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Bone infarct transformation into undifferentiated pleomorphic sarcoma in sickle cell disease: A case report

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ABSTRACT

INTRODUCTION: Avascular necrosis of the bone is a very common finding in sickle cell disease (SCD). The malignant transformation of a pre-existing bone infarct is extremely rare, only few cases has been reported related to different etiologies one of which is SCD.

PRESENTATION OF CASE: 40 years old male, known to have SCD, he presented as a case of avascular necrosis of the left proximal femur. Upon further investigations the lesion has transformed into undifferentiated pleomorphic sarcoma also known as Malignant Fibrous Histiocytoma (MFH).

DISCUSSION: The exact mechanism of the malignant transformation of bone infarcts is not fully understood and yet to be investigated. Few cases were reported in literature of similar malignant transformation of a pre-existing bone infarct and only one was linked to SCD.

CONCLUSION: In reporting this case we hope that further cases worldwide will be reported. A high index of suspicion should be present when encountering bone infarct lesion with an unusual course.

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1. Introduction

Osteonecrosis is a common finding in sickle cell disease (SCD). This is mostly related to vaso-occlusion and sickling of red blood cells causing bone ischemia. It is estimated to affect 10% of sickle cell disease patients [1,2]. The process may appear at any part of the skeleton and long bones. It is agreed that when they affect the epiphysis, then it is called “avascular necrosis”, whereas in the metaphysis and diaphysis, it’s commonly called “bone infarct” [3].

Although rare, bone infarct associated sarcoma (BIAS) has been reported in the literature [4–9]. In a sickle cell anemia patient, this transformation is much less likely. In this report, we present a known case of sickle cell disease, with a known primary proximal femur bone infarct, that has transformed into undifferentiated pleomorphic sarcoma.

The patient was informed that data concerning this case would be submitted for publication, and he agreed. This case was reported in accordance with the SCARE Guidelines [10].

2. Case report

A 40 years old male, known to have sickle cell anemia, was admitted to King Faisal Specialist Hospital and Research Center with a left proximal femur impending pathological fracture, on November 2019. Early on October 2016, he was evaluated for right hip pain and diagnosed with avascular necrosis (AVN) of right hip (Fig. 1).

Surgical history, family history, and psychosocial history were unremarkable. So, the patient was offered total hip replacement surgery, but he preferred to go for conservative management. During his follow up MRI with contrast on January 2018 indicated serpiginous bone infarcts involving the right proximal femoral shaft as well as left femoral head and intertrochanteric region demonstrating high T2 signal intensity and low T1 signal intensity (Fig. 2).

The patient remained on regular follow up with a stable condition until he presented on November 2019 with increasing pain in the left thigh and decreased in the level of activity, there was no palpable masses alongside a left hip painful range of motion with intact distal neurovascular status. X-ray showed osteolytic lesion, involving the left femoral sub-trochanteric area and the lateral cortex, with a picture of an impending fracture (Fig. 3).

Further skeletal survey showed multiple scattered bone infarcts, mainly at the diaphysis of both lower extremities, as well as, bilateral shoulder and hip joints AVN. MRI of the left proximal femur at that time, showed a background of bone osteonecrosis superimposed by an aggressive intramedullary lesion involving the left

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Fig. 1. AP pelvis x rays from 9/11/2017 demonstrating advanced right-sided femoral head AVN with associated deformity and secondary osteoarthritic changes. Mild sclerosis of the left femoral head suggestive of early AVN.

