

Stage IV follicular lymphoma (Grade II) arising from skeletal muscle — a case report and literature review

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Abstract

This is a case report of a middle-aged male who was diagnosed to have extranodal non-Hodgkin lymphoma (NHL) appearing to arise from skeletal muscle of the left thigh. Presentation of the lymphoma with infiltration of skeletal muscle is an exceedingly rare event. We present the clinical course of the disease along with the computed tomography scan and magnetic resonance imaging findings of this case. NHL should be included as a differential diagnosis in patients (immunocompromised or non-immunodeficient) with a soft tissue involvement along with other inflammatory or neoplastic conditions.

Keywords: Follicular lymphoma, Extranodal non-Hodgkin lymphoma, Skeletal muscle.

Introduction

Extranodal origin of non-Hodgkin lymphoma (NHL) has been noted in at least one fourth of the cases¹ though some believe that it may comprise 24-48% of cases and the incidence is increasing in recent decades.² Among the various sites of involvement, muscles have been occasionally reported to be affected. Investigators have observed these cases to represent only 0.11%-2% of the extranodal lymphomas.³⁻⁶ Mechanism for muscle involvement in malignant lymphoma is mostly "secondary" to direct extension from adjacent lymph nodes and bone or by dissemination; however, "primary" cases of muscular involvement by lymphoma have been described as well. In this article, a case of lymphoma that was initially diagnosed by biopsy of a soft tissue mass is described. To the best of our knowledge, this appears to be the first report of its kind in Pakistan as there is an apparent paucity of documented cases of soft tissue lymphomas in the country.

Case Report

A 51-year-old man initially presented with 3-months history of a painful, slowly growing lump in the left thigh. He was otherwise healthy, with no significant medical history. He received antibiotics and analgesics for a

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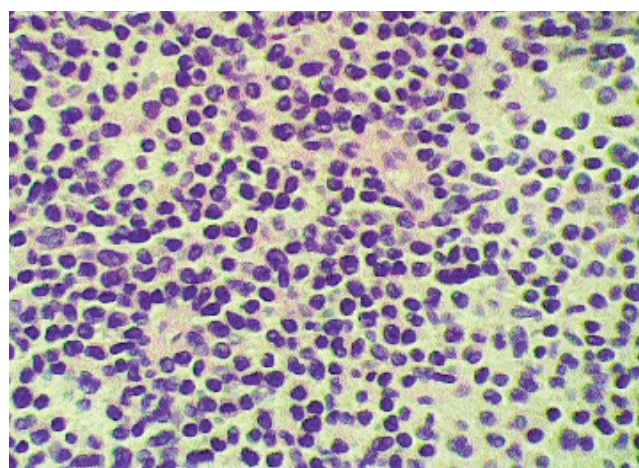


Figure-1: Mixture of small and large sized atypical mononuclear cells arranged in patternless sheets. The cells have irregular nuclear contours with nuclear grooving and hyperchromatic nuclei, scant to no cytoplasm. (Haematoxylin-eosin stain, magnification x400).

provisional diagnosis of abscess but his condition did not improve. Later he developed obstructive jaundice and was admitted via emergency to a tertiary care hospital. Ultrasound of the abdomen showed distended gallbladder, mildly dilated intra- and extrahepatic ducts; common bile duct was also dilated. Endoscopic retrograde cholangiopancreatography (ERCP) was carried out and a stent was placed. Computed tomography (CT) scan of the upper abdomen showed a hypodense mass (4.1x4.0 cm) in the pancreatic head region and distal common bile duct. Enlarged peripancreatic and paraaortic nodes were seen. Findings suggested neoplastic lesion in the pancreatic head and the differential diagnosis included lymphoma. Biopsy of the left thigh mass revealed NHL of B-cell phenotype with morphology suggestive of grade II follicular lymphoma (Figure-1 and 2). MRI of the left thigh demonstrated abnormal signal intensity (isointense to muscle on T1 and hyperintense on T2-weighted images) involving rectus femoris, tensor fasciae latae, vastus lateralis, vastus medialis and adjacent adductor muscles with no evidence of erosion or abnormal signal within underlying bone (Figure-3). Bone marrow aspirate and trephine

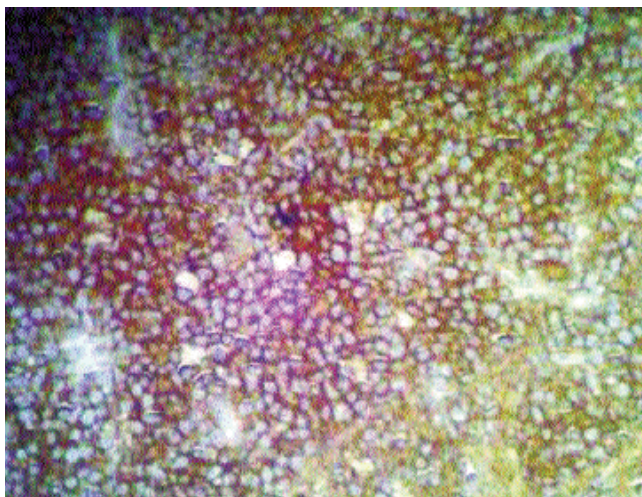


Figure-2: Immunohistochemistry by Dako Envision method showed Pan B and Bcl 2 positive. Cytokeratin AE1/AE3 was negative.



