

Secondary Amyloidosis Manifesting as Bilateral Blepharodema

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Sir,

Secondary amyloidosis is an important complication of rheumatoid arthritis (RA). It is sometimes life-shortening, but it rarely produces specific skin lesions. We describe here a case of secondary amyloid A amyloidosis arising as a complication of RA and presenting bilateral blepharodema without purpura.

CASE REPORT

A 61-year-old Japanese woman had received treatment with several agents, but not gold, for rheumatoid arthritis (RA) and severe destructive joint disease at another hospital for more than 30 years. She had had proteinuria of uncertain cause for more than 20 years. Several months prior to her current consultation, she had noticed leg oedema and body weight gain, and was diagnosed as having chronic renal failure. She was transferred to our hospital and initiated on haemodialysis for chronic renal failure; soon thereafter, the patient noticed bilateral blepharodema without purpura (Fig. 1). A skin biopsy was performed from her eyelids. The histopathological findings showed oedema in the upper dermis and slightly eosinophilic amorphous deposits in the vessel walls, without leukocytic infiltration. Congo red and Dylon (Pagoda red) staining revealed amorphous masses of amyloid in the vessel walls, which were susceptible to oxidation treatment with potassium permanganate (Fig. 2). Immunohistochemical staining with anti-amyloid A

protein (Kyodo Byori Inc. Kobe, Japan) was positive, but that with anti- β 2 microglobulin (Kyodo Byori Inc. Kobe, Japan) was negative (1). Laboratory studies revealed chronic renal failure, slight increase in serum C reactive protein, increase in serum rheumatoid factor (197 IU/ml), serum anti-amyloid A protein (SAA) (112 μ g/ml; normal range, < 5 IU/ml) and serum brain natriuretic peptide (1660.7 pg/dl; normal range < 8 pg/ml), slight increase in serum troponin I (0.33 ng/ml; normal range, < 0.01 ng/ml), and normal thyroid test results. The SAA was investigated using the latex method (SRL Inc., Tokyo, Japan), which has been commercially available in Japan for several years. An electrocardiogram showed generalized low voltage and segment elevation which indicated old myocardial infarction, and echocardiography revealed a granular speckled pattern and a hypertrophic left ventricle with normal cavity size; features characteristic of amyloid cardiac involvement (2). A duodenal biopsy obtained by upper gastrointestinal endoscopy revealed amyloid deposits. The patient was diagnosed as having secondary amyloid A amyloidosis arising as a complication of RA and presenting with cardiac, renal, and cutaneous involvement without purpura.

DISCUSSION

Secondary amyloidosis is an important complication of RA and is derived from circulatory SAA. SAA synthesis and secretion by hepatocytes is mediated by the cytokines interleukin-1 and tumour necrosis factor- α (3). Skin involvement in patients with secondary amyloidosis is rare, and clinical evidence of amyloid deposition is difficult to find (4). The detection of the mass of amyloid deposition is performed using stains, including PAS methods, Congo red stain, and thioflavin T stain. Congo red stain is the most specific of these for detecting amyloid deposits; however, it sometimes gives false positive, and it is inadequate for detecting small deposits of amyloid (5). The Pagoda red method was specificity simple, practical, and can be applied routinely in the laboratory (6). Histopathological examination reveals amyloid A deposits around blood vessels in the areas of involvement (5). Amyloid deposits alter the barrier function of the endothelium and may cause injury to vessels in the deep dermis. The connective tissue in the eyelids is scant and is more delicate than in other body surface areas; therefore, amyloid deposits might have prevented capillary or microcirculation



Fig. 1. Clinical findings at initial visit. Oedema of the eyelids without fever, tenderness or purpura was observed.

