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Case Report

Chronic Osteomyelitis Associated Primary Diffuse Large B-Cell Lymphoma of Femur. Report of a Diagnostically Challenging Case

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ABSTRACT

Diffuse Large B Cell Lymphoma (DLBCL) associated with chronic inflammation is a recently described entity associated with Epstein Barr virus (EBV) infection. Here we report a case of DLBCL developing in a background of chronic osteomyelitis and metallic implant following fracture after 17 years. Radiographs revealed a mixed lytic and sclerotic lesion at the distal end of right femur. Sinus tract biopsy showed plasmacytoid cells which were positive for EMA, MUM1 and CD138 and negative for routine B-cell markers like CD20, Pax-5 and CD79a. The cells were also diffusely positive for EBV encoded RNA by in situ hybridization (EBER-ISH). A high index of suspicion in all cases of long standing chronic osteomyelitis is essential for diagnosis. Diagnosis is challenging in a subset of cases with plasmablastic differentiation which are negative for B cell markers.

INTRODUCTION

Primary bone lymphoma accounts for 3% of primary bone tumors and 5% of extranodal lymphomas. Patient presents with a wide range of non-specific symptoms clinically mimicking osteomyelitis, small round cell tumors and primary bone tumors [1]. Lack of pathognomic signs on imaging leads to diagnostic dilemma. Diagnosis is evident on histopathology after the symptoms persist for a long time despite adequate treatment with antibiotics. Crush artefact and sampling of soft tissue component with florid inflammation often obscures the morphology. Diffuse Large B Cell Lymphoma (DLBCL) associated with chronic inflammation encompasses a specific group of lymphoma morphologically characterized by diffuse large B cell lymphoma occurring in an enclosed environment with clinical or histological evidence of chronic inflammation. It shows B-cell immunophenotype and is associated with Epstein Barr virus (EBV) infection. Here we report a case of DLBCL associated with chronic inflammation developing in a background of chronic osteomyelitis and long standing metallic implant insertion for a fracture.

CASE SUMMARY

A 49 year old male presented with ulcer and discharging sinus over the lateral aspect of distal part of the right thigh for 1 year. Seventeen years prior he was involved in a road traffic accident during which he had sustained multiple fractures of long bones of right lower limb. These included supracondylar fracture of right femur for which he was operated with dynamic condylar screws. In addition he had borne compound

distal third fractures of right tibia and fibula, which were treated with external fixator and flap cover followed by Ilizarov application. The Ilizarov was removed after 9 months and mobilized by patellar tendon bearing orthosis.

He remained asymptomatic until last year when he developed discharging sinus over lateral aspect of distal part right thigh. The discharge was on and off and was not associated with fever or significant pain. Two months prior he presented with recurrent trauma to right leg and was treated with slab. At current presentation his routine hematological and biochemical parameters were within normal limits. On examination he was found to have infected implant in situ with chronic discharging sinus. Microbiological tests including gram stain, culture and sensitivity of the discharge was negative. Radiographs of distal right femur including the knee joint showed plate and screw internal fixation device transfixing fracture lower end of femur with associated areas of mixed lysis and sclerosis. There was well formed callus around the fracture site (Figure 1A,B). Implant removal was planned and at surgery the tissues around the implant were found to be friable and there was profuse bleeding. Hence the implant could not be completely removed leaving behind one of the distal screws in-situ. A sinus tract biopsy was taken and submitted for histopathological examination. The wound was examined on post-operative day 3. As there was no discharge the drain was removed and radiograph was taken (Figure 1C,D).

