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

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## ARTICLE INFO

## 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

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 $3 \times 10^9$/L with an unremarkable differential, hematocrit of 43%, and platelet count of $100 \times 10^9$/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 $\beta_2$ 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
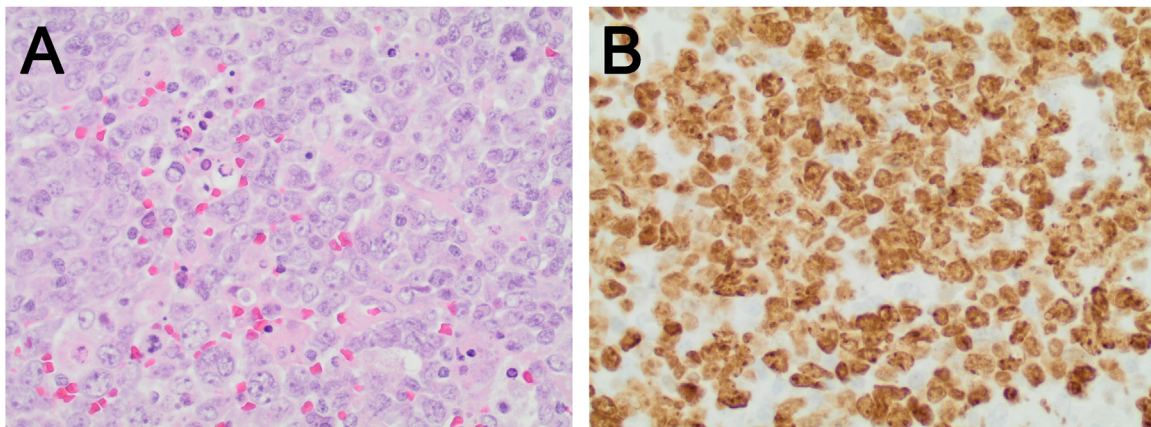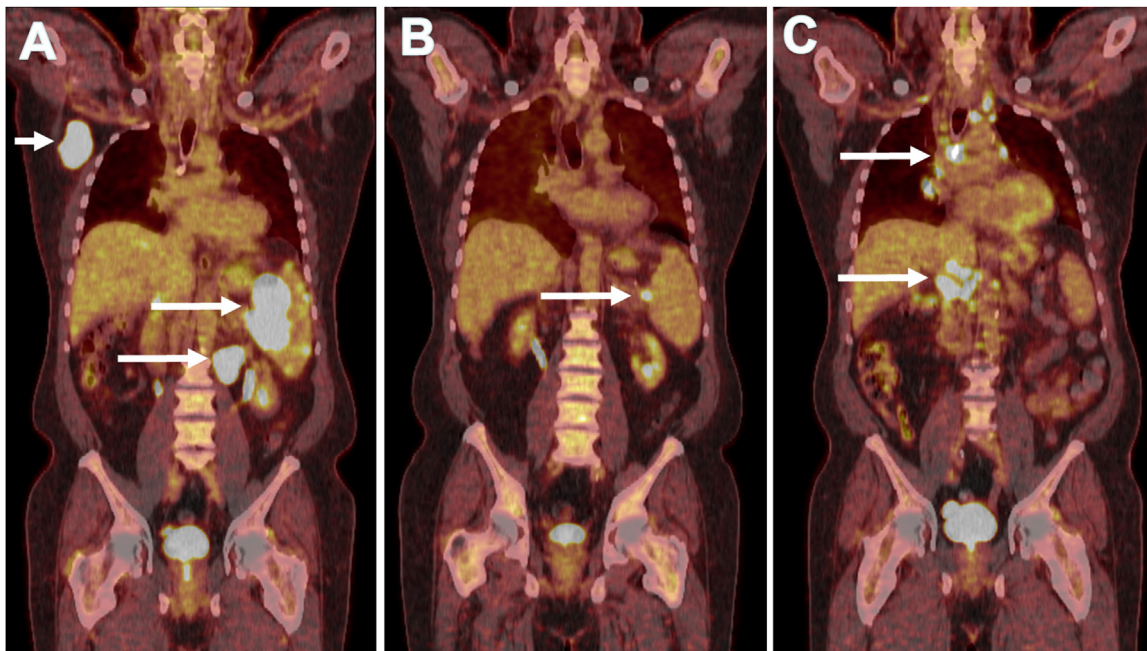


