Case Report

Spinal polyostotic fibrous dysplasia in two adults: Does only biopsy unravel the mystery?

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ABSTRACT

Polyostotic fibrous dysplasia is a rare non-inheritable genetic disease due to mutation in GNAS gene. Here we present two adults who were accidentally detected lytic lesions in spine and after extensive evaluation for malignancies; was diagnosed on biopsy. Current concept of the disease and management is discussed.

Key words: Fibrous dysplasia, McCune albright syndrome, thyrotoxicosis

Introduction

Fibrous dysplasia is a genetic, non-inheritable bone disease due to activating mutations of α subunit of stimulatory G-protein ($G_s\alpha$) resulting in defective osteoblast differentiation.[1] The presentation is characterised by bone pains, fractures and bone deformities. It can present as a mono-ostotic or poly-ostotic variant. When associated with endocrine dysfunction and/or café-au-lait spots it is termed as McCune-Albright syndrome (MAS).[2] The classical presentation is the skeletal involvement of long bones, ribs and craniofacial bones.[1] Here we present two cases of polyostotic fibrous dysplasia diagnosed in adulthood with predominant spinal involvement. The first case had hyperthyroidism in addition to his skeletal lesions constituting MAS. We also report ^{18}F-FDG PET findings and its value in assessment of fibrous dysplasia.

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Case Reports

Case 1

A 44 year old male presented with insidious onset gradually progressive symmetrical, inflammatory polyarthralgia predominantly involving small joints of hands of six months duration; diagnosed and treated as seronegative arthritis with analgesics and methotrexate. There was no history of bone pains, deformity of the joints/bones or systemic symptoms. General and systemic examination was unremarkable except arthritis, of which clinical disease activity index was 32 (maximum of 76; ≥21 indicating severe disease activity).

Laboratory evaluation revealed a haemoglobin of 15.1 g/dL, total leucocyte count of 8,700 cells/cu.mm, normal differential count, erythrocyte sedimentation rate of 45 mm fall at one hour (0-10). All his biochemical parameters were normal except for elevated alkaline phosphatase – 350 IU/L. C-reactive protein was 12 mg/dL (<10), rheumatoid factor was 7.0 IU/mL, anti-cyclic citrullinated peptide antibody was 4.2 IU/mL (<5), anti-nuclear antibody was 4.8 U (<20), anti-dsDNA was 32.2 IU/mL (<35), HLA-B27 negative and anti-neutrophilcytoplasmic autoantibodies were negative. Skeletal survey revealed multiple mixed lytic and sclerotic lesions in vertebral bodies and posterior elements from 8th thoracic to 5th lumbar vertebra [Figure 1] and expansile

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lytic lesions were seen in 8th, 11th and 12th rib. Magnetic resonant image (MRI) of the spine showed destructive changes in the vertebral bodies and posterior elements from 8th dorsal vertebrae to 5th lumbar vertebrae. Bone scan showed increased uptake in the areas described above [Figure 2]. His bone mineral density (BMD) by dual energy X-ray absorptiometry (DXA) was normal (T-score-0.9 and Z-score-0.4 at lumbar spine). Serum electrophoresis didn't reveal M band and bone marrow aspiration was cellular and reactive. Oncological markers such as serum prostate specific agent (PSA), carcino-embryogenic agent (CEA) and carbohydrate antigen (CA)-19.9 were within normal limits. An open biopsy from left 8th rib revealed the diagnosis of fibrous dysplasia in 2005. Severity of fibrous dysplasia as interpreted by bone scan[1] was 0.66. There was no evidence of café-au-lait spots and his endocrinal evaluation including thyroid adrenal and pituitary function tests were normal.

