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Case Report

Primary Pulmonary Peripheral T-cell Lymphoma Mimicking Metastatic Carcinoma to the Lung in a Patient with Prior History of Breast Carcinoma. Case Report with Uncommon Clinical Presentation and Brief Review of the Literature

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Abstract

Primary pulmonary lymphomas (PPLs) are very uncommon types of lymphomas, usually B-cell-derived lymphomas; reports of primary pulmonary peripheral T-cell lymphoma (PTCL) are not commonly reported. These patients are diagnosed with PTCL-not otherwise specified (PTCL-NOS) since they cannot be further categorized into discrete disease categories. PTCL-NOS is the most common subtype, accounting for about 22% of PTCL cases in Asia and 30–35% of PTCL cases in Europe and North America. Most cases with PTCL-NOS manifest as nodal lymphomas, yet extra-nodal involvement during the disease's early stages or relapses is not unusual. We present a case of a 59-year-old female with a history of left breast mucinous ductal carcinoma who presented with multiple lung nodules initially mistaken for metastatic breast carcinoma. Specific histomorphologic features and immunohistochemistry analysis confirmed the diagnosis of primary peripheral pulmonary T-cell lymphoma, not otherwise specified. We review the pertinent literature, including clinical presentation, diagnosis, pathology, and management.

Keywords: T-cell lymphoma, Carcinoma, Pulmonary, Primary, Metastasis

Abbreviations

Primary pulmonary lymphoma (**PPL**), Primary pulmonary peripheral T-cell lymphoma (**PTCL**), Primary pulmonary peripheral T-cell lymphoma, not otherwise specified (**PTCL-NOS**). Non-Hodgkin Lymphoma (**NHL**), Immunohistochemistry studies (**IHC**).

INTRODUCTION

Primary pulmonary lymphoma (PPL) is a rare malignancy, which affects one or both lungs (parenchyma, bronchi, and trachea) and shows no signs of extrapulmonary metastasis for three months after onset [1]. It generally accounts for less than 1% of Non-Hodgkin Lymphoma (NHL) and 3-4% of extranodal NHL. Among lung malignancies, its contribution is only 0.5-1% [2,15]. On radiographs, these may appear as consolidations, well-defined masses, or nodules [2]. 70-80% of PPL cases are of B-cell origin, often arising from bronchial mucosa-associated lymphoid tissue (MALT). [1]. Most cases of primary pulmonary lymphoma are of the B-cell lineage, and the disease is often localized to bronchi-associated lymphoid tissue. Very few cases of primary pulmonary peripheral T-cell lymphoma (PTCL) have been reported, and the imaging features of this rare malignancy are poorly characterized [3]. Metastasis to the lung is the most common cause of multiple well-demarcated lesions in the elderly. Primary cancers usually arise in the lungs, breast, or abdomen. Therefore, radiographically, when PPL appears as multiple masses and nodules, it can easily be mistaken for primary lung cancer or metastasis. [2].We present a primary pulmonary peripheral T-cell lymphoma case that was initially mistaken for metastatic breast carcinoma, and we review the pertinent literature. The reported studies on PPL and the number of cases are limited. Understanding this type of disease needs to be strengthened. [4]

CASE PRESENTATION

A 59-year-old female with a history of left breast mucinous ductal carcinoma seven years ago presented with shortness of

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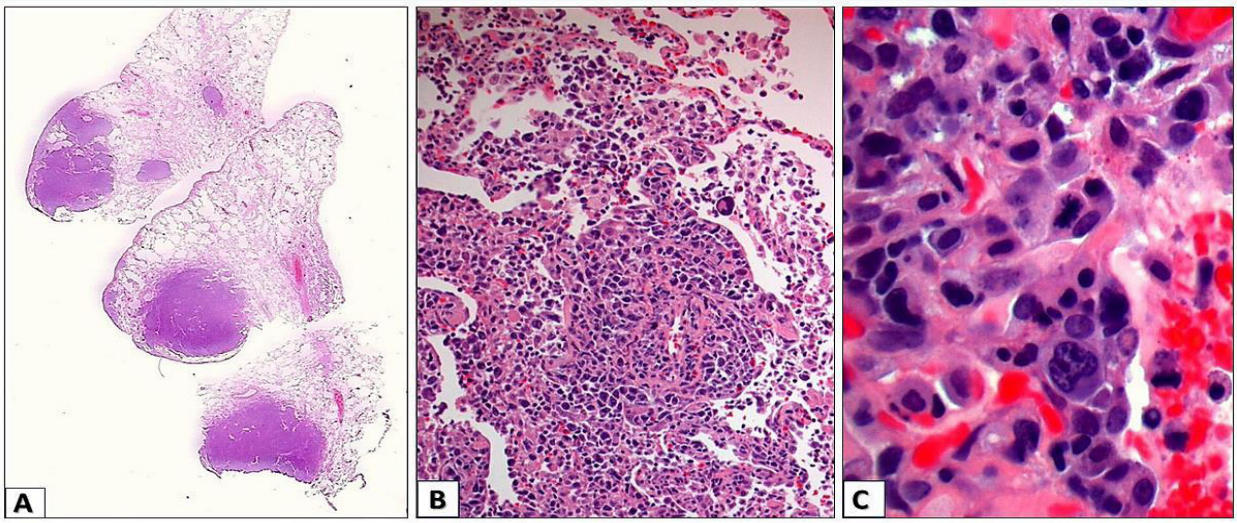
breath, fever, cough, and dyspnea. In addition, the patient noticed an enlarging 2.5 cm nodule at the site of prior surgery of the left breast carcinoma. Initial Chest Computer Tomography (CT) scans showed bilateral pulmonary nodules, the largest measuring 3 cm and the smallest measuring 1.2 cm, mimicking metastatic carcinoma in the lung.

