IgA linear bullous dermatosis. A case report

J. Korsika-Mrak, A. Vizjak, M. Penko and A. Kansky

SUMMARY

A case of linear IgA dermatosis in a 71-year-old female patient is reported. She was previously treated with enalapril for arterial hypertension in the course of several years. At the last admission she mentioned that oral lesions have been appearing periodically, blister have been noticed about 2 months before. Histopathology revealed a subepidermal blister, and direct immunofluorescence disclosed linear IgA as well as granular C3 deposits along the epidermal basement membrane. The treatment with methylprednisolon starting with a dosis of 125 mg i.m. was successful. Additionally, dapsone was applied in a dosis of 100 mg daily, but it had to be discontinued because of methemoglobinemia. The dosis of methylprednisolon was gradually decreased and she left the hospital with 32 mg daily.

KEY WORDS

linear IgA dermatosis, drug induced, case report, immuno-fluorescence microscopy

Introduction

Linear IgA dermatosis (LAD) is an autoimmune vesicobullous subepidermal dermatosis rarely observed in Western Europe. Infections, drugs or malignant processes may provoke it, but sometimes it is of idiopathic origin. It seems to be more frequent in China, Malaysia, Sri Lanka and Thailand (1). Clinically it bears resemblance to bullous pemphigoid or to dermatitis herpetiformis. Both children and adults may be involved. The diagnosis can be confirmed by direct immunofluorescence (DIF), displaying linear IgA deposits along the epidermal basement membrane. The autoantibodies are of the IgA class, which is a rather rare event among the autoimmune disorders. A complexity and heterogeneity of the target antigens in different patients with LAD have been established (2). Incriminated antigens are proteins with molecular weight of 285 kD as well as the 97 kDa and 120 kDa which appear to be fragments of extracellular domain of bullous pemphigoid antigen BP 180 (type XVII collagen). BP 230 antigen located in the lamina lucida of the basal membrane, collagen VII, which is a component of anchoring fibrils as well as some still non-identified antigens, may also be involved (2). A strong association between the disease and autoimmune haplotypes HLA-B8, CW7 and DR3 has been reported (3).

The disease affects people of all ages, but two peaks can be observed: *the chronic bullous disease of childhood* appearing before the age of five and the *adult linear IgA disease* appearing after the age of sixty years (4). In children the onset is usually acute, papules, urticarial plaques and polycyclic lesions with blisters are situated mainly on the face and perineum, however the trunk, thighs, limbs, as well as hands and feet may also be involved. Mucosal involvement is common (mouth, nose or esophagus) so that erosions and ulcers are not uncommon. A mild or severe pruritus or burning sensation accompanies these lesions.

In cases triggered off by drugs, e.g. vancomycin, phenitoin, somatostatin, amiodarone, lithium or captopril, a remission may follow the withdrawal of the incriminated drug (5). In idiopathic cases the treatment should be started with a dosis of 25-50 mg of dapsone daily, which has to be increased stepwise to 100-150 mg daily. As dapsone may cause a hemolytic anemia, decreased hemoglobin values or even methemoglobinemia, the enzyme glucose-6-phosphate dehydrogenase has to be assayed before beginning the treatment. Clinical symptoms of methemoglobinemia are cyanosis, breathlessness and stenocardia. As an alternative drug sulphapyridine 250 mg to 3 g daily can be administered.

In resistant cases where the above mention treatment has failed systemic corticosteroids should be used, in a few patients beneficial effects after an application of azathioprine or cyclosporin have been reported (2).

Case report

A 71-year-old female patient appeared for consultation in July 1998. Two months before she had observed a blister on her left arm, followed by more blisters on various areas of the skin. She also complained of the oral mucosa lesions and told that she was taking 2 x 20 mg enalapril (Olivin®) daily during a couple of years for her arterial hypertension. A skin biopsy was performed at that time and the slide No. 774/98 was read as bullous pemphigoid or pemphigus vulgaris. DIF revealed a faintly positive linear IgA and IgG deposits associated with fine granular immunostaining for C3 at the epidermal basement membrane zone. Diffuse interstitial deposits of fibrin/fibrinogen were observed in the dermis. The pathologist expressed the opinion that the IgA deposits were faint and did not justify the diagnosis of linear IgA dermatosis and the diagnosis bullous pemphigoid was suggested.