Fig. 1. Representative photos of the patient's excisional biopsy of a left inguinal lymph node. A) Hematoxylin and eosin stain showing diffuse large B-cell lymphoma. B) Immunohistochemistry showing Ki-67 index greater than 95%.

**Fig. 2.** Computerized tomography and positron emission tomography (CT-PET) scan from skull base to mid-thigh, coronal view. A) Staging CT-PET scan noted right axillary, splenic, and retroperitoneal adenopathy (white arrows) with intense fluorodeoxyglucose uptake. The maximum standardized uptake value was 26. B) CT-PET scan after completion of six cycles of R-CHOP revealed marked reduction in lymphadenopathy and associated hypermetabolic disease, though with a persistent small focus of hypermetabolic activity at the splenic hilum (white arrow) with a standardized uptake value of 11.5. C) Surveillance CT-PET scan three months after completion of consolidative radiotherapy displayed significant interval lymphadenopathy, with multiple, new, fluorodeoxyglucose-avid mediastinal, *peri*-hilar, peri-portal, and retroperitoneal lymph nodes (white arrows) with standardized uptake values ranging from 12.6 to 25.

anti-CD45 radiolabeled antibody and BEAM (carmustine, etoposide, cytarabine, melphalan) as a prelude to ASCT. And lastly, he was presented with the option of participating in a clinical trial of chimeric antigen receptor (CAR) T-cell therapy with a novel anti-CD19 construct plus durvalumab (a PD-L1 antibody). This was the choice he ultimately settled on after much deliberation and angst.

To confirm pathologic recurrence as a necessary requisite prior to clinical trial participation, the patient underwent an endo-bronchial ultrasound with trans-bronchial biopsies of several enlarged mediastinal and para-tracheal nodes. Fine needle biopsy revealed multiple non-necrotizing granulomas, without evidence of recurrent lymphoma. He additionally underwent a core needle biopsy of a right supraclavicular lymph node which also revealed granulomatous lymphadenitis with nearly complete replacement of normal lymph node architecture with non-caseating granuloma and no evidence of recurrent lymphoma, and with findings clearly favoring sarcoidosis (Fig. 3, A-C).

Pulmonary function tests (PFTs) showed a normal forced vital capacity (FVC) with an FVC ≥ 80% of predicted, with normal forced expiratory volume in one second (FEV1) with a FEV1 ≥ 80% predicted, normal FEV1/FVC ≥ 0.7, and only a mildly reduced diffusing capacity (DLCO) of 64%. Serum angiotensin converting enzyme (ACE) was mildly elevated at 79 U/L (normal 8–53). No ocular manifestations of sarcoidosis were identified by exam or magnetic resonance imaging of the brain.

Although intensely anxious due to persistent concerns that he might have recurrent DLBCL, he experienced no pulmonary symptoms (i.e., cough, dyspnea), nor did he have fevers, night sweats, or weight loss. He was diagnosed with stage I sarcoidosis and no systemic therapy was recommended. Twelve months later the patient remains well and without recurrent DLBCL.

## 3. Discussion

Our patient experienced significant hardship in the evaluation for relapsed lymphoma. While approximately 50–60% of patients with

DLBCL achieve and maintain a CR after first-line therapy, 30–40% of patients relapse, and 10% of patients are destined to have refractory disease [10]. s-line chemotherapy followed by ASCT, as well as new therapeutic agents including those currently available through clinical trials do, however, offer the possibility of cure for patients with relapsed or refractory disease [11–13].

