Drug induced linear IgA dermatosis

Case report and a short review

A. Benedičič Pilih, A. Vizjak, F. Wojnarowska, M. Berčič, A. Pejovnik Pustinek, J. Arzenšek and A. Kansky

SUMMARY

A significant number of reports incriminate various drugs, especially vancomycin and amiodarone of provoking bullous linear IgA dermatosis. This entity also includes the subset of IgA-mediated epidermolysis bullosa acquisita.

We report on a patient with histopathologically and immunologically proven bullous linear IgA dermatosis, who developed this condition during treatment for hypertension with enalapril. Treatment with low doses of dapsone, 25 mg daily, was efficient. There is strong evidence that the condition was triggered by enalapril.

KEY WORDS

linear IgA dermatosis, drug induced, enalapril, captopril, treatment, dapsone

Introduction

There are many publications asserting that bullous autoimmune diseases, such as pemphigus, bullous pemphigoid and linear IgA dermatosis (LAD) may be provoked by medication. Inhibitors of the angiotensin converting enzyme (ACE) like captopril or diuretics like furosemide have frequently been incriminated as causing bullous pemphigoid (BP), as well as other skin conditions (1,2). Litt mentioned in his publication (3) that captopril was held responsilble in 38 references as the cause of angioedema, in 31 it was associated with exanthema and lichenoid eruptions, in 23 with bullous manifestations, mostly pemphigus and in three reports with LAD. Enalapril was reported to have induced angioedema in 55 cases, and has also been reported as having induced exanthema and rash, urticaria and other skin manifestations (3). There is ample evidence in literature that a number of drugs have been incriminated as provoking LAD (Table 1) including vancomycin, somatostatin, rifampin, captopril, trimethoprim, sulfamethoxazole, phenytoin, atorvastin, piroxicam, lithium carbonate, amiodarone, cyclosporine, cefamandole and diclofene (4,5).

The diagnosis of LAD is based on the following criteria:

- itchy vesicobullous lesions on skin and/or mucous membranes

Table 1. Reports on drugs incriminated as inducing linear IgA dermatosis

Author	Journal	Incriminated drug
Gabrielsen T et al	Acta Dermatol (Stockh) 1981; 51: 439-41	Diclophenac
Castel T et al	Clin Dermatol 1981; 6: 635	Furosemide
Mc Whirter JD et al	Arch Dermatol 1987; 123: 1120-2	Lithium carbonate
Rasmussen H et al	J Cutan Pathol 1989; 16: 154	Penicillamine
Kuechle MK et al	J Am Acad Dermatol 1994; 39: 187-92	Somatostatin, Vancomycin
Plunkett RW et al	J Am Acad Dermatol 2001; 45: 691-6	Piroxicam
Klein PA, Callen JP	J Am Acad Dermatol 2000; 42: 4316-23	Vancomycin
König C et al	J Am Acad Dermatol 2001; 44: 689-92	Atorvastin
Avci O et al	J Am Acad Dermatol 2003; 48: 299-301	Acetaminophen
Dellavalle RP et al	J Am Acad Dermatol 2003; 48: S56-7	Vancomycin
Lesueur A et al	Press Med 2003; 32: 1078	Vancomycin
Bachot N et al	J Am Acad Dermatol 2003; 49: e1-2	Amiodarone

- subepidermal bulla with neutrophilic infiltrate
- linear IgA deposits along the epidermal basement membrane
- prompt response to treatment with dapsone (4).

Two main subsets of IgA antibodies have been identified in LAD, binding to the opposing sides of salt split human skin. The *first subset* comprises antibodies directed against bullous pemphigoid 230 kDa antigen BP 230 and 180 kDa antigen BP 180 (collagen XVII). They bind to the roof of the salt split skin and are responsible for the development of classic LAD. The second subset comprises antibodies against type VII collagen, which bind to the floor of the salt split skin and characterize IgA mediated epidermolysis bullosa acquisita (4). Wojnarowska et al demonstrated by indirect immunofluorescence on salt split skin that autoantibodies in LAD patients may bind to the epidermal side, to the dermal side or in a combined pattern (6). They suggested that autoantibodies in LAD targeted multiple antigens associated with hemidesmosomes and anchoring fibrils (7).