He was started on intravenous pamidronate, along with calcium and vitamin D supplements. Six months later he noted weight loss of 12 kgs in spite of preserved appetite. He also had noted palpitations, heat intolerance and tremulousness. There was no goitre, ophthalmopathy or dermopathy. His thyroid function test was consistent with thyrotoxicosis [Tri-iodothyronine (T3) - 2.9 mg/dL (0.9-2.6), thyroxin (T4) -20.0 μg/dL (5.5-13.0) and thyroid stimulating hormone (TSH) - 0.04 μIU/mL]. Thyroid antibodies were negative. ^{99m}Technicium scan showed homogenous increased uptake in the thyroid with suppressed salivary uptake suggestive of hyperthyroid status. He was also detected to have diabetes mellitus (DM) by oral glucose tolerance test (OGTT, fasting 142 mg/dL and two hour 219 mg/dL). There was also evidence of transaminitis (SGOT/SGPT – 134/175) which persisted even after stopping methotrexate and test was positive for anti-HCV antibodies; however HCV viral count was zero. Modified KnodellIshak score showed grade 1/18 and stage 1/6 on liver biopsy. In view of association of hyperthyroidism with fibrous dysplasia and underlying HCV infection he was radioablated with 10 mCi of radioiodine and in addition advised diabetic diet. He developed post ablative hypothyroidism three months later and has been on thyroxine replacement since then. Once euthyroidism was achieved, result of repeat OGTT was suggestive of DM and started on metformin. Presently he is receiving zoledronic acid 4 mg twice yearly, methotrexate 7.5 mg weekly, thyroxine, metformin, calcium and vitamin D supplements. His annual bone scans have showed stable disease. At his latest review ^{18}F-FDG PET was performed for the first time which showed both active and healed osseous lesions [Figure 4]. He has not sustained any fracture till date.

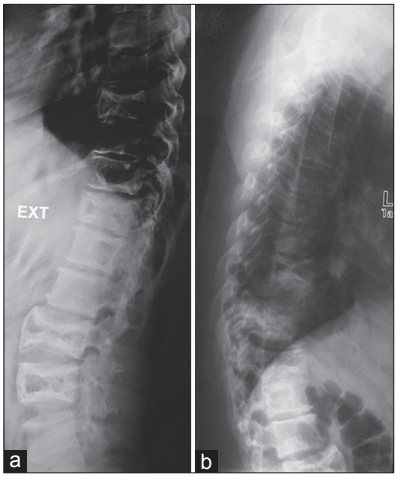

Figure 1: Radiograph of case one showing multiple osteolytic and expansile lesions in the spine

Case 2

A 27 year old man became symptomatic following repeated falls on a slippery surface with chronic low backache and neck pain for one year. He also noticed bone pains and the severity progressed over six months to an extent that he had gross limitations of his daily activities, had to be bed bound and developed chronic insomnia. He didn't have arthralgia, deformity of the joints/bones or systemic symptoms. He weighed 69 kgs for a height of 170 cm (he reported his height was 173 cm at the age of 18 years). He had tenderness at lower thoracic and lumbar spine. He had no deformity. His general and systemic examination was normal.

Investigations revealed a haemoglobin of 14.2 g/dL (14 ± 2.5), total leucocyte count 7,500/cu.mm (4,000-11,000), platelets 1,87,000/cu.mm (1,50,000-4,50,000), erythrocyte sedimentation rate 5mm fall at first hour (0-10), fasting blood glucose 97mg/dL (70-100), blood urea nitrogen 12 mg/dL (7-19), creatinine 0.8mg/dL (0.5-1.6), sodium 140 mEq/L (135-149), potassium 4.1mEq/L (3.5-5.0), bilirubin 0.9mg/dL (<1), aspartate trasaminase 85 U/L (<40), alanine trasaminase 78 U/L (<40), alkaline phosphatase 354 U/L (<250), protein 7.9 g/dL, albumin 4.2 g/dL,

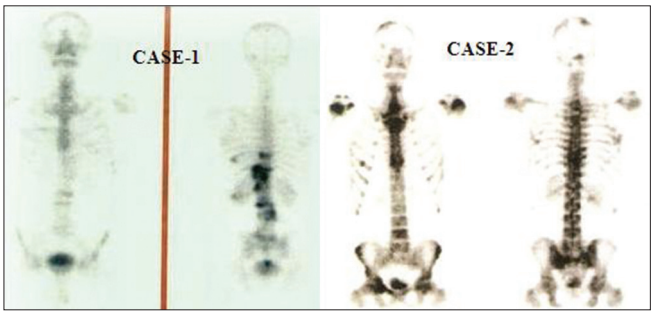

Figure 2: Anterior and posterior view of bone scan. In case one increased uptake is seen only in lower thoracic and lumbar spine, whereas in case two spine, humerus, sternum, rib and pelvic bone is involved

