Pure Motor Axonal Neuropathy, Organomegaly, Impaired Glucose Tolerance, M Protein, Skin Changes, Multiple Plasmacytomas & Acute Interstitial Nephritis in Osteolytic Myeloma: Beyond POEMS!

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Abstract The authors describe a case of 52-year-old male who presented with sudden onset deterioration of weakness of both lower limbs and retention of urine. He had 1 month history of gradually progressive weakness of legs. On examination, there were lower motor neuron signs in lower extremity, digital clubbing and a lump over left iliac fossa. Routine blood tests showed impaired glucose tolerance, confirmed by oral glucose tolerance test while renal parameters were normal. Magnetic resonance imaging of spine documented osteolytic lesions, long segment epidural mass in thoracic spine and a mass overlying the left iliac bone, both were revealed to be plasmacytoma following cytology. Ultrasonography of abdomen showed splenomegaly. Nerve conduction studies showed gross axonal, motor, asymmetric polyneuropathy with conduction block involving all the four extremities, mainly lower limbs with sensory sparing. Serum protein electrophoresis showed M spike, and bone marrow showed diffuse neoplastic plasma cell proliferation. Osteolytic lesion was present in skull

radiograph. Then in the course of illness the patient developed acute renal failure due to acute interstitial nephritis as evidenced from proteinuria and kidney biopsy, which improved with steroids and chemotherapy but unfortunately we lost the patient after 2 weeks of initiation of chemotherapy.

Keywords Epidural mass · Osteolytic lesions · Magnetic resonance imaging · Polyneuropathy · Acute interstitial nephritis

Introduction

Multiple myeloma (MM) is characterized by bone marrow infiltration with plasma cell, the presence of serum and urine monoclonal protein and usually osteolytic lesions [1]. Chronic interstitial nephritis is common findings in myeloma patients [2]. However, acute interstitial nephritis amenable to the corticosteroid therapy is quite rare in the setting of MM, and only handful of cases has been reported in the medical literature [3].

Polyneuropathy seen in MM are mostly mild distal sensori-motor polyneuropathy and less frequently, a pure sensory neuropathy or amyloid neuropathy. The common neurological complications of MM are related to cord and root compression from lytic vertebral lesions. Whereas, the neuropathy of osteosclerotic myeloma bears a striking resemblance to chronic inflammatory demyelinating polyradiculopathy (CIDP). Chronic dysimmune neuropathies may also present as multifocal motor neuropathy (MMN) [4]. A subacute, pure motor, gross axonal neuropathy involving the extremities asymmetrically mainly in lower extremities unlike MMN is exceedingly rare. POEMS or Crow–Fukase syndrome is the acronym for polyneuropathy,

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organomegaly, endocrinopathy, M protein, and skin changes described in osteosclerotic myeloma [4]. However, POEMS like features in an osteolytic myeloma is less frequently described.

Plasmacytoma is one of the plasma cell neoplasms locally infiltrating bones or spreading to extramedullary sites from the bones. Wiltshaw classified soft tissue plasmacytoma into three clinical stages: (I) limited to an extramedullary site, (II) involvement to regional lymph nodes, and (III) multiple metastases [5]. The patient in the present case had plasmacytomas, one over iliac bone and another involving long segment in thoracic spine.

Case Report

A 52-year-old non-diabetic, normotensive man presented to the emergency department for sudden onset weakness of weakness of both lower limbs and retention of urine. Patient was otherwise well 1 month back when he started to experience progressive weakness of right lower limb followed by left and involving both distal as well as proximal lower limb musculature. He did not mention any weakness of the upper limb muscles. There was sudden deterioration of weakness and the patient became bedridden 2 days prior to admission. He also complained of marked wasting of the lower extremity muscles. He did not give any history of diurnal variation of weakness, stiffness in the limbs, any abnormal movements. There was neither any history suggestive of radicular pain nor any history of aggravation of symptoms with coughing, straining or movement. He mentioned about an upper back pain during work since past few months. He denied any history of trauma, fever, gum bleeding or other hemorrhagic manifestations, cough, and significant weight loss in recent past. He was nonsmoker and had no history of contact of tuberculosis in family, relevant drug use or abuse or any exposure to toxic agents.

On physical examination, there was mild pallor and digital clubbing. There was wasting of both proximal and distal muscles of lower limbs. Tone was decreased in lower extremities. The weakness was found to be of grade 0/5 in both lower limbs and normal in upper extremities. All tendon reflexes of lower extremity were diminished. In the upper limb biceps and triceps jerks were exaggerated bilaterally. Plantar reflex was non-responsive bilaterally. Abdominal examination showed no obvious organomegaly however, the Traube's space was dull on percussion. Palpation in the left iliac fossa revealed a non tender, soft, non mobile lump (9 cm × 6 cm).

