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LEUKOCYTOCLASTIC VASCULITIS IN A CHILD WITH EPIDERMOLYSIS BULLOSA SIMPLEX*

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A 10-year-old boy with epidermolysis bullosa simplex (Weber-Cockayne variant) together with leukocytoclastic vasculitis is presented. He was admitted to the hospital with the provisional diagnoses of infected epidermolysis bullosa simplex or drug eruption. On the sixth day of hospitalization he developed palpable purpura, abdominal pain and bloody diarrhea, together with hematuria and proteinuria. A generalized tonic-clonic convulsion, changes in mental status, fluctuations in arterial blood pressure and intractable pain in his extremities occurred during the course of hospitalization. Systemic pulse steroid therapy, antibiotics, and antihypertensive and anticonvulsive drugs were given. On the 30th day of hospitalization, a skin graft was performed to replace a large tissue defect on his left hand. Despite high dose steroid therapy, his hematuria, proteinuria and hypertension continued after his discharge, suggesting a steroid-resistant renal pathology, such as focal glomerulosclerosis, that occurred secondary to leukocytoclastic vasculitis. *Key words: epidermolysis bullosa simplex, leukocytoclastic vasculitis, childhood.*

Epidermolysis bullosa (EB) is a group of genetically determined diseases characterized by abnormal fragility of the skin and mucosa. It may be divided into three major inherited forms (simplex, junctional and dystrophic), based on the presence or absence of scarring, the mode of inheritance and the level of skin cleavage following minor trauma, and an acquired form (EB acquisita). Depending on the specific type of EB, prognosis varies considerably. At present there is no cure for any form of EB. Epidermolysis bullosa EB simplex is characterized by autosomal dominant inheritance. Blisters generally heal without scarring and mucosal involvement is mild. the commonest type of EB simplex is the Weber-Cockayne variant in which the blisters occur mainly on the hands and feet. Cytolysis of the epidermal cells is the essential histological feature of the EB simplex. Epidermal cleavage usually occurs in the midsquamous area but it may be noted anywhere from the suprabasal to the lower granular layers of the epidermis[2].

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Leukocytoclastic vasculitis is a necrotizing vasculitis affecting small blood vessels in which the polymorphonuclear leukocytes (PMNL) infiltrate the necrotic vessel wall, and scattered nuclear debris accumulates around the lesions. This is the predominant reaction in Henoch-Schönlein purpura (HSP), mixed cryoglobulinemia, hypersensitivity angiitis, hypocomplementemic urticarial vasculitis and other connective tissue diseases such as systemic lupus erythematosus (SLE). In the literature, there are a few reports of epidermolysis bulosa acquisita occurring in association with systemic lupus erythematosus[5, 6], but no report exists on the development of leukocytoclastic vasculitis in a patient with a hereditary form of epidermolysis bullosa.

Thus, we present herein a case of leukocytoclastic vasculitis in a child with epidermolysis bullosa simplex.

Case Report

A 10-year-old boy presented to Hacettepe University Children's Hospital Infectious Disease Unit, Ankara, in April 1996 with a diagnosis of infected EB simplex and a suspected drug eruption.

The diagnosis of EB simplex was first suspected when he was admitted to another hospital at 18 months of age with recurrent attacks since his neonatal period of bullous lesions confined to his hands and feet following minor trauma. One week before his admission at that time he developed erythema and papular lesions on his legs, and the bullous lesions that were present on his legs and feet increased. He was examined by a dermatologist and prescribed a topical steroid and an oral antihistaminic which were of no benefit.

He was the fourth child of healthy nonconsanguineous parents. He had one brother who had similar lesions beginning from birth who had died of a convulsion after vaccination with DPT at two months of age. There was no family history of autoimmune disease. He had no history of photosensitivity, malar rash, arthritis, serositis or renal, neurological or hematological disorders.

Clinical examination revealed multiple bullous lesions on his hands, feet, forearms, and legs; widespread erythema and maculopapular eruptions on thighs; and significant erythema on left ankle, lateral part of right foot, third finger of the left hand and right hand. Involvement of the soles made ambulation impossible and palmar lesions interfered with routine hand functions. Bullae were tense, measuring up to 2 cm in diameter and filled with clear yellow fluid. Physical examination was otherwise normal. Sulbactam-ampicillin was started at a dose of 100 mg/kg/day i.v. On the 6th day of his admission sulbactam-ampicillin was changed to ciprofloxacin because of the palpable purpura on his thighs and gluteal region and of the petechiae and aphthous lesions in his oral mucosa. At this time, the patient had intractable pain caused by his tense bullous lesions as well as from his palpable purpuric lesions, which required codeine preparation (Fig. 1).

