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The fear of lymphadenopathy: A cautionary case of sarcoidosis masquerading as recurrent diffuse large b-cell lymphoma (DLBCL)

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ABSTRACT

We describe the cautionary case of a patient with advanced-stage large B-cell lymphoma (DLBCL). After combination chemotherapy, CT-PET revealed a persistent focus of likely DLBCL for which he received radiotherapy. Follow-up CT-PET showed diffuse hypermetabolic adenopathy and recurrent DLBCL was presumed. As part of clinical trial assessment, multiple biopsies showed non-caseating lymphadenitis consistent with sarcoidosis. No treatment for asymptomatic sarcoidosis was required and 18 months later he remains cancer-free. The presentation of sarcoidosis masquerading as recurrent DLBCL highlights the importance of tissue sampling prior to engaging in toxic and potentially life-threatening chemotherapy and the interesting link between DLBCL and sarcoidosis.

1. Introduction

Non-Hodgkin Lymphomas (NHL) are a heterogeneous group of malignancies arising from lymphoid tissue with varied clinical and biological features. In 2012, roughly 6500 cases of diffuse large B-cell lymphoma (DLBCL) were diagnosed in the United States [1–3]. Diagnosis and staging is designed to identify all sites of known disease and to determine prognosis relative to known clinical risk factors. The revised International Prognostic Index (R-IPI) identifies specific groups of patients who are more or less likely to be cured with standard therapy [4]. DLBCL, while aggressive, is curable, and with treatment, approximately 50% of patients with advanced-stage DLBCL will attain cure [5,6].

Efforts to evaluate for complete remission (CR) are often clouded by interim assessments through surveillance imaging with computerized tomography (CT) or CT - positron emission tomography (PET). For treated lymphoma, surveillance and restaging imaging with CT-PET scans can yield false-positive results and should not be used to guide changes in therapy without overt evidence of progressive disease (PD) through tissue analysis [4]. The National Comprehensive Cancer Network (NCCN) guidelines do not recommend the use of CT or CT-PET for routine surveillance for patients with stage I-II disease who have achieved a CR following initial therapy. For patients with stage III-IV disease who achieve a CR, the NCCN recommends CT scans no more than once every six months for up to two years after completion of treatment [4]. Evaluating for PD or recurrence should, however, include regular history and physical exams and serial laboratory assessments, typically every three-to-six months for the first five years after induction therapy.

We describe the case of a previously healthy man with stage IVA DLBCL. He received R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) chemotherapy. A CT-PET scan after six cycles of treatment revealed a persistent focus of likely DLBCL involving the splenic hilum for which he received involved field external beam radiation therapy. Three months later, a CT-PET scan showed increased mediastinal, perihilar and retroperitoneal fluorodeoxyglucose (FDG) -avid lymphadenopathy. At the time of our consultation, the patient was exploring further treatment options and had received recommendations elsewhere to consider salvage chemotherapy followed by consolidation high-dose chemotherapy and autologous stem cell transplantation (ASCT) and was also considering chimeric antigen receptor (CAR) T-cell therapy through a clinical trial. He was anxious, had difficulty sleeping at night and had begun plans to liquidate his estate.

Lymphadenopathy (localized or widespread) found during routine physical exam or with imaging is a nonspecific finding, but can elicit intense fear and anxiety from both the patient and clinician, particularly in the post-lymphoma induction or reassessment period [7]. The

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overlap of clinical symptoms and radiographic findings between lymphoma and other causes of lymphadenopathy underscores the challenge of disease surveillance while highlighting an opportunity for potential new diagnostic technologies [8]. When confronted with evidence of hypermetabolic lymphadenopathy, clinicians must remain aware of sarcoidosis (among other infectious, inflammatory, or granulomatous etiologies) as an alternative diagnosis even in the backdrop of recently treated DLBCL [9].

2. Case report

A 70-year-old Caucasian man with a past medical history which included gastroesophageal reflux disease, episodic gout, and benign prostatic hypertrophy presented to medical attention with asymptomatic and painless left groin adenopathy of several weeks duration. After a concerted effort to lose thirty pounds through diet and exercise, he no longer required medications to control hypertension or hyperlipidemia. His family history was unremarkable. He had never been a smoker, but did report exposure to Agent Orange in Vietnam 50 years earlier.

His physical exam was within normal limits, except for bilateral shotty groin adenopathy, and a 2.5 cm palpable right axillary node. An ultrasound of the left groin showed a 2.5 cm cystic-appearing mass. A core needle biopsy of the mass revealed lymphoma. Flow cytometry findings included a monoclonal B-cell population expressing CD20, CD5, CD10 (partial), CD19, CD38, CD22, CD25 (partial), CD11c (partial), and CD8 (partial). B cells were negative for CD23, CD3, CD103, and FMC-7. He subsequently underwent an excisional biopsy of a left inguinal lymph node, which revealed DLBCL not otherwise specified (Fig. 1A). By immunohistochemistry analysis, the cells expressed CD5, CD10 (weak), CD79a, BCL-2, BCL-6, MUM-1, and Pax-5. Cells were negative for CD3, CD30, and Cyclin D1. The Ki-67 index was greater than 95% (Fig. 1B). Given the high Ki-67 index and unusual co-expression of CD5 and CD10 antigens, the tissue was sent to the lymphoma branch at the National Institutes of Health for further review where the diagnosis of non-germinal CD5+ DLBCL was confirmed. There was further agreement that the expression of CD10 was unusual, but given the strong MUM1 expression, activated B-cell phenotype (ABC type) was favored. Additional laboratory studies included the following: a normal complete blood count and hepatic panel; lactate dehydrogenase (LDH) of 530 U/L (normal < 243); and beta-2 microglobulin of 3.0 mcg/mL (normal < 2.70). Hepatitis A, B and C viral assays were pan negative as was an HIV enzyme-linked immunosorbent assay (ELISA) test.

