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CASE REPORT

Variegate porphyria complicated by systemic AA amyloidosis: a case report

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Abstract

We report a Japanese woman with variegate porphyria accompanied by amyloid A (AA) amyloidosis. Arthropathy involving multiple joints occurred at 35 years old and persisted. C-reactive protein was 4.0 mg/dL, but rheumatoid factor was negative. Radiographs did not reveal any loss or narrowing of the joint spaces. Two years later, blister formation after sun exposure and reddish urine were first noted. At the age of 45 years, she developed abdominal pain, nausea, vomiting and seizures. After administration of phenobarbital, reddish urine was noted and muscular weakness progressed to atonic quadraparesis. Porphyria attack was diagnosed from high urinary levels of ∂ aminolevulinic acid and porphobilinogen. At the age of 47 years, hemodialysis was started. At the age of 49 years, progression of her gastrointestinal event resulted in death. Autopsy showed massive deposits of AA amyloidosis in various organs, including the kidneys and digestive tract. Thus, amyloid deposition may have contributed to both end-stage renal failure and her gastrointestinal symptoms. This is the first report about the coexistence of porphyria and AA amyloidosis. Chronic inflammation related to this patient's seronegative arthropathy, although atypical for porphyria, might have contributed to the development of AA amyloidosis.

Abbreviations: AIP, acute intermittent porphyria; ALA, aminolevulinic acid; PBG, porphobilinogen; PCT, porphyria cutanea tarda; SAA, serum amyloid A protein; VP, variegate porphyria

Keywords

Amyloid A amyloidosis, arthropathy, porphyria, variegate porphyria

History

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Introduction

The porphyrias are a group of metabolic disorders, each of which results from deficiency of a specific enzyme in the heme biosynthesis pathway. These enzyme deficiencies are usually inherited as autosomal-dominant or -recessive traits, but rare sporadic cases also occur. Variegate porphyria (VP) is usually an autosomal-dominant hepatic porphyria that results from deficiency in the activity of protoporphyrinogen oxidase (the seventh enzyme in the heme pathway), which converts protoporphyrinogen to protoporphyrin. It presents with acute neurovisceral crisis and skin lesions due to photosensitivity. Acute attacks are identical to those in patients with acute intermittent porphyria (AIP), and mainly feature gastrointestinal symptoms (abdominal pain, nausea and vomiting) and neurological symptoms (muscular weakness, confusion and seizures). Blistering of the skin is similar to that seen in porphyria cutanea tarda. Acute attacks are often triggered by exposure to precipitating factors, including a wide range of common prescription medications [1–3].

There have only been a few reports of renal disease in patients with porphyria, including VP [4–6]. Here, we present the first case of VP associated with end-stage renal disease due to amyloid A (AA) amyloidosis.

Case report

A 35-year-old Japanese woman was admitted to our hospital for the evaluation of bilateral arthropathy affecting the joints of her hands, feet, knees, ankles, shoulders and hips. She complained of pain in multiple joints, but swelling was not apparent. C-reactive protein was 4.0 mg/dL, but rheumatoid factor was negative. Radiographs did not disclose any loss or narrowing of the joint spaces. She did not have a family history of such arthropathy or of autoimmune disease, including rheumatoid arthritis. Two years later, blister formation after exposure to the sun and reddish urine were noted, and these symptoms showed repeated remission and exacerbation. At 40 years old, evaluation of the urinary excretion of porphyrin metabolites showed that daily ∂

