Cranial Neuropathy and Bone Involvement in Primary Systemic Amyloidosis

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Abstract
Bone involvement in primary systemic amyloidosis is rare. Intracranial involvement in primary amyloidosis has not been reported so far. We report two cases of bone involvement in primary amyloidosis. The first patient also had combined deficiencies of factor IX and XII, while the second patient had associated intracranial involvement and XIIth cranial nerve palsy. Both these cases are unique in that, destructive bone lesions with intracranial involvement and combined factor deficiencies have not been reported in primary amyloidosis previously. ©

INTRODUCTION
Primary systemic amyloidosis is a clonal plasma cell disorder characterized by the deposition of a congophilic beta-pleated fibrillary protein containing monoclonal light-chain fragments in affected organs, in the absence of multiple myeloma. Many organs are affected in this disease, but bone involvement is rare. We report two cases of primary systemic amyloidosis with bone involvement, associated with combined factor IX and XII deficiency in one case and, XIIth cranial neuropathy due to intracranial involvement in the other.

CASE REPORT
Case 1
A 53 years woman with no pre-existing illness came to us in November 2004 with complaints of generalised weakness of 10 months and left hip pain with difficulty in walking of 6 months duration. There was no history of trauma or fever. No history of bleeding tendencies. Clinical examination revealed bilateral pitting pedal oedema with a tender firm to hard liver palpable 13 cms below the coastal margin in the right midclavicular line. Haemogram was normal except for a platelet count of 8,39,000/mm³. The erythrocyte sedimentation rate (ESR) was 70 mm/hr. Prothrombin time (PT) was 13.9 sec (normal: 10.8-14.2 sec) and activated partial thromboplastin time (aPTT) was prolonged at 41.4 sec with a control of 27.5 secs. Factor IX assay was 43.6% (Normal: 60-140) and that of Factor XII: 34.4% (Normal: 60-140) with normal Factor VIII and XI levels. Renal and liver functions were normal but for an alkaline phosphatase of 384 IU/L. Total cholesterol was 267mg/dL with triglycerides: 219 mg/dL. Urine for Bence Jones protein was negative with 24 hr urine protein: 10.4 gm. Ultrasound of abdomen and pelvis showed hepatomegaly and enlarged kidneys with increased echogenicity. There was no M band seen on serum electrophoresis. Quantitative immunoelectrophoresis showed IgG: 924 mg/dL (630-1700), IgA: 215 mg/dL (76-370) and IgM: 60 mg/dL (58-210). Beta 2 Microglobulin (b₂M) level was 6.87. A skeletal survey showed a lytic lesion of left pubic body. Short term inversion recovery (STIR) sequence on magnetic resonance imaging (MRI) of pelvis and dorsolumbar spine revealed an osteolytic lesion in S3 with small prevertebral soft tissue and high signal areas in the entire sacrum, superior pubic rami bilaterally and inferior pubic ramus on left side with normal dorsolumbar spine (Fig 1). ⁹⁹ᵐ⁻Tc – Methylene Diphosphonate (MDP) bone scan showed increased tracer uptake in bilateral bones and extra-osseous soft tissue on left side.

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sacroiliac joints, sacrum, symphysis pubis, body of bilateral pubis and left pubic crest with normal ribs and skull. An open biopsy taken from the sacrum showed large amounts of amorphous eosinophilic material with Congo red positivity. Immunohistochemistry showed positivity for Kappa and negative for Lambda. Iliac crest marrow aspiration revealed a normocellular marrow with less than 10% plasma cells and a trephine biopsy showed amorphous eosinophilic material with Congo red stain positivity. An electrocardiogram (EKG) and echocardiogram revealed normal cardiac status. Nerve conduction study showed evidence for a mild degree of bilateral axonal type of sensory neuropathy with no evidence of autonomic neuropathy on sympathetic skin response testing. The patient was treated with analgesics, started on high dose dexamethasone with interferon protocol. She is on regular follow and is symptomatically better.