Primary breast carcinoma records from seven years ago showed a 2.2 cm infiltrating moderately differentiated mucinous ductal carcinoma of the left breast. Six left axillary lymph nodes were removed and were negative for metastatic carcinoma; however, the tumor displayed vascular invasion, and one surgical margin was close to the tumor. The breast carcinoma was 90% positive for estrogen, negative for progesterone, negative for Her-2, high proliferation with 20% nuclear staining with Ki-67, and had diploid DNA. The tumor was surgically excised with safe but close margins. The patient received postoperative radiotherapy and hormonal therapy.

At the current presentation, a fine needle aspiration cytology specimen with cell block was obtained from the new breast nodule, and the pathology diagnosis confirmed a recurrent breast ductal carcinoma [Figure 1]. The lung nodules were clinically consistent with recurrent metastatic carcinoma. For further investigation of the lung masses, tissue cultures for bacteria and fungus were negative. A transbronchial biopsy of one of the lung nodules showed interstitial fibrosis with moderate lymphocyte infiltration and focal necrosis but was nondiagnostic and insufficient to clarify the condition. Surgical lung wedge biopsies were done. Microscopic examination showed a tumor consisting of atypical cellular infiltrates without a specific pattern, infiltrating lung parenchyma, frequently around blood vessels. The infiltrating tumor cells displayed anaplastic features, with large cells showing moderate to abundant pale cytoplasm and large pleomorphic nuclei with coarse chromatin and prominent eosinophilic nucleoli. Mitotic figures and apoptotic debris were ample (>12 mitosis/10 HPF) [**Figure 1 A-B-C**]. Although the infiltrates were clinically consistent with metastatic disease, the histomorphology was more consistent with an anaplastic malignant tumor with a possible differential diagnosis, including carcinoma, sarcoma, lymphoma, or melanoma. Immunohistochemistry studies were utilized for a definitive diagnosis. The tumor cells did not express CD15, PAX-5, or ALK. In situ hybridization for EBV (EBER) was negative. Other immunohistochemical stains, including cytokeratin AE-1/AE-3, TTF-1, GCDFP-15, ER, PR, CD20, S100, HMB45, CAM52, HMWCK, CK903, EMA, CD34, CD45, CD56, DESMIN, MYOGENIN, NSE, SMA, and SYN, were negative. VIMENTIN, FLI1, and CD31 were focally but strongly positive.

Consultation requested additional studies that showed a subset of cells expressing CD30, and the addition of CD3 to the panel was strongly positive. Although the lung infiltrates were clinically strongly consistent with metastatic disease from the primary breast carcinoma, the histomorphology and immunohistochemical studies were not supportive of metastasis from the primary breast carcinoma, and the final diagnosis of the case was primary pulmonary peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS).

The recurrent breast nodule was surgically excised with safe margins, followed by radiation. The lung T-cell lymphoma was treated with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP). The patient showed significant improvement



Figurere 1 Microscopic examination of lung biopsy
1A: Low power view showing infiltrating lung nodules (H&E stain X20)
1B: Intermediate power view showing atypical cellular infiltrates without a specific pattern, infiltrating lung parenchyma, frequently around blood vessels (H&E stain X40)
1C: High power view showing tumor cells displaying anaplastic features, with large cells showing moderate to abundant pale cytoplasm and large pleomorphic nuclei with coarse chromatin, frequent mitosis and prominent eosinophilic nucleoli. (H&E stain X60)

with a gradual decrease in the size of the lung nodules, followed by their disappearance on follow-up CT scans. The patient was followed up for 32 months with no evidence of treatment failure or spread of the disease.

DISCUSSION

Primary pulmonary lymphoma (PPL) is more commonly of B cell origin, but the disease course can be aggressive when of the uncommon T cell origin [5]. PPL is more common in the elderly, and older than 60 years is significantly associated with a poor prognosis [4]. Patients aged 60 years or older with elevated LDH and β2-MG and clinical stage II2E or higher and those who did not receive surgical treatment had a poor prognosis [4]. However, smoking, PS score (which describes the status of symptoms and functions concerning ambulatory status and need for care), tumor location, and degree of involvement often influence prognosis in patients with PPL [5]. Chen et al. found that higher β2-MG levels were significantly associated with higher invasive potential and greater tumor burden. [6].

