Colchicine for epidermolysis bullosa acquisita

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Background: Epidermolysis bullosa acquisita (EBA) is a chronic subepidermal blistering disease that is difficult to treat. Recently one patient with severe EBA was described who responded dramatically to colchicine.

Objective: Our purpose was to determine the efficacy of colchicine in the treatment of EBA.

Methods: Four patients with severe EBA refractory to conventional therapy were treated with colchicine 0.6 to 1.5 mg a day for up to 4 years.

Results: In all four patients the lessening of skin fragility and the decrease in spontaneous blister formation were dramatic; few side effects were noted.

Conclusion: Colchicine should be considered in the treatment of EBA.

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Epidermolysis bullosa acquisita (EBA) is an acquired subepidermal blistering disease associated with autoimmunity to type VII collagen. 1-3 Patients with EBA have autoantibodies to anchoring fibrils within and below the lamina densa zone of the dermoepidermal junction (DEJ). 2 Autoantibodies in patients with EBA are specifically directed against the NC1 (noncollagen) domain of the amino terminus of the type VII collagen. 2 EBA is a mechanobullous disease associated with skin fragility in trauma-prone areas and blisters and erosions that heal with scarring and milia. 3 There is often dystrophy of the nails and a predominant acral distribution of the lesions. The disease resembles hereditary forms of dystrophic EB. 3 There is no consistently effective therapy, although various forms of immunosuppression such as systemic steroids, azathioprine, methotrexate, cyclophosphamide, and cyclosporine 4 have been used.

Although biopsy specimens of EBA often reveal a sparse inflammatory dermal infiltrate, some patients have improved with dapsone, especially if a neutrophilic infiltrate is present. Moreover, as demonstrated by Gammon et al., 5 EBA may present as an inflammatory, widespread, vesiculobullous eruption reminiscent of bullous pemphigoid. In this pre-

sentation, there is often a mixed dermal infiltrate of neutrophils, lymphocytes, and histiocytes. Dahl 6 has emphasized that EBA may also present with clinical features similar to cicatricial pemphigoid.

Recently, one patient with severe EBA that was refractory to conventional treatment had a complete remission with colchicine. 1 We describe four additional patients with EBA who were successfully treated with colchicine.

CASE REPORTS

In these four patients the diagnosis was based on clinical presentation, a subepidermal blistering process, IgG deposits at the DEJ and on the dermal floor of perilesional skin after 1 mol/L salt separation, 7 IgG deposits beneath the lamina densa zone of the basement membrane, and the exclusion of porphyria cutanea tarda and systemic lupus erythematosus. All four patients had HLA typing for MHC class II antigens. Only patient 4 had HLA-DR2.

Case 1

A 74-year-old white man had a 2-month history of blisters in trauma-prone areas. He had ileitis that had been treated with sulfasalazine several years before the onset of EBA. Examination revealed tense blisters on his elbows, knees, and the dorsal aspect of his feet. An initial biopsy specimen revealed a subepidermal blister with a sparse lymphocytic dermal infiltrate without eosinophils. Direct immunofluorescence of perilesional skin revealed linear IgG deposition at the DEJ. He was treated with prednisone for bullous pemphigoid and had no clinical improvement.

Our laboratory findings were consistent with EBA. He was treated with colchicine, 0.5 mg/day. Within 2 weeks his blisters had decreased and his colchicine was in-
increased to 1 mg/day. After 2 months he began to reduce the prednisone by 5 mg/week. After stopping prednisone he has remained lesion-free for 1 year with a maintenance dosage of colchicine, 1 mg/day.

Case 2

A 71-year-old white woman had blisters after minor trauma on her elbows, fingers, palms, soles, knees, and lower extremities for 1 year. She was in good health and her only medication was conjugated estrogens (Premarin). Examination showed numerous milia within erythematous scarred plaques on her knees, elbows, hands, and feet. The results of laboratory studies confirmed the diagnosis of EBA.

The patient was treated with 0.6 mg colchicine per day, which was later increased to 1.2 mg/day. She improved and had no blisters for several months. Subsequently, however, a few new blisters developed on her hands. She was unable to tolerate higher doses of colchicine because of diarrhea, so dapsone, 50 mg/day, was added. Within 1 month, the patient reported an absence of new spontaneous blister formation and less skin fragility. Her disease currently remains stable with occasional trauma-induced lesions; her maintenance regimen is colchicine, 1 mg/day, and dapsone, 50 mg/day.

Case 3

Since 1984, a 75-year-old white woman had had a widespread inflammatory bullous eruption; it was diagnosed as bullous pemphigoid. She had been treated with sulfapyridine, azathioprine, dapsone, and prednisone. Four years later trauma-induced blisters and numerous milia developed on her elbows, knees, hands, and feet. Her blisters healed with scarring. The distribution of her disease included truncal and acral blisters (Fig. 1), deep erosions on her buttocks and 1 to 2 cm erosions on the tongue and hard palate. The blistering and scarring of the soles of her feet prevented her from walking (Fig. 2).