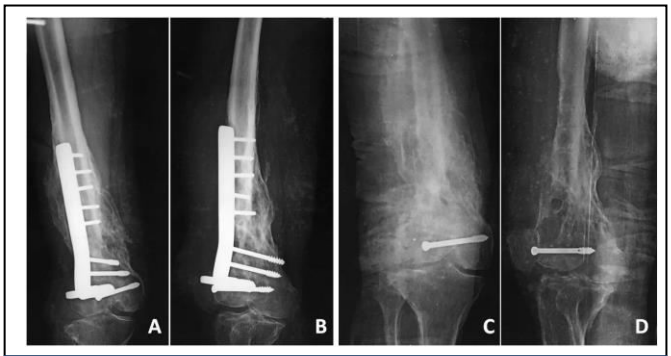

Figure 1: Antero-posterior (A) and Lateral (B) radiographs of distal right femur including the knee joint (taken 1 month prior to implant removal) showing plate and screw internal fixation device seen transfixing fracture lower end of femur. There is well formed callus around the fracture site. Antero-posterior (C) and Lateral (D) radiographs of distal right femur including the knee joints (taken 4 days after implant removal) showing cortical screw insitu in lower end of femur. There is well formed callus around the fracture site.

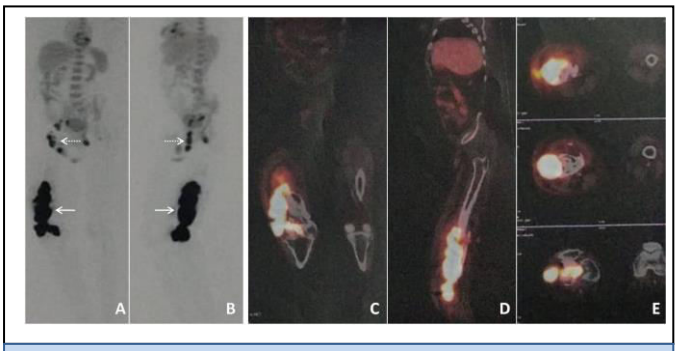

Figure 2: Antero-posterior (A) and Lateral (B) PET images demonstrating differential FDG uptake in lower end of femur and adjacent soft tissue (white arrow). Differential FDG uptake is also seen in right iliac and inguinal nodes (dashed white arrow). Antero-posterior (C), Lateral (D) and Axial (E) Fused PET-CT images demonstrating intense hypermetabolism in lower end of femur and adjacent soft tissue.

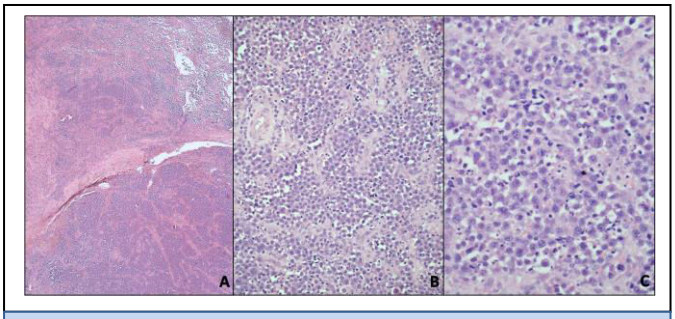

Figure 3: Sections (A) & (B) show diffusely arranged relatively monomorphous population cells separated into lobules and nests by fibrous septae (H&E; AX40, BX200). (C) On higher magnification these are round to oval cells with central to eccentrically placed round vesicular nuclei and moderate amount of eosinophilic cytoplasm. Nuclei show coarse chromatin and distinct nucleoli at places. Prominent mitotic and apoptotic activity can also be seen (H&E;CX200).

Microscopically, the biopsy bits were lined by keratinized stratified squamous epithelium showing areas of ulceration and underlying granulation tissue. In addition there were diffuse sheets of plasmacytoid cells with moderate amount of eosinophilic cytoplasm, central to eccentrically placed vesicular nuclei. Nuclei of some of these cells had distinct nucleoli. Binucleate forms, areas of coagulative necrosis, prominent mitoses and apoptotic activity were also seen (Figure3). On immunohistochemistry, these cells were positive for EMA, MUM1 and CD138. The cells were negative for lymphoid cell/ lymphoma related LCA, CD20, PAX5, CD79a, CD43, CD56, CD3, CD30 and ALK (Figure 4). Additional IHC markers tested and also found to be negative included S-100, SALL4, PanCK and HMB45 (Figure 5). Furthermore, these abnormal cells were

positive for Epstein–Barr virus encoded RNA (EBER) on in situ hybridization (Figure 5). The proliferation index (evaluated with Ki67) was about 70%. So a diagnosis of diffuse large B-cell lymphoma (plasmablastic type) associated with chronic inflammation and long standing metal implant insertion was rendered.