Case report

History.

A 66-year-old male patient with linear IgA bullous dermatosis is presented. He appeared for consultation in April 2002 because of an erythematous vesicular rash on his legs. He had observed a few erythematous lesions on legs about one year prior to admission. He was treated for hypertension with enalapril tablets, 2.5 to 5.0 mg daily for approximately six months. He had one kidney removed due to tuberculosis at the age of 17 years, but otherwise enjoyed good health.

Multiple erythematous lesions, some of them slightly vesicular, were seen on his thighs and legs, when he appeared for consultation in October 2002. Figure 1.

Table 2. Reports on angiotensin receptor antagonists and angiotensin converting enzyme inhibitors inducing linear IgA dermatosis or bullous pemphigoid

Author	Journal	Incriminated drug	Confirmed diagnosis
Kuechle MK et al	J Am Acad Dermatol 1944;30:187-92	Captopril	LAD
Friedman IS et al	Int J Dermatol 1998;37:608-12	Captopril	LAD
Pena-Penabad C et al	Am J Med 2003;114:163-4	AR antagonists	LAD
Femiano F et al	Oral Surg 2003,95:169-73	Benazepril	LAD
Smith EP et al	J Amer Acad Dermatol 1993;29:879	Enalapril	BP
Mullins PD, Choudhury SL	BMJ 1994;309:1411	Enalapril	BP

Abbreviations: AR antagonist – angiotensin receptor antagonist
LAD – linear IgA dermatosis
BP – bullous pemphigoid

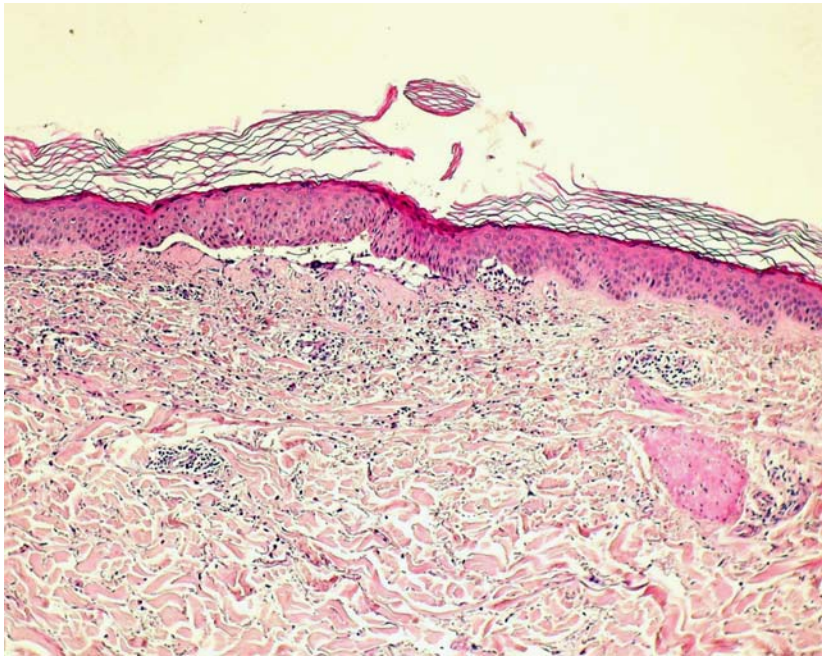


Figure 2. Light microscopy, H&E - Small subepidermal bulla and an inflammatory infiltrate in the superficial dermis, including lymphocytes and some neutrophils and eosinophils.