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aminolevulinic acid (ALA) excretion was 1.68 mg/dL (normal range: <0.5 mg/dL), while the daily excretion of porphobilinogen (PBG) was 1.42 mg (normal range: <0.8 mg) and coproporphyrin was 0.274 mg (normal range: <0.10 mg). Accordingly, VP was diagnosed. In addition to avoidance of sun exposure, administration of prednisolone (20 mg daily) was effective for her skin lesions and arthropathy, but symptoms recurred after tapering. She also noted that a low-dose contraceptive improved her symptoms. At the age of 45 years, her renal function declined with a serum creatinine of 3.4 mg/dL. In addition, she had nausea, vomiting, abdominal pain without rebound tenderness and clonic convulsions. After administration of phenobarbital, reddish urine appeared and muscular weakness progressed to atonic quadraparesis. Acute porphyria was diagnosed because of elevated urinary excretion of PBG to 51.296 mg daily (normal range: <0.8 mg) and coproporphyrinogen to 0.271 mg daily (normal range: <0.16 mg). Her symptoms subsided after plasma exchange plus high-dose glucose therapy. In addition, hematin therapy was effective for her porphyria after four months. However, hypertension became refractory and renal dysfunction progressed. At the age of 47 years, hemodialysis was started when her serum creatinine was 11.0 mg/dL and congestive heart failure had developed. At the age of 49 years, her gastrointestinal symptoms and skin lesions became worse. Gastroduodenoscopy and colonoscopy did not reveal any ulcerated lesions. However, she died of refractory thrombocytopenia and anemia due to bleeding from the gastrointestinal tract. Throughout the clinical course, C-reactive protein (CRP) remained positive, rheumatoid factor was negative, serum AA protein was over 20 μg/mL (normal range: <8.0 μg/mL) and radiographs did not show any joint deformities consistent with rheumatoid arthritis.

Autopsy findings

The weight of both kidneys was 80 g. Amorphous material was deposited in almost all of the glomeruli, small arteries and tubules (Figure 1a). This material was positive for amyloid by Congo red staining (Figure 1b) and showed apple green birefringence under polarizing light. Immunohistochemical staining was positive for AA (Figure 1c) and amyloid P protein, but negative for kappa and lambda chain, beta-2 microglobulin and prealbumin. Electron microscopy showed randomly arranged fibrils that measured 8–12 nm in diameter at the sites of the amyloid deposits (Figure 1d). Accordingly, AA amyloidosis was diagnosed. The liver weighed 1120 g. Amyloid deposition was localized to the small hepatic arteries. The cardiac weight was 400 g. Amyloid deposition was localized to the peripheral branches of the coronary arteries and the tissues surrounding myocardial bundles. Amyloid deposition was also apparent in the small arteries of the spleen, pancreas, adrenal glands and ovaries. In the lungs, amyloid was found in the subpleural alveolar septae, but was not noted in the small pulmonary arteries. The gastrointestinal tract showed massive amyloid deposition in the submucosal and subserosal layers, but ulcerated lesions that could be a source of bleeding were not noted. Her thyroid gland and major salivary glands, such as the parotid, sublingual and submandibular glands, were totally replaced by amyloid. Her joints showed synovial inflammation, but there was only minor resorption of the articular cartilage.

Discussion

VP is quite prevalent in South Africa, where most cases have been traced to a couple who migrated from Holland in the late 1600s. Patients with VP show approximately 50% reduction

