Pemphigus foliaceus

Claire Galambrun, Frédéric Cambazard, Catherine Clavel, Pascale Versini, Jean Louis Stéphan

Abstract

Pemphigus foliaceus is a skin disease in which antibodies against the cell surface of keratinocytes destroy the adhesion between epidermal cells, thereby producing blisters. It is a rare disease in childhood, and treatment guidelines for juvenile pemphigus foliaceus are lacking. An 8 year old boy with pemphigus foliaceus is described. He did not respond to topical steroids, and the condition flared up when high dose oral steroids were tapered. The lesions resolved completely in four weeks on dapsone, which was maintained for nine months with no major adverse effects, except for a moderate increase of the methaemoglobin concentration at the outset of treatment. There has been no evidence of disease reactivation in more than nine months of follow up since dapsone withdrawal.

(*Arch Dis Child* 1997;**77**:255–257)

Keywords: pemphigus foliaceus; dapsone

Pemphigus is the term used to describe a group of diseases that have in common superficial blistering of the skin and mucous membranes. These organ specific autoimmune skin diseases have been linked to antibodies directed against specific proteins found in human skin.[1] They are exceptionally rare in children.[2]

We describe a new case, in a young boy, of a major variant of the pemphigus group, pemphigus foliaceus, which responded well to dapsone.

Case report

An 8 year old boy of Turkish origin was referred with a 15 day history of a polymorphous bullous eruption. He had received empiric oxacillin treatment for suspected staphylococcal impetigo. He had multiple small crusted lesions with raised edges and blisters containing clear fluid; they were initially restricted to the trunk, then spread to the face and limbs. The mucosal membranes were respected (fig 1), and Nikolsky's sign was positive. Histological studies of a lesion showed splitting of the upper epidermis. The blisters contained acantholytic cells, eosinophilic polymorphonuclear cells, and neutrophils. IgG and C3 deposits were found between keratinocytes by means of direct immunofluorescence in the upper half of the epidermis, performed in perilesional skin according to well established techniques (fig 2).[3] Immunoblotting with

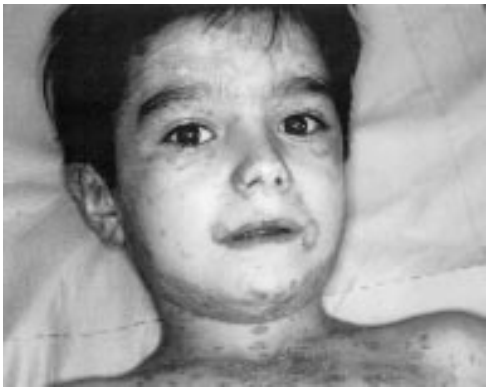

Figure 1 Superficial erosions and crust formation on the head, trunk, and neck.

normal bovine tongue desmosomal extract was performed as follows. Cow tongue was cut into small fragments and incubated for 72 hours in 1 M sodium chloride containing 50 mM phenylmethylsulphonyl fluoride and 0.1 M EDTA at 4°C. The surface epithelium was then physically stripped from the dermis. Proteins were extracted from the culture flasks with an extraction buffer and were separated by sodium dodecyl sulphate-polyacrylamide slab gel conditions as previously described.[4] A characteristic protein band at 160 kDa was present, indicative of pemphigus foliaceus. As a positive control, a commercially available monoclonal antidesmoglein antibody (clone 3.10, Progen, Heidelberg, Germany) was also used (fig 3). Other investigations were of little contribution, except for polyclonal hypergammaglobulinaemia involving all isotypes (IgG: 17.8 g/l, total IgE: 198 kU/l). Microbiological studies were all negative. Neither antinuclear nor organ specific autoantibodies were detected. No potential drug related cause was

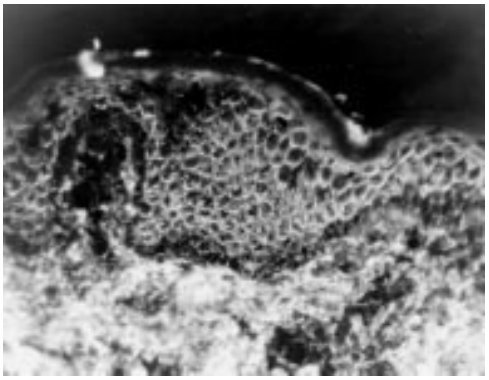

Figure 2 Direct immunofluorescence of perilesional, normal appearing skin by using antibody directed against human IgG. Cell surface IgG deposits are seen on epidermal keratinocytes.

Hôpital Nord, Saint Etienne, France
C Galambrun
F Cambazard
C Clavel
P Versini
J L Stéphan

Correspondence to:
Dr J L Stéphan, Unité d'Immuno-Hématologie et d'Oncologie Pédiatrique, Hôpital Nord, CHRU St Etienne, Avenue A Raymond, 42055 St Etienne Cedex 02, France.