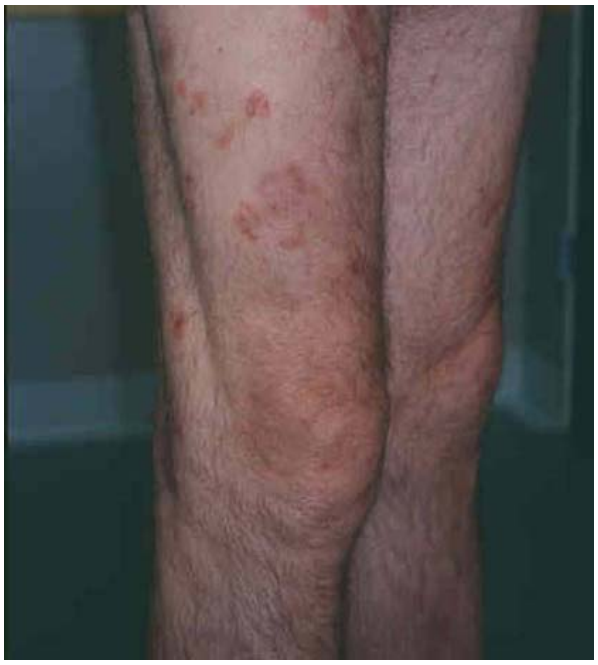


Figure 1. Erythematous lesions on the thigh, some are slightly vesicular, first consultation October 2002.

Figure 3. Direct immunofluorescence shows continuous linear IgA deposits along the epidermal basement membrane zone.

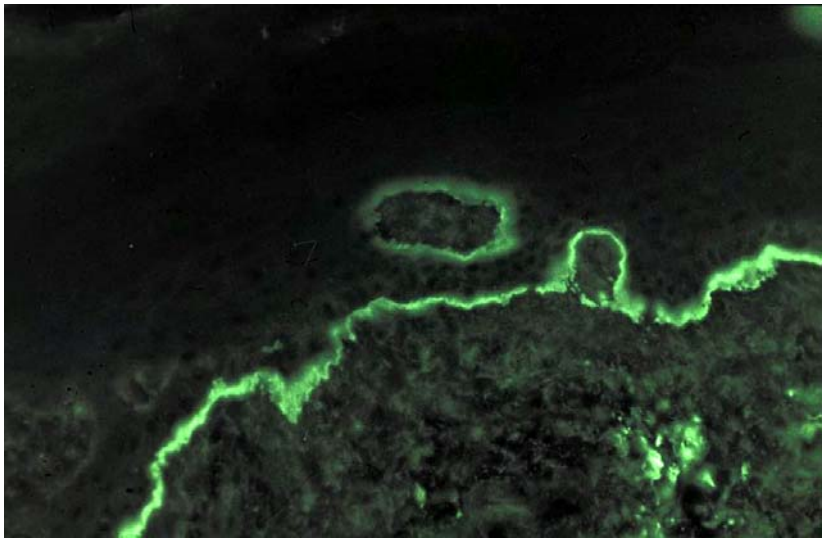
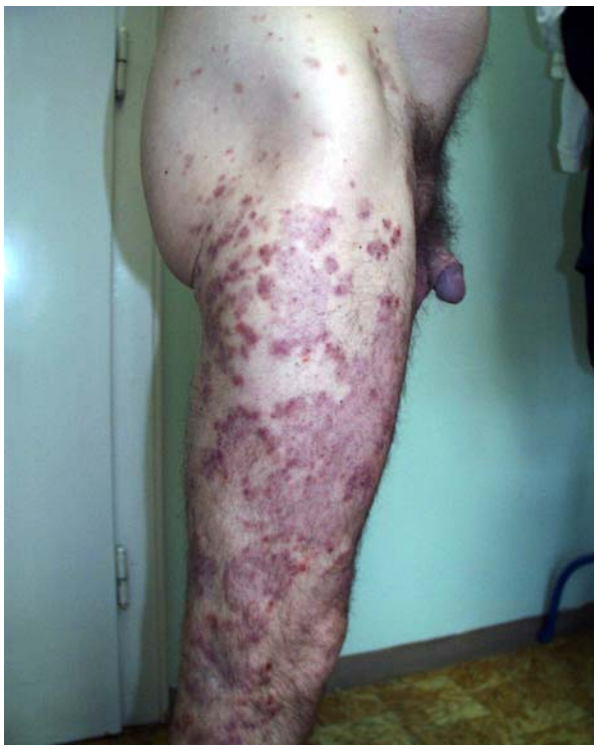


