Case Report

Sarcomatous transformation (Leiomyosarcoma) in polyostotic fibrous dysplagia

M. K. Garg, Reena Bhardwaj[1], Srishti Gupta[1], Navdeep Mann[1], Sandeep Kharb, Aditi Pandit

Departments of Endocrinology, [1]Pathology, Army Hospital (Research and Referral), Delhi, India

ABSTRACT

Malignant changes in polyostotic fibrous dysplasia are very rare. Most common malignancies reported are osteosarcoma and fibrosarcoma, chondrosarcoma and malignant fibrous histiocytoma. Here, we report a previously diagnosed case of fibrous dysplasia who has developed leiomyosarcoma; diagnosis of which was delayed for about one year despite repeated fine needle aspiration and open biopsy.

Key words: Fibrous dysplasia, leiomyosarcoma, metastasis

Introduction

Fibrous dysplasia is a rare 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] It can present as a mono-ostotic or polyostotic variant and when associated with endocrine dysfunction and/or café-au-lait spots, it is termed as McCune-Albright syndrome.[2] Malignant changes in fibrous dysplasia is very rare and were first reported by Coley and Stewart in 1945,[3] and Schwartz and Alpert collected and analyzed 28 cases including their own two cases till 1964,[4] and 100 cases were reviewed till 1997 by Ozaki *et al*.[5] This indicates that about two new cases are reported every year in the medical literature. The largest series of development of sarcoma in fibrous dysplasia is published by Mayo clinic consisted of 28 cases among 1122 cases analyzed retrospectively.[6] Here, we report a case of polyostotic fibrous dysplasia, who was under observation and evaluation for one year,[7,8] terminally detected with sarcomatous changes with extensive metastasis.

Access this article online	
Quick Response Code:	Website: www.ijem.in
	DOI: 10.4103/2230-8210.122645

Case Report

We have previously reported detailed history of this case and follow-up in our journal.[7,8] In brief, this 27-year-old male presented with pain in neck and extensive osteolytic lesion in the spine. After extensive evaluation for malignancy on biopsy, he was diagnosed as a case of polyostotic fibrous dysplasia.[7] On follow-up, he developed severe pain and weight loss; and repeat investigation showed progression of lesion with increased CA19.9 levels, hepatic space occupying lesion, and increased standardized uptake value (SUV) on Fluoro-deoxy-glucose positron emmission tomography (18-FDG-PET) in liver and anterior superior iliac spine. However, open biopsy from anterior superior iliac spine did not reveal any malignancies and was consistent with diagnosis of polyostotic fibrous dysplasia. He was on treatment with injection zoledronic acid, vitamin D, and narcotic analgesics.[8]

Patient continued to deteriorate and presented with complaints of jaundice and breathlessness for last 2 weeks in August 2012. Breathlessness was present at rest and progressive in nature. Patient was bed-ridden since last 4-5 days. On examination, he was sick looking and his vitals were normal. He had pallor, icterus, pedal edema, bilateral

Corresponding Author: Prof. M. K. Garg, Department of Endocrinology, Army Hospital (Research and Referral), Delhi Cantt - 10, India.
E-mail: mkgargs@gmail.com

axillary, left supraclavicular and left cervical lymph nodes, and a single, tender, bony swelling of 3.0 × 2.0 cm in size on right chest wall near right nipple. Systemic examination revealed tender hepatomegaly and bilateral basal crepts with occasional rhonchi on right side. On central nervous system examination, he had generalized muscular wasting, mainly of small ones of hands and feet with power of 3/5 in left lower limb and 4/5 in rest all other limbs. Tone was decreased in all muscles. Deep tendon reflexes were absent; left ankle and depressed in right suggestive of lower motor neuron type of weakness. Cardiovascular system examination was within normal limits. His laboratory investigation showed - Hb-7.5 gm/dl, TLC-12300/cumm, platelets- 81000/cumm, total protein-5.4 mg/dl, albumin-1.7 mg/dl/SGOT/SGPT- 86/39 IU/ml, serum alkaline phosphatase-332, GGT- 389, LDH-43, calcium/phosphate-8.0/2.9. On USG abdomen, liver was 17 cm in longitudinal scan with heteroechoeic texture. There was evidence of multiple rounded, nodular, iso- to hypo-echoeic lesions studded in both lobes of liver; largest measuring 2.5 × 3.5 cm in segment II, leading a variegated appearance of the parenchyma with evidence of necrosis within the lesion and bilobar dilatation of intra-hepatic biliary radicles. These lesions showed mild to moderate color flow on color Doppler application. Portal vein was 8.7 mm at confluence, and 9 mm at porta. Patient was treated with broad-spectrum antibiotics in addition to analgesics. Repeat fine needle aspiration cytology of right chest wall lesion was performed, which was suggestive of spindle cell tumor. Patient's condition deteriorated and was kept on inotropic support along with ventilatory support. However, he did not respond and succumb to his illness.