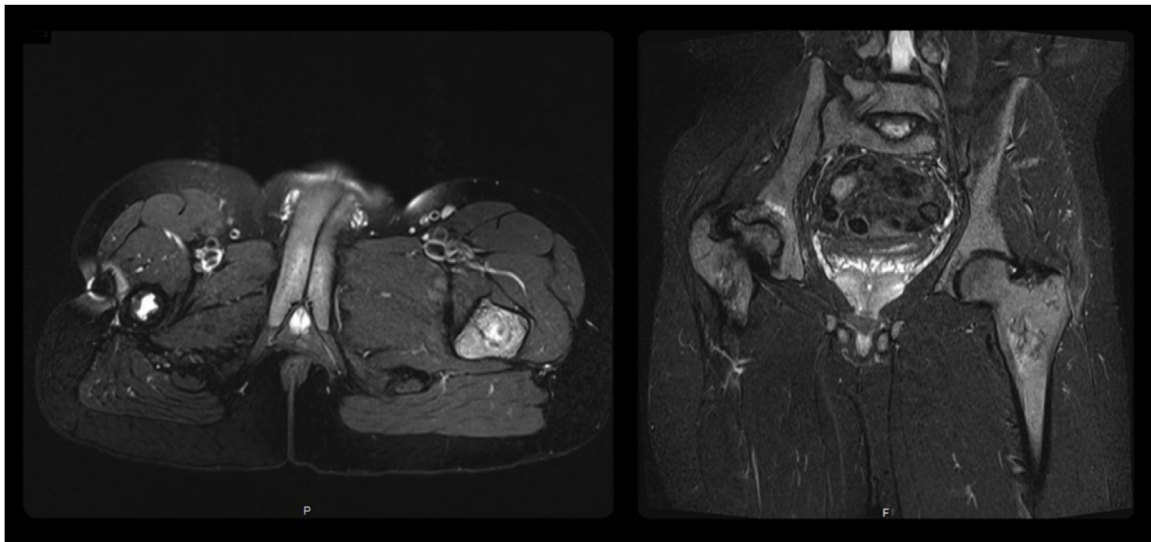


Fig. 2. MRI obtained 22/01/2018 shows serpiginous bone infarctions involving the right proximal femur as well as left femoral head and intertrochanteric region.

intertrochanteric area with cortical destruction. These imaging features highly indicate malignant transformation of the osteonecrosis (Fig. 4).

Systemic staging in the form of CT chest with contrast was free of any metastatic lesion and bone scan showed radiotracer uptake at the left intertrochanteric region consistent with the aggressive lesion. Radio Tracer uptake was also observed at the left distal femur, left proximal tibia and right proximal tibia, all of which represent bone infarcts (Fig. 5).

Open biopsy of the left proximal femur lesion displayed malignant spindle/epithelioid neoplasm consistent with high-grade sarcoma, undifferentiated pleomorphic sarcoma (Fig. 6). Laboratory investigations were also consistent with patients' condition of SCD. After adequate preparation, the patient was taken for resection of the proximal femur and reconstruction with mega-prosthesis (Fig. 7). The surgery was done by the senior authors (MS and RP). Histopathology analysis of the specimen showed high-grade pleomorphic sarcoma consistent with malignant fibrous histiocytoma of bone, all margins were free of tumor.

Post-intervention considerations included referring the patient to medical oncology department where adjuvant chemotherapy was started. He is still under chemotherapy treatment up to the time of this report. His overall health status is fair, started weight bearing without any complications related to surgery, and no local recurrence up to date. CT chest in follow up on January 2020, showed no evidence of metastatic disease.

The patient was satisfied about his general medical condition and surgical treatment that he received. The patient is being followed every 3 months with proper imaging.

3. Discussion

Bone infarct, also known as AVN of the bone, are commonly seen in orthopedics surgery practice and mostly involving the hips and the knees [4]. Development of bone infarct might be idiopathic and also has been linked to several medical and environmental conditions including sickle cell disease, sickle cell trait, Gaucher disease, Cushing disease, pancreatitis, collagen diseases, pregnancy, steroid



Fig. 3. AP pelvis x rays obtained 01/11/2019 showing no significant interval change in bilateral avascular necrosis with the finding of new osteolytic lesion involving the left femoral subtrochanteric region with involvement of the lateral cortex.