Case 2

A 59 years woman, a known diabetic for 7 years and hypertensive for 7 months, presented to us with complaints of low backache of 6 months and right-sided throbbing headache of 2 weeks’ duration. There was no history suggestive of vascular headache or any other neurological symptoms. She had also noticed a painless swelling in the left lateral chest for the past one-year, which was slowly increasing in size and not associated with any local symptoms. Clinical examination revealed a 6 x 6 cm, hard, immobile, non-tender swelling in the upper outer quadrant of left breast, which appeared to be arising from the chest wall. The left breast was clinically normal and there was no fixity to the mass. Systemic examination was normal except for a right LMN XIIth cranial nerve palsy (Fig. 2). Ocular fundi were normal. Haemogram was normal. The ESR was 78 mm/hr. PT and aPTT were within normal limits. BUN was 40 mg/dl and serum creatinine was 2.4 mg/dl. Liver function tests were normal; except for alkaline phosphatase of 147 IU/L. 24 hour urine protein was 1.8 gm. Ultrasound of abdomen and pelvis was within normal limits. There was no M band seen on serum electrophoresis. Quantitative immunoelectrophoresis showed IgG: 1810 mg/dl, IgA: 118 mg/dl and IgM: 191.8 mg/dl. Urine protein electrophoresis showed a single clear band in the gamma globulin region. A contrast CT chest done showed multiple lytic expansile well defined bone lesions in bilateral 3rd, 4th, 5th and 6th ribs with a soft tissue lesion associated with the left 5th rib lesion measuring 7.8 x 6.3 cms (Fig. 3). Multiple lytic lesions were noted from T3 to L2 vertebrae. Mediastinum and lung fields were normal. A skeletal survey revealed multiple well-defined punched out lesions in the skull and multiple lytic lesions in right ischial tuberosity and over right anterosuperior iliac spine in addition to the vertebral and rib lesions. 99mTc-Methylene Diphosphonate (MDP) bone scan showed increased tracer uptake in right mastoid and mandible, sternum, bilateral anterior and posterior ribs, scapulae, bilateral sacroiliac joints, sacrum, right ilium, pubis and right ischial tuberosity, dorsal and lumbar vertebrae. A contrast enhanced fat saturated MRI brain in T1 weighted images was done in view of the cranial neuropathy, which revealed a well-defined intradiploic lesion with extension through the inner table measuring 4 x 1.3 cms in the region of the right edge of foramen magnum extending into right jugular foramen causing mild compression of internal jugular vein (Fig. 4). Another well-defined similar lesion was seen in the region of the left petrous apex and left cavernous sinus measuring 2.7 x 1.6 cms and encasing the left internal carotid artery. Three small intradiploic lesions, two on the right side and one on left side were seen with enhancing lesion in right mandibular condyle. An incision biopsy from the left 5th rib lesion was positive for Congo red. Immunohistochemistry showed positivity for Lambda and negative for Kappa. Bone marrow aspiration and biopsy were normal except for mild erythroid hyperplasia. The patient was treated with analgesics, started on high dose dexamethasone with interferon protocol. She is on regular follow up and is doing well.
DISCUSSION

Bone involvement in primary amyloidosis is rare, but has been reported.\textsuperscript{1-6} The skeletal involvement can be (a) solitary amyloid tumor of bone involving the ribs and skull; (b) periarthritic lytic lesions with soft tissue masses along with demineralization of adjoining bones due to amyloid infiltration of the bone and bone marrow, especially in the proximal humeri and the femoral necks (shoulders, hips). Amyloid deposits in and around joints causing capsular and pericapsular infiltration cause the soft tissue swelling. The amyloid may fill the joint space and produce erosion of the articular surface.\textsuperscript{1,5} (c) Diffuse spinal osteoporosis with vertebral collapse.\textsuperscript{4}

(d) Neuropathic joint or avascular necrosis causing pathological fracture.\textsuperscript{5}

Literature search revealed 7 additional cases after the review by Kramer \textit{et al}\textsuperscript{1} making a total of 27 cases, including ours (Table 1). The age of all these patients ranged from 42 to 72 years. There were 17 males and 10 females. Bone lesions were most commonly encountered in the long bones and spine in 17/27, pelvis in 12 cases, ribs in 6 and skull in 4 cases. Joints were involved in 13 cases. Fractures were observed in 14 patients, spine in 7 and neck of femur in 6 cases. Osteolytic lesions were seen in 16 cases, osteopenia in 7 and osteoblastic bone lesions in 1 case. Seven patients had paraproteinemia and notably radionuclide bone scan showed increased tracer uptake in all the 13 cases in which this test was performed.

Primary amyloidosis can be divided into (1) AL (primary idiopathic amyloidosis) and (2) AL associated with multiple myeloma. In myeloma, bone lesions are common in the skull and spine; they rarely involve the joint, generally do not take up 99mTc-PP (cold lesions) and have a normal serum acid phosphatase.\textsuperscript{1} Presence of 10% or more plasma cells in the bone marrow is more in favour of multiple myeloma. Immunohistochemical staining of the biopsied amyloid deposits with Kappa and Lambda antisera confirms the diagnosis of amyloidosis.