Autopsy was performed. Salient findings on internal gross examination were heavy boggy congested lungs with multiple sub-pleural white patches, enlarged liver with congested spleen. Multiple grey-white nodules were present in liver, spleen, greater omentum of stomach, small and large intestine, left lobe of thyroid, expanded right rib, right and left sacro-iliac joints and L4-L5 [Figure 1]. On histopathological examination, effacement of normal bony architecture by tumor cells arranged in fascicles, intersecting bundles and storiform pattern was observed. These tumor cells were elongated spindle-shaped cells with abundant eosinophilic cytoplasm, cigar-shaped nucleus [Figure 2]. Occasional multinucleated giant cells were noted. Mitosis was present (>10/10 hpf), and pleomorphic areas were noted. On immunohistochemistry, tumor was positive for smooth muscle antigen (SMA) and vimentin and negative for CD-117, S-100, HMB-45, CK, epithelial membrane antigen (EMA), myogenin, desmin, Myo D1, BCl2, CD68, Mic 2, and Ki-67. With these finding, a diagnosis of leiomyosarcoma of bone with metastasis to pancreas, liver, spleen, left kidney, thyroid, small and large intestine, lungs, and heart was made.

Discussion

Malignant transformation of benign bone conditions have been reported in Paget's disease, osteoblastoma, osteochondroma, giant cell tumor, enchondroma, and fibrous dysplasia. Malignant transformation in fibrous dysplasia has been reported at a rate varying from 0.4-2.5%.[4,9] Cole *et al*.,[3] were the first to describe two cases of spindle cell sarcoma in 39 and 42 year old patients who also had histological feature suggestive of fibrous dysplasia. There are only two large series published till date. One from Mayo clinic[5] and other from Cancer Center in New York[10] consisted of 28 and 12 cases, respectively. Others have reported malignant transformation in 1 and 4 cases over 5-20 year of follow-up among 36 cases[11] and 128 case,[12] respectively. To best of our knowledge, this is the first case report of malignant transformation of fibrous dysplasia from India.

Malignant transformation in fibrous dysplasia always occurs in abnormal bone and do not occurs in normal bone.[13] In our cases, we have also observed that malignant changes were evident only in abnormal bone [Figure 2]. The most common mesenchymal malignant transformation is reported to osteosarcoma, followed by fibrosarcoma, chondrosarcoma, and malignant fibrous histiocytoma.[5,12] The positivity for SMA confirmed a smooth muscle origin of malignancy and negativity to S-100, CD-117, HMB-45, and CK ruled out malignant peripheral nerve sheath tumor, extra-gastrointestinal stromal tumor, spindle cell malignant melanoma, and sarcomatoid carcinoma, respectively. Synovial sarcoma was excluded by negative staining for Bcl 2, Mic 2, EMA, and skeletal muscle sarcoma like rhabdomyosarcoma by absence of positivity for myogenin, desmin, and Myo D1. SMA positivity has high specificity for leiomyosarcoma. Other tumors reported in fibrous dysplasia are admantinoma,[14] chondroblastic osteosarcoma,[15] papillary thyroid carcinoma,[16] and benign intramuscular myxoma.[17] Till date, leiomyosarcomatous changes have not been reported in the literature as seen in our case. Most of the cases of malignancy and fibrous dysplasia were diagnosed on biopsy simultaneously,[4] but many cases have been reported to develop malignancy in a previously diagnosed cases of fibrous dysplasia.[10,11]