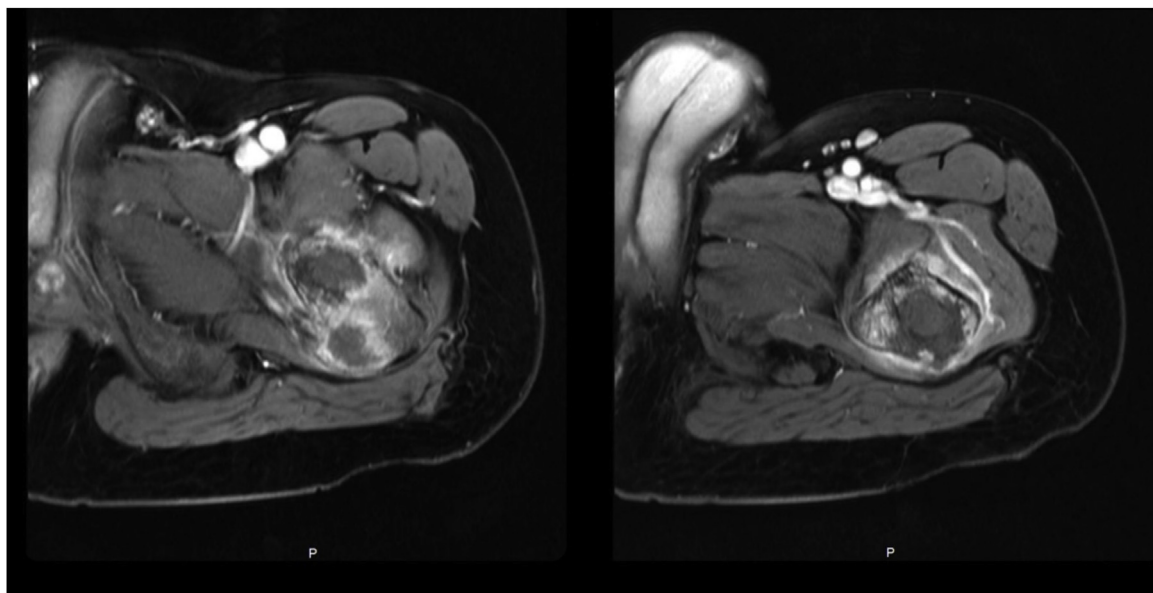


Fig. 4. MRI pelvis obtained 05/11/2019 demonstrated. Background of bone osteonecrosis superimposed by an aggressive intramedullary lesion involving the left intertrochanteric region with cortical destruction.

therapy, radiation exposure, diving and caisson disease, high room pressure exposure, mine working, and alcohol abuse [5].

Bone infarct starts as an acute process of bone ischemia. In sickle cell disease, it is linked to vaso-occlusive crises and sequestration of red blood cells in the bone marrow causing pain. This acute inflammatory process will eventually develop tissue ischemia [11].

The transformation of the bone infarct in this reported case of a sickle disease patient, into a high-grade sarcoma, is very rare. To the best of our knowledge, only one other case of a patient with known sickle cell disease and a bone infarct transformation to bone sarcoma, was reported in the literature [6].

Sarcomas arising from a subsequent existing bone infarct, are extremely uncommon. It was first documented by Furey et al. reporting a fibrosarcoma in 1960 [8]. Since that time,

few infarct-associated sarcomas have been reported, with diverse histopathological types including malignant fibrous histiocytoma, osteosarcoma, angiosarcoma, fibrous sarcoma and epithelioid hemangioendothelioma. Secondary sarcoma originating from a pre-existing bone infarct are usually found during the sixth decade of life, mostly men, and it has been reported that 60% of the cases from the knee and most of them are MFH [4]. Over the decades, it has been proven that sarcomas can arise from infarcts of the long bone, the incidence of which has been reported to be 1% of all diagnosed bone sarcomas [12].

