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Interesting Case

Unusual manifestation of AL amyloidosis—stenosis of inferior vena cava

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Introduction

Systematic AL (Ig light-chain) amyloidosis is a protein conformation disorder associated with a clonal plasma cell dyscrasia. A rare disease with an incidence of 9 per million per year in the USA, it is characterized by the tissue deposition of fragments of monoclonal immunoglobulin light chains in the form of fibrils. In approximately 75% of cases, the fibrils in primary amyloidosis are derived from the variable region of lambda light chains [1,2].

The diagnosis of AL amyloidosis may be suspected on clinical grounds. Its presenting symptoms include weight loss, fatigue, oedema, pain or numbness due to peripheral neuropathy, and purpura, and patients may have hepatosplenomegaly, enlarged lymph nodes or carpal tunnel syndrome. Multisystem organ involvement is typical—with the most commonly affected organs being the kidney (50%), heart (40%), and peripheral nerves (up to 25%). The serum or urine of a majority of primary amyloid patients will show paraprotein spikes or free light chains [3]. The gastrointestinal tract is also commonly involved [4]. To confirm the diagnosis, it is necessary to do a biospy that shows amyloid deposition.

The treatment of AL amyloidosis is aimed at the underlying plasma cell dyscrasia, however, the outcomes of treatments are still unsatisfactory. Its long-term prognosis is poor, with mean survival as short as 1 year if treated with melphalan and prednisone. Better survival rates are reported after myeloablative chemotherapy (with melphalan) with autologous stem-cell support, some patients having complete clinical recovery [5].

We report on a patient with an unusual clinical manifestation of AL amyloidosis.

Case report

A 58-year-old woman was admitted to our nephrology unit in May 2001 because of massive oedema of her lower trunk. Her medical history was unremarkable. She had had mild arterial hypertension, since 1997. In 1989 she had undergone a hysterectomy with adnexectomy, for myomatosis. In April 2001, shortly before her admission, she had an operation on her left carpal tunnel in her hometown, but tissue was not taken for histologic analysis. The oedema had first appeared in December 2000. In March 2001, radionuclide phlebography had shown phlebothrombosis of both legs, with the veins in the pelvic region patent. She had been started on anticoagulation treatment. At about this time, she had been referred to the neurology department in her hometown because of neck and arm stiffness. Based on a muscle biopsy, she was diagnosed to have the stiff-man syndrome. Repeated neurologic examinations and a test negative anti-GAD (anti-glutamic acid decarboxylase antibodies) later excluded this diagnosis.

On admission to our unit, she complained of stiffness and weakness of her lower extremities and limited mobility because of oedema. She had gained 12 kg in 5 months. She also had lower back pain and chronic pain in both shoulders with radiation to both arms and paresthesias. She did not complain of any gastrointestinal symptoms.

On physical examination, she had huge, stiff and symmetric oedema of both lower extremities extending up to her waist. Her blood pressure was 145/100 mmHg.

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Laboratory tests showed an erythrocyte sedimentation rate of 80 mm/h, serum albumin 28 g/l, cholesterol 7.15 mmol/l and creatinine 73 μmol/l. Her blood count and the rest of biochemical analyses were within normal ranges. Electrophoresis of blood proteins showed no pathologic peaks (tests to detect free light chains were not available at that time). The urinalysis revealed proteinuria of 1.9–2.6 g/24 h (glomerular selective type of proteinuria); the examination of her urine was otherwise negative.

A lymphatic origin for the oedema was excluded by lymphoscintigraphy, a cardiac etiology by echocardiography. According to a CT scan, thrombosis of the suprarenal segment of the inferior vena cava (VCI) seemed probable; but this was not confirmed by phlebography, where the thrombosis appeared minor and incomplete. A renal contribution to the oedema could not be ruled out, and therefore, a renal biopsy was performed. It revealed no morphologic changes on light microscopy. On immunofluorescent examination, IgG was slightly positive in the tubular epithelium, IgA positive in the cylinders and C3 positive in the vessels. IgM, fibrinogen, C1q, kappa, lambda and AA amyloid remained negative. Based on the results of electron microscopy a diagnosis of minimal change glomerulonephritis (MCGN) could not be ruled out. Therefore, a course of corticosteroids (0.5 mg/kg/day of prednisone) was given and gradually tapered during the next 3 months. The proteinuria remained refractory to this treatment.