The most common sites of malignant transformation related to the common sites of fibrous dysplasia in decreasing order-craniofacial bones, proximal femur, humerus, and pelvis.[5,6] In our case, tumor most likely developed at rib or ileum, which has shown very high

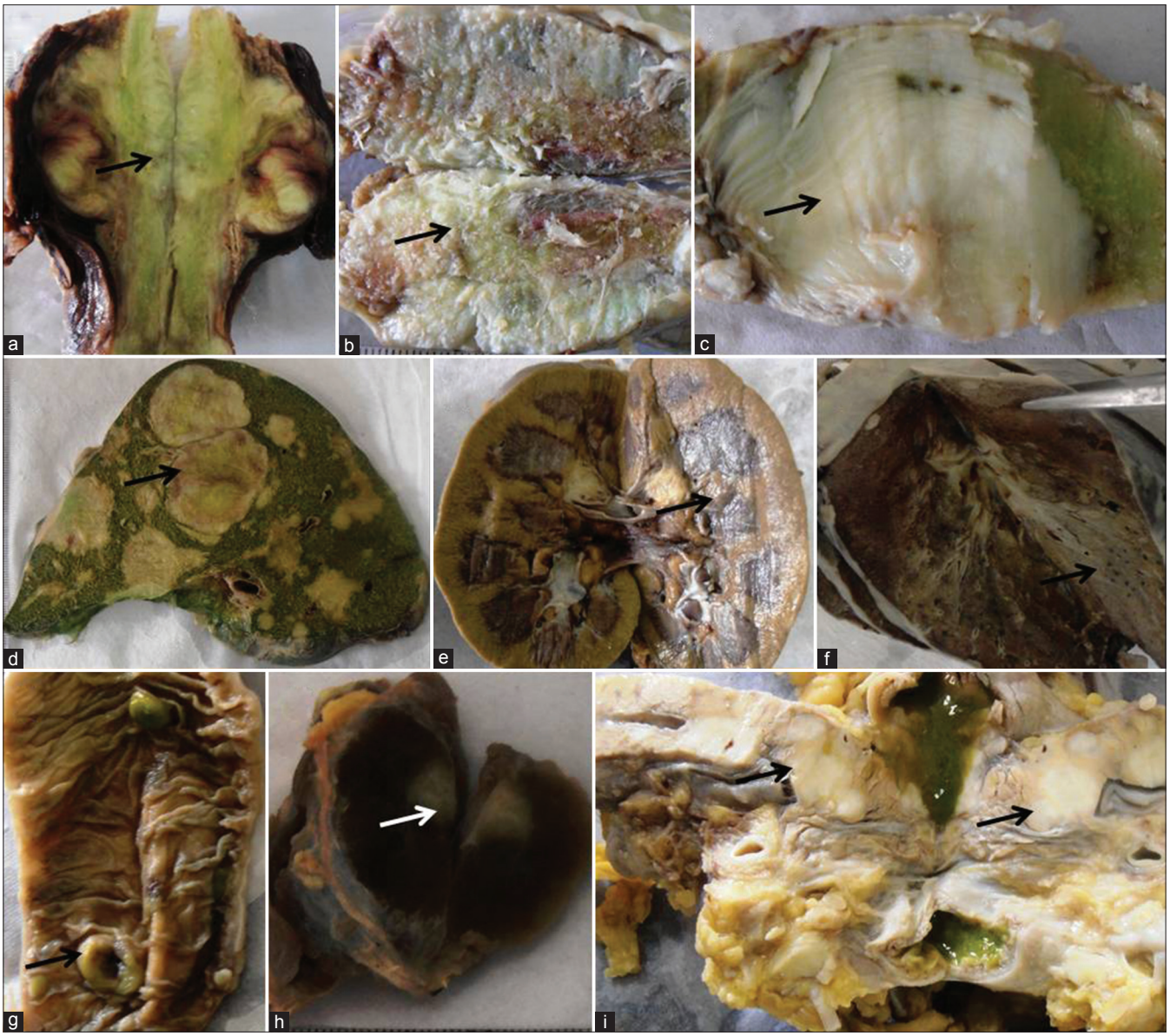

Figure 1: Gross examination showing grey-white tumor in rib (a) Sternum (b) Sacrum (c) Cut surface of liver (d) Kidney (e) Lung (f) Intestine (g) Thyroid (h) and pancreas (i)