Figure 4. Erythematous lesions at the time of recurrence, February 2003, are very similar to those presented in Figure 1.



Under local treatment with steroids, bullous eruptions continued to appear, the erosions left over healed, but brown pigmentation became visible. The withdrawal of enalapril was followed by a remission lasting a few weeks. A vesicular rash later appeared on the legs and also on the trunk

Laboratory investigations.

Basic blood findings were within the normal range. Pemphigoid, pemphigus, antigliadin and antimyosin antibodies in blood serum were negative. Histopathology of lesional and perilesioal skin revealed a subepidermal bulla filled with fluid, fibrin and a few eosinophils. Figure 2. Direct immunofluorescence (DIF) revealed continuous linear IgA deposits, as well as granular C3 and fibrin deposits along the epidermal basement membrane zone. There were no IgG deposits and only a few fine granular deposits of IgM along the dermo-epidermal zone and in the upper dermis.

After three months, erythematous skin lesions on his lower extremities recurred and the biopsy was repeated (February 2003). Histopathology again showed two small subepidermal vesicles. In the superficial dermis there was a lymphocytic inflammatory infiltrate, including some neutrophils and eosinophils. DIF again showed linear IgA deposits characteristic for LAD. Indirect immunofluorescence with the patient's sera on intact and salt split skin was negative for IgG and C3. An IgA antibody was detected in the basement membrane zone of intact skin and on the epidermal side of the split skin at low dilutions (1:5 and 1:10). By immunoblotting, IgA and IgG antibodies to BP 180 (collagen XVII) were detected in low titers. Immunologic tests confirmed the diagnosis of LAD. Figure 4.

Therapy.

Our patient refused the recommended dose of 100-150 mg dapsone daily, because of his single kidney, although his renal function was within the normal limits. We started treatment with 25 mg of dapsone daily, but after 10 days he stopped the therapy due to impaired vision. During the 10-day treatment, the bullous skin lesions cleared and the patient refused further treatment with dapsone. After two months the bullous lesions reappeared. Treatment with 25 mg of dapsone was reintroduced and within one month the skin manifestations again cleared. This time, there were no side effects, the patient continued the therapy for three months, when he again discontinued the treatment. He was still without symptoms three months after the discontinuation of the treatment.

Discussion

There are an increasing number of reports that mention various drugs provoking LAD. In the past, penicillamine (8) and furosemide (9) were repeatedly mentioned as being associated with LAD. Cases of LAD induced by piroxicam (5), statins (10), lithium carbonate (11), acetaminophenon (12), amiodarone (13,14) and diclophenac (15) have also been reported (Table 1). In the last few years, vancomycin has been the most frequently incriminated drug (16-22). The majority of these conditions were clinically similar to our case, with fairly small vesicles, mostly on the legs, thighs and forearms. However, cases of drug-induced LAD with more severe lesions, such as erythema multiforme (23) or lesions mimicking toxic necrolysis (14) have also been described. Furthermore, LAD cases limited to gingiva have been reported (24).

Only limited data are available so far on LAD attributed to inhibitors of ACE. One reported case was associated with captopril (25) and a few cases with other ACE inhibitors (26-28). There have been more reports connecting the ACE inhibitors with bullous pemphigoid, and at least two reports incriminated enalapril (29,30) (Table 2).

