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A 47-year-old woman with persistent watery diarrhea, proteinuria, proximal weakness and monoclonal gammopathy

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Case report

A 47-year old woman was admitted to our hospital because of severe watery diarrhea, edema and profound weakness. The patient had been well until 5 months earlier when progressive, prominent, proximal weakness developed. The patient had difficulty in walking, rising from a chair and raising her arms. Gradually pedal edema developed. Three months earlier the patient was complaining of intermittent pain in both temporomandibular joint regions with radiation to the teeth and progressive difficulty in opening her mouth. Twenty days before admission she had an abrupt onset of nausea, vomiting, cramping abdominal pain and watery diarrhea. The patient passed approximately 15 watery stools daily without blood. Three days before her admission she began to have dysphagia.

The patient was a medical doctor and the mother of two children, with a normal menstrual cycle and a history free of disease, tobacco smoking, and alcohol consumption. Her temperature was 37°C, pulse 110/min and respirations 20/min. Her blood pressure was 120/80 mmHg without signs of orthostatic hypotension. The patient appeared lethargic and had dysphonia. The lungs and heart were found to be normal. The skin was pale without abnormal pigmentation or rash. No lymphadenopathy was found. The neck was supple and the thyroid gland was not palpable. Attempts to open the patient's jaw by applying pressure to the chin were unsuccessful (lockjaw) and she was unable to protrude her tongue. The abdomen was tense but not tender and the liver and spleen were not palpable. A subcutaneous nodule was palpable in the upper right part of the abdomen. There was 3+ edema in the feet and legs and trace edema in the hands. The joints were normal. Rectal examination was negative; a greenish watery liquid was present within the rectum and gave a negative test for occult blood. The genitalia were normal. There was a reduction of strength (grade 3/5) in the proximal muscles of both limbs. Tendon reflexes, vibration, joint position, pin prick and temperature sensations were normal. There was marked wasting of both masseter muscles. The optic fundi appeared normal; the pupils were normal in size and shape, and reacted normally to light and accommodation. No other neurological abnormalities were detected.

The patient's hematocrit was 37% and her white cell count was 6,800/mm^3 with 57% neutrophils, 14% lymphocytes, and 24% monocytes. The platelet count was 320,000/mm^3 and the ESR 75 mm/hr. C-reactive protein was 268 mg/dl. Urinalysis gave a ++ positive test for protein; the sediment contained 8 red cells per high power field; no red cell casts were seen. In a 24-hr urine specimen the protein was 1 gr. The prothrombin time and partial thromboplastin time were normal. The urea nitrogen was 51 mg/dl, creatine 1.5 mg/dl, bilirubin 1 mg/dl, calcium 11.5 mg/dl, uric acid 8.8 mg/dl and protein 4.8 g/dl (albumin 2.8 g and globulin 2 g/dl). The sodium was 147 mmol and the potassium 4.4 mmol/L. ASAT was 17 U/L, ALAT 20 U/L, LDH 300 U/L, creatinophosphokinase 48 U/L, amylase 92 U/L and alkaline phosphatase 229 U/L. Tests for hepatitis B surface antigen and human immunodeficiency virus antibodies were negative. Rheumatoid factor and cryoglobulins were negative. C3 was 104 mg/dl and C4 was 46 mg/dl. A thyroid function test was normal. Serum protein electrophoresis revealed a discrete band in the region of the γ-globulins and severe hypoglobulinemia. Immunofixation of the serum showed a

monoclonal IgG-κ immunoglobulin. There was also a monoclonal κ light chain in the urine. An electrocardiogram showed a normal rhythm at a rate of 105 with non-specific ST-segment and T-wave abnormalities. An ultrasound examination of the heart was normal. X-ray films of the chest, bones, and abdomen were normal. A CT scan of the abdomen was negative.