The rationale for surveillance imaging is detection of preclinical relapse with the expectation of improvement in survival when tumor burden is low and remains sensitive to second-line chemotherapy. For DLBCL, however, the large majority of relapses are detected clinically and there is no compelling data to support routine imaging as a strategy that leads to improved patient outcomes [14–16]. In a prospective study of 552 patients with DLBCL who achieved a CR after induction chemotherapy, 104 (19%) relapsed [14]. The majority of those relapses (67; 64%) were identified before scheduled follow-up due to symptomatic disease. The remaining 37 relapses (36%) were detected at a scheduled follow-up visit, of which 24 had symptoms or abnormal physical exam findings. Of the 13 (12.5%) asymptomatic patients with imaging suggestive of recurrent disease, 4 were of other NHL subtypes. Surveillance imaging detected asymptomatic DLBCL relapse in only 9 of the 552 patients (1.6%) and there was no difference in survival among these individuals when compared to patients whose relapse was discovered clinically [14].

The utility of CT-PET scans is further diminished in the DLBCL surveillance period due to false positive findings that often lead to unnecessary, extensive and invasive evaluations. Among 151 patients with mediastinal lymphoma (57 with Hodgkin Lymphoma; 94 with NHL) who were followed with CT-PET scans after completion of front-line therapy, radiographic imaging suggested relapsed lymphoma in 30 of the 151 patients (20%) [17]. Histologic analysis confirmed relapse in only 17 of the 30 patients (57%), whereas the remaining 13 patients (43%) demonstrated either benign disease (nine patients with fibrosis; three patients with sarcoid-like granulomatosis) or an unrelated neoplastic condition (one patient). The importance of obtaining tissue for analysis if a CT-PET scan suggests relapse was further underscored in a
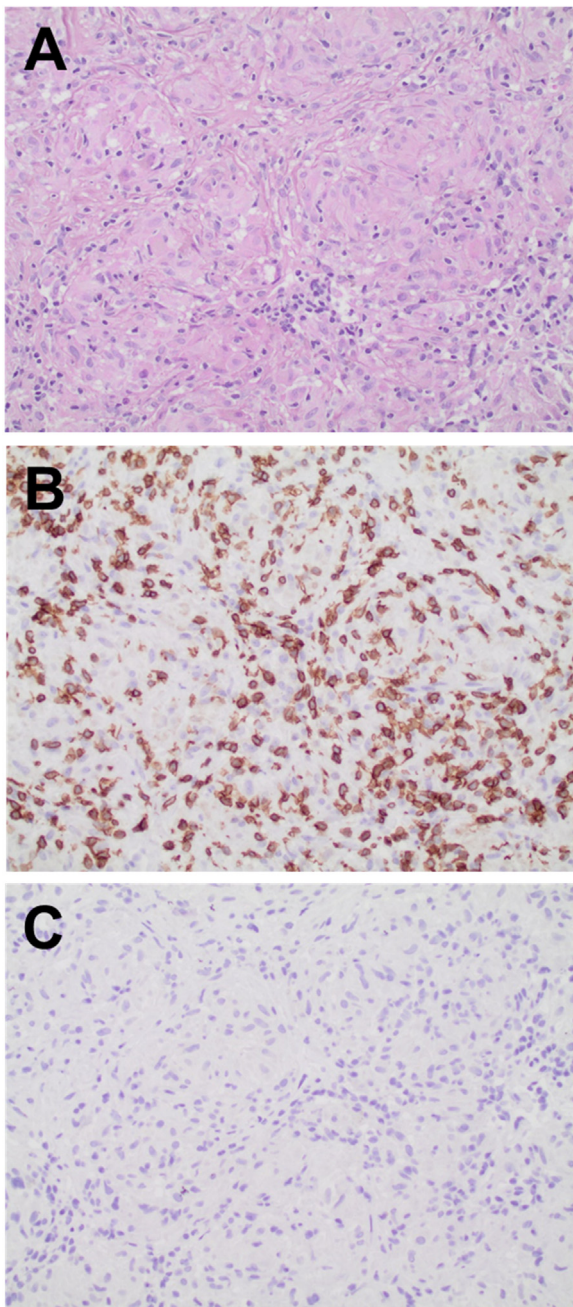
Fig. 3. Representative images of the patient's supraclavicular lymph node biopsy. A) Hematoxylin and eosin showing non-necrotizing granulomas. Immunohistochemical staining for CD3 (B) highlights small T cells (brown) and for CD19 (C) which was negative, without any B cells present.

study involving 103 patients with NHL, 49 of whom had scans which revealed findings suggestive of recurrent lymphoma [18]. Of those with suspected relapse, seven (14%) were found to have alternative diagnoses (aspergillosis in one, sarcoidosis in one, and secondary malignancy in five).