Figure-3: Axial T2-weighted contrast enhanced magnetic resonance image of the left thigh showing hyperintense signals arising from within the anterior compartment muscles with a small area of necrosis (arrow) and sparing the femur.

examination was consistent with infiltration of marrow by the follicular lymphoma.

Chemotherapy with CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) regimen followed by radiotherapy was planned. After 2-cycles of chemotherapy, significant reduction in the size of the thigh lesion was noticed clinically, although a repeat MRI after four cycles did not mention significant reduction in the mass (but adductor muscles returned to normal signals now). Maximal axial diameter of the thigh mass was noted to be almost 15 cm. However, CT scan of the abdomen noted a slight decrease in the pancreatic lesion (now 4.0x3.8 cm). At this point, the patient developed diplopia due to 6th nerve palsy and ptosis of left eye. MRI of the brain showed meningeal enhancement along with the left side of midbrain, medial temporal lobe and left side of the cerebellum but no cerebral oedema, or hydrocephalus. Diagnostic cerebrospinal fluid (CSF) cytology revealed predominantly lymphoid cells with degenerated cells against a fibrinous background.

Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were raised while autoimmune profile was negative. Neurological opinion recommended chemotherapy should continue, with the addition of dexamethasone. A good response was observed following initiation of dexamethasone.

CT scan of the abdomen after the 7th-cycle of chemotherapy mentioned a marked reduction in the hypodense area near the head of pancreas, now measuring 1.8x1.8 cm. MRI of the left thigh showed a significant improvement at this stage with the maximal axial diameter now being 8 cm. After the patient had received 8-cycles of chemotherapy, he developed positional vertigo that was later followed by difficulty in swallowing. MRI of the brain was done which showed multiple lymphomatous deposits in the right temporal and left parietal, thalamus and hemispheric regions. Intrathecal chemotherapy with methotrexate was initiated. Simultaneously, the patient underwent a post-treatment positron emission tomography - computer tomography (PET-CT) scan which showed subtle uptake of fluorodeoxyglucose (FDG) in the left thigh lesion which was attributed to the therapy change. It appeared diffuse and neither a discrete focal mass nor any bone involvement was seen. He was admitted twice for worsening of his latest complaints of difficulty in swallowing, vertigo; CSF cytology revealed atypical mononuclear cells suggestive of central nervous system (CNS) involvement by the NHL. He expired one week after discharge from the hospital.

Discussion

NHL comprises of a heterogeneous group of lymphoproliferative disorders and is common in developing countries like Pakistan. Bhurgri et al have reported a double-fold increase in the incidence rates in 2002 compared to that in 1995 with a higher preponderance in men and marginally higher risk in ethnicities belonging to Northern and North-Western Pakistan.⁷ A substantial number of NHLs arise from extranodal tissues. An operational definition considers lymphoma as extranodal, when after routine staging procedures, there is either no or only 'minor' nodal involvement along with a clinically 'dominant' extranodal component, to which primary treatment must often be directed⁸ (another less accepted addition to this definition defines nodal and extranodal as <25% and >75% respectively, of the total tumour volume.)²

Most frequent site for primary extranodal lymphoma is gastrointestinal tract followed by head and neck localisations. Skin cases constitute 10% and primary CNS lymphoma constitutes 3-4%. Less common sites include

bone, respiratory tract, breast, testis, soft tissue etc. Travis et al³ reported 8 instances involving muscle out of 7000 cases of malignant lymphoma in a ten-year time period, Komatsuda et al⁴ found 31 cases from 2147 lymphoma cases from pathologic autopsy in two years and Damron et al¹⁰ presented a series of 4 cases from a group of 241 malignant lymphomas. Despite such scant occurrence, lymphoma affecting skeletal muscle is a relatively well-described entity, especially in pathology literature.

The involvement of muscle in lymphoma has been broken down into two categories. By the purest of definitions,³ cases that are considered 'primary' soft tissue lymphoma are those that present without concomitant involvement of any other region, even the regional lymph nodes, i.e., stage 1E. Although rare, well-documented cases have been mentioned following this definition.^{3,11,12,16} But other investigators have included patients with disseminated or nodal disease who present with extranodal soft tissue lymphoma as well because of reports of confusion between cases of stage 1E disease and sarcoma that have led to inappropriate surgery.¹¹ However, even by the latter definition, the main bulk of the disease should be extranodal thereby necessitating treatment in that direction.

