Letters to the Editor

Exuberant macroglossia in a patient with primary systemic amyloidosis

Sirs,

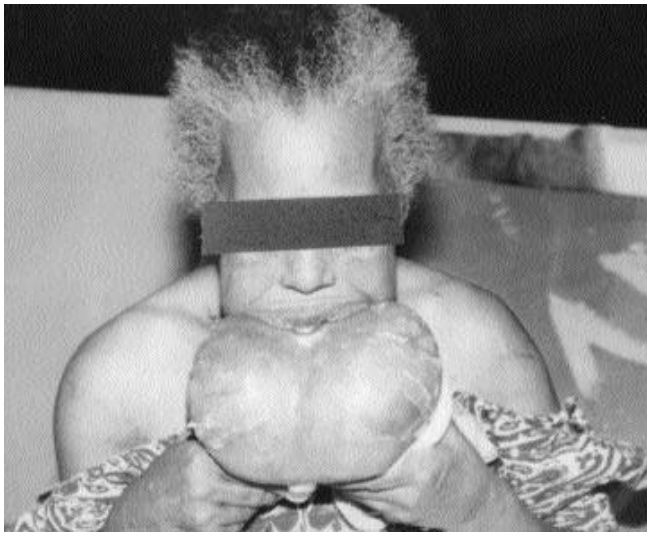
A 60-year-old woman was admitted to our hospital in November 1999 because of weakness and paresthesia in the right hand that had begun 2 years earlier. In 1998, she noted periorbital purpura and progressive enlargement of the tongue. There was no history of chronic inflamatory diseases such as rheumatoid arthritis, osteomyelitis, malaria or tuberculosis, as well as no history of amyloidosis.

On physical examination, there was bilateral periorbital purpura and submandibular swelling; extreme macroglossia that precluded closing the mouth and visualization of the throat was observed (Fig. 1). The Tinel sign was positive in the right superior limb. Cardiac and abdominal examination were normal. Selected laboratory investigations revealed a hemoglobin concentration of 10.5 g/dLand a normal leukocyte count; total serum protein and albumin were 6.9 g/dLand 4.3 g/dL, respectively. Renal functional impairment was not present and urinalysis was normal. Serum monoclonal paraprotein was detected by immunoelectrophoresis. X-ray studies of the chest and peripheral skeleton were normal. The electrocardiogram showed low voltage. The echocardiographic study was normal. Electromyography demonstrated prominent motor axonal neuropathy in the right superior limb. Tongue biopsy detected the presence of amyloid, and a bone marrow biopsy showed a normal number of plasma cells (4%). After the diagnosis surgery was performed, but the patient died of massive pulmonary embolism on the fifth post-operative day.

Systemic amyloidosis is a rare disorder that usually begins after the age of 40 and is associated with rapid progression, multisystemic involvement and short survival. The age-adjusted incidence of AL amyloidosis is estimated to be 5.1 to 12.8 per million person-years (1). In this type of amyloidosis, the deposits consist of monoclonal light chains produced by an indolent plasma cell dyscrasia in the bone marrow.The initial symptoms are frequently fatigue and weight loss, but the diagnosis is rarely made until symptoms or signs involving a particular organ appear (2). The median survival in a group of Mayo Clinic was 20 months, with a 5-year-survival of 20% (3).

As is often the case, in this patient an early diagnosis was not made because the initial complaints were unspecific. In the late stages of the disease, she developed periorbital purpura (racoon sign) and macroglossia; oral and skin involvement are important clues in diagnosing systemic amyloidosis. In the oral cavity, amyloid deposition may exhibit many forms. The best known oral finding is macroglossia, often associated with submandibular swelling (4). Periorbital purpura has been noted as the most characteristic form of cutaneous involvement in systemic amyloidosis (5).

Fig. 1. Patient suffering from exuberant macroglossia.



Autonomic and sensory neuropathy and carpal tunnel syndrome are relatively common features. The kidneys and heart – the organs most commonly involved in AL amiloidosis (6) – were not clinically affected in this case. In 90% of patients with AL amyloidosis, serum or urinary monoclonal immunoglobulins or light chains are detected by immunofixation electrophoresis. In most a clonal dominance of plasma cells is identified in bone marrow biopsy specimens (6). In this case, the monoclonal paraprotein detected by immunoelectrophoresis and a positive biopsy of the tongue established the diagnostic of ALamyloidosis, but the bone marrow biopsy did not reveal a plasma cell dyscrasia.

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Pulmonary granuloma, polyarthritis and antiphospholipids in common variable immunodeficiency: resolution after IVIG and the role of immunoglobulin A

Sirs,

Common variable immunodeficiency (CVI) is a heterogeneous immunodeficiency syndrome characterized by defective production of one or several immunoglobulin (Ig) isotypes, recurrent bacterial infections and an increased risk of autoimmune diseases, malignancies and granulomatous lesions (1, 2). The treatment of autoimmune diseases and granulomatous lesions is usually based on the steroids, but few report have shown the benefit of intravenous immunoglobulin (IVIG) (3-5). We report a case of CVI that seems original due to several points: its association antiphopholipid syndrome (APS), a favorable outcome of the granulomatous lesion with IVIG and a differential outcome according to the IVIG combination used.