Current recommendations take these and other studies into account [19–23]. Surveillance CT and CT-PET scans are generally discouraged as their use does not offer survival benefit, are associated with significant false-positive rates, and expose patients to unnecessary radiation, biopsies, expense and anxiety, the latter of which was particularly salient to our patient's experience.

While our patient was clinically stable after completing chemotherapy and radiation therapy, there remained concerns for relapse

due to his high R-IPI score at diagnosis and a tumor biopsy which showed a high nuclear protein Ki-67 index. Ki-67 is synthesized at the beginning of cell division and is expressed during all active phases of the cell cycle ($G_1$, S, $G_2$, and mitosis) [24]. Ki-67 expression has been widely used in clinical practice as an index for the proliferative activity of numerous cancers, including NHL, and offers prognosis for survival; the higher the Ki-67 index, the poorer prognosis of survival [25].

With the introduction of immunotherapy (rituximab) to CHOP therapy, the survival rate for patients with DLBCL has considerably improved [26]. The R-IPI scoring system was developed to create a model for predicting outcomes in patients with aggressive NHL on the basis of clinical characteristics before treatment [27]. The scoring system utilizes a patient's clinical and disease characteristics at diagnosis (age > 60, Ann Arbor stage III-IV, Eastern Cooperative Oncology Group [ECOG] performance status $\geq$ 2, serum LDH, and extra-nodal disease sites) to provide a score that correlates with a particular prognosis for progression-free survival (PFS) and overall survival (OS). The R-IPI identifies three distinct prognostic groups, ascribing patients a very good (R-IPI score of 0; four-year PFS of 94%, four-year OS of 94%), good (R-IPI score of 1–2; four-year PFS 80%, four-year OS 79%), or a poor (R-IPI score of 3–5; four-year PFS 53%, four-year OS 55%) outcome, respectively [26]. Our patient's elevated R-IPI score, as consistent with a poor prognosis, raised concerns for potential relapse and likely contributed towards the overreliance on imaging studies in surveillance.

While this case highlights the challenges of monitoring patients for relapsed lymphoma and reinforces the recommendations against regularly scheduled imaging studies, it also serves to remind us that other causes of lymphadenopathy may be present even in the context of advanced stage NHL. Etiologies for lymphadenopathy are numerous and can be recalled by the pneumonic "MAGIC" which broadly includes malignancy, allergic and autoimmune disorders, granulomatous disease, infection and iatrogenic causes, and chronic disease states (Table 1) [28–32].

As was evident in this case, sarcoidosis, a multisystem inflammatory disorder of undetermined etiology, can manifest as diffuse hypermetabolic adenopathy on imaging. The disorder is characterized by T-lymphocyte infiltration, granuloma formation, and distortion of normal microarchitecture. The prevailing theory holds that sarcoidosis develops in genetically susceptible individuals from a cell-mediated immune response to one or more unidentified antigens [33]. The cell-mediated response to antigenic stimuli results in well-formed, non-caseating epithelioid granulomas [34].

Sarcoidosis is commonly associated with systemic symptoms such as fatigue, night sweats, and weight loss, which can mimic symptoms associated with malignancy. Pulmonary symptoms, however, are the most common and thoracic involvement (i.e., hilar adenopathy on radiograph) is seen in more than 90% of patients with sarcoidosis. PFTs often yield decreased DLCO and a restrictive physiology [33]. Sarcoidosis, usually an insidious and chronic disease, can present through involvement in the skin, eyes, and with lesser frequency, as cardiac and CNS manifestations [33–35]. Sarcoidosis may also present acutely as Lofgren syndrome. Lofgren syndrome is typically manifest by erythema nodosum, bilateral hilar adenopathy, and poly-arthralgia, whereby a presumptive diagnosis can be made without biopsy [29,33].