July 31, 1998 she was admitted to the Department of Dermatology of the University Medical Center in Ljubljana. A second biopsy was performed.

Immunopathology displayed a definite linear deposition of IgA along the basement membrane (++), accompanied by less expressed linear IgG deposits (+) as well as granular and partially linear C 3 deposits (+/++).

The definite diagnosis at that time was linear IgA dermatosis, which was confirmed also by indirect immunofluorescence test (IIF) on normal skin. Positive IgA but not IgG pemphigoid autoantibodies were demonstrated.

The routine laboratory tests as well as the x-ray and the ultrasound examinations were within normal limits.

Treatment with methylprednisolon (Solumedrol®) 125 mg i.m. daily was introduced, the dosis being gradually decreased. After 18 days 84 mg of methylprednisolon (Medrol®) were given orally per day. Additionally, she received 100 mg of diaminosulphon (Dapson®) daily, but the drug had to be discontinued because of methemoglobinemia. She was given also ranitidin (Ranital®) and nystatin (Mycostatin®). The oral lesions were treated with 0.1% triamcinolone and 1% xylocain. The patient also received antibiotics twice: the first time due to an infection following the biopsy, and the second time because of a paronychia.

The skin lesions healed in two weeks after the introduction of treatment, but mucosal lesions resolved two-month later. She was discharged from the hospital after 72 days being still on 32 mg of Medrol and was advised to reduce its dosis gradually. Olivine was supplemented by losartane (Cozaar®) 50 mg daily.

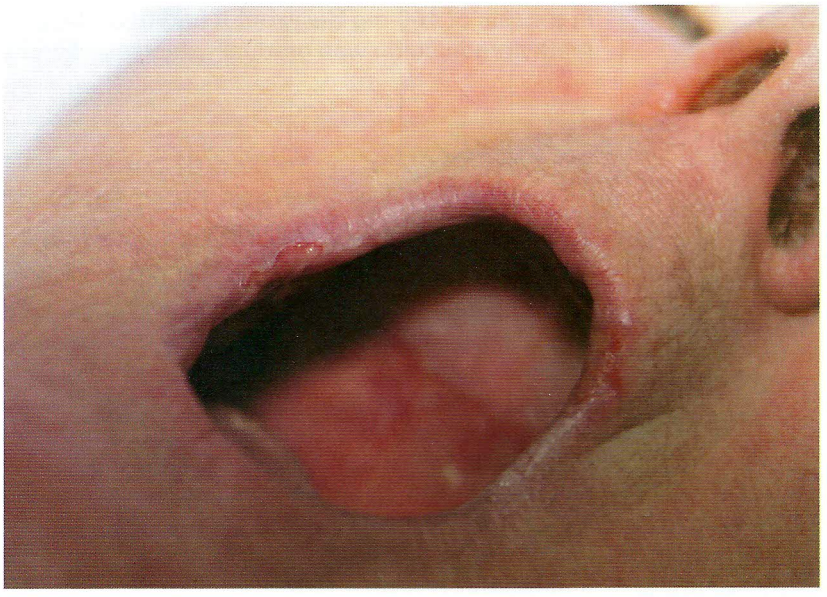

Figure 1. The 71-year-old patient with linear IgA dermatosis: oral lesions.

