Case report

Benign pulmonary nodular lymphoid hyperplasia (NLH) in an HIV infected patient; A diagnostic dilemma

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1. Introduction

Pulmonary lymphoid disorders span from benign lesions to various forms of malignant lymphoma. Interestingly, they may have similar clinical and radiographic presentations, making histopathological exam vital in differentiation. We present one such diagnostic conundrum. (see Tables 1 and 2)

2. Case

A 62-year-old Hispanic male presented with complaints of progressive shortness of breath for two weeks. This was initially with exertion; however, it progressed to shortness of breath at rest.

The patient described associated cough that had been present for over a month productive of yellow-brown phlegm with intermittent streaks of blood; along with generalized chest pain, rated 9/10 in severity, non-radiating, worse with coughing and exertion. He did not describe any alleviating factors. This constellation of symptoms was associated with fatigue, subjective fevers, chills, and a 10-pound weight loss.

The patient stated that he had visited his primary care physician who prescribed him a short course of prednisone 20 mg for an asthma exacerbation; however, this did not relieve his symptoms. He went back, and his dose was increased to 40 mg also without effect, prompting his visit to the ER.

His past medical history was significant for asthma and short stature. He had no significant surgical history. He denied alcohol use, described past drug abuse with marijuana and cocaine, and was a former cigarette smoker who quit 15 years ago with a 20 pack year smoking history. The patient emigrated from Puerto Rico approximately 15 years ago and was a farmer by profession. His family history was non-contributory. His home medications included prednisone 40 mg, Advair, Spiriva, guaifenesin, zolpidem and benzonatate. When examined in the ER, the patient’s vital signs were BP 125/78, HR 120, RR 20, SpO2 of 95%, and temp of 36.8 °C. He was a pleasant, well-groomed, well-nourished, mildly anxious male laying in bed in no acute physical distress. His head/eyes/ears/nose/throat exam was unremarkable. There was no palpable lymphadenopathy, or JVD noted. Chest exam revealed bilateral diminished breath sounds with fine crackles at the bases. Pericardial, abdominal, and skin exam were all unremarkable. Laboratory data was significant for hemoglobin 12.6 g/dL, WBC 20.5, calcium 8.4, AST 77, ALT 300, albumin 2.2 and glucose 116. Troponin was negative. EKG showed sinus tachycardia. Chest X-ray showed: Elevated diaphragm, small lung volumes, mild-moderate cardiomegaly and widened mediastinum along with bilateral patchy airspace opacities with a left mid lung round density measuring approximately 40 mm in largest diameter. A previous CXR obtained one week prior also showed this density but it was smaller at 25 mm. A CT scan showed multiple round masses throughout the lung fields (Fig. 1). The patient was admitted to the hospital for further work-up and covered broadly with vancomycin and zosyn. Sputum, blood cultures, and urinary antigens were negative. He was found to have Hepatitis C (viral load: 2161510) and was HIV positive (CD4 of 222). Aspergillus, Cryptococcus, G6PD, RPR, Toxoplasmosis work-up were negative. AFP, PSA, CEA were negative. Autoimmune workup including ANA, C-ANCA, P-ANCA were negative. Atypical PANCa antibodies were positive at 1:32.

The patient’s clinical course waxed and waned. He remained febrile on broad-spectrum antibiotic coverage and ultimately underwent a BAL with biopsy of the left upper lobe lesion. Cultures grew Staphylococcus aureus, which was treated with vancomycin. AFB and fungal cultures were negative. TEE did not show any vegetations. The biopsy was insufficient for pathological diagnosis. However, the patient continued to be febrile after treatment and ultimately underwent a right thoracoscopy and biopsy of the right lobe lung lesion. AFB, fungal, and bacterial cultures were negative. The preliminary diagnosis was lymphomatoid granulomatous. EBV and CMV were checked both of which were positive. EBV levels in the serum < 200 and CMV serum levels 4227. Final pathological diagnosis showed: lymphoplasmacytic infiltrate with fibrosis, focal necrotizing granulomatous inflammation, without vasculitis. CD20-positive B cells were distributed as nodules with PAX-5

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Table 1
Classification of pulmonary lymphoproliferative disorders.

| Pulmonary Lymphoproliferative Disorders |
|-----------------------------------------|
| Non-Neoplastic                           |
| Nodular lymphoid hyperplasia             |
| Follicular bronchiolitis                 |
| Lymphoid interstitial pneumonia          |
| Neoplastic                               |
| Extra-nodal marginal zone lymphoma of MALT |
| Diffuse large B cell lymphoma            |
| Lymphomatoid granulomatosis             |
| Secondary                                |
| Non-Hodgkins lymphoma                    |
| Hodgkins lymphoma                        |
| Immunocompromised States                 |
| Acquired immune deficiency syndrome (AIDS)-related lymphoma (ARL) |
| Post-transplantation lymphoproliferative disorder |

staining limited to germinal center lymphocytes. There was a pre-dominant population of CD3, 2, 5, and seven positive T cells and CD8 > CD4 cells. ISH recognized EBV RNA in scattered small lymphocytes. No evidence of malignancy or organisms. Two independent outside pathologists from different institutions confirmed this. The final pathological diagnosis was necrotizing granulomatous inflammation with lymphoid hyperplasia.

