Chronic Bullous Dermatosis of Childhood Associated with Coeliac Disease in a 6-year-old Boy

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Sir,

Many of the diseases reported in association with coeliac disease (CD) are linked to the histocompatibility antigen HLA-DR3, such as dermatitis herpetiformis (DH) and Type 1 diabetes mellitus (1, 2). DH is characterized by granular IgA deposits in the basement membrane zone. It has recently been shown that epidermal transglutaminase is the autoantigen of DH, as opposed to CD, in which tissue transglutaminase is the main autoantigen (3). DH is rare in coeliac children. Thus, in our Paediatric Clinic we have over the past 25 years diagnosed only one case of DH among 220 consecutive cases of CD. The bullous disease referred to as chronic bullous dermatosis of childhood (CBDC) typically presents as itchy, urticated papules and plaques as well as polycyclic lesions with blisters at the edge, located in the face and perineum (4). CBDC is distinguished from DH, apart from differences in clinical appearance and age at onset, by exhibiting linear deposits of IgA at the basement membrane zone. The same pattern of IgA is seen in linear IgA disease of adults. There is much overlap between these diseases (5). However, according to the literature, CBDC, unlike DH, is not associated with gluten-sensitive enteropathy (6), although this is contradicted by the present case report.

CASE REPORT

A 3.5-year-old boy, who had previously been healthy and had normal growth, was first seen by a dermatologist because of itchy blisters on the arms. A diagnosis of impetigo contagiosa had previously been made, but since the condition had deteriorated the boy came under specialist care. There were no gastrointestinal symptoms. At presentation he had blisters on the arms, legs, neck and in the genital region (Fig. 1). The blisters were arranged in an annular pattern. No mucosal changes were observed. Histological examination of a skin biopsy showed subepidermal blisters. Direct immunofluorescence analysis of another skin biopsy obtained at the same time showed marked linear deposits of IgA along the junction zone, as well as granular deposits of IgM and complement at the same level. A diagnosis of CBDC was made. Treatment with dapsone was instituted at a daily dose of 1.67 mg kg^{-1}, giving a fairly good response. The dose was obviously not optimal, but was kept at this level owing to the parents' fear of side effects. Bouts of new lesions kept appearing at an interval of some months, and topical steroids and topical antibiotics were added.

At 4 years of age, subnormal levels of serum iron and zinc were found. Further haematology investigation revealed normal Hb, WBC count, thrombocyte count, liver function tests, serum folate and cobalamine, and S-IgA anti-gliadin antibodies (AGA), whereas S-IgA anti-endomysium antibody (EMA) was positive at titre 1/20 (ref value $<1/10$). A peroral small-bowel capsule biopsy from the distal duodenum showed a light microscopically normal mucosa without an increased number of intraepithelial lymphocytes. The boy was kept on a normal diet including gluten.

