dermal adherence. By binding type-VII collagen, it is postulated that EBA antibodies interfere with the normal type-VII collagen-fibronectin interaction, leading to impaired adherence and consequent blister formation at the dermo-epidermal junction.[4]

It has been shown that patients with inflammatory bowel disease, especially Crohn's disease have a high prevalence of circulating antibodies against type-VII collagen, and the same authors have demonstrated type-VII collagen to be present in the intestinal epithelium.[5] As type-VII collagen is the antigenic target for autoantibodies in patients with EBA, it has been speculated that autoimmunity to type-VII collagen, which exists in both gut and skin may explain why these patients frequently have inflammatory bowel disease.

Epidermolysis bullosa acquisita is chronic, disabling and difficult to treat. Many therapeutic options have been tried including systemic glucocorticoids, vitamin E, azathioprine, methotrexate, cyclophosphamide, dapsone, cyclosporine, colchicine, photophoresis and intravenous immunoglobulins with variable results.[6] As EBA is an incurable disease without a consistent therapeutic modality, supportive therapy is of the utmost importance. Useful measures include avoiding friction trauma and harsh soaps or overuse of hot water; avoiding sun exposure and using sunscreen; and careful wound management with antibiotics.

Received 13th June 2004. Accepted for publication in final form 5th July 2004.

From the Department of Dermatology (Al-Ratrout), Qatif Central Hospital, Qatif, Kingdom of Saudi Arabia, and the Department of Pathology (Ansari), College of Medicine and Medical Sciences, Arabian Gulf University, Bahrain. Address correspondence and reprint requests to Dr. Naseem A. Ansari, Consultant Histopathologist, Arabian Gulf University, PO Box 22979, Bahrain. Tel. +973 17239870. Fax. +973 17271090. E-mail: ansarnas@hotmail.com

References

1. Roenigk HH, Ryan JG, Bergfeld WF. Epidermolysis bullosa acquisita: report of three cases and review of all published cases. ***Arch Derm*** 1971; 103: 1-10.
2. Lee CW. Prevalences of subacute cutaneous lupus erythematosus and epidermolysis bullosa acquisita among Korean/Oriental populations. ***Dermatology*** 1998; 197: 187.
3. Ray TL, Levine JB, Weiss W, Ward PA. Epidermolysis bullosa acquisita and inflammatory bowel disease. ***J Am Acad Dermatol*** 1982; 6: 242-252.
4. Chen M, Chan LS, Cai X, O'Toole EA, Sample JC, Woodley DT. Development of an ELISA for rapid detection of anti-type VII collagen autoantibodies in epidermolysis bullosa acquisita. ***J Invest Dermatol*** 1997; 108: 68-72.
5. Chen M, O'Toole EA, Sanghavi J, Mahmud N, Kelleher D, Weir D, et al. The epidermolysis bullosa acquisita antigen (type VII collagen) is present in human colon and patients with Crohn's disease have autoantibodies to type VII collagen. ***J Invest Dermatol*** 2002; 118: 1059-1064.
6. Hughes AP, Callen JP. Epidermolysis bullosa acquisita responsive to dapsone therapy. ***J Cutan Med Surg*** 2001; 5: 397-399.