The patient had complete radiological resolution after a few months when he had a repeat CT scan which did not show any lesions as seen before (Fig. 1F). It is unclear whether the resolution of the primary process was due to the use of steroids, antibiotics or antiretrovirals since he received all these therapies subsequent to each other.

The findings in his case favor a diagnosis of early (grade 1) PLG or nodular lymphoid hyperplasia (NLH), further supported by resolution of disease after treatment with antibiotics and antiretroviral therapy. Pathologically and clinically nodular lymphocytic hyperplasia was the most likely diagnosis.

3. Discussion

Primary lymphoid lesions of the lung embody a vast array of pathologies principally divided into non-neoplastic, neoplastic, secondary and those associated with immunocompromised states [1,2]. The differentiation between these subgroups is chiefly based on pathological study due to the significant overlap in the clinical and radiological presentation; almost always-requiring immunohistochemistry and genetic analysis along with a favorable clinical outcome done at the Armed Forces Institute of Pathology. This study represents a large portion of our current understanding of the diagnostic criteria and disease characteristics [7].

Table 2
Comparison of Nodular lymphoid hyperplasia, MALT and lymphomatoid granulomatosis.

| Lymphoproliferative Disorder | Nodular Hyperplasia | MALT | Lymphomatoid Granulomatosis |
|------------------------------|---------------------|------|-----------------------------|
| Clinical Presentation       | Usually asymptomatic; cough, dyspnea and fatigue | Usually asymptomatic; cough, dyspnea, weight loss, hemoptysis | Symptoms: cough, fever, ras; Evidence of underlying immunocompromised state: drugs, HIV/AIDS and autoimmune disease |
| Radiographic findings       | Associations with collagen vascular disease or gammaglobulinemia | Autoimmune disease association, smoking and HIV | CT: nodules, masses, and/or areas of consolidation; single or multiple lesions; bronchovascular distribution; air bronchograms often present; mediastinal and hilar lymphadenopathy PET/CT: hypometabolic lesions present though reports of minimal to no uptake have been cited |
| Pathological features       | Polyclonal hyperplasia; reactive lymphocytes, peribronchial location; may have some infiltration into alveolar septa though without invasion | Monoclonal proliferation of lymphocytes with plasma cells (Dutch bodies may be present) and germinal centers present (some with features of being reactive); lymphangitis spread, invasion, | Angioinvasive/angiodestructive lesion; proliferation of CD30 B cells, atypical EBV B cells, necrosis and reactive T cells |

Due to the rarity of this disease, radiological findings have been gleaned from case reports and descriptions of chest radiographs. Classically, it has been described as a single pulmonary nodule, consolidation, or mass; however multiple nodules were first described in 2005 [2,3,9-11]. Nodules usually range in size from 0.6 to 6 cm in diameter with an average of 2 cm; though up to 10 cm have been described. Occasionally 2-3 nodules may coalesce to form a larger mass. These nodules may be associated with ground glass opacities. Mild focal lymphangitic spread may be noted [2,3,7]. Utility of PET-CT scan has not been established, though reports indicate that there may be some uptake further confounding the radiological differentiation between neoplastic conditions (MALT) and nodular hyperplasia [12].

The pathological features consist of numerous reactive germinal centers with preserved mantle zones and mature plasma cells. The lymphocytes and plasma cells are polyclonal. The plasma cells may

disease is based on clonal proliferation; non-neoplastic being polyclonal in nature while neoplastic is monoclonal [2]. Furthermore, the degree of pulmonary involvement largely differentiates between the various benign lymphocytic disease: nodular lymphoid hyperplasia, follicular bronchiolitis, and lymphoid interstitial pneumonia [1].

Follicular nodular hyperplasia represents a rare disease entity surrounded by much controversy. The disease was first described by Saltzstein in 1963 who coined the term "psudolymphoma" due to the low grade appearance of the small lymphocytes, mixed population of plasma and lymphocyte cells along with follicle centers and a re-assuring clinical course. The disease later fell into dispute in the 1980s upon discovery that many of these lesions even those with reactive germinal centers actually represented low grade B cell lymphomas of mucosa-associated lymphoid tissue (MALT). The term "psudolymphoma" fell out of favor in support of this thought process [5,6]. The confirmation of follicular nodular hyperplasia as a separate entity was later established in a small case series of 14 patients by immunohistochemistry and genetic analysis along with a favorable clinical outcome done at the Armed Forces Institute of Pathology. This study represents a large portion of our current understanding of the diagnostic criteria and disease characteristics [7].