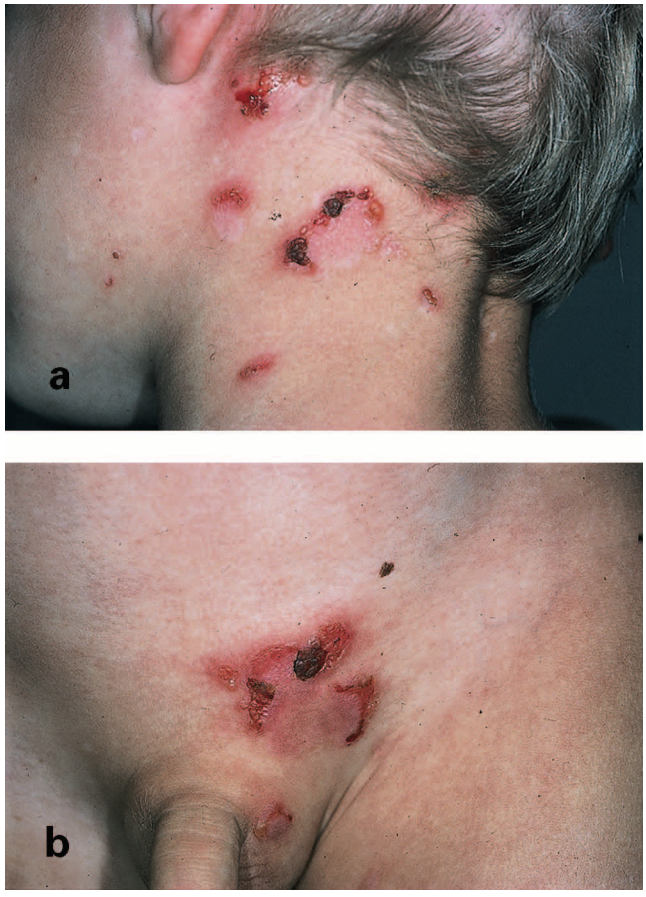

Fig. 1. Child with chronic bullous dermatosis of childhood. Blisters on the neck (a) and in the genital region (b) arranged in an annular pattern.

At 6.1 years of age AGA were still normal but EMA had increased to 1/640. Six months later EMA was even higher, 1/1,280. The boy still had no obvious gastrointestinal symptoms. A re-biopsy of the small bowel now showed hyperplastic villous atrophy of the crypts, severe inflammatory activity and increased numbers of intraepithelial lymphocytes – changes all consistent with CD. A gluten-free diet was instituted and the dapsone dose was reduced to half of the original dose. At follow-up 4 months later, the boy had only slight perioral changes. Serological markers of CD, now including both EMA and IgA anti-transglutaminase antibodies, were negative. The treatment with dapsone was stopped. A small-bowel biopsy after one year of gluten-free diet showed a normal mucosa.

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DISCUSSION

There are some previous case reports of a suspected association between CBDC and CD. However, in those cases small-bowel biopsy was either not performed or showed a result not fully consistent with a diagnosis of CD. To our knowledge this is the first report of an association between CBDC and biopsy-verified CD meeting the current revised criteria for the diagnosis of CD in children (7). Of course the simultaneous occurrence of CBDS and CD may have been coincidental. The remission of CBDC 3 years after debut could have been spontaneous. It could also be that our diagnosis of CBDC was incorrect and that the boy's bullous disease was in fact DH. However, the finding of linear IgA deposits in the skin biopsy of our patient strongly indicates CBDC.

There is some evidence that serum antibodies to gliadin and/or endomysium increase above normal levels in patients with CD (8) or DH (9) prior to the development of an obvious mucosal abnormality. This seems to be the case in our patient, in whom the EMA level was elevated at the time of the first small-bowel biopsy, which showed a histologically normal mucosa. It may also be that our patient had a patchy mucosal lesion, which is the usual finding in adults with DH (10), and that the first capsule biopsy missed the pathology.

In spite of low serum iron and zinc indicating malabsorption and a positive EMA as early signs of CD, the first small-bowel biopsy did not show an enteropathy on light microscopy. In particular, there was no increase in the number of intraepithelial lymphocytes (IEL), which is supposed to be the first light-microscopically detectable alteration of the small intestinal mucosa in CD (8). In fact, increased IEL is reported to occur prior to an increase in lamina propria lymphocytes or other changes of the small-bowel mucosal architecture in patients with CD (8) and DH (11). Taken together, these observations indicate that patients with CBDC may have an atypical form of CD with an immunopathogenesis that differs from current concepts in CD.

CD is one of the most common chronic disorders in Swedish children (12). It is well documented that a child with an undiagnosed or inadequately treated CD runs a definite risk of impaired growth, delayed pubertal development, various nutritional deficiencies, osteoporosis, infertility, decreased well-being and possibly an increased risk for autoimmune disorders (13). The gastrointestinal symptoms of an undiagnosed CD are often less clear-cut in older children than in infants and toddlers. The present case illustrates this fact. The boy had no obvious gastrointestinal complaints, which is also a common finding in children with DH (14). This indicates that children with long-standing or relapsing itchy, bullous skin lesions appearing in the face or in the perineal region should be serologically screened for CD and, if seropositive, submitted to small-bowel biopsy even in the absence of gastrointestinal symptoms.

Finally, our case illustrates that serological screening for CD may need to be repeated in children with CBDC in order not to miss a coeliac diagnosis. HLA-typing of the patient may increase the efficacy of serological screening, since the HLA combination DQA1*0501, DQB1*0201 coding for DQ2 molecules is found in 98% of CD patients in Northern Europe (15).

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