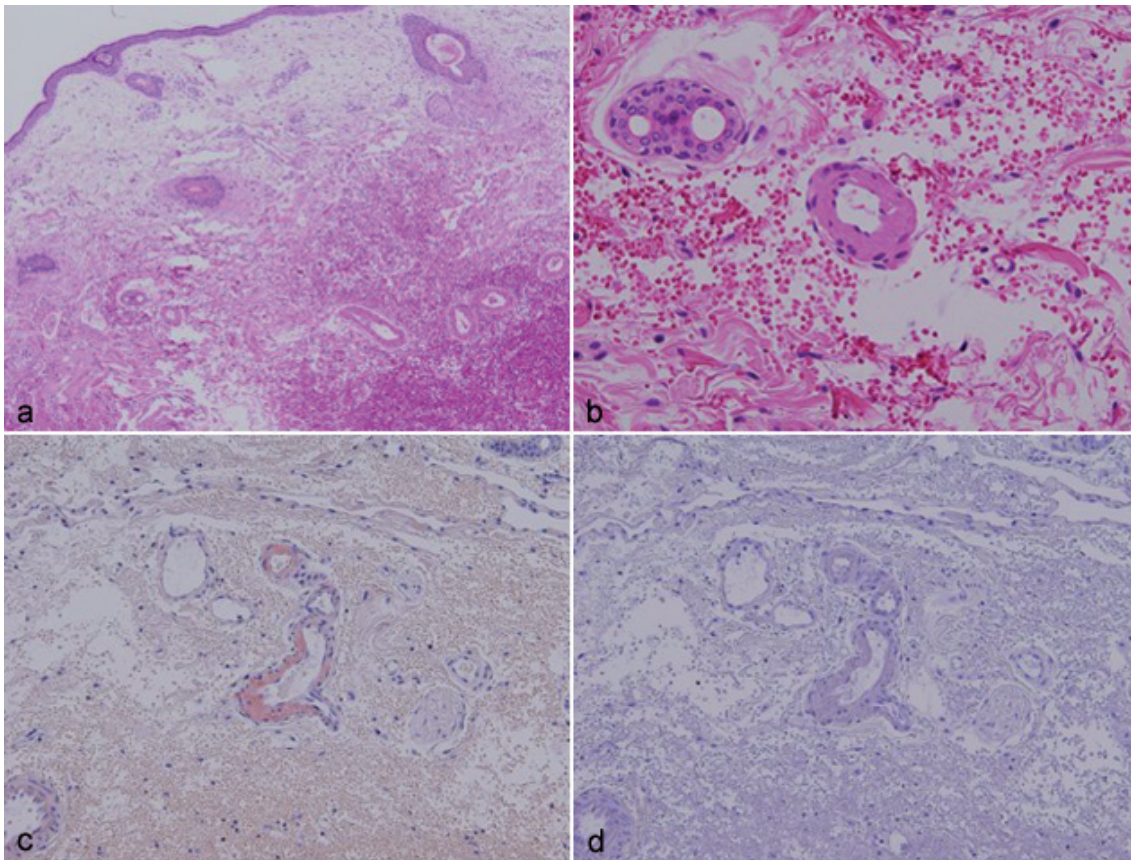


Fig. 2. (a) Skin biopsy specimens from eyelids. Oedema was seen in the upper dermis. The vascular wall was thick and contained eosinophilic amorphous deposits (H&E, $\times 40$). (b) Skin biopsy specimens in high magnification. Amorphous deposits existed around vessels (H&E, $\times 200$). (c) Congo red staining revealed a mass of amyloid in the endothelium (original magnification, $\times 100$). (d) The mass of amyloid disappeared with oxidation treatment with potassium permanganate (Congo red staining, original magnification, $\times 100$).

in this region, leading to bilateral blepharoeidema in the case described here, presumably by the same mechanism that led to abnormalities in the other organs. The diagnosis is usually based on histopathological examination of upper gastrointestinal or rectal biopsy specimens (7), or deep skin biopsy specimens that can easily and usefully reveal secondary amyloidosis in patients with RA (8). Skin manifestations induced by secondary amyloidosis are rare and unclear, but are recognized as a serious problem.

REFERENCES

1. Pepys MB. Amyloid, familial Mediterranean fever, and acute phase response. In: Doyle D, Hanks GWC, Chemy NI, Calman SK, editors. Oxford textbook of medicine, 3rd edn. Oxford: Oxford University Press, 1996: p. 1512–1532.
2. Falk RH, Comenzo RL, Skinner M. The systemic amyloidosis. *N Engl J Med* 1997; 337: 898–910.
3. Husby G, Marhaug G, Dowton B, Sletten K, Sipe JD. Serum amyloid A (SAA): biochemistry, genetics and the pathogenesis of AA amyloidosis. *Amyloid* 1994; 1: 119–137.
4. Breathnach SM. Amyloid and the amyloidoses of the skin. In: Burns DA, Breathnach SM, Cox N, Griffith CE, editors. Rook's textbook of dermatology, 4th edn. Oxford: Blackwell Science, 2004: ch. 57, p. 36–51.
5. Yanagihara M, Mehregan AH, Mehregan DR. Staining of amyloid with cotton dyes. *Arch Dermatol* 1984; 120: 1184–1185.
6. Garcia-Garcia M, Mourad G, Durfort M, Garcia-Valero J, Argiles A. Vascular involvement and cell damage in experimental AA and clinical $\beta 2$ -microglobulin amyloidosis. *Nephrol Dial Transplant* 2002; 17: 1450–1456.
7. Kobayashi H, Tada S, Fuchigami T, Okuda Y, Takasugi K, Matsumoto T, et al. Secondary amyloidosis in patients with rheumatoid arthritis: diagnostic and prognostic value of gastroduodenal biopsy. *Br J Rheumatol* 1996; 35: 44–49.
8. Tiitinen S, Kaarela K, Helin H, Kautiainen H, Isomäki H. Amyloidosis-incidence and early risk factors in patients with rheumatoid arthritis. *Scand J Rheumatol* 1993; 22: 158–161.