It has also been suggested that LAD could be associated with various malignant conditions, e.g. renal carcinoma (31) and myeloproliferative disease (32). It seems that LAD is a polymorphic disorder (33).

Conclusion

Dapsone is accepted as the drug of choice in LAD. The recommended doses used to be 100-150 mg daily until clearing of the skin lesions, followed by gradually reducing the dose to a maintenance dose of 50 mg every other day. It has recently been suggested that it is possible to start the treatment of LAD with a lower dose, <0.5 mg/kg body weight, and to increase the dose later, if necessary, until the complete control of blistering and pruritus. Our patient refused the usually recommended dose of dapsone, because of his single kidney, although his renal function was normal. Treatment with low doses of dapsone, 25 mg daily, was efficient.

The fact that the skin lesions did not reappere after discontinuing enalapril, strongly suggest its etiologic role in our case.

REFERENCES

1. Wojnarowska F, Eady RAJ, Burge SM. Bullous eruptions. In Rook A et al. Textbook of Dermatology, 6th Ed, Champion RH et al eds, Blackwell, Oxford, 1998.

2. Braun Falco O, Plewig G, Wolff HH, Burgdorf WHC. Dermatology 2nd ed, Springer, Berlin 2000: 648-95.

3. Litt J. Drug eruption Reference Manual. 8th Ed, Parthenon Publishing Group, 2002.

4. Vodegel RM, de Jong MCJM, Pas HH, Jonkman MF. IgA mediated epidermolysis bullosa acquisita. Two cases and review of literature. J Am Acad Dermatol 2002; 47: 919-25.

5. Plunkett RW, Chiarello SE, Beutner EH. Linear bullous dermatosis in one of two piroxicam induced eruptions: a distinct immunofluorescence trend revealed by the literature. J Am Acad Dermatol 2001; 45: 691-6.

6. Wojnarowska F, Collier P, Allen J, Millard P. The localization of the target antigens and antibodies in linear IgA is heterogeneous and dependent on the methods used. Br J Dermatol 1995; 132: 750-7.

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

8. Rasmussen HB, Jepsen LV, Brandrup F. Penicillamine induced bullous pemphigoid with pemphigus-like antibodies. J Cutan Pathol 1989; 16: 154-7.

9. Castel T, Gratacos R, Castro J et al. Bullous pemphigoid induced by furosemide. Clin Dermatol 1981; 6: 635-8.

10. König C, Eickert A, Scharfetter-Kochanek K et al. Linear bullous IgA dermatosis induced by atorvastin. J Amer Acad Dermatol 2001; 44: 689-92.

11. Mc Whirter JD, Hashimoto K, Fayne S, Ito K. Linear IgA bullous dermatosis related to lithium. Arch Dermatol 1987; 123: 1120-2.

12. Avci O, Okmen M, Cetiner S. Acetaminophen induced linear IgA bullous dermatosis. J Am Acad Dematol 2003; 48: 299-301.

13. Roupe G. Larko O, Olsson SB. Amiodarone photoreaction. Acta Derm Venereol (Stockh), 1987: 67: 76-9.

14. Bachot N, Wechsler J, Demoule A, Roujeau JC. Amiodarone related linear IgA bullous dermatosis. J Am Acad Dermatol 2003; 49:e2.

15. Gabrielsen T, Staerfelt F, Thune P et al. Drug induced linear IgA deposits along the basement membrane, Acta Dermatol (Stockh) 1981; 61: 439-41.

16. Nousari HC, Kimyal-Asadi A, Caeiro JP, Anhalt GJ. Clinical, demographic and immunohistologic features of vancomycin-induced linear bullous disease of the skin. Medicine 1999; 78:1-8.

17. Dellavale RP, Burch JM, Tayal S et al. Vancomycin-associated linear IgA bullous dermatosis mimicking toxic epidermal necrolysis J Am Acad Dermatol 2003; 48: S56-7.