Fig. 1: Right hand and arm with blistering and scalded purpuric lesions.

Laboratory examination revealed normochromic normocytic anemia (HB: 11.5 g/dl, Htc: 32%, MCV: 84 fl), a white blood cell count of 18,600/mm^3 with predominance of PMNL on peripheral blood smear and normal platelet count. Erythrocyte sedimentation rate was 75 mm/hr. The urine was 3 (+) for protein and sediment contained 3-4 leukocytes and 3-4 erythrocytes per high power field. The values for urea nitrogen, creatinine, calcium, phosphorus, uric acid, total protein, and albumin were normal. Abdominal ultrasound showed increased echogenitcity in both kidneys such that the cortex and the medulla could not be distinguished and there was edema in the intestine, especially in the duodenum. Protein/creatinine ratio in spot urine specimen was 3.4 and creatinine clearance was 94 ml/min/1.73 m^2 (normal: 89-165 ml/min/1.73 m^2 for this age group). ASO titer was 244 U/ml (normal: 166-250 U/ml). Quantitative c-reactive protein (CRP) was 53 mg/L (Normal: 0-8 mg/L). C_3, C_4, CH_{50} values and serum immunoelectrophoresis for IgA, IgM, and IgG were normal.

Our preliminary clinical differential diagnosis favored HSP together with EB simplex.

On the fourth day following occurrence of his lesions the patient demonstrated edema and erythema of his eyelids, and prednisolone at 1 mg/kg/day was started. During the follow-up the patient also had a generalized tonic-clonic seizure. Magnetic resonance imaging revealed cortical and subcortical lesions in the posterior temporal, occipital, posterior parietal and frontal regions bilaterally (Fig. 2). These lesions were thought to be secondary to sinus thrombosis or vasculitis.

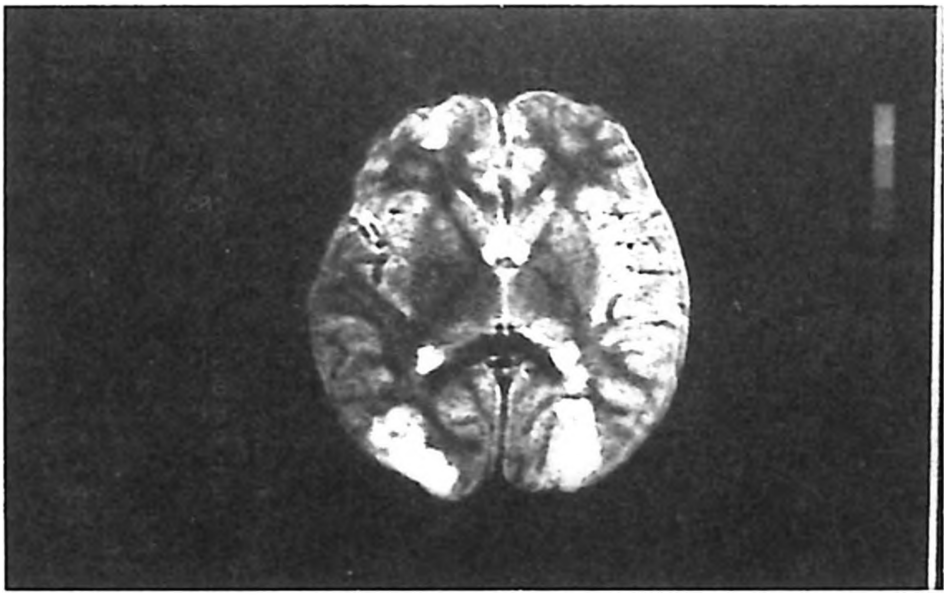

Fig. 2: Bilateral cortical and subcortical areas of increased density on cerebral magnetic resonance imaging (MRI).

As our patient's episodes of unconsciousness continued, we increased the dose of prednisolone first up to 2 mg/kg/day and then to 30 mg/kg/day. a punch biopsy specimen from the purpuric lesions revealed leukocytoclastic vasculitis. Direct immunofluorescence staining performed on the punch hiopsy specimen taken on the 7^{th} day of steroid therapy showed nonspecific C_4, IgA, IgM and fibrinogen positivity in the interstitial area of the upper dermis. Electron microscopic examination showed degeneration of the basal layer and cleavage of the epidermis above the basal lamina, both of which are correlated with the diagnosis of EB simplex.

