Hemophilic pseudotumor-is there a role of radiotherapy? A case report with review of literature

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ABSTRACT

Hemophilic pseudotumors are a rare but serious complication. They are more common in the weight-bearing joints. These lesions could be treated by conservative measures using factor VIII cryoprecipitate or by radiation therapy as an alternative to surgery with good results. We present a case of chronic hemophilia with pseudotumor of the right knee joint who was treated with low dose external beam radiation with fair results.

Key Words: Hemophilia, Pseudotumor, Radiotherapy.

INTRODUCTION

Hemophilic pseudotumor is an uncommon complication of factor VIII and IX deficiencies in the coagulation cascade and occurs in a wide spectrum of bones and soft tissues. A pseudotumor consists of chronically encapsulated blood collection due to recurrent extra-articular hemorrhage in either bone or soft tissues. As the swelling progresses, the increasing pressure within the hematoma leads to the slow destruction of adjacent structures[1]. Even though treatment of hemophilia has undergone rapid development in the past decade, at present the management of hemophilia-induced pseudotumors lacks standard therapy. Further complicating the issue is the rarity of the lesion, which is a hindrance to establishing standard management guidelines In this report we present a case of hemophilic pseudotumor which was resistant to conservative treatment and was treated with external beam radiation with good results.

A CASE REPORT

The propositus, a thirty year old male diagnosed as severe form of hemophilia-A and on cryoprecipitate treatment was referred to

the radiotherapy department of a tertiary care hospital (PGIMER) with history of pain and swelling in the right knee that had not responded to any form of conservative treatment for the past 3-4 months. On examination, the swelling present over the right knee joint was tender, progressive and impairing joint mobility. He was put in a plaster of Paris cast in view of impending fracture due to rapidly accumulating effusion. Blood factor VIII level was < 1%. X-ray of the right leg and knee joint showed lytic expansile lesion of the tibia and the fibula with fracture of medial cortex of the tibia. Extensive periosteal reactions and soft tissue calcifications were seen with overgrowth of distal femoral epiphysis with osteoporosis and prominent coarse trabeculations due to chronic recurrent intra-osseous hemorrhage (Figure 1). Pretreatment sagittal T1 spin echo and Flash T2-weighted magnetic resonance imaging (MRI) (Figure 3) images revealed grossly expansile hyperintense lesion in the proximal epiphyseal region of the right tibia with heterogeneous signal intensity on both T1-and T2-weighted images with a concentric layered appearance suggestive of presence of blood degeneration products as well as thrombus. However, post contrast T1-weighted images showed no enhancement. Postradiotherapy, MRI scans (Figure 4) revealed minimal reduction in the size of the lesion. However there was some alteration in signal intensity due to evolution of the hemorrhagic products.

Based on the X-ray and MRI features, in a chronic case of hemophilia, a clinical diagnosis of hemophilic pseudotumor was made and the patient was treated with external beam radiotherapy to the right knee (Figure 2) to a dose of 2500 cGy in 10 Fractions over a period of two weeks by parallel opposed AP-PA portals using telecobalt unit with the field size of 10 x 8 cm. However the patient was continued on cryoprecipitate while on treatment. On his first follow-up one month after

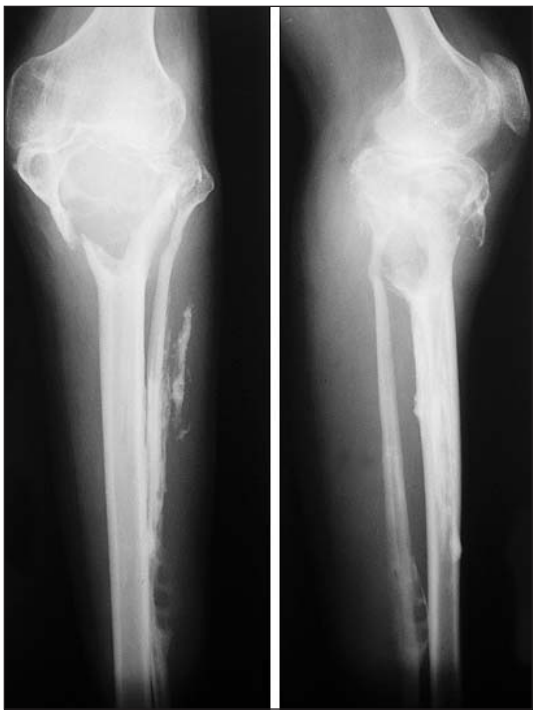

Figure 1. X-ray of the right leg and knee joint showing lytic expansile lesion of the tibia and the fibula with fracture of medial cortex of the tibia with extensive periosteal reactions, soft tissue calcifications and prominent coarse trabeculations.