SUV value on ^{18}FDG-PET, but was missed in spite of open biopsy from ileum.[8] Pain, which is rapidly becoming worse over a short period unrelated to trauma, is the most alarming symptom.[18] Our patient had persistent intolerable pain for past one year requiring narcotic analgesics. Radiological features which suggest sarcomatous transformation on computerized tomography are moth-eaten or cystic areas of osteolysis, cortical destruction, and gradual formation of a soft tissue mass.[19] Our patient had soft tissue mass related to rib, fine needle aspiration of this lesion gave clue to presence of sarcomatous changes during present admission. Patient's clinical findings were consistent with rapidly expanding and metastasizing aggressive tumor with neurological involvement of lumbar vertebra with metastasis and fibrous dysplasia. Prognosis of secondary sarcomatous changes in fibrous dysplasia is usually poor.[4-6]

Mutation in $G_s\alpha$ protein leads to constitutive activation adenylate cyclase and overproduction of cyclic adenosine monophosphate with an increase in intracellular interleukin 6, c-fos, c-myc proto-oncogene expression, which is related to development of osteosarcomas. Overexpression of p53 protein has been reported in fibrous dysplasia with malignant transformation.[20] Other has demonstrated trisomies of chromosomes 5 and 7 in the fibrous dysplasia and osteosarcoma by fluorescence *in situ* hybridization and comparative genomic hybridization.[21] Early genetic analysis may give clue to the malignant transformation of fibrous dysplasia, as it may be

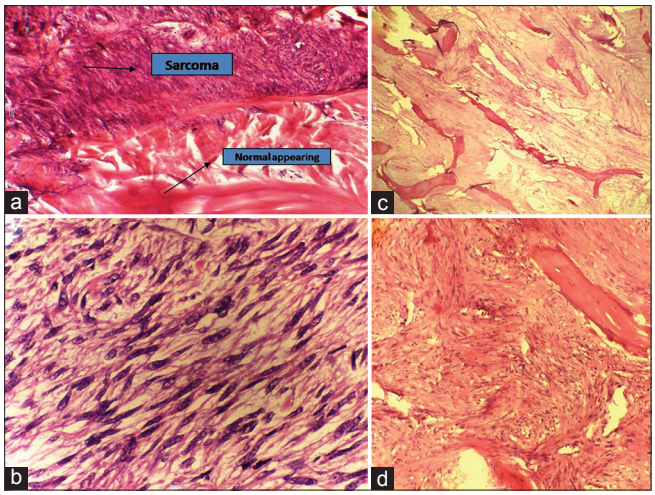

Figure 2: (a) Normal-appearing bone with sarcomatous transformation (H and E, x4). (b) High power view showing spindle-shaped cells with cigar-shaped nuclei (H and E, x40). (c) Benign appearing – manubrium sternal lesion, Chinese letter pattern (H and E, x4). (d) Areas with increased cellularity in manubrium sterni (H and E, x4)

difficult to diagnose low-grade osteosarcoma from fibrous dysplasia on histology.[22]