Microscopical examination of a stained stool specimen revealed no neutrophils; a stool culture yielded no pathogenic microorganisms. A fiberoptic colonoscopic examination revealed mucosal edema and submucosal hemorrhages. A CT scan of the brain was normal. Cerebrospinal fluid analysis was not revealing. Needle electromyography (EMG) revealed fibrillations and neurogenic motor unit potentials in tibial anterior, deltoid and both masseter muscles. Nerve conduction studies of the median and ulnar nerves showed no features of prolonged distal latencies or slowed conduction velocities, but a reduced amplitude of the motor-evoked responses of the right ulnar nerve. A diagnostic procedure was performed.

Differential diagnosis

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This woman had a recent onset of symmetrical proximal weakness, lethargy, proteinuria, watery diarrhea, dysphagia, dysphonia and marked wasting of both masseter muscles associated with lockjaw and inability to protrude the tongue. Electrophysiological testing showed no features of demyelination, but a reduced amplitude of motor evoked responses compatible with axonal neuropathy. EMG revealed fibrillations and neurogenic motor unit potentials. In addition, hypercalcemia was present and protein immunofixation of the serum and urine revealed a monoclonal IgG κ immunoglobulin.

Patients with axonal neuropathy and monoclonal protein should be evaluated for underlying disorders such as multiple myeloma, macroglobulinemia, cryoglobulinemia, lymphoma, and primary amyloidosis.

Primary amyloidosis is a multi-system disorder characterized by the extracellular deposition of fibrillar protein arranged in a β-pleated sheet conformation in tissues throughout the body. Amyloid is classified on the basis of the biochemical composition of its protein. Primary or myeloma-associated amyloid is composed of the amino-terminus variable segment of immunoglobulin light chains, and hence is designated as AL. AL amyloidosis occurs in association with multiple myeloma, Waldestrom's macroglobulinemia and certain neoplasms or in primary plasma cell dyscrasia, without any underlying disease. Patients are predominantly men at or past middle age (1).

Neural involvement is present in 15% to 35% of patients with AL amyloidosis (2). Patients have clinical and electrodiagnostic features consistent with an axonal sensorimotor polyneuropathy frequently associated with autonomic neuropathy. Amyloid neuropathy is related to a prominent involvement of small myelinated and unmyelinated fibers and is present with distal sensory symptoms including dysesthesia, sensation loss, pain and orthostatic hypotension. Distal symmetric motor involvement is usually present but is rarely observed as an early manifestation (3). Nerve conduction studies commonly showed axonal degeneration without conduction block or demyelination (4).

Our patient had progressive, prominent proximal weakness and electrophysiological features compatible with axonal neuropathy, but sensory signs and symptoms as well as orthostatic hypotension were not recorded. Furthermore, the normal conduction and active tendon jerk mimicked motor neuron disease.

Cases of AL amyloidosis with peripheral neuropathy and sings of motor neuron disease have been described (5), indicating the multiple phenotypes of the neural involvement in AL amyloidosis. The pathogenic mechanism of the nerve fiber damage remains uncertain. Various hypotheses have been proposed, including ischemia due to amyloid infiltration of the versa nervosum, nerve fiber compression by endoneural amyloid deposits, and distal axonopathy caused by a massive proximal neurotoxic effect of the monoclonal protein (6).

Our patient exhibited numerous other features compatible with AL amyloidosis, such as proteinuria, subcutaneous nodule, lockjaw, diarrhea, dysphagia and dysphonia.

Renal disease occurs in almost every type of amyloidosis. Proteinuria is the most common presentation and is usually progressive and responds poorly to therapy. The most frequent histopathologic finding is amyloid deposition in the mesangial and subendothelial regions of the glomerulus as well as in the arteriolar walls.

Cutaneous manifestations are seen in 40% to 60% of patients, including waxy indurated papules, purpura, skin thickening and subcutaneous nodules.

Amyloid arthropathy is generally a chronic symmetric arthropathy that involves shoulders, wrists, knees and fingers (7). A case of amyloidosis with temporomandibular arthopathy has been reported and could explain the lockjaw sign in our patient (8).