A 28-year-old woman was referred to our center in October 2000 for relapse of a chronic polyarthritis. She had a medical history of recurrent sinusitis and pneumonia and in 1991 of post-infectious glomerulonephritis. Hypogammaglobulinemia was noticed at that time (4.6 g/L). In 1994 she was hospitalized for pulmonary embolism and iliac venous thrombosis revealing antiphospholipids [IgG 2 IU/ml; IgM 26 IU/ml (normal <20)], anticardiolipids (28 IU/ml; nor-

mal <20) and lupus anticoagulant, with laboratory confirmation 6 weeks later. From 1999 she presented a chronic symetrical polyarthritis that was treated with steroids 10 to 20 mg/day. At the end of 2000, with 20 mg/day of prednisolone, laboratory findings were: erythrocyte sedimentation rate (ESR) 13 mm/1sthour; C-reactive protein < 3 mg/L, albuminemia 32 g/L (normal range 30.7 –50.4), immunoglobulin (Ig) G 3.5 g/L (normal range 6.75-12.8), IgA2.8 g/L (0.8-3.4), IgM 1.9 g/L (0.6-1.9). Pulmonary X-ray revealed a round regular opacity at the top of the right lung of 15 mm confirmed on CT-scan, without mediastinal adenopathy, suggesting a granulomatous lesion.

The diagnosis of CVI was retained and the patient received IVIG (40 g on one day every 4 weeks) resulting in a dramatic improvement of polyarthritis. Steroids were progressively tapered and stopped in December 2001. The size of the pulmonary granuloma decreased to 5 mm at the same time. In August 2002, she presented a Quincke oedema during the 14th infusion of IVIG. The search for anti-IgA antibodies was positive. Due to a relapse of sinusitis, we proposed IgA depleted IVIG (40 g on one day every 4 weeks). Before the second infusion, the level of total Ig was 6.5 g/dL (normal range: 7.0–15.0). Ten days after this second infusion, she complained of a relapse of polyarthritis. Laboratory findings were as follow: ESR 76 mm/1sthour; C-reactive protein 51 mg/L. Electrophoresis showed hypoalbuminemia (30 g/L) but Ig were in the normal range (10.2 g/dL). Despite a new perfusion of depleted IgA-IVIG, her clinical condition deteriorated, justifying starting prednisone again, 30 mg/day. Steroids were progressively tapered but the polyarthritis remained cortico-dependant despite regular IgA-depleted IVIG infusions.

This is the first report of an association of antiphospholipid syndrome and CVI. The relationship between systemic lupus erythematosus and CVI has been established for several years and it could be supposed that those beween APS and CVI are similar (6, 7). The present case suggests that IVIG could have a favorable impact on pulmonary granulomatous lesion. Two previous reports have also shown resolution of cutaneous granulomatous lesions and polymorphic light eruption with IVIG, suggesting, in addition to our case, that it has steroid-sparing and immunosuppressive effects in patients with CIV(4, 5).

Finally, we noticed a lower efficacy against rheumatologic manifestations of IgA-depleted IVIG than of non-depleted IVIG. As the only difference between these two types of immunoglobulin preparations lies in the level of IgA (2.1 mg/ml for non-depleted IVIG and 2.2 µg/ml for IgA-depleted IVIG) it is suggested that IgA played a role in the control of immune disease in our patient. *In vitro* studies have shown that IgA antibodies had a better antiinflammatory activity and regulates complement activity (8, 9), and that IgA/IgM enriched IVIG may be a more potent immunomodulator than pure IgG preparations (10). Our observation suggests that the IgAcomposition of immunoglobulin preparations could also lead to a difference in antiinflammatory effects in some patients.

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Development of myositis after hepatitis C virus infection

Sirs,

Persistent hepatitis C virus (HCV) infection leads to the development of chronic hepatitis, cirrhosis, hepatocellular carcinoma, and a wide spectrum of extrahepatic manifestations. Viruses have long been suspected as potential etiologic or triggering agents in the pathogenesis of many autoimmune diseases. Some immunological disorders have a well established association with HCV infection, the presence of cryoglobulins being the most common (1-3). An association between polymyositis/dermatomyositis (PM/DM) with lung fibrosis and chronic HCV infection has previously been reported (4-6). We recently observed a patient who developed myositis in association with chronic HCVinfection.

The patient, a 68-year-old woman, presented with a 4-week history of progressive muscle weakness of upper and lower limbs, and weight loss (10 kg). Seven days before she was unable to rise from her bed or to walk. She had a 4-year history of histologically confirmed liver cirrhosis and HCV seropositivity. Thirty years ago she had been operated on and received a blood transfusion. She was seen in our rheumatology unit in July 2004. On presentation the patient had a blood pressure of 200/100 mmHg and a normal temperature. No skin rashes or lymphadenopathy were found. Head and neck examination revealed non-icteric sclerae. There was truncal vascular spiders. The spleen was palpable. Ascites was absent. There was severe proximal muscle weakness with marked wasting. Laboratory test results showed hemoglobin 15 g/dl, leukocytes 11.300/mm^3 and 23,000/mm^3, alanine aminotransferase (ALT) 310 IU/L and 867 IU/L, aspartate aminotransferase (AST) 1,626 IU/Land 924 IU/L, lactate dehydrogenase 761 IU/L and 1.980 IU/L, and gammaglutamyl-transferase (GGT) normal (49 IU/L). Creatine kinase (CK) was increased at 40,000 IU/L. Total bilirrubin was 1.6 mg/dl; and albumin and alkaline phosphatase were normal. Serum creatinine was elevated (6.9 mg/dl) and there was hyperkalemia (7.6 mmol/L). Serum level of alpha-fetoprotein was within nor-