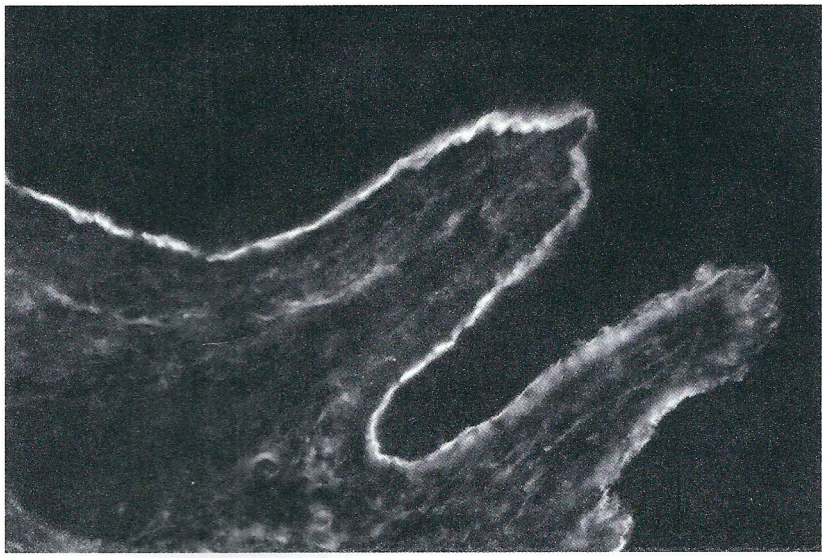

Figure 2. Direct immunofluorescence showing fine linear deposition of IgA along the epidermal basement membrane zone. Original magnification x 130.

Discussion

LAD is clinically and immunologically a relatively well-defined nosologic entity.

The disease is characterized by circulating and tissue bound IgA antibodies against heterogeneous antigens located in the cutaneous basement membrane zone. Some of these antibodies were defined by molecular weight and localization. Application of split skin technique has demonstrated that the majority of antibodies bind to the epidermal side of the lamina lucida, whereas the rest adheres to the dermal side of the artificial blister, and a few are of a combined pattern (6,7). Certain authors distinguish between *specific LAD antigens* (285 kDa, 97/120 kDa, ladinin) and *shared LAD antigens* (BP 230, BP 180, collagen VII and some further antigens) (8,9). The described immunological heterogeneity could be responsible for variations in the clinical course of LAD.

It has been demonstrated in recent studies that the basal keratinocyte surface antigen, BP 180, known to be type XVII collagen, is a major shared target antigen for autoantibodies produced by patients with various blistering diseases, including bullous and cicatricial pemphigoid, herpes gestationis, lichen planus pemphigoides, and LAD (10). A characteristic finding of linear immunoglobulin binding mostly associated by complement deposits along the epidermal basement membrane zone is of major significance in the diagnosis of bullous dermatoses. It is desirable that this observation is confirmed also by indirect immunofluorescence demonstrating positive autoantibodies in the patient's serum.

On the other hand, clinical, histomorphological and immunohistological heterogeneity is presumably caused by differences in fine epitope specificity, the isotype of autoantibodies and associated effector mechanisms. Thus, IgG autoantibodies are distinctive for pemphigoid and herpes gestationis, while IgA autoantibodies characterize LAD. However, the simultaneous positivity for IgG and IgA observed in some patients makes the distinction especially between bullous/cicatricial pemphigoid and LAD difficult. In such cases, the comparison of intensity of particular immunoglobulins is of major relevance for making the proper diagnosis. This is well illustrated with our case report. The patient had in the first skin biopsy scanty positive linear IgG and IgA deposits along the epidermal basement membrane, which did not permit the differentiation between bullous pemphigoid and LAD. Since LAD is a fairly rare condition, bullous pemphigoid was suggested as more likely diagnosis. However, the diagnosis of LAD was enabled by the second skin biopsy showing clear predominance of IgA over IgG in linear epidermal basement membrane deposits. In addition, the diagnosis of LAD was confirmed by positive IgA and negative IgG pemphigoid antibodies detected by indirect immunofluorescence.

Certain observations indicate the possibility that LAD may be provoked by the use of drugs e.g. vancomycin, captopril, phenitoin, and amiodaron (11,12). In this context we would like to express opinion that drugs are important triggering factors.

Reports exist demonstrating that in contrast to dermatitis herpetiformis there is no tissue transglutaminase in the sera of LAD patients (12).

In addition to skin involvement lesions of the oral mucosa and conjunctiva were reported (13). Ulcerative colitis (14) and balanitis (15), as well as psoriasis (16) were also reported appearing simultaneously with skin involvement.