Gastrointestinal involvement occurs in about 50% of patients with amyloidosis and is the result of direct infiltration or autonomic involvement. Clinical manifestations include macroglossia, dysphagia, malabsorption, diarrhea, ulceration, ileus, melena, and hematochesia. The macroglossia may result in dysphonia and difficulties in respiration and deglutition (7). Our patient did not have macroglossia so her dysphonia and inability to protrude her tongue cannot be explained by this mechanism.

The combination in our patient of dysphonia, dysphagia, wasting of both masseter muscles and inability to protrude the tongue generated a suspicion of cranial neuropathy (vagus, glossopharyngeal, trigeminal, hypoglossal). One key feature distinguishing the neuropathy associated with AL amyloidosis from familiar amyloidosis has been the absence of cranial neuropathy in the former. Cranial neuropathy may be the initial manifestations of AL amyloidosis and this diagnosis should be considered in the differential diagnosis of cranial neuropathy when proteinuria is noted or when a monoclonal protein is found in the serum or urine. It is interesting that in half of all patients multiple cranial nerves were involved (9). Isolated amyloidomas may involve the central nervous system, although this event is rare.

There have been a few previous reports of amyloidomas that involved the gasserian ganglion and trigeminal nerve causing unilateral trigeminal neuropathies and bilateral trigeminal neuropathies (10-12). Our patient presented with bilateral wasting of the masseter muscles; an EMG of both muscles showed fibrillations and a neurogenic motor unit potential, but light touch sensation and pinprick in the distribution of both trigeminal nerves were normal. We think that the above discrepancy was artificial since the patient was confused and could not collaborate in the sensation testing. It is interesting that she also noted intermittent tooth pain in the preceding months and this probably was the only sign of trigeminal neuralgia. Magnetic resonance imaging (MRI) is superior to CT scan for detecting these lesions (10-12).

It is also worth discussing the link between gammopathy and neuropathy. Three main pathophysiologic mechanisms can be associated with this relationship. Firstly is that of the direct action of the paraprotein to the neurons. In patients with IgM gammopathy, M proteins frequently have autoantibody activity and are implicated in the pathogenesis of the neuropathy. IgM monoclonal proteins that bind to myelin-associated glycoprotein (MAG) have been shown to cause demyelinating peripheral neuropathy; anti-GM1 ganglioside antibody activity is associated with predominantly motor neuropathy and electrophysiologic abnormalities such as motor conduction block indicative of segmental demyelination; anti-sulfatide or anti-chondroitin sulfate antibodies are associated with sensory neuropathy (13, 14).

Another mechanism of neuropathy is indirect neuron destruction due to cryoglobulinaemia. Sural nerve biopsies show abnormalities of the endoneural vessels ranging from overt vasculitis to occlusive microangiopathy. The neuropathy associated with cryoglobulinaemia may be asymmetric, painful, cryosensitive and associated with cutaneous purpura (15). Finally the third mechanism is amyloidosis. Our patient did not have cryoglobulinaemia and there was no evidence of a demyelinating process, so the clinical and pathogenic patterns support the hypothesis that this woman had a multi-system disorder compatible with AL amyloidosis.

The diagnosis of AL amyloidosis implies the presence of plasma cell dyscrasias. Multiple myeloma (MM), the principal malignant plasma cell dyscrasia, accounts for approximately 10% of all malignant hematological tumors. Bone disease and hypercalcemia are common features of MM, but bone disease as evidenced by lytic lesions has been documented only in 13% of patients. However, the combination of osteoporosis and lytic lesions or fractures was observed in 57% of the cases. Hypercalcemia was also found in 30% of the patients (16). The mechanism of both hypercalcemia and bone disease is related to lymphokine production. Finally, amyloidosis occurs in 5% to 15% of patients with MM. In our patient the bones appeared normal on x-ray films, but she had hypercalcemia and encephalopathy symptoms compatible with increased calcium, so we favored a diagnosis of MM.

