Case Report

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Diffuse large B-cell lymphoma presenting as sternal mass in a patient with ankylosing spondylitis: a case report study

Ali Borhani, MD[a], Mahyar Daskareh, MD[b,*], Samira Gilanchi, PhD[d], Azin Vakilpour, MD[f], Maryam Poursharif, MD[e], Mehdi Vojdanian, MD[c]

Introduction and importance: Primary bone lymphoma is a rare entity that constitutes less than 1% of all non-Hodgkin lymphomas and 3–5% of malignant bone tumors. Chronic immune and inflammatory diseases carry a level of risk for the development of malignancies that is correlated with the disease severity. There is conflicting evidence regarding the risk of lymphoma in spondyloarthritis.

Case presentation: The authors present a rare case of primary diffuse large B-cell lymphoma of the sternum in a 41-year-old Iranian woman with ankylosing spondylitis (AS). Physical examination revealed a 7 × 7.5 cm firm swelling of the anterior midline chest wall above the breasts, and MRI showed a lesion within the sternal marrow with an associated soft-tissue mass in the anterior aspect of the sternum. Following core-needle biopsy under ultrasound guidance, a histopathological study demonstrated diffuse sheets of large noncleaved atypical cells with large multilobated prominent nuclei and fine chromatin compatible with diffuse large B-cell lymphoma.

Clinical discussion: Primary and exclusive involvement of the sternum is an uncommon presentation of lymphoma. Radiological, histological, and clinical characteristics of primary bone lymphoma can resemble those of other medical disorders. Although infrequent, existing evidence shows that AS seems to be associated with a small but significant risk for malignancy.

Conclusion: Even though inflammatory involvement of the anterior chest wall could be a common clinical finding in patients with AS, it is recommended that anterior chest wall pain or any mass almost always needs comprehensive assessment and imaging evaluation in such patients to avoid any delayed diagnosis, misdiagnosis, and ensuing morbidity or mortality.

Keywords case report, diffuse large B-cell lymphoma, lymphoma, spondylitis ankylosing, sternal mass

Introduction

Ankylosing spondylitis (AS) is the main subtype of a class of axial skeleton inflammatory rheumatic conditions gathered under the name of spondyloarthritides. Early inflammation and later ensuing osteoproliferation are the main known underlying causes of the structural changes in AS. Characteristic clinical features of AS are inflammatory back pain, spinal stiffness, and limitation of spinal mobility as a result of sacroiliitis and spondyloarthritis. AS is known to be a disease in young individuals, and men are about two times more likely to be affected than women[1]. Evidence has shown that chronic immune and inflammatory diseases carry a level of risk that is correlated with disease severity for the development of lymphoma[2].

HIGHLIGHTS

- Chronic immune and inflammatory diseases carry a level of risk for the development of lymphoma that is correlated with the severity of the disease.
- Primary and exclusive involvement of the sternum is a rare presentation of lymphoma but needs to be taken into account in any patient with chronic inflammatory or rheumatic disease.
- The radiological, histological, and clinical characteristics of primary bone lymphoma can resemble those of other medical disorders.
- Although the evidence regarding the risk of cancer in spondyloarthritis is still conflicting, anterior chest wall pain or mass in such patients almost always warrants careful assessment and imaging evaluation to prevent delayed diagnosis, misdiagnosis, and subsequent morbidity or mortality.

[a]Department of Radiology, Imam Khomeini Hospital, [b]Department of Radiology, Ziaeian Hospital, [c]Rheumatology Research Center, Tehran University of Medical Sciences, [d]Proteomics Research Center, Shahid Beheshti University of Medical Science, [e]Department of Radiology, Mashhad University of Medical Sciences, Tehran and [f]School of Medicine, Guilan University of Medical Sciences, Rasht, Iran

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*Corresponding author. Address: Ziaeian Hospital, Tehran University of Medical Sciences, Tehran 1366736511, Iran. Tel.: +989129463241; fax: +9855751333. E-mail: daskarehmahyar@gmail.com (M. Daskareh).

