Destructive bone lesions in primary amyloidosis

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Summary: We describe a patient with primary amyloidosis in whom multiple osteolytic lesions caused by amyloid bone tumours developed, and review the clinical features of the 18 cases with primary amyloidosis in whom destructive bone lesions have been reported. In contrast to amyloidosis associated with multiple myeloma, destructive lesions in the primary disease are mainly located to long bones; joint involvement is common, and radionuclide bone scan shows pronounced uptake of ^{99m}Tc -PP by the destructive bone lesions. Despite the superficial similarity between the destructive bone lesions associated with primary amyloidosis and multiple myeloma, distinction between these entities on clinical grounds is possible and may be easily confirmed by direct aspiration of the osteolytic infiltrates.

Introduction

Primary amyloidosis is a systemic disease involving mainly the heart, tongue, gastrointestinal tract, peripheral nerves and skin (Kyle & Bayrd, 1975; Kyle *et al.*, 1966; Kyle & Griep, 1983). In contrast to amyloidosis associated with multiple myeloma in which destructive bone lesions are common (Kyle & Griep, 1983), gross bone involvement in primary amyloidosis is rare.

In this paper we describe a patient with primary amyloidosis in whom severe osteoporosis, pathological fractures and multiple osteolytic lesions developed during the course of the disease. Experience in the 18 cases of primary amyloidosis with destructive bone lesions previously published is summarized, and the difference in the clinical features of bone lesions in primary amyloidosis and in amyloidosis associated with multiple myeloma is emphasized.

Case report

A previously healthy 76 year old Arab female was admitted in February 1984 because of nausea and upper abdominal pain of 4 months' duration. Physical examination revealed a hard liver palpable 15 cm below the costal margin. Laboratory results at the time of admission showed a normal complete blood count. The erythrocyte sedimentation rate was 80 mm/h. Serum electrolytes, BUN, creatinine, calcium and phosphorus were within normal limits. There was no proteinuria. The total serum protein was 72 g/l with

42 g/dl albumin. Serum electrophoresis showed the presence of a paraprotein which was identified by immunoelectrophoresis as IgG kappa monoclonal protein. The serum alkaline phosphatase was 284 IU (normal 30–85), and the acid phosphatase was 0.93 IU (normal 0.1–0.65). Iliac crest marrow aspiration disclosed a normocellular marrow with less than 5% plasma cells. Rectal biopsy showed Congo red positive tissue deposits with green birefringence on polarised microscopy. Gastrointestinal radiographic studies and oesophageal manometry were normal. At this stage the patient was discharged from hospital with a diagnosis of primary amyloidosis, receiving symptomatic treatment.

Eight months later she was admitted to another hospital because of a subtrochanteric fracture of the left femur. A sliding nail was introduced without any attempt at histological examination of the bone or marrow tissue.

In July 1985, 17 months after her initial diagnosis, she was readmitted to our department because of severe back pain and difficulty in walking. Her gross hepatomegaly was unchanged. In addition, there was marked tenderness over the lumbar vertebrae L4–L5 and movement of the left hip was painful with difficulty in stepping on that foot. Haematological and biochemical findings were unchanged. Protein electrophoresis showed persistence of the IgG kappa paraprotein. Quantitative immunoelectrophoresis showed IgG 1777 mg/dl, (normal 750–1500), IgA 185 mg (normal 100–350) and IgM 90 mg (normal 50–150). Skeletal radiograms showed severe generalized osteoporosis, a compressed fracture of L4, fracture of the upper ramus of the left pubis, and bilateral multiple osteolytic lesions of the proximal

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Figure 1 Radiogram of distal humerus and elbow showing multiple osteolytic lesions.

Figure 2 Massive amyloid infiltration of bone marrow aspirate interspersed with normal cellular elements of haemopoietic tissue.

and distal ends of the humerus and along the radius (Figure 1). Severe bone resorption was seen around the nail inserted into the left femur. The left knee showed degenerative changes with soft tissue thickening. The skull was intact. ^{99m}Tc -pyrophosphate (PP) bone scan showed foci of increased uptake in the lumbar vertebrae, pelvic bones, left femur and ribs.

Iliac crest biopsy and sternal aspiration showed a normocellular bone marrow with about 5% plasma cells. There were large amounts of amorphous eosinophilic material with a strongly positive staining for Congo red. A fine needle aspiration biopsy taken from the osteolytic lesions in the right radius showed large amounts of amyloid material with no evidence of plasma cell infiltration. (Figure 2).

The patient was treated with analgesics and epidural infiltration with morphine sulphate resulting in symptomatic relief. Four months after having left hospital and 23 months after diagnosis she died at her home.

Discussion

Our patient presented with massive hepatomegaly and gastrointestinal symptoms associated with amyloidosis. This was followed by the rapid development of multiple destructive skeletal lesions involving mainly the long bones. There was no anaemia or hypercalcaemia and repeated bone marrow aspirates as well as direct biopsy of the bone lesions failed to show plasma cell infiltration in spite of the presence of IgG kappa paraprotein in the plasma. Massive amyloid infiltrates were found in all bone marrow samples.

A systematic review revealed 17 previously published cases of primary amyloidosis with destructive bone lesions within the last 50 years (Table I). We have excluded all cases of amyloidosis associated with myeloma or with other malignant disorders.

The age of these patients with destructive bone lesions ranged from 42 to 72 years. There were 13 males and 5 females. Destructive bone lesions were most commonly encountered in the long bones: the femur, humerus or radius were involved in 15 cases. Lesions in the spinal vertebrae were described in 11 cases. The pelvis, ribs and skull were involved in 8 cases. Joints were involved in 8 cases limited to hips, shoulders or elbows. Spontaneous (pathological) bone fractures were observed in 10 patients involving the neck of the femur (5 cases), spinal vertebrae (5 cases) and one each of the humerus, pubis and odontoid process. Discrete osteolytic lesions were seen in 11 cases and diffuse demineralization (osteopenia) in 4 patients.