Follicular nodular hyperplasia is a rare, benign, localized lymphoproliferative disorder of unknown etiology. As previously stated, in a review done at the Armed Forces Institute of Pathology, only 14 cases were identified and proven. A more recent review of the literature described 22 cases reported [8]. Consensus among these reports indicate that the median age of presentation is 65 years (range of 19-80) and that the majority of patients were asymptomatic (60–70%). When symptoms occurred they were cough, dyspnea, generalized malaise, pleuritic chest pain and/or hemoptysis [7,8].
show Russell or Mott bodies. These areas are sharply demarcated from surrounding parenchyma and usually have central scarring. Features of organizing pneumonia are usually present around the periphery. Giant cells may also be present. Local lymphangitic spread may also be present, however invasion is not a characteristic. A reactive \( \sim \) arrangement is seen upon staining, with germinal centers predominantly consisting of CD20 B cells and interfollicular lymphocytes consisting of CD3, CD5, and CD43. There is no evidence of immunoglobulin light or heavy chain gene re-arrangement [3,13].

Classically, much overlap exists between MALT and FNH. A histopathological confirmation is absolutely crucial in establishing the diagnosis. Coincidentally, MALT are usually asymptomatic lesions discovered incidentally. Clinical features are similar to both pathologies: dyspnea, fatigue and cough. Radiologically, the lesions range from single nodule/opacity to multiple nodules or areas of consolidation with bronchiectasis, bronchiolitis, air bronchograms and diffuse interstitial lung disease. Evidence of peribronchiolar invasion or hilar lymphadenopathy may be present. Histologically, the tumors are composed of small lymphocytes, plasmacytoid lymphocytes with Dutcher bodies, and some immunoblasts. These tumors are dense at their core but have striking lymphangitic invasion into the airways, vessels and pleural space. In contrast, the lesions of follicular nodular hyperplasia never demonstrate invasion even when located subpleurally. Another overlapping feature between reactive lesions and MALT lymphomas are the presence of multinucleated giant cells or sarcoid-like granulomas (20–50% of cases) and reactive germinal centers (20–85% of cases). Interestingly, a major portion of these centers stain polyclonal. The granulomatous inflammation and reactive germinal centers are non-specific but give another layer of complexity to the diagnosis requiring adequate tissue sample and expert reading. Immunohistochemical stains demonstrate B cells expressing CD 19, 20, Bcl2 and occasionally CD43 along with lymphoid infiltrate with invasion of follicular structures to the bronchial and bronchiolar epithelium. The preponderance of tumors demonstrate monoclonal immunoglobulin light chains in paraffin sections. 60-70% of tumors show clonal re-arrangements of joining regions of the heavy chains, a useful differentiating feature. Overall, lymphangitic spread, pleural invasion, bronchial destruction and the above mentioned immunohistochemical and molecular patterns differentiate MALT from a reactive lesion [2,3,6,13–16].

Intriguingly, the above case was initially thought to represent pulmonary lymphomatoid granulomatosis; first described in the literature by Liebow et al. It is characterized by an angioinvasive/angiodestructive character. The disorder itself is very rare and usually associated with an underlying immunocompromised state, such as AIDS, Wiskott-Aldrich syndrome and those who have received a transplant. Clinically, it is a multi-organ disease present in the lung, skin or CNS. Radiologically, most patients will have bilateral peripheral lung nodules, measuring up to 9 cm in diameter and commonly in the lower zones. These nodules may coalesce and cavitate mimicking Wegner's granulomatosis or metastatic disease. Of note, nodules may disappear or migrate due to the waxing and waning nature of the disease. Histologically, there is a triad of nodular lymphoid infiltrate of lymphocytes, plasma cells and inconstant amount of macrophages. There is transmural infiltration to the arteries and veins along with necrosis within the nodules. The lesions around the arteries or veins (angiocentric) demonstrate lymphocytes with elongated, twisted nuclei and atypical large mononuclear lymphoid cells. These atypical cells stain positive for CD20, CD79a, and EBV and negative for CD15. The small lymphocytes are reactive in nature and polyclonal with CD4 positive outweighing CD8. The degree of EBV infected atypical cells, amount of necrosis and number of large atypical cells stratifies the disease into different grades; a determinant of prognosis and treatment course.
Lymphoid Interstitial pneumonia (LIP) was on the list of differential diagnoses given the nodular lesions and immunodeficiency, but presence of granulomatous inflammation in our case made it less likely. Typical features of LIP include diffuse interstitial infiltration with predominantly alveolar septal distribution, mostly with T/B Lymphocytes, plasma cells, and macrophages and lack of Dutcher bodies and necro-tizing granulomas [20].

As previously noted, much clinical overlap exists between the lymphoid-lymphoproliferative disorders of the lung. This spectrum of disease is emerging in diagnostic consideration due to awareness and improved management of underlying immunocompromised states. Clinically and radiologically, the presentations of these diseases may mimic each other as well as other pathologies. The cornerstone of diagnosis remains on obtaining an adequate sample and diligent pathological analysis. Advances in immunohistochemical techniques, molecular biology and FISH subtly differentiate among the various pathologies as such improving patient stratification and clinical outcome.

Disclosure
No conflicts of Interest.

Appendix A. Supplementary data
Supplementary data to this article can be found online at https://doi.org/10.1016/j.rmcr.2018.10.024.

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