Accepted 16 June 1997

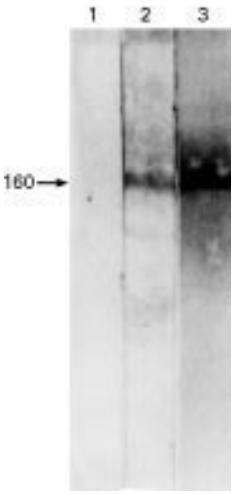

Figure 3 Immunoblotting studies. The patient's serum recognised a 160 kDa protein (lane 2). No reactivity with normal human serum (lane 1). Positive control with a monoclonal antidesmoglein antibody (lane 3).

identified in the recent history. Topical betamethasone was started, but was replaced by prednisolone, 2 mg/kg/day, because of lesion spreading, severe pruritus, and disturbed sleep. After a certain improvement, at a cost of marked weight gain and a Cushing-like appearance, a marked aggravation of the lesions occurred when the steroid was tapered. Dapsone was then started at a dose of 50 mg/day, after ensuring that the patient had no glucose-6-phosphate dehydrogenase deficiency. A rapid increase in methaemoglobinaemia (9%, normal < 2) led to a dose adjustment to 25 mg every second day, which was maintained for nine months, stable normal methaemoglobinaemia ensued. A complete remission was achieved in four weeks, and prednisolone was withdrawn. The child has been in complete remission since dapsone withdrawal, with a follow up of nine months. No circulating autoantibodies are currently detectable.

Discussion

Pemphigus foliaceus is a rare disease in children, with the exception of endemic forms of pemphigus foliaceus observed in Parana state in Brazil (Fogo selvagem = 'wild fire'), the epidemiology of which points to an infectious cause.[5]

Sometimes confused with impetigo or seborrheic dermatitis, the diagnosis is based on the presence of disseminated bullous and erythemous lesions covered with seborrheic scabs; Nikolsky's sign is positive. To our knowledge, only seven pediatric cases have been reported since 1986. One case involved a newborn with passive transfer of maternal autoantibodies across the placenta.[2 6–11]

Pemphigus foliaceus is due to the loss of malphigian cell coherence through binding of an IgG +/− C3 antibody directed against a polypeptide antigen complex on the keratinocyte surface. Although immunofluorescence patterns are virtually identical in pemphigus foliaceus and pemphigus vulgaris (the most severe variant of pemphigus), the antigenic target of the autoantibodies is different. IgG from patients with pemphigus foliaceus binds to the 160 kDa glycoprotein desmoglein I (DsgI), a key structure involved in adhesion of keratinocytes. In contrast, IgG from patients with pemphigus vulgaris binds to a distinct 130 kDa glycoprotein (cadherin) with significant homology with DsgI.[4] The autoantibodies are disease specific, predominantly restricted to the IgG_4 subclass, and pathogenic, as shown by passive transfer studies.[12] The exact mechanism by which these autoantibodies cause acantholysis is not known. Certain case reports underline the role of drugs as triggering factors in adults (amoxicillin, d-penicillamine, and captopril), together with viral causes (herpesviruses).[13]

The first case of paraneoplastic pemphigus foliaceus in children, associated with a T lymphoma, was reported very recently.[14] Neither infectious nor neoplastic cause was found in the case we describe, despite extensive investigations.

The prognosis of pemphigus foliaceus is markedly better than that of pemphigus vulgaris, probably because of the more superficial nature of the blistering process, and treatment should be chosen with this in mind, especially in children. Given its rarity, treatment guidelines for juvenile pemphigus foliaceus are lacking. Many adults with limited disease are treated with high potency topical steroids. Systemic steroids and immunosuppressants (cyclosporin A, azathioprine, methotrexate, or cyclophosphamide) are the drugs of choice for patients with severe pemphigus foliaceus.[15] However, the adverse effects of continuous high dose steroids or immunosuppressants must be weighed up carefully in children, and it is noteworthy that our patient had a flare up when steroids were tapered.

Dapsone (4,4' -diaminodiphenylsulfone) has proved the mainstay of treatment for patients with intraepidermal IgA neutrophil infiltrates, another autoantibody mediated blistering skin disease, and has been used with success in adults with pemphigus foliaceus.[16]

Leibowitz and Voss suggested that this product could be effective in children.[11] A rapid response to dapsone was seen in our patient, thus avoiding large doses of oral steroids (and their side effects) and immunosuppressants. The potential toxicity of this well known product at this age calls for very close haematological monitoring. Indeed, methaemoglobinaemia and haemolysis are well known complications of dapsone treatment, the latter being frequent in individuals deficient in erythrocyte glucose-6-phosphate dehydrogenase.[17]

Life threatening neutropenia and agranulocytosis can also occur. The apparent efficacy of dapsone in childhood pemphigus foliaceus must be confirmed.