Anti-nuclear antibodies, anti-DNA antibodies, anti-neutrophilic cytoplasmic antigen, anticardiolipin antibodies, lupus anticoagulant and rheumatoid factor were negative. Serology for CMV, EBV, Mycoplasma pneumoniae, Herpes simplex virus type I and type II, and markers for HBV and HCV were negative. Echocardiography was normal. Plasma proteins C and S and antithrombin III were normal. On the 30^{th} day of hospitalization, a skin graft taken from the right inguinal area was placed on his left hand where a tissue defect occurred. Pulse steroid therapy of 30 mg/kg/day was continued for four days and then gradually decreased to 2 mg/kg/day. All other bullous lesions and purpuric lesions healed without scarring and the inguinal area from which the skin graft was removed demonstrated no scarring. Before his discharge from the hospital his urea nitrogen, uric acid, creatinine, calcium and phosphorus were normal. The urine was still 3 (+) for protein and the sediment contained 2-3 erythrocytes per high power field. Creatinine clearance was 44 ml/min/1.73m^2 and protein/creatinine

ratio was 14 in 24-hour urine specimen.Although he has been on extended steroid therapy, the persistence of hematuria, proteinuria and hypertension may suggest a steroid-resistant renal pathology which occurred secondary to the vasculitic process that developed on the basis of a hereditary disease, EB simplex.

Discussion

The presence in this case of clinical symptoms such as non-thrombocytopenic palpable purpura, abdominal pain, bloody diarrhea, proteinuria, hematuria, generalized seizure, and mental status changes agreed with our diagnosis of HSP. Although our diagnosis was HSP together with EB simplex, we were not able to rule out hypersensitivity angiitis.

The diagnostic criteria for hypersensitivity angiitis was outlined in 1990 by the American College of Rheumatology (ACR)[1]. The presence of medication at disease onset, palpable purpura, maculopapular rash, and histological changes showing granulocytes in perivascular or extravascular locations suggested the diagnosis of Henoch-Schönlein nephritis, and hypersensitivity angiitis together with EB simplex. Belmen et al[3]. described three patients with HSP who developed prominent neurological smyptoms and signs during the course of their illness. Based on their experience and a review of the literature they suggested that nervous system involvement is more common than previously believed. Headaches and mental status changes are the most frequent complications of HSP followed by seizures, focal neurological deficits, mononeuropathies and polyradiculopathies. In our case the cause of the generalized seizure andperiods of mental status changes could also be attributed to fluctuations in blood pressure, but it is difficult to comment on whether it is a consequence of hypertension or secondary to the vasculitic process. Although we know from recent studies that glucocorticoids do not demonstrate any advantage over supportive therapy in gastrointestinal hemorrhage or renal disease[1], we administered with an increasing dose regimen because of the intractable pain and the possible central nervous system involvement.

Review of the literature gives no information related to EB simplex together with leukocytoclastic vasculitis. There are only reports regarding EB acquisita with clinical features of bullous lupus erythematosus[5,6]. Epidermolysis bullosa EB acquisita is thought to be an autoimmune disease in which patients have antibodies to the amino-terminal of type VII collagen[4]. It is a chronic progressive disease with periods of relapses and remissions and is resistant to systemic glucocorticoids. The diagnostic criteria of EB acquisita were originally outlined by Prussick et al.[5] and were subsequently modified. Patients with SLE, especially those with the bullous type, may produce antibodies to the EB acquisita antigen in addition to other autoantibodies[5,6]. In our patient, a diagnosis of EB acquisita

was ruled out in view of the family history of EB in a brother; the electron microscopic, light microscopic and direct immunofluorescence findings; and the clinical picture. In recent studies, it is suggested that autoantibodies to collagen types III, IV, V and laminin may be detectable in serum samples from patients with hereditary EB[4]. These serum antibodies would be of different molecular characteristics than those of EB acquisita autoantibodies. In our patient, death of one brother with EB at two months of age after vaccination and the development of hypersensitivity angiitis and Henoch-Schönlein nephritis suggest that some unknown autoimmune mechanisms based on EB simplex may also play a role.

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