References

1. Weinstein LS, Shenker A, Gejman PV, Merino MJ, Friedman E, Spiegel AM. Activating mutations of the stimulatory G protein in the McCune-Albright syndrome. N Engl J Med 1991;325:1688-95.
2. Collins MT. Spectrum and natural history of fibrous dysplasia of bone. J Bone Miner Res 2006;21(Suppl 2):99-104.
3. Coley BL, Stewart FW. Bone sarcoma in polyostotic fibrous dysplasia. Ann Surg 1945;121:872-81.
4. Schwartz DT, Alpert M. The malignant transformation of fibrous dysplasia. Am J Med Sci 1964:247:1-20.
5. Ozaki T, Lindner N, Blasius S. Dedifferentiated chondrosarcoma in Albright syndrome. A case report and review of the literature. J Bone Joint Surg Am 1997;79:1545-51.
6. Ruggieri P, Sim FH, Bond JR, Unni KK. Malignancies in fibrous dysplasia. Cancer 1994;73:1411-24.
7. Gundgurthi A, Garg MK, Bhardwaj R, Kharb S, Pandit A, Brar KS, *et al.* Spinal polyostotic fibrous dysplasia in two adults: Does only biopsy unravel the mystery? Indian J Endocrinol Metab 2013;17:178-83.
8. Pandit A, Kharb S, Garg MK. RaisedCA19.9 and hepatic space occupying lesion after teriparatide therapy in a case of polyostotic fibrous dysplasia (PFD). Indian J Endocrinol Metab 2013;17:947-9.
9. Horvai A, Unni KK. Premalignant conditions of bone. J Orthop Sci 2006;11:412-23.
10. Huvos AG, Higinbotham NL, Miller TR. Bone sarcomas arising infibrous dysplasia. J Bone Joint Surg Am 1972;54:1047-56.
11. Saglik Y, Atalar H, Yildiz Y, Basarir K, Erekul S. Management of fibrous dysplasia. A report on 36 cases. Acta Orthop Belg 2007;73:96-101.
12. Hoshi M, Matsumoto S, Manabe J, Tanizawa T, Shigemitsu T, Izawa N, *et al.* Malignant change secondary to fibrous dysplasia. Int J Clin Oncol 2006;11:229-35.
13. Singer FR. Fibrous dysplasia of bone: The bone lesion unmasked. Am J Pathol 1997;151:1511-5.
14. Nouri H, Jaafoura H, Bouaziz M, Ouertatani M, Abid L, Meherzi MH, *et al.* Dedifferentiated adamantinoma associated with fibrous dysplasia. Orthop Traumatol Surg Res 2011;97:770-5.
15. Kaushik S, Smoker WR, Frable WJ. Malignant transformation of fibrous dysplasia into chondroblastic osteosarcoma. Skeletal Radiol 2002;31:103-6.
16. Collins MT, Sarlis NJ, Merino MJ, Monroe J, Crawford SE, Krakoff JA, *et al.* Thyroid carcinoma in the McCune-Albright syndrome: Contributory role of activating Gs alpha mutations. J Clin Endocrinol Metab 2003;88:4413-7.
17. Prayson MA, Leeson MC. Soft-tissue myxomas and fibrous dysplasia of bone. A case report and review of the literature. Clin Orthop Relat Res 1993;291:222-8.
18. Doganavsargil B, Argin M, Kececi B, Sezak M, Sanli UA, Oztop F. Secondary osteosarcoma arising in fibrous dysplasia, case report. Arch Orthop Trauma Surg 2009;129:439-44.
19. Reis C, Genden EM, Bederson JB, Som PM. A rare spontaneous osteosarcoma of the calvarium in a patient with long-standing fibrous dysplasia: CT and MR findings. Br J Radiol 2008;81:e31-4.
20. Tang J, Zhao HY, Zheng L, Zhang HZ, Jiang ZM. [Abnormal expression of c-myc, p53, p16 protein and GNAS1 gene mutation in fibrous dysplasia]. Zhonghua Bing Li Xue Za Zhi 2009;38:292-7.
21. Jhala DN, Eltoum I, Carroll AJ, Lopez-Ben R, Lopez-Terrada D, Rao PH, *et al.* Osteosarcoma in a patient with McCune-Albright syndrome and Mazabraud's syndrome: A case report emphasizing the cytological and cytogenetic findings. Hum Pathol 2003;34:1354-7.
22. Bertoni F, Fernando Arias L, Alberghini M, Bacchini P. Fibrous dysplasia with degenerative atypia: A benign lesion potentially mistaken for sarcoma. Arch Pathol Lab Med 2004;128:794-6.

Cite this article as: Garg MK, Bhardwaj R, Gupta S, Mann N, Kharb S, Pandit A. Sarcomatous transformation (Leiomyosarcoma) in polyostotic fibrous dysplagia. Indian J Endocr Metab 2013;17:1120-3.

Source of Support: Nil, **Conflict of Interest:** None declared.