Supported in part by grant from Association pour le Développement et La Recherche en Pédiatrie à St Etienne (ADERPS).

We thank J Kanitakis from the Laboratory of Dermatopathology/Department of Dermatology, Hopital Edouard Herriot, Lyon, France, for technical assistance with the immunoblotting study.

1 Korman NJ, Eyre RW, Klaus-Kovtun V, Stanley JR. Demonstration of an adhering-junction molecule in the autoantigens of pemphigus foliaceus and pemphigus vulgaris. *N Engl J Med* 1989;**321**:631-5.
2 Jones SK, Schwab HP, Norris DA. Childhood pemphigus foliaceus: case report and review of the literature. *Pediatr Dermatol* 1986;**3**:459-63.
3 Bhogal BS, Black MM. Diagnosis, diagnostic and research techniques. In: Wojnarowska F, Briggaman RA, eds. *Management of blistering diseases*. London: Chapman and Hall, 1990:15-32.
4 Cozzani E, Kanitakis J, Nicolas JF, Schmitt D, Thivolet J. Comparative study of indirect immunofluorescence and immunoblotting for the diagnosis of autoimmune pemphigus. *Arch Dermatol Res* 1994;**286**:295-9.
5 Empinotti JC, Diaz LA, Martins CR, *et al.* Endemic pemphigus foliaceus in western Parana, Brazil (1976-1988). Cooperative group for fogo selvagem research. *Br J Dermatol* 1990;**123**:431-7.
6 Walker DC, Kolar KA, Hebert AA, Jordon RE. Neonatal pemphigus foliaceus. *Arch Dermatol* 1995;**131**:1308-11.
7 Kanwar AJ, Dhar S, Kaur S. Further experience with pemphigus in children. *Pediatr Dermatol* 1994;**11**:107-11.
8 Goodyear HM, Abrahamson EL, Harper JI. Childhood pemphigus foliaceus. *Clin Exp Dermatol* 1991;**16**:229-30.
9 Kanwar AJ, Kaur S. Pemphigus in children. *Int J Dermatol* 199;**30**:343-6.
10 Yorav S, Trau H, Schewach-Millet M. Pemphigus foliaceus in an 8-year-old girl. *Int J Dermatol* 1989;**28**:125-6.
11 Leibowitz MR, Voss SP. Juvenile pemphigus foliaceus: response to dapsone [letter]. *Arch Dermatol* 1993;**129**:910.

12 Rock B, Martins CR, Theofilopoulos AN, *et al*. The pathogenic effect of IgG_4 autoantibodies in endemic pemphigus foliaceus (fogo selvagem). *N Engl J Med* 1989;**320**:1463-9.
13 Anhalt GJ. Drug induced pemphigus. *Semin Dermatol* 1989; 8:166-70.
14 Rybojad M, Leblanc T, Flageul B, *et al*. Paraneoplastic pemphigus in a child with a T-cell lymphoblastic lymphoma. *Br J Dermatol* 1993;**128**:418-22.
15 Piamphongsant T, Ophaswongse S. Treatment of pemphigus. *Int J Dermatol* 1991;**30**:139-46.
16 Basset N, Guillot B, Bruno M, Meynadier J, Guilhou JJ. Dapsone as initial treatment in superficial pemphigus. *Arch Dermatol* 1987;**123**:783-5.
17 Tracqui A, Gutbub AM, Kintz P, Mangin P. A case of acute dapsone poisoning: toxicological data and review of the literature. *J Anal Toxicol* 1995;**19**:229-35.

Beta cells, potassium channels, and insulin

It seems that the term, nesidioblastosis, is out and persistent hyperinsulinaemic hypoglycaemia of infancy (PHHI) is in. In familial PHHI mutations have been found in the gene on the short arm of chromosome 11 which codes for a β cell potassium channel protein, the sulfonylurea receptor. Now work in Sheffield, Leicester, and London (Charlotte Kane and colleagues, *Nature Medicine* 1996;**2**:1344-7) has shown a potassium channel defect in non-familial PHHI.

The β cells from partial pancreatectomy specimens from five infants were studied in culture and electrophysiological recordings demonstrated the absence of ATP-sensitive potassium (K_{ATP}) channel activity in all five. In normal β cells glucose entry produces more ATP which closes K_{ATP} channels. The resultant membrane depolarisation opens calcium channels and an influx of calcium brings about insulin release. Increased intracellular calcium was demonstrated in the PHHI β cells from these five infants.

It appears, therefore, that PHHI is caused by a lack of K_{ATP} activity which results in spontaneous electrical activity and insulin release. In an article in this journal in 1996 (**74**:373-8) the same workers reported a favourable response to calcium channel blockade in an infant with PHHI.

ARCHIVIST