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Primary bone lymphoma (PBL) is a rare entity that constitutes less than 1% of all non-Hodgkin lymphomas and 3–5% of malignant bone tumors[3,4]. The most common histological type of PBL is diffuse large B-cell lymphoma (DLBCL), and long bones, particularly the femur, are the most frequent site of involvement[3,4]. PBL commonly affects male individuals within the age range of mid-40 and mid-60 years and usually presents with local pain, and swelling or is diagnosed after a pathologic fracture. Fever, night sweats, and weight loss (B-symptoms) are less likely to be encountered in comparison with other lymphomas[4,5]. Primary bone lymphoma of the sternum is extremely rare, with only seven cases reported in the literature up to now[4,6,7]. Although there have been identified correlations between PBL and other bone disorders, infectious processes, and autoimmune disorders, none of these associations are well established as risk factors for the development of this disease[7]. In this case report study, we present a case of primary DLBCL of the sternum in a patient with AS and briefly review the latest information on the risk of lymphoma in AS as well as causes of sternal mass in AS patients. This case report has been reported in line with the SCARE 2020 Criteria[8].

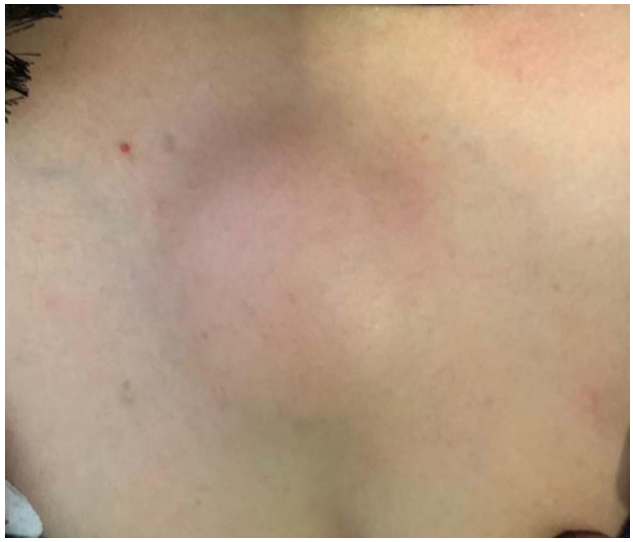

Figure 1. Clinical photograph shows midline anterior chest wall swelling above breasts.

Presentation of case

A 41-year-old Iranian woman who had been a known case of AS for 1 year was referred to the Radiology Department of our hospital for imaging of an enlarging sternal mass. The patient was a nonsmoker and had no remarkable past medical history. She also had no previous history of chest radiation, surgery, or trauma and had no history of diagnosed cancer in her first-degree family. She had been receiving sulfasalazine 2 g and indomethacin 150 mg daily for the past year under the diagnosis of AS from his rheumatologist. The patient initially reported having a lump on the sternum 4 months before being referred to our department and was assured that the lump was due to manubriosternal enthesopathy at the time. However, the patient was concerned about the sternum lump both for cosmetic issues and also due to the progressive growth of the mass over time. She also reported nonspecific generalized bone and muscle pain as well as malaise for the past 4 months. In physical examination, she had a 7×7.5 cm firm swelling in the anterior midline chest wall above the breasts that was mildly tender on palpation (Fig. 1). She was clinically well and had no B-symptoms (weight loss, fever, and night sweats). The systemic examination was not remarkable, and no palpable lymphadenopathy was noted on the physical examinations.

Laboratory data showed a positive C-reactive protein, an increased erythrocyte sedimentation rate (34 mm/h), mildly increased serum glutamic oxaloacetic transaminase and serum glutamate pyruvate transaminase, as well as microcytic hypochromic anemia. The levels of electrolytes, lactate dehydrogenase, renal function tests, and urine analysis were all within the normal limits. Serology and immunology tests, including rheumatoid factor, anticyclic citrullinated peptide, antinuclear antibody, anti-DNA antibodies, wright, coombs wright, and 2-Methoxyestradiol, were also normal, and Human leukocyte antigen B27 was negative.