In relation to haemoglobinopathies, the majority of bone infarct lesions transformations into sarcoma reported are linked to sickle cell trait (SCT). Sickle cell trait patients has one sickle beta globin

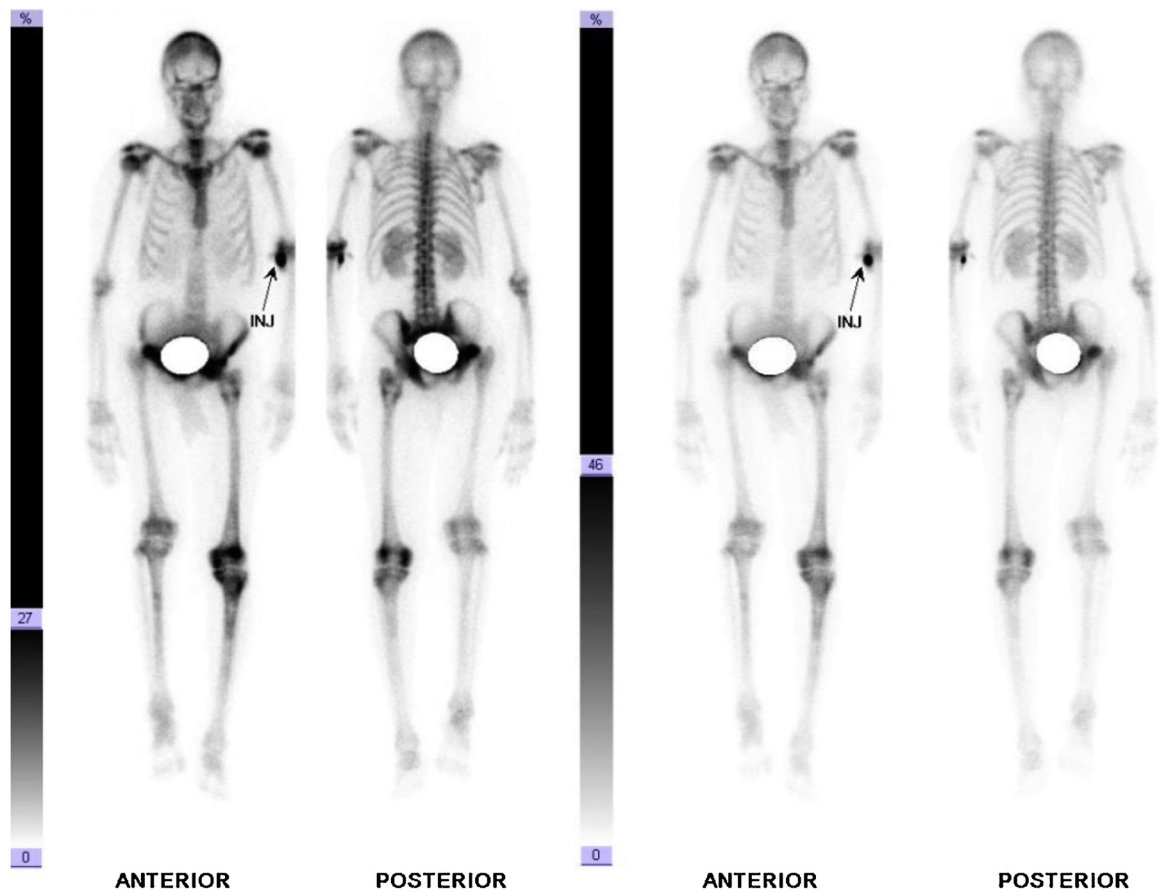


Fig. 5. Bone scan showing.

- 1- Heterogeneous radiotracer uptake seen in the distal femur and proximal left and right tibia consistent with osteonecrosis.
- 2- Heterogeneous radiotracer uptake seen in the left intertrochanteric region consistent with patient known aggressive lesion in the prior MRI.



Fig. 6. Intra-operative image of the resected tumor in the left proximal femur.

gene and one normal gene, making it a heterozygous condition, while sickle cell disease is a homozygous condition with two sickle beta globin genes. Patients with SCT are less symptomatic than SCD

patients. Bone infarct are more common in sickle cell disease than in sickle cell trait [13,7].

In reviewing the history of related studies, we have found four cases of sickle cell trait with bone infarct associated sarcoma, and one case of sickle cell disease indicating that bone infarct associated sarcoma are more common in SCT than SCD. All of the five cases occurred in males. Doung [7] related this gender predominance to working conditions including dysbaric exposures. In our case the patient was never exposed to pressure related environment.