Investigations after admission to medical ward showed hemoglobin concentration of 8.7 g/dl, and a leucocyte count of 9000/ μ L. ESR was raised (65 mm/1st hr). Renal

parameters showed urea —44 mg/dl and a creatinine level of 1.23 mg/dl. Fasting blood glucose was 120 mg/dl and 2-h blood glucose (after oral glucose challenge) was 187 mg/dl. Liver function tests revealed raised globulin level (4.1 g/dl). Magnetic resonance imaging (MRI) of dorsolumbar spine showed a long segment epidural mass extending from D4 to D10 (Fig. 1a) and multiple areas of destructive lesions in D4, D5, D6, and D11 vertebral bodies (Fig. 1b). Most strikingly, a soft tissue mass over left iliac fossa was found (Fig. 1c). Nerve conduction velocity study showed mildly prolonged distal latencies of right median nerve, reduced compound muscle action potential (CMAP) in right ulnar and bilateral inexcitable tibial nerve. Bilateral peroneal nerves were also inexcitable. Sensory nerve action potential (SNAP) of median, ulnar and sural nerves were normal on both sides. Radiograph of skull showed punched out lytic lesion (Fig. 2).

The patient eventually became oliguric and general condition deteriorated. Bone marrow aspiration was performed to investigate the cause of unexplained anemia which revealed 22 % plasma cells with atypical plasma cells and Mott cells (Fig. 3). Serum protein electrophoresis revealed total protein: 10.15 g/dl, albumin: 2.62 g/dl, alpha-1: 0.69 g/dl, alpha-2: 1.14 g/dl, beta-1: 0.31 g/dl, beta-2: 0.61 g/dl, gamma: 4.58 g/dl with "M"-band (4.03 gm/dl) seen in gamma region. Immunofixation electrophoresis showed bands which immunologically correspond to IgG and κ region. Ultrasound of abdomen showed enlarged spleen (13.5 cm), mildly increased parenchymal echogenicity of both kidneys and a soft tissue mass (7.9 × 4.6 cm) over left psoas muscle. Repeat blood tests showed urea- 326 mg/dl and creatinine level of 9.2 mg/dl. Serum calcium was 7.6 mg/dl. Uric acid was normal. Arterial blood gas analysis revealed uncompensated metabolic acidosis. Urinalysis showed proteinuria (774.2 mg in 24 h) and a positive Bradshaw test for Bence-Jones protein. Serum vascular endothelial growth factor (VEGF) level could not be contemplated due to economic constraints. With suspicion of acute renal failure, per-cutaneous renal biopsy was performed and hemodialysis was done in two sittings.

The patient was placed on chemotherapy with intravenous cyclophosphamide, doxorubicin, and vincristine for 5 consecutive days and intravenous pulse methylprednisolone (1 g/day) for 3 days followed by oral prednisolone (50 mg/day). After 4 days of steroid therapy, urinary output increased and patient improved a bit. Renal biopsy showed interstitial mononuclear proliferation with intratubular amorphous material and tubular dilatation with focal necrosis (Fig. 4a, b). Congo red staining didn't show any amyloid deposit. Computed tomography (CT) guided aspiration from the epidural mass and subsequent cytology revealed scattered atypical plasma cells suggestive of

Fig. 1 **a** Magnetic resonance imaging of dorsolumbar spine showing a long segment epidural mass from D4 to D10 (*white arrows*); **b** Focal areas of destructive lesion in D4, D5, D6, and D11 vertebral bodies

(*white arrow*); **c** Coronal image showing a soft tissue mass over left iliac bone (*white arrow*)

Fig. 2 Radiograph of skull showing punched out lytic lesion (*black arrowheads*)

Fig. 3 Bone marrow aspiration findings (original magnification, ×400): Plasma cells constituting 22 % of bone marrow with atypical plasma cells, Mott cells, and trilobed plasma cells

plasmacytoma (Fig. 5a). Immunohistochemical analysis of the iliac fossa mass showed a small round cell tumor with CD138 positive staining (Fig. 5b). Unfortunately, despite best supportive care for complications, we lost the patient after 2 weeks of initiation of chemotherapy.

Discussion

Multiple myeloma (MM) is a neoplastic proliferation of a single clone of plasma cells producing a monoclonal immunoglobulin. Active MM is defined by the presence of

M protein in serum and/or urine, bone marrow (clonal) plasma cells or plasmacytoma and myeloma-related organ or tissue impairment (end organ damage, including bone lesions) [6].