The patient was referred to our imaging department for further evaluation. On ultrasound examination, a well-defined hypoechoic mass was identified located under subcutaneous fat and above the sternum with internal hyperechoic strands (Fig. 2A). MRI depicted a lesion within the sternal marrow with associated soft-tissue mass off the anterior aspect of the sternum (Fig. 2B). It was challenging to establish a diagnosis based on clinical findings and radiological examination; hence, a decision was made to obtain a tissue sample using core-needle biopsy under ultrasound guidance and local anesthesia. The biopsy was performed by a faculty member interventional radiologist. Histopathology revealed diffuse sheets of large noncleaved atypical cells with large multilobated prominent nuclei and fine chromatin. Immunohistochemistry examination showed that the biopsy specimen was positive for CD10, CD20, B-cell lymphoma (BCL)-6, however, it was negative for CD5, CD3, anaplastic lymphoma kinase, CD30, *BCL2*, and MUM 1 representing germinal center B (GCB) subtype. Also, regarding proliferative status, a Ki-67 of 70% was detected (Fig. 3). All pathological findings were compatible with the final diagnosis of DLBCL.

Thereafter, the patient underwent a whole-body evaluation by ^{18}F-fluorodeoxyglucose (FDG)-positron emission tomography (PET)/computed tomography, in which other sites of the body did not have an obvious abnormal increase in FDG metabolism. The patient was diagnosed with stage I DLBCL.

She was then referred to the medical oncology department for systemic treatment. She was given chemoimmunotherapy with the R-CHOP regimen (rituximab 375 mg/m^2, cyclophosphamide 750 mg/m^2, doxorubicin 50 mg/m^2, vincristine 1.4 mg/m^2, and 100 mg prednisolone) every 21 days for six cycles. Following the completion of chemoimmunotherapy, the patient was evaluated by a FDG-PET exam in order to determine the rate of response. Due to the partial response to the treatment according to the FDG-PET scan results, external beam radiotherapy was administered to the involved site with a total dose of 50 Gy in 25 fractions for 5 weeks. Grade 2 radiation-induced dermatitis was the only adverse effect found during the course of radiotherapy. Over the 12-month follow-

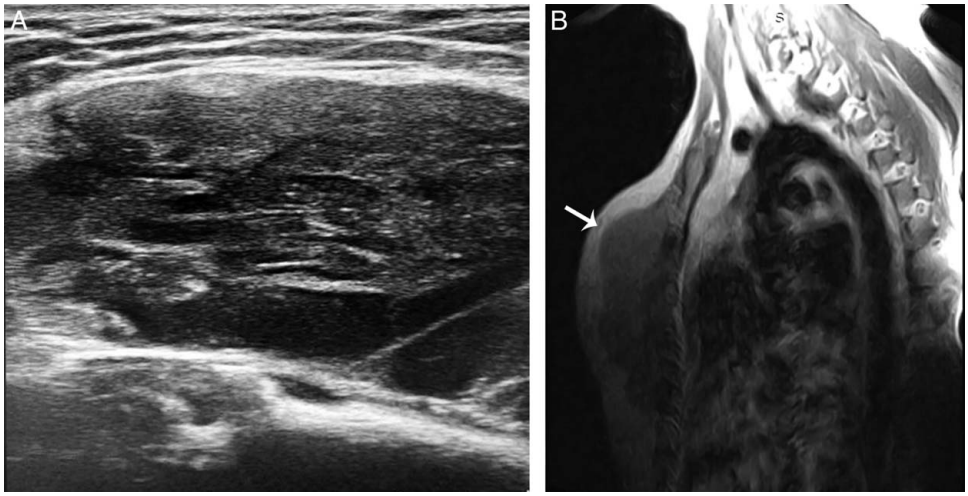

Figure 2. (A) Ultrasound with a linear probe shows a well-defined hypoechoic mass located under subcutaneous fat and above sternum with internal hyperechoic strands. (B) Sagittal T1-weighted MRI of chest demonstrates a lesion within the sternal marrow with associated soft-tissue mass off the anterior aspect of the sternum.

up period, she remained asymptomatic and showed no evidence of recurrence.