In conclusion we would like to point out that the treatment with methylprednisolon was efficient in our patient. After almost two years there are no skin lesions and just mild erosions are appearing on the pressure sites exhibited by the artificial denture. She is still on a maintaining dosis of 20 mg methylprednisolon (Medrol®).

REFERENCES

1. Jin P, Shao C, Ye G. Chronic bullous dermatoses in China. Int J Dermatol 1993; 32: 89-91.

2. Wojnarovska F, Eady RAJ, Burge S. Bullous eruptions. In: Rook et al. Textbook of Dermatology 6 ed,Champion RH et al eds., Blackwell, Oxford 1998; 1880-3.

3. Collier PM, Wojnarovska F. MHC class I and II antigens in linear IgA dermatosis. J Invest Dermatol 1992; 98: 526 (Abstract).

4. Wojnarovska F, Marsden R, Bhogal B, Black M. Chronic bullous disease of childhood, childhood cicatricial pemphioid and linear IgA disease of adults, a comparative study demonstrating clinical and immunopathological overlap. J Am Acad Dermatol 1988; 19: 792-805.

5. Baden LA, Apovian C, Imber MJ, et al. Vancomycin induced linear IgA bullous dermatosis (Letter). Arch Dermatol 1988; 124: 1186-8.

6. Wojnarovska F, Allen J, Collier PM, Leigh IM. A comparison of the expression of known basement membrane components with the linear IgA disease antigens using the novel substrate cylindroma. Br J Dermatol 1999; 141: 62-70.

7. Allen J, Zhou S, Wakelin SH, Collier PM, Wojnarovska F. Linear IgA disease: a report of two dermal binding sera which recognize a pepsin-sensitive epitope (NC-1 domain) of collagen type VII. Br J Dermatol 1997; 137(4): 526-33.

8. Wakelin SH, Allen J, Zhou S, Wojnarovska F. Drug induced linear IgA disease with antibodies to collagen VII. Br J Dermatol 1998; 138(2): 310-4.

9. Moll R, Moll I. Epidermal adhesion molecules and basement membrane components as target structures of avtoimmunty. Virchows Archiv 1998; 432(6): 487-504.

10. Zillikens D, Herzele K, Georgi M, et al. Autoantibodies in a subgroup of patients with linear IgA disease react with the NC16A domain of BP180. J Invest Dermatol 1999; 113: 947-953

11. Kuechle MK, Stegermeir E, Maynard B, et al. Drug induced Linear IgA bullous dermatosis : Report of six cases and review of the literature. J Am Acad Dermatol 1994; 30: 187-92.

12. Friedman IS, Rudikoff D, Phelps GP, Sapadin AN. Captopril - triggered linear IgA bullous dermatosis. Int J Dermatol 1998; 37: 600-616.

13. Smith JR, Kupa A, Coster DJ. Linear IgA disease. Austral New Zealand J Ophtal 1999; 27(6): 443-6.

14. De Simone C, Guerriero C, Pellicano R. Linear IgA disease and ulcerative colitis. J Europ Dermatol 1998; 8(1): 48-50.

15. Kirtschig G, Mengel R, Mittag H, Flores-De Jacoby L, Happle R. Desquamative gingivitis and balanitis - linear IgA disease or cicatricial pemphioid. Clin Exp Dermatol 1998; 23(4): 173-7.

16. Takagi Y, Sawada S, Yamauchi M, Amagai M, Nimura M. Coexistence of psoriasis and linear IgA bullous dermatosis. Br J Dermatol 2000; 142(3): 513-6.

AUTHORS' ADDRESSES

Jadranka Korsika-Mrak MD, dermatologist, Department of Dermatology, University Medical Centre, Zaloška 2, 1525 Ljubljana, Slovenia.
Alenka Vizjak PhD, research associate, Institute of Pathology, Faculty of Medicine, University of Ljubljana, Korytkova 2, Ljubljana, Slovenia.
Marta Penko MD, dermatologist, Chairman of Department of Dermatology, University Medical Centre, Zaloška 2, 1525Ljubljana, Slovenia.
Aleksej Kansky MD, PhD, professor of dermatology, same address