In September 2001, she was readmitted because of progression of the oedema. Her proteinuria was almost 5 g/24 h, serum albumin 23 g/l, and the rest of her laboratory findings were unchanged. A repeated Doppler ultrasound of the VCI and pelvic and renal veins did not show any evidence of thrombosis. She was treated symptomatically with diuretics, with a partial effect on hyperhydration. In December 2001, immunoelectrophoreses of her serum and urine was reperformed. They revealed a very small concentration of lambda light chains in the urine (0.422 g/l) and kappa light chains (4.18 g/l) in the serum. These findings were not considered significant, especially in view of the negative finding in the renal biopsy.

At about this time, a control CT scan of the patient's abdomen was performed, which raised a suspicion of stenosis of the VCI, with no pathologic findings in the peritoneal cavity or retroperitoneum. This was confirmed by venography. A stenosis at the level of the diaphragm was obstructing 85% of the VCI lumen (Figure 1). A metallic stent was successfully placed in the VCI in January 2002, and a susbstantial loss of fluid (10 kg of body weight) ensued. From January to June 2002, restenosis of VCI occurred under the stent repeatedly, and a total of three metallic stents were placed. Partial obstruction of the VCI was,

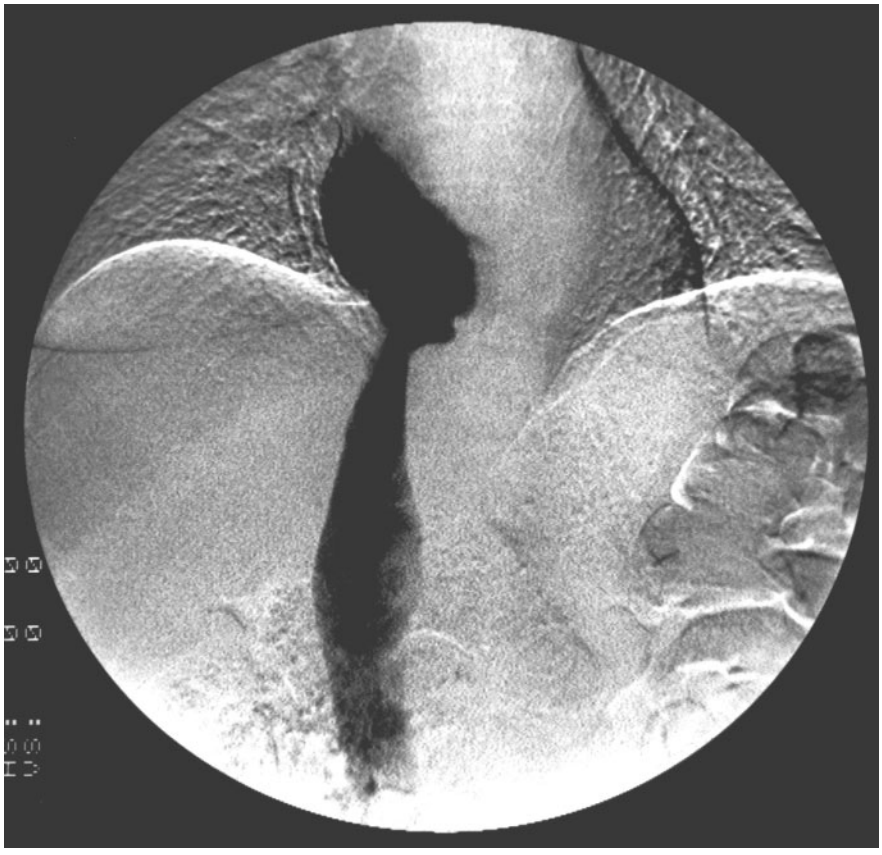

Fig. 1. Cavography—the stenosis in the area of diaphragm obstructing 85% of VCI lumen.

nevertheless, detected distally from the third stent soon after its placement. Despite extensive examination with repeated CT scans, magnetic resonance imaging (MRI) and positron emission tomography (PET), we found neither external expansion nor pathological involvement of the vessel wall to explain this recurrent process. The anticoagulant treatment was never stopped.

In January 2002, gastrointestinal and nutritional problems, related to frank gastric atonia and gastrectasy and malabsorption, appeared and slowly progressed. The patient's serum albumin dropped to 21 g/l. A biopsy performed during gastroscopy was negative. Despite substantial enteral and parenteral nutritional support the patient's condition worsened. She started to have constipation, and a macroglossia became apparent. Suddenly, she developed ileus. An urgent exploratory laparotomy revealed adhesions in the pelvis—a late complication of her past hysterectomy. The tissue specimen gained from the incidental appendectomy during this exploration made the clinical situation clear. It showed Congo red-staining deposits, resistant to permanganate oxidation, i.e. AL amyloid. At this time, light chain lambda was detecable in both the serum (2.99 g/l) and the urine (1.53 g/l). A trephine biopsy showed normocellular, trilinear bone marrow with interstitial, predominantly lambda-positive plasmocytic infiltrate, whose proportion of plasma cells was 6.2%. The X-ray of the bones subsequently revealed a single 1 cm osteolytic lesion in the skull—a finding that does not exclude multiple myeloma. A few weeks later, in June 2002, the patient died of heart failure—most probably due to a malignant arrhythmia.