Discussion

The bulging on the sternum of our patient was initially misdiagnosed as hyperostosis due to manubriosternal arthropathy, and only after rapid enlargement was referred for imaging. The most likely other potential diagnostic pitfalls in a similar situation include lipoma, osteochondroma, and cavernous hemangioma of the anterior chest wall[9]. There were some clues that signaled a malignant etiology in our patient: the timeline of the enlargement of the mass was not consistent with a benign condition, and increased blood inflammatory markers also indicated an underlying serious pathology rather than benign tumors of the chest wall. Moreover, although primary bone lymphoma of the sternum is exceedingly rare, manubriosternal joint involvement in AS is also rarely reported in the literature[10]. Therefore, it is fairly sensible that patients with spondyloarthropathies who present with anterior chest pain or a mass sensation are at least referred for an ultrasound exam, as the ultrasound provides satisfactory soft-tissue contrast and is now widely accepted in the evaluation of pathologies that affect superficial joints. From a diagnostic imaging perspective, it was pivotal to evaluate whether the mass had any involvement with the sternal bone marrow or not. MRI yields high-resolution visualization of the bone marrow[11,12]. Therefore, we chose MRI as a radiation-free imaging modality with incomparable soft-tissue contrast for the next diagnostic step[13].

Initial involvement of the sternum is a very rare presentation of the PBL, and the most common sites of involvement in this rare entity are the extremities. PBL mostly presents with pain, swelling and pathologic fractures, while systemic symptoms such as fever,

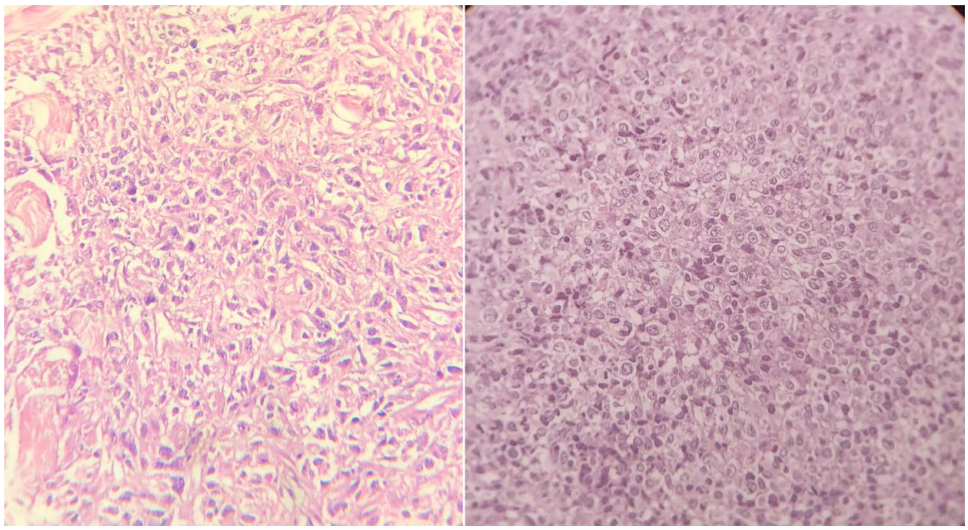

Figure 3. Histopathology reveals diffuse sheets of large noncleaved atypical cells with large multilobated prominent nuclei and fine chromatin compatible with diffuse large B-cell lymphoma.

night sweats, and weight loss are reported less frequently in PBL compared with other non-Hodgkin lymphomas[4]. To the best of our knowledge, only seven cases with the primary involvement of the sternum have been reported in the literature so far[4,6,14–17]. The majority of patients in previous case studies had multifocal disease and no history of spondylarthritis[4,14–16].

Raised levels of cytokines, chemokines, and growth factors in chronic inflammatory diseases could result in DNA damage, chromosomal instability, and a change in the chemical structure of DNA which put affected cells at risk of malignant transformation[18]. Among rheumatic diseases, it is well-documented that rheumatoid arthritis is linked with an overall additional risk of cancer, particularly lymphoma[19]. However, in regard to the risk of cancer in other rheumatic disorders including spondyloarthritis, the evidence is still conflicting[20]. There are several studies including a recent meta-analysis that have sought to specifically address this knowledge gap. The results of Deng and colleagues meta-analysis demonstrated that AS is associated with a small but significant risk for malignancy [pooled relative risk (RR): 1.14; 95% CI: 1.03–1.25] and that the RR of lymphoma in AS found to be 1.32 (95% CI: 1.11–1.57). However, in subgroup analysis, this increased RR was only found in Asian populations, not western populations[20]. Accordingly, a case–control study that was conducted exclusively on a Swedish population, did not demonstrate a significant association between lymphoma and AS (RR: 1.0; 95% CI: 0.6–1.7)[21] and a recent study that included only Korean male patients found that RR of cancer is increased in this population group[22].