calcium 8.6 mg/dL (8.5-10.5), phosphorous 3.8 mg/dL (2.5-4.5), lactate dehydrogenase 811 U/L (230-460) and uric acid 7.2 mg/dL (2-6). CRP was 6mg/L (<6), HLA-B 27 was negative. X-ray of spine showed multiple lytic lesions with collapse of 8th dorsal vertebra and ill-defined radiolucencies in both pubic rami and ischium [Figure 5]. Computed tomography of spine showed extensive involvement of spine, sternum, pelvis, heads of humerus and femur [Figure 6]. MRI spine showed extensive marrow infiltration of spine and pelvic bone and collapse of C3, D1 and D8 vertebrae [Figure 7]. He was evaluated for multiple myeloma with serum electrophoresis which was negative for "M" band, light chain assay was negative and bone marrow aspiration was dry and bone marrow biopsy showed extensive fibrosis (?secondary). Bone scan showed increased uptake in involved areas [Figure 2]. FDG-PET confirmed increased metabolic activity in above area and was suggestive of malignancy with highest SUV of 7.6 in sacrum [Figure 4]. Parathormone (PTH) was 13 pg/mL (10-65), 25(OH) vitamin-D was 65 ng/mL (30-150) and endocrinal evaluations (thyroid, adrenal and pituitary function tests) were normal. Oncological markers including PSA, CEA and CA 19.9 were normal. BMD z-score at spine, hip and forearm were -2.6, -0.8 and 0.5 respectively. With the suspicion of lymphoma, infective etiology, or secondary a CT guided fine needle aspiration was done; but was inconclusive. To obtain tissue diagnosis an open biopsy of left sacral ala and a repeat bone marrow aspiration and biopsy from matched involved area from bone scan and CT scan at iliac spine was performed. Histopathology of bone biopsy was consistent with fibrous dysplasia [Figure 3]. Severity of fibrous dysplasia as interpreted by bone scan[1] was 11%. He was started on intravenous zoledronic acid 4 mg quarterly, calcium and vitamin D supplements. Opioid analgesics were required to control his bone pain.

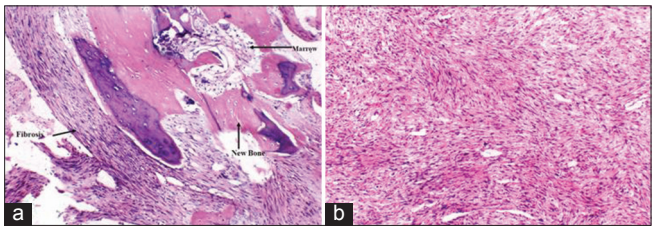

Figure 3: H and E, x40 (Case two). Spindle cell proliferation with immature new bone formation (a) and extensive fibrous tissue proliferation forming cartwheel pattern (b)

Discussion

The term polyostotic fibrous dysplasia (PFD) was introduced by Lichenstein in 1938.[2] A year earlier McCune and Albright had described association of skeletal lesion similar to FD in association with café-au-lait spots and endocrinopathy which later was termed McCune-Albright syndrome (MAS).[3,4] About five decades later MAS and FD were shown to be due to activating somatic mutations $G_s\alpha$ (mosaic type).[5] The presentation depends on the timing of mutation during the development of the embryo and the germ cell layer involved. There is involvement of multiple tissues that are known to originate from the three embryonic germ layers - ectoderm (e.g., skin, craniofacial bone), endoderm (e.g., thyroid), and mesoderm (e.g., axial and appendicular bone).[2] The mutation in ectoderm leads to café-au-lait spots with craniofacial FD, involvement of endoderm results in endocrinopathies and mesoderm

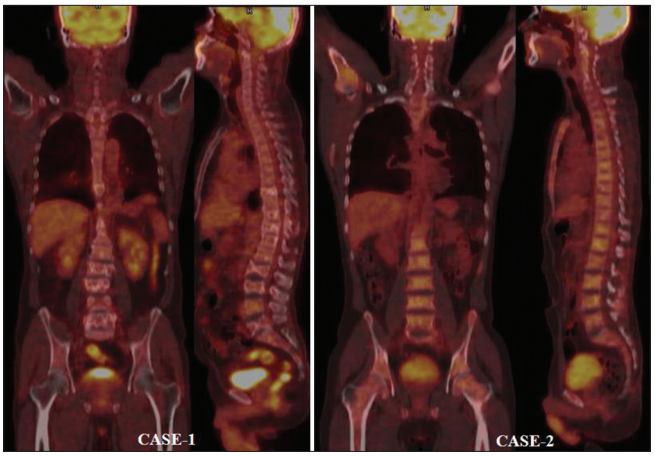

Figure 4: PET-Scan showing increased uptake in spine (both cases), head of humerus, pelvis and head of femur (Case two)