Myeloma nephropathy occurs when tubular absorptive capacity of light chains is exceeded and, intratubular casts lead to tubular obstruction. Light chain molecules are also direct tubular toxins. Interstitial cell infiltration and fibrosis as in chronic interstitial nephritis are late findings. Acute renal failure secondary to volume loss, infection, hypercalcemia, use of radiocontrast studies and nonsteroidal

Fig. 4 **a** Kidney biopsy specimen showing interstitial edema (*black star*) and leucocytic tubulointerstitial infiltration (*black arrow*); **b** Focal tubular necrosis and atrophy (*black arrow*)

Fig. 5 **a** Fine needle aspiration from the epidural mass showing plasma cells; **b** Immunohistochemical findings of the iliac plasmacytoma ($\times 600$). Plasma cells in the iliac tumor showed CD138 expression

anti-inflammatory drugs (NSDAIDs) can occur in the myeloma patients [7]. Amyloidosis and hyperuricemia are addition to the list [2]. However, acute interstitial nephritis amenable to the corticosteroid therapy is very rare in the MM, and literature search revealed only one case report. In a series of 118 myeloma patients [8], renal biopsy revealed cast nephropathy in 40.7 %, amyloidosis in 29.7 %, light-chain deposit and tubulointerstitial diseases in 18.6 and 10.2 % of the patients, respectively. However, all of them were chronic tubulointerstitial lesions rather than acute.

Polyneuropathy occurs in ~5 % of patients with MM. One third of patients are found to have abnormalities on careful electrophysiological studies. The common neurological complications of MM are due to extramedullary cord and root compression from lytic vertebral lesions. The clinical manifestations of myeloma neuropathy are variable. Most patients present with mild distal sensori-motor polyneuropathy. Less frequently, a pure sensory neuropathy is seen. Moreover, AL amyloidosis complicates MM in 30–40 % of cases, and these patients have a high mortality. Painful dysesthesias due to preferential small fibre sensory involvement, autonomic dysfunction, and carpal tunnel syndrome suggest amyloid neuropathy. Nerve conduction and sural nerve biopsy studies are consistent with an axonal process with loss of myelinated fibres. Treatment of the

underlying myeloma may sometimes improve the neuropathy.

In contrast, the neuropathy of osteosclerotic myeloma occurs at an early age, mostly in men, and it is demyelinating, predominantly motor and bears striking similarities to CIDP with symmetrical proximal and distal weakness with variable sensory loss. Cranial nerves are usually spared [4, 9]. An M protein is found in 90 % of cases and virtually always composed of a light chains associated with IgG and IgA heavy chains. It responds to irradiation or excision of the isolated plasmacytoma and is associated with systemic manifestations referred to as Crow–Fukase or POEMS syndrome [4]. Whereas, MMN is characterized by a pure motor syndrome. The age at onset is generally 20–75 years, and men are more commonly affected than women. Clinically, MMN is characterized by asymmetrical, slowly progressive weakness that most commonly begins in the distal upper extremities in the distribution of two or more individual peripheral nerves. Muscle weakness is usually greater than would be expected from the degree of muscle atrophy. MMN may also affect the lower extremities, often with slowly progressive foot drop or focal leg weakness and atrophy. Nerve conduction shows focal conduction block along two or more motor nerve fibres, particularly at sites that are anatomically distinct

from common entrapment sites [4, 9]. In our case, there was pure motor, axonal, asymmetric polyneuropathy with conduction block—a pattern resembling MMN, though the age of presentation and area of involvement didn't match.

POEMS is the acronym for polyneuropathy, organomegaly, endocrinopathy, M protein, and skin changes. In osteosclerotic myeloma, 85 % of patients have peripheral neuropathy. Hepatosplenomegaly is often associated. Common endocrinopathies include gynecomastia and impotence in male, secondary amenorrhea in women, diabetes mellitus, and hypothyroidism are the most. Hyperpigmentation, hypertrichosis, diffuse skin thickening, hemangiomas, and white nail beds, pitting edema of the lower limbs and clubbing fall under skin changes. Approximately one fourth of patients with POEMS syndrome have no associated bone lesions. Some of these patients have Castleman's syndrome (a non-malignant form of angiofollicular lymphadenopathy), and others have a plasma cell dyscrasias restricted to the lymphoreticular system. Elevated levels of tumour necrosis factor- α (TNF- α), interleukins, and vascular endothelial growth factor have been implicated in the multisystem manifestations [4]. The POEMS syndrome is associated with elevated VEGF levels, which is useful in differentiating POEMS from other plasma cell dyscrasias, neuropathic processes, and multisystem illnesses. Moreover, plasma VEGF is also useful in monitoring disease activity after treatment and correlates with clinical improvements better than hematologic response [10].

In the present case there was polyneuropathy, splenomegaly, impaired glucose tolerance, M spike and clubbing in the setting of an osteolytic myeloma. The most intriguing aspects of the case are (1) MM presentation with acute interstitial nephritis, (2) Polyneuropathy in the form of a pure motor, axonal, asymmetric polyneuropathy with conduction block—a pattern resembling MMN, (3) Osteolytic myeloma gives rise to multisystem involvement like POEMS syndrome classically seen in osteosclerotic myeloma and (4) MM leads to epidural long segment

plasmacytoma causing cord and root compression and occurrence in unusual sites like iliac bones.

Conflict of interest None.

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