In 1988 her disease was reevaluated and a diagnosis of EBA was confirmed. She was initially treated with the addition of cyclosporine, 6 mg/kg daily, to her existing regimen of prednisone, 1 mg/kg daily; sulfapyridine, 500 mg, four times daily, and azathioprine, 150 mg/day). Some improvement ensued, but a rapid decrease in her creatinine clearance necessitated the withdrawal of cyclosporine. She then had a severe flare of her eruption. Prednisone was increased to 1 mg/kg daily, and the blisters on her trunk responded slightly. Each attempt at reducing the dose of prednisone, however, led to increased blistering. In 1990, colchicine at 0.5 mg/day was initiated and gradually increased to tolerance over a 2-month period. After 4 months of treatment with colchicine, 2 mg/day, there was a marked decrease in new blister formation and skin fragility (Fig. 3). Her dosages of prednisone, sulfapyridine, and azathioprine were gradually decreased and discontinued. With colchicine, 0.6 mg/day, alone the patient has had no new lesions for 24 months.

Case 4

A 35-year-old black man had a 5-year history of mucosal ulcerations and blisters confined mostly to the head and neck but occasionally on the arms and hands. He also had conjunctival, esophageal, and urethral strictures. Examination showed scarring alopecia and bullae of the scalp. Fibrous bands and scarring were noted in the conjunctivae. There were small scattered erosions on the tongue and gingiva. No milia were present. Laboratory studies confirmed the diagnosis of EBA.

The patient had been taking prednisone, 0.5 to 1 mg/kg, for 6 years without improvement. One year after dis-
continuing prednisone, he was treated with colchicine, 0.5 mg/day. The colchicine was increased to 1.5 mg/day (his maximal tolerated dose). After 2 months he had no new blisters on his scalp, face, and hands; he had only occasional blisters on his oral mucosa. He did well for 4 years while taking colchicine and then had a recurrence of lesions in his mouth and upper larynx. Cyclophosphamide, 50 mg/day, was added. He is currently receiving a maintenance regimen of colchicine, 1.5 mg, and cyclophosphamide, 50 mg, daily.

DISCUSSION

The mechanisms by which colchicine exerts its antiinflammatory effects are numerous. Colchicine inhibits cell division by binding to tubulin dimers and preventing polymerization into microtubules. It also interferes with polymorphonuclear leukocyte chemotaxis.

The mechanism by which colchicine appears to reduce the signs of EBA is unknown. Although EBA is not a neutrophil-rich dermatosis, several cases have demonstrated a predominance of polymorphonuclear leukocytes early in the disease process. It is conceivable that the neutrophil infiltrate in early EBA may initiate the inflammatory cascade. Furthermore, the results of a study by Gammon, Inman, and Wheeler suggested that the EBA autoimmune complex activated complement and recruited leukocytes to the DEJs to a greater degree than bullous
pemphigoid immune complexes. Colchicine, by interfering with polymorphonuclear leukocyte chemotaxis, may abrogate the inflammatory cascade and prevent leukocytes from attaching to the basement membrane in EBA.

Colchicine also decreases lysozymal enzyme release by polymorphonuclear leukocytes secondary to an increase in cyclic adenosine monophosphate levels. Colchicine inhibits immunoglobulin secretion from plasma cells in rats. Colchicine may also act by diminishing the production of type VII collagen antibodies in patients with EBA. Furthermore, colchicine may contribute to limiting HLA-DR expression and antigen presentation. Mekori et al. found that colchicine and vinblastine (microtubule inhibitors), but not methotrexate, interfere with the transport of proteins from the proteasome of cells to the cell surface. This mechanism may prevent the appearance of HLA-DR antigens. Mekori et al. speculated that colchicine may block expression of cellular immunity.

Colchicine decreases collagen and increases collagenase production, resulting in intracellular accumulation of procollagen with a subsequent reduction in procollagen synthesis. Intuitively, these changes would seem to exacerbate a mechanobullous disease. Berbis and Privat postulated that by decreasing collagen synthesis and increasing collagenase, the antigenicity of type VII collagen might change, making it less recognizable by autoantibodies. Whether colchicine’s potential effect on collagen production is significant in the treatment of EBA remains to be determined.

The long-term administration of colchicine at moderate doses is usually well tolerated. All patients given high doses of colchicine will have diarrhea. Therefore, our approach was to start the patients at a low dose (usually between 0.4 and 0.6 mg/day) and then to increase by 0.6 mg/day each week until diarrhea developed. The patient was then instructed to take the highest tolerable dose.

Although we are actively treating 14 patients with EBA, we have not used colchicine in all of them. Four responded to colchicine and have been described herein. Four patients have inflammatory bowel disease associated with their EBA, and we are reluctant to give them colchicine. Two patients, one an elderly man and the other a middle-aged woman, neither with known bowel disease, were unable to tolerate the diarrhea induced by colchicine at only 0.5 mg/day. In addition, we have treated three middle-aged women who failed to improve while taking colchicine, 1 to 2 mg/day, for 3 to 4 months. Why these patients did not respond is unclear.

REFERENCES