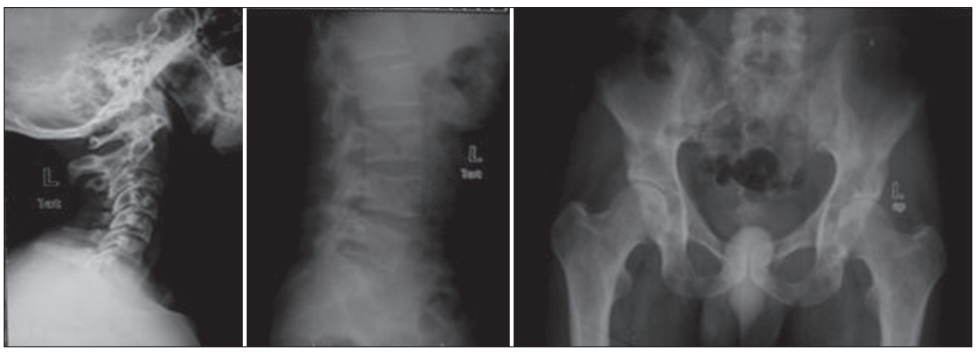

Figure 5: Radiograph showing multiple osteolytic lesions in the cervical, thoracic and lumbar spine and pelvis in case two

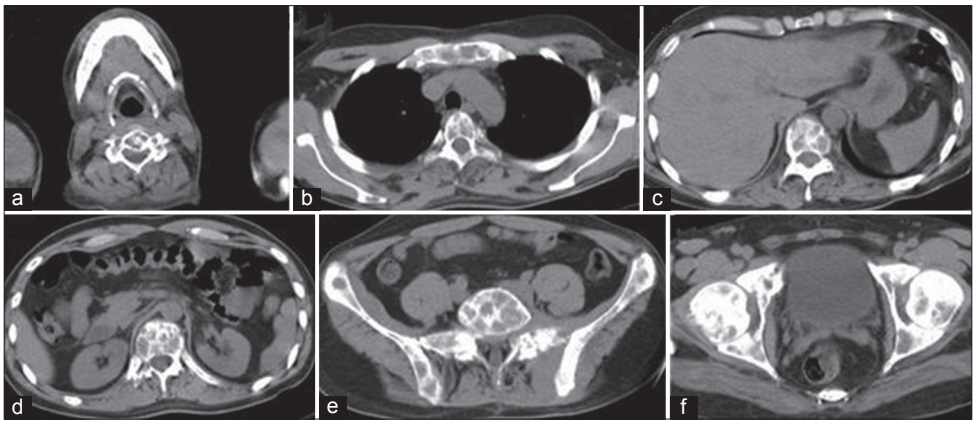

Figure 6: CT scan of spine of case two showing multiple osteolytic lesions in cervical. (a) upper thoracic and sternum (b) Lower thoracic (c) Lumbar (d) Sacrum and pelvis (e) and head of femur (f)