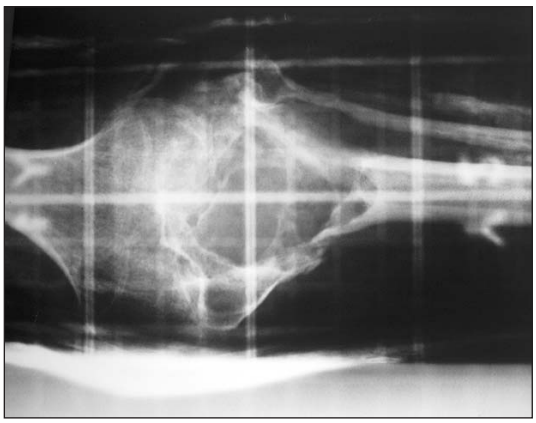

Figure 2. Simulation X-ray shows the target volume consisting of proximal tibia/fibula, the knee joint and distal femur.

the completion of treatment the patient had subjective improvement in pain symptoms. Objectively, the swelling had decreased by

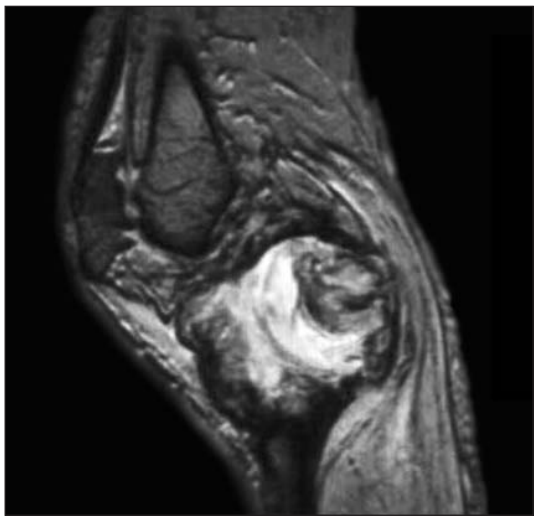

Figure 3. Pre-radiotherapy sagittal T1 spin echo and flash T2-weighted MRI images showing expansile hyperintense lesion in the proximal epiphyseal region of the right tibia with heterogenous signal intensity on both T1- and T2- weighted images with a concentric layered appearance, suggestive of presence of blood degeneration products as well as thrombus.

60% as had the effusion on follow up X-rays however, the lytic lesions persisted.

Presently the patient is fully ambulatory and pain-free, two years after completion of treatment with a much-improved quality of life. Follow up X-rays showed minimal healing of the bone lesion with tell-tale signs of the persisting lesions.

DISCUSSION

Pseudotumors of bone are rare and serious complications of hemophilia occurring in 1-2% of the hemophilic population[2].

Based on the pathogenesis of pseudotumors Gupta et al.[3] have classified pseudotumors of bone into three types:

1. Predominantly occurs in the soft tissue and does not involve bones. Thus it is difficult to detect on plain X-rays and requires MRI or computerized tomography (CT) scan for their delination.

2. Arises from subperiosteal region of bone or adjacent to the bone and causes erosion of bone with periosteal elevation and reaction.