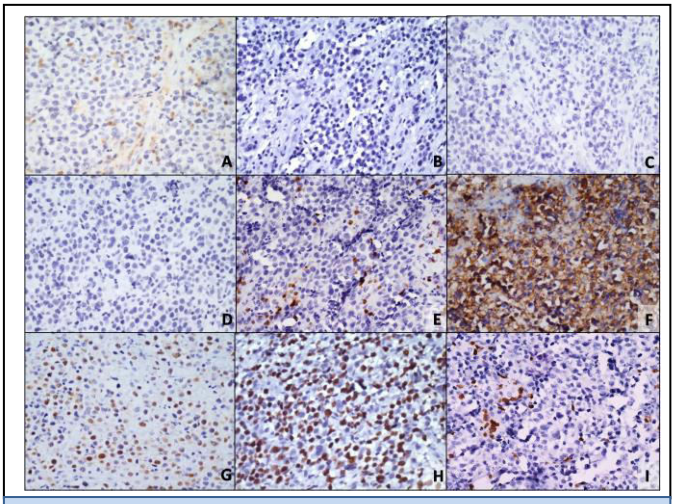

Figure 4: On immunohistochemistry tumour cells were negative for (A) LCA, (B) CD20, (C) CD79a, (D) PAX5, (E) CD3 & (I) CD30 (HRP-Polymer; X400). (F) CD138 showed diffuse membranous positivity and (G) MUM1 showed nuclear staining in tumour cells (HRP-Polymer; X400). (H) Ki67 showed increased label index within the tumour cells (HRP-Polymer; X400).

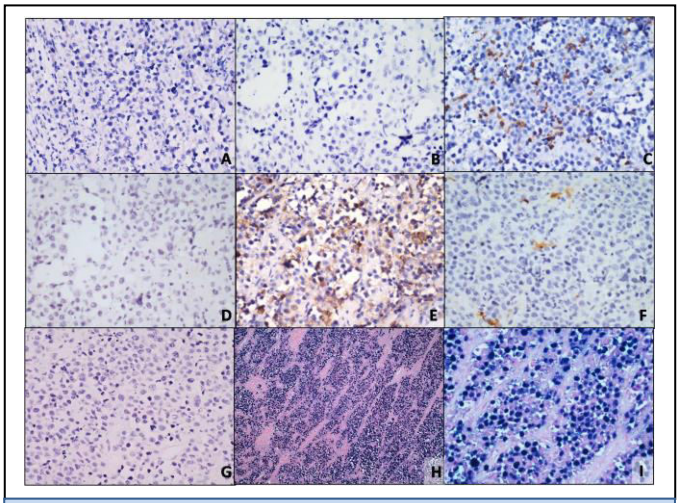

Figure 5: On immunohistochemistry tumour cells were negative for (A) ALK, (B) CD56, (C) CD43, (D) Pan CK, (F) S100 & (G) HMB45 (HRP-Polymer; X400). (E) EMA showed positivity in tumour cells (HRP-Polymer; X400). (H) & (I) EBER ISH showed diffuse positivity in tumour cell nuclei (EBER ISH; HX100, IX400).

Subsequent whole body PET-CT scans showed intense metabolically active ill-defined heterogeneously enhancing lesion involving lateral cortex of right distal femur and multiple metabolically active enlarged right iliac and inguinal lymphnodes. There was no evidence of any other abnormal focal FDG uptake in the rest of the body (Figure 2). The patient was referred to department of Medical Oncology for further management.

DISCUSSION

Oberling first described primary bone lymphoma in 1928[2]. Later in 1939, Parker and Jackson reported series of primary bone lymphoma under the nomenclature of reticulum cell sarcoma of bone [3]. Majority of the primary bone lymphomas are diffuse large B cell lymphoma with a minor subset comprising of follicular, marginal zone, anaplastic large cell, Hodgkin and T-cell Lymphoma [4]. Giudici et al. established criteria for a diagnosis of primary bone lymphoma which included a primary focus involving a single bone at presentation, histological evidence of involvement and the onset of symptoms should precede the distant metastasis by atleast six months [5]. As per WHO 2013 criteria, solitary or multifocal bony masses of malignant lymphoid cells without supraregional or other extranodal involvement constitute primary bone non-Hodgkins lymphomas [4]. The present case full-filled all the above diagnostic criteria.