Most patients have been in their sixth through seventh decades of life with median age falling in the range of 60-65 years.^{2,3,10,12} Among soft tissues, inter-muscular tissue is the most affected whereas skeletal muscle involvement is uncommon.⁸ Although any soft tissue location may be represented, the most common site is the thigh (33%) followed in diminishing frequency by the trunk, upper arm and lower leg.¹² The median size of the soft tissue mass at presentation was noted to be 10cm.^{3,10} Lymphoma of the skeletal muscle can present as a discrete mass or diffuse enlargement of the muscle with loss of normal fascial planes. On biopsy, various types of NHLs are found but diffuse large B-cell lymphoma is the most frequent, though a significant portion are low grade B-cell lymphomas including small lymphocytic and follicular varieties.

Soft tissue masses should be promptly biopsied, since differential diagnosis comprises benign lesions like intramuscular abscesses, haematomas, lipoma etc. as well as sarcoma, lymphoma and metastatic carcinoma. Biopsy should be followed by electron microscopy and immunohistochemical studies if the cell type of the tumour is uncertain. At MRI, NHL involving skeletal muscle has been described as hyperintense or isointense relative to normal muscle on the T1-weighted sequence and hyperintense on the T2-weighted sequence. However, the MRI characteristics of muscle NHL are non-specific and

can be seen in a variety of diseases.⁹ In the past decade, introduction of positron emission tomography - computed tomography (PET-CT) for staging and restaging as well as the treatment response assessment is making an impact on the management of NHL especially the aggressive ones.¹⁸ Also the diagnostic performance was found to be better for extranodal disease. The National Comprehensive Cancer Network has incorporated FDG-PET in the evaluation and management algorithm of most Hodgkin lymphoma (HL) and NHL patients. It must be noted, however, that PET-CT does not obviate the need for a biopsy.¹⁹

For the treatment of follicular lymphoma in muscle, which was found in our patient, there are no specific recommendations. Generally, stage I/II follicular lymphoma can be managed by radiotherapy alone. For advanced disease, CHOP regimen is the world-wide first choice among the anthracycline-based regimens while the variant regimen CVP (that excludes doxorubicin) is reserved for elderly patients. Fludarabine-containing regimens have emerged as a sound alternative but they are poorly effective in cases of histological transformation and follicular large cell lymphoma. Recently, there is a trend of adding rituximab, a passive immunotherapy using humanized anti-CD 20 monoclonal antibody. The added benefits demonstrated for the combination is superior to any chemotherapy alone. Autologous stem cell transplant (SCT) is an alternative strategy to treat advanced follicular lymphoma with curative intent apart from the chemo-immunotherapy mentioned above. Another novel yet effective treatment is radio immunotherapy (RIT) which allows delivery of radiation to lymphoma cells using radioimmunoconjugates ([¹³¹I]-tositumomab and [⁹⁰Y]-ibritumomab tiuxetan have been approved till now) that target the CD20 antigen and are being used in the setting of recurrent follicular lymphoma setting. Important to note is the fact that, RIT spares the non-malignant cells.

The International Prognostic Index (IPI) is widely accepted to identify prognostic factors (which are age >60 years, tumour stage III or IV, serum lactate dehydrogenase (LDH), performance status and extranodal involvement) for NHLs,²⁰ but is only moderately discriminating for follicular lymphoma and therefore, the Follicular Lymphoma International Prognostic Index (FLIPI)²¹ was put forward with some changes in the IPI (performance status and extranodal involvement replaced by haemoglobin level and number of nodal sites). It has been mentioned by investigators that IPI can be applied to primary extranodal NHLs as well^{7,22} although Mok and his co-investigators could not find statistical significance for a number of

extranodal sites as a prognostic factor and advocate 4 rather than 5 prognostic factors from the IPI.²² The case series by Travis et al³ reports that of the eight Stage I patients included, three patients survived disease-free at 3, 8 and 13 years and one died after 4 years from a recurrence; another died after 7 months and two others after 15 months from diagnosis. Hill et al¹⁷ mentioned that patients with stage IE disease (7/19) were followed-up for a mean of 43 months and showed a complete response and no recurrent disease whereas of the 12 remaining (with multifocal disease) only 5 are alive and disease-free; remainder developed recurrence (2/12) or died (5/12). In the series by Damron et al,¹⁰ each of the 4 patients had died of the disease by 2, 3, 21 and 24 months - 2 were stage IV and the other 2 being stage II and III. The sites of recurrence have not been enunciated.

Conclusion

Lymphomatous involvement of muscle, as rare as it may be, must be suspected in non-resolving swelling of the extremities. Biopsy should be followed by electron microscopy and immunohistochemical studies if the cell type of the tumour is uncertain. This is highly imperative because unnecessary radical surgery can be avoided since lymphoma is primarily a non-surgical disease; also excision of mass removes a clinical barometer of response to chemotherapy and radiotherapy. Additionally, for a better understanding of this disease entity, data needs to be collected prospectively from population based registries.

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