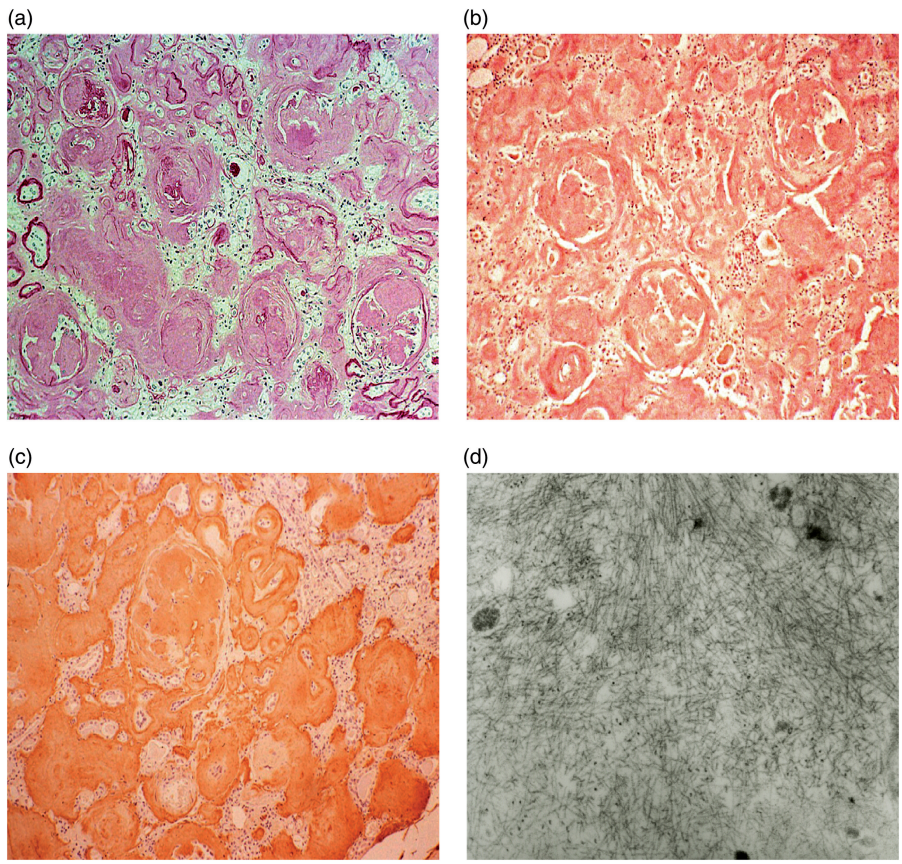

Figure 1. Renal biopsy findings (a) amorphous material is deposited in almost all of the glomeruli, small arteries and tubules (periodic acid-Schiff stain); (b) the amorphous deposits are positive for amyloid by Congo red staining; (c) immunohistochemical staining is positive for AA; (d) electron microscopy shows randomly arranged fibrils measuring 8–12 nm in the amyloid deposits.

in the activity of protoporphyrinogen oxidase. Many different mutations of the genes for this enzyme have been described and a specific mutation is common in South Africa. Levels of ALA and PBG are usually increased during acute attacks, but return to normal more rapidly than in AIP [2].

There have been some reports on the relation between porphyria and renal disease [4,5]. Andersson et al. [5] evaluated 16 patients with AIP. Twelve patients had hypertension and four were normotensive despite renal insufficiency. Renal biopsy diffuse glomerulosclerosis and interstitial changes with additional ischemic lesions, but amyloid staining was negative in all 10 biopsy specimens. No deposits of immune complexes (IgA, IgG, IgM, C3 and C1q) or light chains were found by immunofluorescence microscopy. Protracted arterial and arteriolar vasospasm during acute attacks of porphyria was suggested as a possible mechanism for these renal changes. Sardh et al. [6] reported severe kidney complications in three AIP patients with recurrent acute attacks. In these patients, progression to end-stage renal disease requiring dialysis was associated with a marked increase in the urinary and plasma PBG/ALA ratios [6].

The present Japanese patient was diagnosed as having ''sporadic VP'' based on the elevation of porphyrin metabolites such as ALA, PBG and coproporphyrinogen along with typical symptoms of acute neurovisceral crisis and photosensitivity, as well as the lack of a family history. Autopsy showed that massive deposition of AA amyloidosis may not only have contributed to end-stage renal failure, but also to her gastrointestinal symptoms. A literature search (PubMed) did not identify any reports about the coexistence of porphyria and AA amyloidosis. Our patient also had polyarthropathy, which has not been reported among patients with hereditary porphyria in South Africa. Her arthropathy was due to seronegative arthritis without radiological changes of the joint spaces, although C-reactive protein always remained positive. AA amyloidosis occurs in patients who have chronic inflammatory diseases associated with seronegative arthropathy (excluding definite rheumatoid arthritis), including those with juvenile rheumatoid arthritis [7], familial Mediterranean fever [8], psoriatic arthritis [9], Reiter's disease [10] and ankylosing spondylitis [11]. Thus, our patient' arthropathy might have contributed to the development of AA amyloidosis through chronic inflammation.

Declaration of interest

This study was funded by the Okinaka Memorial Institute for Medical Research. The authors report no conflicts of interest.

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