Three patients had paraproteinaemia: 2 with IgD and one with IgG. Bence Jones proteinuria was documented in only 2 patients. Blood counts were normal in the

Table 1 Clinical features of 18 patients with destructive bone lesions in primary amyloidosis

No.	Age (y)	Sex	Bone involvement					Type of lesion		Fracture	Para- protein	Bence Jones	Bone scan	Reference
			Spine	Long bone	Pelvis	Ribs	Skull	Osteo- penia	Osteo- lytic					
1	51	m	+	+	-	-	-	+	+	-	nr	nr	nr	Von Bonsdorff (1933)
2	44	m	+	+	+	+	-	+	-	spine	nr	nr	nr	Gerber <i>et al.</i> (1934)
3	61	f	-	+	-	-	-	-	-	femur	nr	nr	nr	Koletsky <i>et al.</i> (1939)
4	49	m	-	+	-	-	-	-	+	-	nr	nr	nr	Gardner (1961)
5	56	m	+	-	-	-	-	-	-	spine	nr	nr	nr	Mandl (1924)
6	67	f	-	+	-	-	-	-	+	humerus	neg	neg	nr	Grossman <i>et al.</i> (1967)
7	63	m	+	+	-	-	-	-	+	spine	neg	neg	nr	Axelsson <i>et al.</i> (1970)
8	62	m	-	+	+	-	-	-	+	-	neg	neg	pos	Weinfeld <i>et al.</i> (1970)
9	45	f	+	+	-	-	-	-	+	-	neg	neg	nr	Birchwood (1974)
10	72	m	+	+	-	-	-	-	+	-	IgD	neg	nr	Hannon <i>et al.</i> (1975)
11	42	m	+	+	+	-	-	-	+	-	neg	neg	nr	Tandon <i>et al.</i> (1976)
12	72	m	-	-	-	-	+	-	-	jaw	IgD	neg	nr	Manz <i>et al.</i> (1981)
13	59	m	+	+	+	+	+	-	+	-	neg	pos	pos	Khojasteh <i>et al.</i> (1979)
14	60	m	-	+	-	-	-	-	+	femur	neg	pos	pos	Lai <i>et al.</i> (1984)
15	55	m	+	-	-	-	-	+	-	spine	neg	neg	nr	Stavem <i>et al.</i> (1980)
16	58	f	+	+	+	+	+	-	+	femur	neg	nr	pos	Goldman <i>et al.</i> (1981)
17	57	m	-	+	+	-	-	-	+	femur	neg	neg	nr	Huau <i>et al.</i> (1985)
18	71	f	+	+	+	+	-	+	+	femur & spine	IgG	neg	pos	Present case

neg-negative; pos-positive

Table II Distinctive features of destructive bone lesions in primary amyloidosis and multiple myeloma

	Primary amyloidosis	Multiple myeloma	Reference
Common localization	Long bones	Skull and spine	Kyle & Griep (1983)
Joint involvement	Common	Rare	Bernhard & Heusley (1969)
^{99m} Tc-PP uptake	Strong	Weak or none	Wahner <i>et al.</i> (1975)
Serum acid phosphatase	Increased	Normal	Weinfeld <i>et al.</i> (1970) Khojasteh <i>et al.</i> (1979)

vast majority of patients and calcium levels were normal in all but one case. Radionuclide bone scan showed increased uptake in all 5 cases in whom this test was performed. The survival from diagnosis ranged from one month to several years. The most common causes of mortality were congestive heart failure and renal failure.

The amyloid fibril has recently been identified with the variable region of the immunoglobulin light chain in both primary amyloidosis and amyloidosis complicating multiple myeloma. Despite this similarity in the molecular structure of amyloid, the clinical, radiological and laboratory features of the two clinical entities differ significantly. This is illustrated by the difference in the frequency and distribution of destructive bone lesions in the two conditions. In the extensive series of Kyle & Griep (1983) involving 229 patients, only 5% of the 163 patients with primary amyloidosis had osteoporosis and 3% had pathological fractures. None had osteolytic lesions. By comparison, in patients with amyloidosis associated with multiple myeloma, 38% of subjects had osteolytic lesions.

Skeletal lesions associated with primary amyloidosis may affect primarily the joints or the bones. Amyloid deposits in and around joints result in soft tissue

swelling caused by capsular and pericapsular infiltration. The amyloid may fill the joint space and produce erosion of the articular surface. Clinically such patients suffer from painful swelling and stiffness of the involved joints. The most common sites are large joints such as the shoulders, hips and elbows (Bernhard & Heusley, 1969; Bywaters & Dorling, 1970). Amyloid infiltration of the bone and bone marrow may present with generalized demineralization, destructive bone lesions consisting of massive amyloid deposits, and pathological fractures located most commonly to the femoral neck or the vertebrae.

Table II summarizes the main features distinguishing the destructive bone lesions associated with primary amyloidosis from bone lesions typical of amyloidosis associated with multiple myeloma.

Although destructive bone lesions associated with primary amyloidosis are rare, their distinction from the more common osteolytic lesions of multiple myeloma is important and highly relevant to the management of such patients. A rapid distinction on clinical grounds may be easily made bearing in mind the above points in the differential diagnosis. Direct confirmation of clinical diagnosis may be achieved subsequently by aspiration of the osteolytic infiltrates.

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