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Primary Large B Cell Lymphoma in the Tibia of an Old Individual Relapsing at an Uncommon Location

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Abstract

Involvement of the bones is a rare presentation of diffuse large B cell non-Hodgkin's lymphoma and afects mostly jounger individuals. The tibia, as the initial site of the disease is a rather ucomon target, particularly when it emerges at older age. We present a 94 old individual with large B-cell lymphoma stage IV E that involved the right upper tibia treated by CHOP-R and that relapsed one year later at the right testicle. The rarity of bone invivment, the old age and the unusual site of relaps are disussed.

Keywords: *Large B-cell lymphoma, bones, tibia, testicle, CHOP, rituximab, bendamustine.*

Introduction

It is utterly acepted that primary bone lymphoma is a relatively rare presentation of diffuse B cell non-Hodgkin's lymphoma and it has been observed in <1% of all lymphomas [1]. The tibia, as the primesite of the disease is involved in 13% of the cases [2-4]. The small bones of hands and legs and cervical spine are extremely rare invaded [4,5]. The disease affects predominantly younger and middle-age individuals. In a series encompassing 60 patients 55% were in the pediatric group, while 15% were in the elderly group [5]. While systemic B symptoms are relatively rare, localized bone pain, intensifying with time, is the prominent sign in the majority of patients [6,7]. We present hereby a patient with large B-cell lymphoma depicting unusual presentation comprising advanced age, primary bone involvement and relapse in the testicle.

Case Report

MD, a 94-year old physician was first examined in the outpatient orthopedic clinic at the beginning of 2015 because of pains at the median site of the right proximal tibia and weight loss of about 4kg. The patient's past history was remarkable for a myocardial infarction about 2 months before his present illness with a consequent insertion of two stents and recommendation to start treatment with clopidrogrel. There was no fever or any other symptoms. Family history: his father and sister expired at age 77 and 57 respectively, both from diffuse non-Hodgkin's lymphoma.

On physical examination he was found in a relatively good general condition. The patient felt pains on pressure over the tibia and the ribs. No enlarged lymph nodes were detected, the liver and spleen were not palpable below the costal margin. The rest of the physical examination was without pathological findings.

The orthopedic surgeon's impression was that the pain is due to pes anserinus syndrome and the patient was referred to a physiotherapist. However, the pain progressively increased, the patient started limping and was forced to use a walking stick. Therefore, he was referred to a senior orthopedist that performed x-ray of the tibia and interpreted to be without pathological findings. Therefore, the patient was given steroids,

locally injected and referred to the physiotherapist. His condition rapidly deteriorated, he started to complain of costal and lumbar pains, and became almost unable to walk. A re-examination of the first tibial x-ray film revealed a 2.9/2.4/3.3 cm osteolytic lesion at the upper medial part of the bone. Bone scintigraphy using 99m Tc-diphosphonate showed increased uptake in the majority of the skeleton bones. 18 fluoride-fluorodeoxyglucose positron emission-computerized tomography (FDG-PET-CT) revealed increased FDG uptake in the affected tibial site. Relevant blood examinations: Erythrocyte sedimentation rate was 100 mm/first hour, hemoglobin 11.9 g/dL, WBC 8,750 K/micl with 13,6% lymphocytes, platelets 209 K/micl, lactic dehydrogenase (LDH) 611 U/L (normal range 130-480 U/L). Since aspiration bone biopsy of the iliac crest did not reveal bone marrow pathology a core bone biopsy from the affected site of the tibia was carried out and immune-histiochemical examination showed infiltration with CD20+, Bcl2+, MUM1+, C-myc+, Ki67 90%, CD10-, CD138-, Bcl6 cells. Following the diagnosis of large B-cell lymphoma stage IV E the patient was placed on radiotherapy, total dose of 40GY targeted at the affected tibial site, followed by six cycles of attenuated CHOP-R dosage considering patient's age and his cardiac status. The patient's condition gradually improved, the pains receded and repeated FDG-PET-CT examinations were without pathological findings. He remained on follow-up and was free of complaints till the beginning of 2018, when he noticed the development of an indolent lump in the right testicle. On physical examination except for an enlarged right testicle, approximately 4x5 cm. in size, there were no pathological findings. Lymph nodes and spleen were not palpable. Blood counts, ESR, serum chemistry including LDH, as well as markers for seminoma such as beta-HCG and alfa-feto-protein, were all in normal limits. Ultrasonography revealed hypoechoic right testicle measuring approximately 5 cm in width and 8 cm in length. It showed an infiltrative pattern with increased Doppler flow. The left testicle measured 5×6 cm and was with normal texture. MRI examination confirmed the finding and FDG-PET-CT showed increased uptake in the right testicle lump. The rest of the examination including lungs and brain were without pathological findings. A right inguinal orchiectomy was carried out and histological examination of the testicle showed diffuse infiltration by small and large T and B lymphocytes. Immunochemistry staining was positive for NUM1+; CD-20; BCL6; bcl2, as well as for CD3 and BCL2 for small lymphocytes. The staining was negative for CD10 and CYCLIN D1; CD23; CD56 and CD30. The patient received a total of 28GY irradiation on the left testicle followed by 6 series of i.v. administered bendamustine 70mg/d x 2 q 28 d with rituximab 300 mg/d x 1 q 28 d. The patient's condition gradually improved and is presently on continuous follow up.