Necropsy revealed multiorgan AL amyloidosis. It was present in the VCI wall and in the entire gastrointestinal tract. (A second reading of the gastric tissue histology demonstrated AL amyloid, which had been overlooked in the first reading.) The kidneys were affected only to a small extent—AL amyloid was present in renal blood vessels, but not in the glomeruli (and it was not detected in a second reading of the native kidney biopsy). Smooth muscles and connective tissue, including perineural areas, had heavy amyloid infiltration. The heart was almost unaffected, except for a slight infiltration of the walls, presumed to be clinically insignificant. Not even on the postmortem was any thrombosis found in the VCI lumen.

Discussion

AL amyloidosis should be considered in the differential diagnosis of all patients over 40 who have unexplained proteinuria—even in the absence of a paraprotein in the serum or urine, which is present in only 85–90% of patients with primary amyloid [6]. The absence of AL amyloid in the native kidney biopsy specimen of our patient might seem unusual, as the kidneys are one of the main 'target organs' for amyloidosis. This absence could probably be explained by an only minor involvement of the kidneys at the time of renal biopsy, because small amounts of amyloid in kidney biopsy specimens may be missed during routine examinations. Nevertheless, the misdiagnosis of MCGN in this setting has been previously described; and it appears that the typical 'minimal changes' with flattening and effacement of the epithelial foot processes can be found in capillary loops directly affected by amyloid deposition—as well as in capillary loops of glomeruli with only a mild amyloid deposition in the mesangium, or even in the absence of detectable amyloidosis of the kidney. It has been suggested that proteinuria and epithelial podocyte changes in the last instance are caused by other factors, such as a cytokine release during early fibril formation, which would lead to abnormalities even before the typical structural changes [7].

The oedema in our patient was not, however, entirely renal. She had a stenosis of her VCI due to the AL amyloid deposition in the vessel wall. Nevertheless, the nature of the stenosis could not be established until after her death. The repeated CT, MRI and PET examinations did not contribute to the diagnosis, probably because the wall of the VCI was not enlarged, and the metabolic turnover measured by glucose uptake is not affected by amyloid deposition (serum amyloid P component scintigraphy was not routinely available at that time). Moreover, a case of stenosis of VCI due to the AL amyloid deposition in the vessel wall has, to our best knowledge, not been previously described. Oedema formation in the setting of chronic constriction of the VCI could be caused by a decreased cardiac filling pressure and cardiac output, subsequent augmented rates of renin and aldosterone secretion and resultant marked sodium retention, as has been described in an experimental dog model with caval constriction [8]. However, we do not have data to confirm this mechanism in our patient.

This case was complicated from several points of view. The significance of the carpal tunnel surgery in the medical history was underestimated. The carpal tunnel syndrome was very probably the first symptom of AL amyloid in this patient. Her stiffness and pain were believed to be due to the oedema, although they can be retrospectively attributed to the combination of peripheral neuropathy, vascular claudications, or the polymyalgia rheumatica syndrome repeatedly described in AL amyloidosis [9]. Amyloid infiltration of the digestive tract, with the clinical presentations of gastrointestinal bleeding, chronic intestinal dysmotility or malabsorption, has been repeatedly reported [4,10]. In our patient, clinically discernible gastrointestinal infiltration with amyloid appeared relatively late in the course of her disease, when the clinical condition of the patient would not allow any treatment. Nevertheless, the AL amyloid unrecognized in her gastric biopsy was a laboratory mistake. Furthermore, it should have been suspected that malabsorption or protein-losing gastroenteropathy pariticipated in the hypoalbuminaemia and malnutrition. On the other hand, it must be emphasized that the clinical signs of AL amyloidosis mentioned earlier, together with

several negative histologic examinations and the late appearance of the lambda light chains in her serum and urine were rare and unexpected. In summary, we report on a patient with AL amyloidosis who presented with a combination of confounding symptoms related to the involvement of her vessel walls, connective tissue and digestive tract.

Conflict of interest statement. The authors are not aware of any conflict of interest whatsoever.

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