Diffuse large B cell lymphoma associated with chronic inflammation was considered as a distinct entity in 2008 World Health Organization classification of tumors of hematopoietic and lymphoid tissues [6]. It was first described by Luchi et al in three patients of pleural lymphoma with long standing pyothorax resulting from artificial pneumothrorax used for treatment of tuberculosis in the past [7]. Subsequently these cases were designated as Pyothorax-Associated Lymphoma (PAL) which is a prototypical form arising in pleural cavity. Though majority of the cases involve body cavities, these can be seen in the setting of other chronic inflammatory conditions like chronic osteomyelitis, metallic implant insertion, surgical mesh insertion and skin venous ulcers [8-10]. Loong et al described four cases of DLBCL arising in splenic pseudo cyst, hydrocele , atrial myxoma and metallic-implant wear debris [11]. Literature search has revealed few cases of DLBCL arising in the back ground of chronic inflammation in a metallic

implant. Majority of these cases developed in the background of orthopedic metallic implant rather than prosthesis for joint replacement [11-17].

There is a long period of latency between the insertion of implant and development of lymphoma ranging from 1.2 years to 32 years [18]. Similar to PAL and EBV positive DLBCL of the elderly, simultaneous expression of LMP-1 and EBNA-2, in these lesions indicates type III EBV latency which is a hallmark of EBV associated lymphoma arising in immunodeficient patients [11].

The metallic debris are antigenic and cytokines released by the inflammatory cells leads to proliferation of the EBV transformed B cells resulting in lymphomagenesis [18]. Similar proliferation is also known to facilitated by localized immunodeficiency state resulting from long standing chronic suppuration and inflammation [8,9]. Unlike these primary bone lymphomas which are also mostly DLBCLs, arise de novo and show no EBV association. Lymphoma involving the musculoskeletal system involves femur pelvis and vertebrae and most commonly presents as palpable mass, bone pain and pathological fracture. Accompanying constitutional symptoms like fever, night sweats, weight loss and myalgia are seen. The radiological features are nondiagnostic with blastic, lytic, or mixed appearance [19]. It includes a wide range of differential diagnosis including Ewings tumor, chronic osteomyelitis, Langerhan cell histiocytosis and primary bone tumors. Presence of fever with wound leak and discharging sinus clinically simulates infection and misleads the diagnosis.

This subset of lymphomas on histology is characterized by diffuse large cell lymphoma with centroblastic or immunoblastic morphology. They commonly express CD20 and CD79a with variable expression of CD30. Loonget al. in their study reported non germinal center cell immunophenotype of DLBCL [11]. Few cases may show plasmacytoid differentiation with expression of CD138, MUM-1 and loss of expression of CD20 and CD79a as in this case. The present case had sheets of cells with plasmacytoid morphology and were negative for LCA and B cell markers including CD20, PAX-5 and CD79a. The diagnosis was difficult in this case as the cells were only positive for plasma cell phenotype, CD138 and MUM-1.

EBV can be demonstrated on formalin fixed paraffin embedded tissue sections by in situ hybridization as in this case. The cases reported in the recent years have also shown evidence of EBV association by in situ hybridization [8,10,11,20-22]. Apart from in situ hybridization, Polymerase Chain Reaction (PCR) can be done. Sanchez-Gonzalez et al reported a similar case in which in situ hybridization was negative and the diagnosis was confirmed by PCR [18]. It has an aggressive clinical course and chemotherapy with or without radiotherapy is the treatment of choice. A high index of suspicion in all cases long of standing chronic osteomyelitis with or without implant is warranted for early diagnosis and proper management. Demonstration EBV association not only confirms diagnosis but also suggests its etiological role.

This study was approved by the Institutional Ethics Committee.

CONTRIBUTIONS OF AUTHORS

Manuscript has been read and approved by all the authors, and requirements for authorship as stated earlier in this document have been met, and that each author believes that the manuscript represents honest work.

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