Involvement of the nervous system unrelated to spinal cord or nerve compression by plasma cell tumors is unusual in MM. Polyneuropathy occurs in approximately 5% of patients with MM. The clinical manifestations of myeloma neuropathy are heterogeneous (17) and the pathogenic mechanisms are included in the previous paragraph. Osteosclerotic myeloma accounts for less than 3% of patients with myeloma, but is associated with peripheral neuropathy in almost one half of all cases (18). It is a demyelinating, predominantly motor neuropathy associated with progressive proximal motor weakness. Bone lesions are sclerotic and painless in contrast to the painful lytic bone lesions that occur in MM. About one fourth of reported cases have no detectable bone lesions. It can also be associated with systemic manifestations such as organomegaly, endocrinopathy (hypogonadism, gynecomastia, diabetes, hypothyroidism), and skin changes (hypertrichosis, hyperpigmentation, thickening, hemagioma). This complex is referred as the POEMS syndrome. Anasarca, pitting edema of the lower limbs, ascites, pleural effusion, weight loss, clubbing, polycythemia, thrombocytosis, papilledema, Raynaud's phenomenon and flushing are other signs of this syndrome (19, 20). It is important to recognise this rare syndrome because it is treatable. Our patient showed no hepatomegaly, splenomegaly, lymphadenopathy, or endocrinopathy and although her motor weakness was compatible with the clinical expression of osteosclerotic myeloma neuropathy, there were no prolonged distal latencies or slowing nerve conduction velocities in nerve conduction studies.

In conclusion, our diagnosis was myeloma-associated AL amyloidosis with

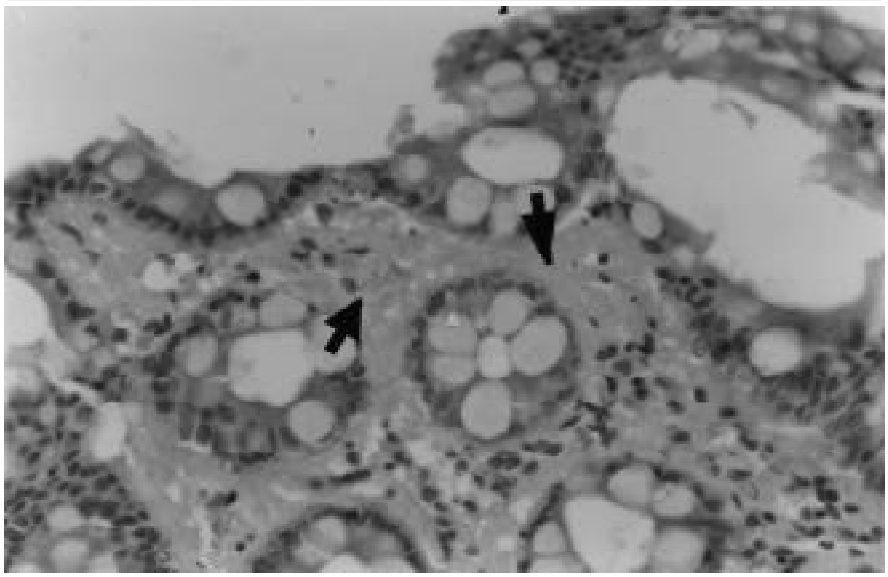

Fig. 1. Rectal biopsy (hematoxylin-eosin stained section, 200x). Deposition of amorphous, eosinophilic material is evident in lamina propria and in the small vessels (**arrows**).

peripheral-central nervous, gastrointestinal, cutaneous, renal and skeletal system involvement.

Pathological description

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The diagnostic procedure undertaken in this patient was the rectal biopsy. Histological examination showed deposits of eosinophilic material in the lamina propria and in the walls of the small vessels (Fig. 1). Congo-red stain gave a green birefringence under polarized light. Bone marrow biopsy and aspiration revealed the presence of 20% plasma cells expressing monoclonal κ-light chains. Finally, peripheral nerve biopsy revealed axonal degeneration and demyelinization without evidence of amyloid deposition. The final diagnosis was myeloma-associated AL-amyloidosis.

Patient follow-up

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After the diagnosis was established, a combination of cyclophosphamide, vincristine, melphalan, and prednisone was started. No improvement was noted. After fifteen days the patient's condition had deteriorated gravely and she died from the symptoms of cerebral hemorrhage.

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