Bleeding disorders may complicate AL amyloidosis. Common abnormalities noted are prolongation of the thrombin time (TT), PT and aPTT. Deficiencies in specific coagulation factors in AL amyloidosis have long been

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Table 1: Clinical features of nine patients with bone involvement in primary amyloidosis.

<table>
<thead>
<tr>
<th>No.</th>
<th>Age (Yrs)</th>
<th>Sex</th>
<th>Bone Involvement</th>
<th>Type of Lesion</th>
<th>Paraprotein</th>
<th>BenceJones Protein</th>
<th>Bone Scan</th>
<th>Reference</th>
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<tbody>
<tr>
<td>1</td>
<td>69</td>
<td>M*</td>
<td>+ – – – – – – – – + – – – – Neg\textsuperscript{6}</td>
<td>NA\textsuperscript{1}</td>
<td>+</td>
<td>Bhattacharya \textit{et al} (1987)</td>
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<tr>
<td>2</td>
<td>63</td>
<td>F†</td>
<td>+ – – – – + – – – + – – – – Neg</td>
<td>NA</td>
<td>+</td>
<td>Bhattacharya \textit{et al} (1987)</td>
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<tr>
<td>3</td>
<td>56</td>
<td>F</td>
<td>+ – – – + – – – + – – – – Neg</td>
<td>NA</td>
<td>+</td>
<td>Schattner \textit{A et al} (1989)</td>
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<tr>
<td>4</td>
<td>47</td>
<td>M</td>
<td>+ – – – + – – – + – – – – Spine</td>
<td>Neg</td>
<td>NA</td>
<td>Brzeski \textit{M et al} (1990)</td>
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<tr>
<td>5</td>
<td>44</td>
<td>M</td>
<td>– + + – – – – – + – – + Femur</td>
<td>Pos\textsuperscript{†}</td>
<td>NA</td>
<td>Venkatachalam \textit{et al} (1996)</td>
<td></td>
<td></td>
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<tr>
<td>6</td>
<td>45</td>
<td>F</td>
<td>– + – – – – – + – – + –</td>
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<td>Venkatachalam \textit{et al} (1996)</td>
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<tr>
<td>7</td>
<td>69</td>
<td>M</td>
<td>+ – – + – – – – – + – – + – Spine</td>
<td>IgA</td>
<td>NA</td>
<td>Pilar \textit{G et al} (1998)</td>
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<tr>
<td>8</td>
<td>53</td>
<td>F</td>
<td>– – + – – – – – + – – + –</td>
<td>Neg</td>
<td>Neg</td>
<td>Our case</td>
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<tr>
<td>9</td>
<td>59</td>
<td>F</td>
<td>+ – + + + + + – + – + –</td>
<td>Neg</td>
<td>IgG</td>
<td>Our case</td>
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* male; † female; ‡ not available; § : Negative; ¶ : Positive
recognized, although factor X deficiency has been the most widely studied. Since the patient did not manifest any bleeding tendencies, the clinical significance of the low levels of factor IX and XII cannot be commented upon. A combined deficiency of factors IX and XII and coexisting bone lesions in a case of primary amyloidosis has not been reported previously.

The neuropathy of AL typically is a painful, distal, symmetrical sensorimotor neuropathy with prominent autonomic features. Loss of pain and temperature sensation was frequently more striking than loss of mechanoreceptor. There is axonal degeneration with predominant, but not exclusive involvement of small myelinated and unmyelinated fibres. Various cranial nerve involvements have been described in primary amyloidosis. They include anosmia, loss of taste sensation and cranial nerves III, IV, V, VI and VII involvement. Diagnosis of amyloid neuropathy depends on the identification of amyloid deposits, usually around capillaries in the endoneurium and in the walls of small blood vessels in the epineurium. Our patient had XIIth cranial nerve involvement, primarily by pressure effect due to the intracranial bony lesions, which has not been reported so far. The patient had marked improvement with high dose dexamethasone therapy.

Both cases were initially worked up as metastatic bone disease. However, only on further investigations, the diagnosis of amyloidosis was revealed. Even though rare, clinicians should consider the possibility of amyloidosis involving the bone, in cases of unusual bone lesions mimicking metastasis, in otherwise good performance status patients.

REFERENCES