18. Baden LA, Apovian C, Imber MJ, Dover JS. Vancomycin-induced linear IgA bullous dermatosis. Arch Dermatol 1988;124:1186-8.

19. Piketti C, Meeus F, Nochy D et al. Linear IgA dermatosis related to vancomycin, Br J Dermatol 1994; 130: 130-1.

20. Carpenter S, Berg D, Sidhu-Malik N et al. Vancomycin associated linear IgA dermatosis. J Amer Acad Dermatol 1992; 26: 45-8.

21. Lesueur A, Lefort C, Gauthier JM, Andrivet P. Vancomycin-induced linear IgA bullous dermatosis. Press Med 2003; 32: 1078

22. Klein PA, Callen JP. Drug induced bullous dermatosis after vancomycin discontinuance in a patient with renal insufficiency. J Amer Acad Dermatol 2000; 42: 316-23.

23. Argenyi ZB, Bergfeld WF, Valenzuela R et al. Linear IgA bullous dermatosis mimicking erythema multiforme in adults. Int J Dermatol 1987; 26: 513-7.

24. del Valle AE, Martinez-Sahutquillo A, Padron JR, Urizar JN. Two case of linear IgA disease with clinical manifestations limited to the gingiva. J Periodontol 2003; 74: 879-92.

25. Friedman IS, Rudikoff D, Sapadin AN. Captopril-triggered linear bullous IgA dermatosis. Int J Dermatol 1998; 37: 608-12.

26. Pena-Penabad C, Rodrigez-Lozano J, del Pozo J, Garcia-Silva. Linear IgA bullous dermatosis induced by angiotensin receptor antagonists. Am J Med 2000; 114: 163-4.

27. Femiano F, Scully C, Gombos F. Linear IgA dermatosis induced by a new angiotensin-converting enzyme inhibitor. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2003; 95: 169-73.

28. Kuechle MK, Stegemeir F, Maynard B et al. Drug-induced linear bullous dermatosis: report of six cases and review of literature. J Amer Acad Dermatol 1994; 30: 187-92.

29. Smith E, Taylor TB, Meyer LJ, Zone JJ. Antigen identification in drug induced bullous pemphigoid. J Am Acad Dermatol 1993; 29: 879-62.

30. Mullins PD, Choudhury SL. Drug points: Enalapril and bullous eruptions. BMJ 1994; 309, 1411.

31. Keller AS, Bouldin MB, Drage LA et al. Linear IgA bullous dermatosis: an association with ulcerative colitis versus renal carcinoma. Dig Dis Sci 2003; 48: 783-9.

32. Hollo P, Preisz K, Nemes L et al. Linear IgA dermatosis associated with chronic clonal proliferative disease. Int J Dermatol 3003; 42: 143-6.

33. Janniger CK,Wiltz H. Schwartz RA et al. Adult linear IgA bullous dermatosis: a plymorphic disorder. Cutis 1990; 45: 37-42.

A U T H O R S ' A D D R E S S E S

Ana Benedičič Pilih MD, MSc, dermatologist, Dept of Dermatology, General Hospital, 3000 Celje, Oblakova 5, Slovenia
Alenka Vizjak PhD, research fellow, Institute of Pathology, Medical Faculty, 1000 Ljubljana, Korytkova 2, Slovenia
Fenella Wojnarowska MD, Professor of Dermatology, Dept of Dermatology, Churchill Hospital, Old Road, Headington, Oxford OX3 7LJ, Great Britain
Marija Berčič MD, PhD, dermatologist, Medvedova 6, 2000 Maribor, Slovenia
Alenka Pejovnik Pustinek MD, MSc, dermatologist, same address as Pilih
Jože Arzenšek MD, MSc, dermatologist, Head of Department, same address
Aleksej Kansky MD, PhD, Professor of Dermatology, Dept of Dermatology, Clinical Centre, 1525 Ljubljana, Zaloška 2, Slovenia