The risk of cancer in AS patients that can be attributed to pharmacotherapy is also noteworthy. In regard to sulfasalazine, limited available data have not shown an increased risk[23] and in the matter of tumor necrosis factor inhibitors, the largest study to date that evaluated the risk of lymphoma in patients that were exposed to tumor necrosis factor inhibitors concluded that there is no added cancer risk in such patients[24].

DLBCL is an aggressive non-Hodgkin lymphoma and the most common type of PBL, and is characterized by heterogeneity with respect to clinical presentation, morphology, and molecular pathogenesis. The introduction of gene expression profiling revealed the existence of at least three distinct molecular subtypes of DLBCL that differ in the expression of thousands of genes and that seem to arise from B cells at different stages of differentiation[25]. According to their gene expression profiles two major subtypes of DLBCL were termed germinal center B-cell-like (GCB) DLBCL, activated B-cell-like (ABC) DLBCL[26]. There are several deregulated oncogenic pathways that contribute to the molecular pathogenesis of this disease. GCB DLBCLs subtype are postulated to originate from light-zone GCB cells[27]. The molecular pathway of DLBCL is very complex and involve various genetic and epigenetic alterations. In summary, previous research has identified that about 45% of GCB DLBCL patients have a detectable *t(14;18)* translocation, which juxtaposes the *BCL2* gene and the immunoglobulin H locus, resulting in constitutive activation of the antiapoptotic *BCL2* protein[25]. GCB DLBCL is also characterized by dysregulation of the *phosphatase and tensin homolog*–phosphatidylinositol 3-kinase signaling pathway. This can occur through *phosphatase and tensin homolog* deletions or amplification of *miR-17-92*, leading to deregulation of the phosphatidylinositol 3-kinase/mTOR pathway. In addition, GCB DLBCLs also exhibit deregulation of genes involved in DNA damage response, such as *TP53* mutation, *MDM2* gain/amplification, deletions of known tumor suppressor genes *TP73* and *ING1*[25,27].

First-line therapy with immunochemotherapy regimens such as R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) now cures up to 60% of patients[28]. However, in some cases, failing in first-line therapy present a significant clinical challenge and a majority of these patients still die due to the disease. Also, evidence revealed that patients with GCB DLBCL have a more favorable respond to a combined approach of the anti-CD20 antibody treatment with rituximab and chemotherapy, compared to the patients with ABC DLBCL[25].

Much research has been done on the molecular pathogenesis of DLBCL in order to understand the targetable oncological pathways and to address the demand for new theopoetic options[28,29]. Nevertheless, none of these studies has achieved its major objectives, and the first-line treatment for DLBCL has not altered in almost 20 years[28].

Conclusion

Primary bone lymphoma, particularly with initial and exclusive involvement of the sternum, is a rare disease but needs to be taken into account in any patient with chronic inflammatory or rheumatic disease. It is recommended that, anterior chest wall pain or mass in such patients almost always warrants careful assessment and imaging evaluation to prevent delayed diagnosis and any subsequent morbidity or mortality.

Ethics approval

The need for ethical approval was waived for this case report study.

Consent for publication

Written informed consent for clinical information and accompanying images to be published in this article was obtained from the patient. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

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This study did not receive any funding.

Author contribution

A.B. and M.D. gathered data and drafted the manuscript. S.G. reviewed the literature. A.V. drafted the manuscript. A.B., M.D., S.G., A.V., M.P., and M.V. revised the manuscript. All authors read and approved the final version of the manuscript for publication.

Conflicts of interest disclosure

All authors declare they have no conflict of interest in any form.

Guarantor

Ali Borhani and Mahyar Daskare.

Provenance and peer review

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