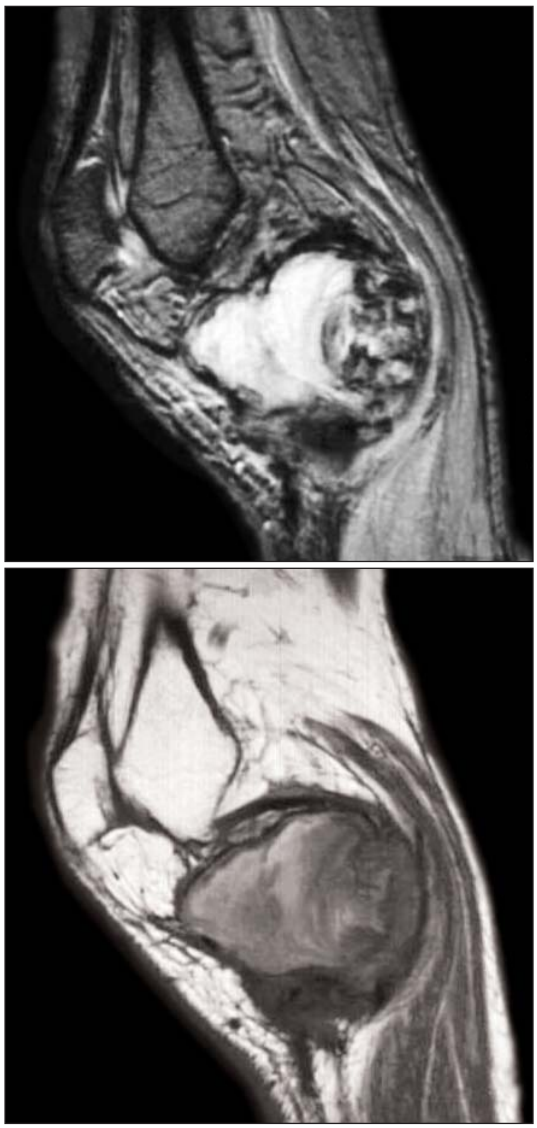

Figure 4. Post-radiotherapy, MRI showing minimal reduction in the size of the lesion with some alteration in signal intensity due to evolution of the hemorrhagic products.

3. Arises from the bone causing expansile lesions and thinning of bony cortex. Our patient belonged to the third subtype.

Gilbert et al.[4] has described two types of pseudotumors:

1. A proximal type of tumor occurring in the long bones of the extremities and pelvis.

2. A distal type localized mainly in the small bones of hands and feet.

The former is more commonly seen in adults while the latter is common in children.

Radiological differential diagnoses of pseudotumor include Ewing's tumor, aneurysmal bone cysts, giant cell tumor, malignant fibrous histiocytoma, neurofibroma and certain malignant neoplasms[5,6]. Benign tumors like aneurysmal bone cysts resolve with radiotherapy doses of 25-30 Gy. However, malignant tumors like Ewing's tumor and malignant fibrous histiocytoma require higher doses of 40 Gy and 50 Gy, respectively.

Magallon et al.[1] reviewed a total of 1831 patients diagnosed with hemophilia A and B and other coagulopathies from 1965-1990. Of the 1831 patients, only 21 patients had pseudotumors, located mainly in the appendicular skeleton and the pelvis. Total number of patients with hemophilia A was 1108, of which only 16 patients (1.44%) had pseudotumor. Total number of patients with hemophilia B was 172, of which 4 (2.32%) had pseudotumor. The number of patients with other coagulopathies was 551, of which only 1 patient (0.18%) had pseudotumor. In their series, replacement therapy and surgery gave the best results, especially in cases whom it surgery was electively choosen. However, patients from their series in whom surgery was performed after failure of replacement therapy showed poorer results.