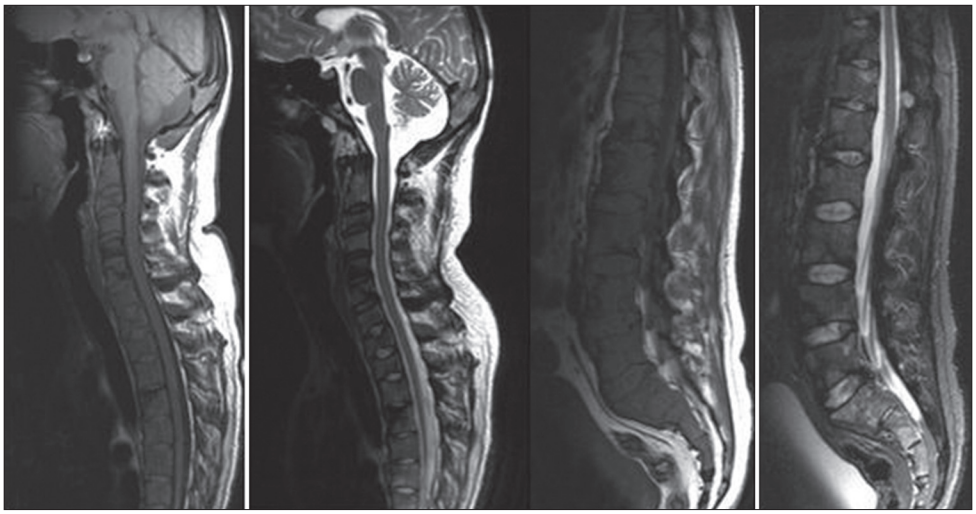

Figure 7: MRI spine showed extensive marrow infiltration of spine and pelvic bone and collapse of C3, D1 and D8 vertebrae in case two

leads to axial and appendicular FD. In our first case there was involvement of mesoderm and endoderm whereas in second case in all probability only mesoderm was involved.

Most patients with FD are diagnosed in childhood as they either present with endocrinopathy or fractures. In two largest studies isolated PFD was seen in only 5-13% of 104 and 113 cases respectively.[1,6] Leet *et al*.[7], found isolated FD in 23% of their 35 patients which included both adults and children. Adults are diagnosed to have FD when they are being evaluated for an unrelated illness or when they present with fracture.[7] A study from India reported that the most of their patients with FD were adult (68%) and 76% of the adults had PFD.[8]

Here we have reported two cases of adult FD and both of them had predominant spinal involvement. The distribution of skeletal lesion is classically described to involve craniofacial bones, ribs and extremities. Studies in the 1960's reported that spine was rarely involved in PFD – five of the 37 patients.[9] A recent study however reported involvement of spine in 39 of the 62 patients studied.[10] Dorso-lumbar spine was the most common location followed by the sacrum and cervical spine. In case-1, it was during evaluation of arthritis that he was diagnosed to have skeletal lesions representative of FD which was confirmed by biopsy. Spine involvement was seen in nine vertebral segments, limited to lower thoracic and lumbar regions. In addition he also had few lesions in ribs and skull. Interestingly he also had seronegative arthritis. Relation between arthritis and PFD is not known. A case has been reported with concomitant rheumatoid arthritis and PFD.[11] In case-2 all four spinal segments were involved. Increase tracer uptake was seen in both anterior and posterior images of bone sac indicating extensive involvement of the spine. Leet *et al*.[10], reported involvement of three or more spinal segments in 23 patients with spinal PFD. In addition he also had compression fracture of multiple vertebrae. Though fracture is a common complication of FD of extremities, it is rarely noted in

spine.[12,13] The fracture in our patient could be due to the multiple falls he sustained.

Case one developed hyperthyroidism few months after diagnosis of PFD. The most common endocrine dysfunction in MAS is peripheral precocious puberty.[14] The next common endocrinopathy is hyperthyroidism.[15] Hyperthyroidism is described as non-autoimmune in origin. It can be subclinical, overt or rarely present with thyrotoxic crisis.[16,17] In a study from India six of the 17 adults had endocrinopathy, the most common being acromegaly in five and hyperthyroidism in one.[8] These patients require definitive form of therapy for hyperthyroidism as the disease invariably recurs after anti-thyroid drugs are stopped. Our patient was treated with radioiodine therapy successfully.

Case two didn't have any evidence of endocrinopathy presently. However, he had persistent transaminitis. A detailed evaluation including virological and autoimmune work-up couldn't point to a cause of this abnormality. Liver biopsy was not done. Many non-endocrine organs can be involved in MAS including liver.[5,6] Hepatic cholestasis is the most common involvement[18] but our case had no abnormalities in serum bilirubin levels. Persistent transaminitis of unexplained nature has been reported in two cases of FD.[5,19] Our case also had raised serum LDH and uric acid; which can be explained by secondary myelofibrosis with rapid cell turnover of cells at un-involved site or extramedullary areas.