Whole-body PET scans may also suggest occult sarcoidosis through display of hypermetabolic activity. According to one study, among 139 patients with sarcoidosis, SUV activity ranged between 2.0 and 15.8 [36]. Imaging can suggest sarcoidosis; however, the diagnosis relies on the pairing of clinical and radiographic findings with histologic evidence of non-caseating granulomas. To obtain tissue, bronchoscopy with trans-bronchial biopsy is heavily utilized and has a diagnostic yield of 85% [33].

While sarcoidosis more often occurs in patients without a history of lymphoma, the overlap between sarcoidosis and lymphoma is an important one. Utilizing a Danish health-registry to review a series of

**Table 1**
MAGIC mnemonic – etiologies of lymphadenopathy.

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| M | Malignancy | Leukemia, lymphoma, solid organ cancer ± metastases [i.e., breast, lung, renal, colon, prostate], Waldenstrom macroglobulinemia; systemic mastocytosis] |
| A | Allergic / Autoimmune | Hypersensitivity pneumonitis, autoimmune diseases (i.e., dermatomyositis, rheumatoid arthritis, Sjögren syndrome, Still disease, systemic lupus erythematosus) |
| G | Granulomatous disease | Sarcoidosis, granulomatosis with polyangiitis, berylliosis, silicosis |
| I | Infection / Iatrogenic | Bacterial (i.e., tuberculosis, melioidosis, cat-scratch disease); viral (i.e., adenovirus, cytomegalovirus, hepatitis,human immunodeficiency virus, infectious mononucleosis (Epstein-Barr virus), herpes zoster, rubella); fungal (i.e., coccidiomycosis, histoplasmosis); parasitic; iatrogenic (i.e., medications, serum sickness) |
| C | Chronic conditions (with reactive lymphadenopathy) | Chronic obstructive pulmonary disease, congestive heart failure, bronchiectasis |

cases of coexistent sarcoidosis and malignant lymphoproliferative disease, Brincker and colleagues found that there were 5.5 times more cases of lymphoma observed in patients with a history of sarcoidosis than in the general population [37]. The syndrome linking sarcoidosis and lymphoma possessed several characteristics: the lymphoma occurred after a patient was found to have sarcoidosis; the diagnosis of sarcoidosis occurred at a later age than was typical in the general sarcoid population; and Hodgkin lymphoma occurred more frequently in sarcoidosis patients than would otherwise have been expected in the general population [9,29,37].

While Brincker's work suggests a mechanism whereby persistent immune system activation by sarcoidosis yields a lymphoproliferative state, there are also instances of sarcoidosis occurring after the diagnosis of lymphoma. London and colleagues reported on 14 such cases and through a literature review identified an additional 25 patients presenting with sarcoidosis following lymphoma [9]. Much like our patient, most of the patients developed sarcoidosis shortly after achieving a PR or a CR with chemotherapy for their lymphoma, arguing that the development of sarcoidosis may be related to an excessive immune response to the lymphoma cells, or reactive to chemotherapy (i.e., R-CHOP) [9]. In these patients, sarcoidosis was most commonly asymptomatic and was manifest by hypermetabolic lymphadenopathy.

## 4. Conclusion

In summary, this case illustrates the unusual presentation of sarcoidosis in an asymptomatic man presumed to have recurrent DLBCL. We highlight the lack of evidence to support routine imaging in surveillance for relapsed DLBCL as well as the importance of tissue sampling before altering the treatment plan. Despite our patient's incredible psychological strain, financial stress, and exposure to a battery of potentially hazardous tests, he remains asymptomatic, without need for systemic therapy for sarcoidosis, and without any suspicion for recurrent lymphoma.

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