Discussion

The patient hereby described showed a distinctive presentation of large B cell non-Hodgkin's lymphoma (LBNHL) consisting of three rare features, i.e. outburst of the disease at an advanced age, the tibia being the primarily affected site and the uncommon relapse location. Statistical analysis of large groups of patients with diffuse large B-cell lymphoma of the bone indicates that the individuals in the fourth and fifth decades are the most affected [2]. In a report comprising 82 patients the median age of the individuals was 48 years (range 11-83 years)[3]. In a series of 161 patients with diffuse large B-cell lymphoma of the bone the mean age was 55 years with a range of 18-99 years [8] and in another larger study consisting of 409 patients, the median age was 56 with a range of 16-89 years [9]. Involvement of the proximal tibia as the primary presentation of the disease in adults and elderly individuals is also rare and only single cases have been reported [10]. According to Subic et al. [11] the median age of 22 patients with tibial lymphoma was 22.5 years and that of all bone lymphomas reviewed from the databases from the Rochester Medical Center was 42 years. The authors stress the point that the proximal tibia was the predominant site in the majority of the patients. In some cases tibial involvement could be bilateral [12]. Inyoung individuals large B-cell lymphoma of the tibia may imitate other malignant tumors [13]. The relapsing site of the disease is an additional feature in the unusual presentation of the large B-cell lymphoma in the described patient. Clinical experience shows that primary testicular lymphoma is an uncommon

form of extranodal non-Hodgkin's lymphomas and has been observed in 1-2% of all types of the disease [14,15]. Kemal et al. [16] reviewed 339 patients with primary testicular lymphoma. Eight of them were at an average age of 67.7 years (range 53-79 years). Systemic manifestations at presentation are rare, but with time the disease tends to spread mostly to extranodal sites particularly to the contralateral testicle, nervous system and lungs [15,17]. Cases with large B cell non-Hodgkin's lymphoma relapsing to the testicle are infrequent. Miyake et al. [18] reviewed 322 patients with malignant lymphoma and have found that there was secondary involvement of the testicle in 5.9% of them. In a series of 69 cases with malignant lymphoma five patients (7.2%) showed relapse to the testicle that appeared 13-37 months after initial diagnosis [19]. In another report, six out of 28 patients with non-Hodgkin's lymphoma showed testicular involvement [20]. However, these cases differ from the clinical features observed in the hereby described patient in whom the testicle became involved after two years remission of the bone located lymphoma. While the clinical features in cases of large B-cell lymphoma are not persuasive, FDG-PET-CT plays a major role in both staging and assessment of the disease progress [1]. Since the cells express mostly B cell markers immunohistochemistry staining with antibodies to CD10, CD20, CD22, MUM1, bcl-2 and cyclin D is of great help for the final validation of the diagnosis [21]. The general concept in the literature is that combined therapy consisting of X-ray irradiation followed by CHOP + rituximab results in a better prognosis and survival [3,22-25]. However, similarly to the above described patient, 30%-40% of older individuals show relapse mostly in the first two years after chemo-immunotherapy [26]. A thorough review of the treatment modalities recommended for elderly patients with LBNHL has been reported by Pfreundschuh[27]. Notable, newer therapeutic agents have been introduced to the therapeutic armamentarium of the large B-cell lymphoma. One of them, bendamustine, a derivative from the alkylating agents group, administered in cases of indolent non-Hodgkin's lymphoma, either as a single agent or in combination with rituximab, exerted an effect not inferior to the widely accepted CHOP-R schedule[28-30]. However, following an extensive review of the literature we were not able to find any reports as for the effect of bendamustine in cases with primary or secondary lymphoma of the testicles.

In short, a rare case of primary large B-cell lymphoma of the tibia remarkable for the advanced age of the patient and peculiar course of the disease is hereby presented. The applied therapeutic modalities are discussed.

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