Bone scintigraphy has a significant utility in FD.[20] It aids in diagnosis, extent of skeletal involvement, prognostication and monitoring of therapy. Bone scan shows increased tracer uptake in the skeletal lesion either due to increased vascularity of these lesions or due to pathologic fractures. Bone scintigraphy can also pick up lesions which are not picked up by other imaging modalities and thus help in gauging the extent of disease. In case two, scintigraphy picked up lesions which were not picked up by x-ray or MRI. However, CT scan was able to pick up the skeletal lesions similar to scintigraphy. A scoring system for disease burden has been developed using scintigraphy.[1] It involves the quantification of lesions in 11 different skeletal areas. A score of more than 30 predicts need for assisted ambulation in adulthood. Our cases (one and two) had a score of 0.66 and 12 respectively, which indicates a favorable outcome with respect to ambulation.

Other imaging modalities like CT scan and MRI though not necessary for diagnosis, usually done to exclude other conditions during evaluation and can be used to study the extent of the disease.[21] CT scan shows classically ground glass lesions with well-defined borders. Presence of lytic lesions, expansile nature, cortical disruption, sclerotic rim, decrease in body height and contour deformity can also be appreciated on CT scan.MRI shows hypointense lesions in T1-weighted sequences and hyperintense in T2-weighted sequences with occasional heterogeneous hyperintense enhancement in post-contrast images.

We were able to characterize the imaging findings on FDG-PET in both of our patients. There have been numerous reports of FD, mimicking skeletal metastases, being diagnosed during work up of underlying malignancy.[21,22] In a recent study of FDG-PET imaging in FD, the average standardized uptake value (SUV) was 3.76 ± 2.40 in early images and 4.51 ± 3.07 in delayed images. A high SUV of 11.42 has been observed in FD, which is usually seen in malignancy. It has been postulated that the increased SUV could be due to metabolic turnover in the proliferating fibroblasts in the lesions. In case one we were unable to have a baseline FDG-PET images as facilities became available recently at our centre. The FDG-PET images taken at the latest follow up had showed both healed and active lesions, but scintigraphy had showed increased uptake in the corresponding lesion. The dichotomy between scintigraphy and FDG-PET has not been reported. If this is confirmed in subsequent studies FDG-PET could be superior to follow the treatment response of FD. FDG-PET in case two also showed increased SUV mimicking skeletal metastases.

The standard treatment of FD is bisphosphonate therapy.[23] Bisphosphonate suppress osteoclast which are the target of excess interleukin-6 (known to activate osteoclasts) secreted by fibrous cells and postulated as possible mechanism of lytic lesions in FD.[24] Case one was initiated on intravenous pamidronate and is subsequently receiving zoledronic acid twice yearly. He has stable disease and in fact the latest bone scintigraphy shows regression in the some lesions.

There is gradual improvement in bone lesions over the time in FD. The basic pathophysiology in FD is abnormal differentiation of osteoblast.[1,25] The skeletal lesion shows mosaic pattern i.e., both normal and abnormal cells are present. The abnormal cells over a period of time undergo apoptosis and there is proliferation of normal cells. This phenomenon can be clinically appreciated by the fact that the incidence of fractures decreases as the patient age increases.[1] We postulate that therapy with teriparatide could be a novel option. Teriparatide is known for its anabolic action on osteoblasts. Hence, teriparatide may accelerate apoptosis of abnormal cells and stimulate normal cells which will enhance normal bone formation. Another potential drug in treatment of FD is tocilizumab,

an anti-IL6 receptor human monoclonal antibody;[26] as IL-6 has been implicated in pathogenesis of FD. Successful vertebroplasty has been performed in cases of FD with severe kyphosis and neurological involvement due to compression by expanding FD lesions or fracture.[12,13]

The main limitation of this case report is absence of genetic analysis, which could not be performed due to lack of in house facility and financial constraints.

Conclusions

Polyostotic fibrous dysplasia is a rare disease; which can present in adults when investigated for unrelated cause. It usually leads to many investigations to rule out common etiology of multiple osteolytic lesions like multiple myeloma; myelo- and lympho-proliferative disorders; infections and secondaries from primary malignant disease. Diagnosis is usually clinched on adequately performed bone biopsy. Disease shows gradual improvement with aging and presently bisphosphonates remains cornerstone of treatment. However; being a stem cell disease the cure of disease may lie in mesenchymal stem cell transplantation.[27]

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