Sickle cell disease and trait are seen more in black race, all the five cases mentioned above also had this in common. Our reported case is of a dark-skinned man and not considered of a black race background. The age of diagnosis had ranged from 20 to 69 years old. Bone infarcts are usually asymptomatic, and it's hard to predict the exact timing of which the process was first developed. Taking this in consideration, the exact timing of transformation of the infarct into sarcoma is hard to predict.

The exact mechanism of transformation is yet to be investigated. It was hypothesized by Mirra that the reparative process leads the transformation into sarcoma in the bone infarct lesions [6]. This process might be more active in SCT than in SCD which could be the reason of having more bone infarct associated sarcoma in SCT than in SCD. The type of sarcoma of all patients varied. There were two cases of Malignant Fibrous Histiocytoma of Bone (MFHB) in SCT, one case of osteosarcoma and high grade of pleomorphic osteosarcoma in SCT, and the other case of SCD, had a fibrosarcoma (Table 1).

In the case of SCD with BIAS reported by Mirra, the patient was a 26 years old black male. His lesion was located in the distal tibia and management consisted of radiation therapy then the

Table 1
Displaying other cases that showed an infarct developing into a malignancy.

Author/year	SCT/SCD	Sarcoma type	Location	Time from Bi to S	Age	Gender	Survival	Race	Other sites of bone infarct	Mets/lung	Management
Friestron/1987	SCT + alcohol	MFHB	Distal Femur	4 years	42	M	Died 12 months after DX	black	Ipsilateral tibia, both femur metaphysis	Lung died	Resection-failed then amputation above knee.
Duong/2004	SCT	MFHB	Distal Tibia	Unknown	69	M	14 months after resection – no f/u after	black	Ipsilateral calcaneus	Lung/progressing	Amputation below knee
Mirra/1977 (the first case of sickle and sarcoma ever reported)	SCA	Fibrosarcoma	Distal Tibia	Unknown	26	M	15 months after amputation	black	Humerus, vertebra, femur, pelvis	Lung/9 months after amputation/pleura/vertebra	Above knee amputation
Resnik/1993	SCT	High grade pleomorphic Osteosarcoma	Proximal Tibia	Unknown	53	M	Unknown	black	Ipsilateral femur, contralateral tibia	Unknown	En block resection and allograft
Neuhauser/1969	SCT	Osteosarcoma	Proximal Tibia	Unknown	20	M	8 months after biopsy	black	Non	lung	Amputation



Fig. 7. Left hip x rays described status post resection of the proximal femur with placement of hip prosthesis.

leg was perfused with phenylalanine mustard and actinomycin D followed by “above knee amputation”. Unfortunately, the patient developed aggressive lung metastatic lesion and died 15 months after his surgery [6].

It has been reported that most of these sarcomas are malignant fibrous histiocytoma (MFH), which is a rare primary sarcoma of the bone. On the other hand, osteosarcoma, which is the most common primary bone sarcoma, has been rarely reported in a pre-existing bone infarct [9].

4. Conclusion

In our experience at King Faisal Specialist Hospital and Research Center, we reviewed 1900 cases of bone sarcoma and this is the only case of BIAS arising in SCD.

The pathophysiology behind the sarcoma arising from bone infarct is still not fully understood. All cases reviewed were managed differently. Although rare one should have a high index of suspicion when encountering bone infarct that undergoes atypical changes with time.

In reporting this case we hope that further attention is provoked in the medical community to report such cases when encountered; and accordingly, evidence of such associations can be established alongside a solid evidence-based treatment algorithm.

Declaration of Competing Interest

The authors report no declarations of interest.

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Consent

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Author's contribution

Case design and writing – Alhamdan, Altayeb.
Case collection – Alhamdan, Altayeb, Alrifai.
Literature review – Alhamdan, Altayeb, Alraifai, Shaheen, Pant.
Figures – Altayeb, Alhamdan, Alraifai, Shaheen, Pant.
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