A CT-PET scan showed hypermetabolic axillary, splenic, and retroperitoneal adenopathy with standardized uptake values (SUV) ranging between 25 and 30 (Fig. 2A). A bone marrow aspirate and biopsy showed no morphologic or immunophenotypic evidence of DLBCL. A multi-gated acquisition (MUGA) scan revealed a normal left ventricular ejection fracture of 64%, and a lumbar spinal puncture to assess for leptomeningeal lymphoma proved unremarkable. The patient was diagnosed with stage IVA DLBCL with an R-IPI score of four (i.e., age greater than 60, advanced stage, more than one extra-nodal site, and elevated LDH).

After three cycles of R-CHOP, an interim CT scan of the chest, abdomen, and pelvis revealed marked interval improvement in the diffuse adenopathy with shrinkage of his axillary and para-aortic lymph nodes as well as his liver and splenic nodules. His first four cycles proved otherwise uneventful but with his fifth cycle, he was hospitalized for treatment of a neutropenic fever. He received empiric parenteral antibiotics for culture-negative pneumonia. There was a two-week delay in treatment before he received a sixth and final cycle of chemotherapy.

A post-treatment CT-PET scan showed an excellent response to chemotherapy with marked reduction in hypermetabolic lymphadenopathy and resolution of splenic and hepatic nodules. There was, however, continued hypermetabolic activity involving the splenic hilum corresponding with an SUV of 11.5 (Fig. 2B). He received 40 Gy of consolidative radiotherapy over four weeks to that area.

Three months later, a repeat CT-PET scan showed multiple enlarged FDG-avid lymph nodes above and below the diaphragm with an SUV range from 12.6 to 25 (Fig. 2C). Brain magnetic resonance imaging and a lumbar puncture proved unremarkable and further laboratory assessment included a white blood cell count of 3×10^9/L with an unremarkable differential, hematocrit of 43%, and platelet count of 100×10^9/L. Electrolytes and renal function were all in the normal range, and aspartate transaminase (AST) and alanine transaminase (ALT) were 47 U/L (normal < 40) and 51 U/L (normal < 44), respectively. Serum LDH was 192 U/L and β_2 microglobulin was 2.94 mcg/mL. Quantitative immunoglobulins were within normal limits and a serum protein electrophoresis did not reveal a monoclonal gammopathy.

Given the CT-PET scan findings suggestive of relapsed DLBCL and the known aggressive nature of lymphoma recurring within 12 months of R-CHOP, the patient sought opinions at various medical centers. Options that he received for presumed relapsed DLBCL included standard salvage therapy with R-ICE (ifosfamide, carboplatin, etoposide), R-DHAP (dexamethasone, cytarabine, cisplatin), and R-GDP (gemcitabine, dexamethasone, cisplatin) for 2–3 cycles, followed by high-dose therapy and autologous stem cell transplantation (ASCT) if his DLBCL proved chemo-sensitive. The patient was further offered participation in a randomized trial of R-ICE alone versus R-ICE with an anti-CD19 antibody-drug conjugate. Another potential choice included high-dose

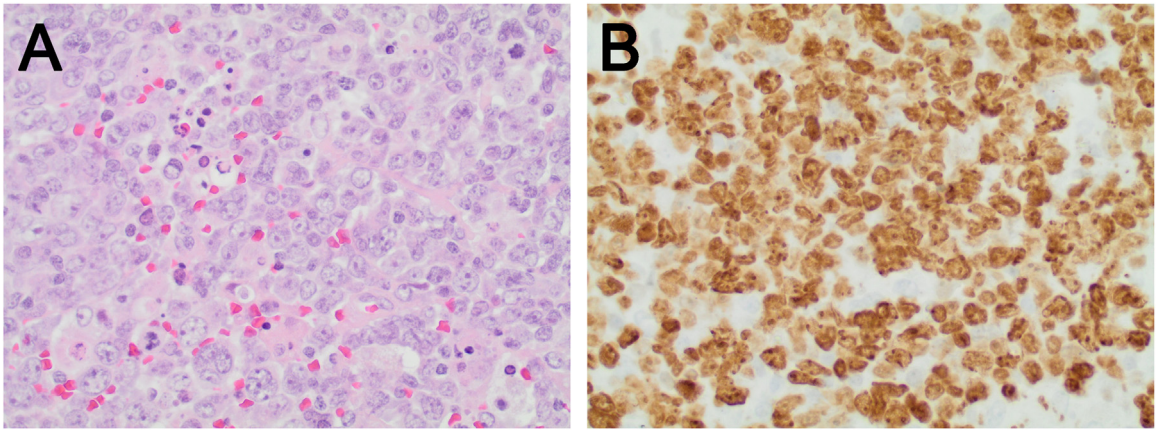

Fig. 1. Representative photos of the patient's excisional biopsy of a left inguinal lymph node. A) Hematoxylin and eosin stain showing diffuse large B-cell lymphoma. B) Immunohistochemistry showing Ki-67 index greater than 95%.