Radiotherapy with or without replacement therapy has shown promising results in the treatment of hemophilic pseudotumor as an alternative to a more mutilating amputation. Medline database search of patients with hemophilic pseudotumors receiving radiotherapy with or without factor VIII replacement yielded 21 cases (Table 1). To the best of our knowledge our case is the 22nd case. The most common site of involvement was the femur 5/22 (22.7%), followed by tibia 4/22 (18.18%), mandible 3/22 (13.6%), calcaneus 2/22 (9%), orbit 1/22 (4.5%), thumb 1/22 (4.5%), pubic bone 1/22 (4.5%), and ankle joint 1/22 (4.5%); paranasal sinus (PNS) involvement was seen in 1/22 (4.5%). Twelve of 22 (54.54%) patients received only radiotherapy while 10/22 (45.45%) received radiotherapy and replacement factors. In 19/22 (66.36%) patients, the lesions had either resolved or were ihthe process of resolving, 1 (4.5%) patient did not show any improvement, and 2/22 (9%) patients had stable disease. Ten of 19 (52.63%) patients who received only radiotherapy had complete resolution of the lesions, while 9/19 (47.36%) patients who received both radiotherapy and replacement therapy showed complete resolution of the lesions. The mechanism of action of radiation is postulated to be the derangement of microvascular architecture of the pseudotumor, resulting in increased fibroblastic activity leading to fibrosis[7,8]. Secondary calcification occurs in four weeks and complete healing occurs in 8-12 weeks. Literature provides evidence that low dose radiation for hemophilic pseudotumors is sufficient. However, a dose response relationship has not been studied. Fractionated doses between 750cGy-2350 cGy have been recommended. Our patient received 2500 cGy in 10 fractions. Castaneda et al.[9] have reviewed 17 pseudotumors treated with radiation either alone or in combination with factor replacement. The radiation dose varied between 750 cGy to 2350 cGy. Fourteen of 17 (82%) patients showed complete resolution, while 3/17 (18%) patients with factor VIII inhibitors also responded to radiotherapy and factor VIII therapy. Krill and Mauer[10] reviewed eight cases of hemophilic hemarthrosis over a period of seven years and showed that the patient treated with radiotherapy had rapid resolution of tumor without any recurrence. Review of literature from medline database (Table 1) suggests that there is a lot of heterogeneity in the radiotherapy dose fractionation. Doses as low as 600 cGy to as high as 2350 cGy with or without factor VIII rep-

Table 1. Outcome of patients with hemophilic pseudotumors treated with radiotherapy-Review of literature

Year	No of cases	Age (years) /sex	Bones involved	Treatment	RT dose	Outcome	Author
1942	1	30	Femur	RT	NA	Resolved	Muller et al.[11]
1943	1	13	Tibia	RT	16 Gy	Resolved	Echternacht et al.[12]
1948	1	51	Femur	RT	NA	No improvement	Ghormley et al.[13]
1959	1	65	Pubis	RT	23.50 Gy	Stable for 2 years	Horwitz et al.[14]
1965	2	11, 13	Calcaneum and cuboid	RT	15.76 Gy and 16.72 Gy	Resolved	Chen et al.[15]
1968	2	11, 15	Mandible and fifth metacarpal	RT	8 Gy and 10 Gy	Resolved	Lazarovits et al.[16]
1972	3	18, 13, 57	B/L tibia, femur	RT	16 Gy, 18 Gy, 20 Gy	Resolved	Brant et al.[17]
1975	1	2	Femur	F-VIII Cryoprecipitate + RT	7.5 Gy	Resolved	Hilgartner et al.[8]
1984	1	12	Mandible	F-IX + RT	6 Gy	Resolved	Correra et al.[18]
1985	1	14	Orbit	Proplex + RT	7.5 Gy	Resolving	Meyers et al.[19]
1991	2	3, 13	Mandible and fifth metacarpal	F-IX + RT	6 Gy, 16 Gy	Resolved	Castaneda et al.[9]
1996	1	13/M	Tibia	RT	6 Gy	Resolved	Ozbek et al.[20]
1998	1	15/M	Calcaneum	F-VIII Cryoprecipitate + RT	15 Gy/10 days	Resolved	Kashyap et al.[21]
1998	1	14/M	Ankle joint	F-VIII Cryoprecipitate + RT	14 Gy/7 Fr	Resolved	Lal et al.[22]
2001	1	20/M	PNS	F-VIII Cryoprecipitate + RT	500 cGy/10 days	Resolved	Gupta et al.[3]
2004	1	NA	Thumb	F-VIII Cryoprecipitate + RT	NA	Resolved	Issaivanan et al.[23]
2005	1	30/M	Knee joint (femur + tibia)	F-VIII enriched Cryoprecipitate + RT	25 Gy/10 Fr	Stable	Kapoor et al.

RT: Radiotherapy, PNS: Paranasal sinus, Fr: Fractions, NA: Data not available.

lacement have shown good responses with complete resolution of lesions. Based on the evidence, we suggest that radiation therapy should be attempted in cases where surgery is not possible.

CONCLUSION

Even though there is no consensus in the management of hemophilic pseudotumors, radiotherapy either alone or with factor VIII replacement seems to be an attractive modality with good response rates.

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