The clinical features of primary pulmonary peripheral T-cell lymphoma (PTCL) include very nonspecific symptoms such as fever, productive cough, and dyspnea [5]. The not-otherwise-specified (NOS) subtype also presents with generalized lymphadenopathy, with or without extranodal disease [7]. The lymphadenopathy may be associated with weakness and fatigue depending on the grade and rate at which the nodes are growing. High-grade nodes grow rapidly and are more associated with constitutional/ B cell symptoms. Low-grade nodes are slower growing over months to years and are associated with hepatosplenomegaly and evidence of cytopenias such as anemia, bleeding, or increased susceptibility to infections [7]. Extranodal disease is dependent on the affected tissue and is not always present. If present, it can involve the GI tract, where the patient may experience early satiety and GI bleeding, neurological symptoms such as headache, and thyroid involvement [8].

PTCL, not otherwise specified (PTCL-NOS) is a diagnosis of exclusion and is the most common subtype. Other subtypes and possible differential diagnoses include anaplastic large cell lymphoma (primary systemic), T follicular helper cell lymphoma (Tfh), extranodal NK/T cell lymphoma (nasal type), subcutaneous panniculitis-like T cell lymphoma, enteropathy associated T cell lymphoma, monomorphic epitheliotropic intestinal T cell lymphoma, and hepatosplenic T cell lymphoma [7, 8]. Many of these subtypes carry similar clinical presentations with only slight variations and can be better differentiated using immunohistochemistry (IHC) studies and histomorphologic criteria, while some of the latter originate outside of lung tissue [8]. T follicular helper cell lymphoma also presents clinically with generalized lymphadenopathy and constitutional symptoms; however, involved lymph nodes can display a paracortical infiltrate of atypical lymphoid cells and inflammatory cells [7]. PTCL-NOS does not display the same morphologic features of Tfh lymphomas and lacks tumor markers expressed by normal T follicular helper cells. Anaplastic large cell lymphoma presents with painless lymphadenopathy, with or without systemic symptoms, and has a diffuse pattern of CD30 positive cells [7]. Adult T cell leukemia-lymphoma can be clinically distinguished by lytic bone lesions and skin lesions in addition to HTLV-I studies [7]. Only a few non-malignant diseases can resemble PTCL-NOS, namely autoimmune lymphoproliferative syndrome (ALPS) [7]. Since ALPS is inherited, it is easily distinguished from PTCL by its early age of onset and organomegaly; thus, it is an easier differential diagnosis to rule out.

Due to the overlap in histology and pathology of the various lymphomas, it is crucial to understand the nuances of imaging studies to make the correct diagnosis. After gathering a pertinent history and physical exam, the initial chest CT often displays bilateral pulmonary nodules. However, this leads to a broad differential [9]. Pulmonary T cell lymphoma is diagnosed by transbronchial or computed tomography (CT) guided needle biopsy to analyze morphology [9]. As in our presented case, if this is inconclusive, a surgical lung wedge biopsy can be performed for further investigation of tumor cells since PTCL-NOS is a diagnosis of exclusion [9].

Extranodal PTCL is challenging to diagnose by histology alone because it can often be difficult to delineate from a reactive process. Although certain lymphomas can have striking atypia in large cells, like diffuse large B-cells, immunohistochemistry is necessary to demonstrate monoclonality. However, in obvious cytologic malignancy, stains showing specific B-cell or T-cell origin are all needed to confirm lymphoma [10]. In our case, the patient was definitively diagnosed with T-cell lymphoma based on strong CD3 positivity, CD20 negativity, and degree of histomorphologic malignant features, i.e. (nuclear pleomorphism, lung invasion, and robust mitosis). Peripheral T-cell lymphoma NOS is a heterogeneous category of mature T-cell lymphomas that do not fall into the specifically defined mature T-cell lymphomas [11]. The histomorphology of PTCL-NOS broadly consists of medium-sized and large cells with irregular, pleomorphic, hyperchromatic nuclei and many mitotic figures [12]. Due to our immunophenotype (ALK-and Partial CD30+), ALK negative-Anaplastic Large Cell Lymphoma was a specifically defined T-cell lymphoma high in the differential. However, the characteristic histomorphologic, hallmark cells and strong CD30 positivity indicative of Anaplastic Large Cell Lymphoma were not present in our case. Furthermore, on the genomic level, two types of PTCL-NOS are characterized by over-expression of TBX21 and GATA3; the latter is associated with a poorer clinical course and shorter overall survival [13]. At the time of diagnosis, these gene expression profiling alterations were not well defined or described and thus unavailable.

Peripheral T-cell lymphoma (PTCL) represents a diverse group of T-cell lymphomas. Generally, the prognosis for PTCL patients is unfavorable. Currently, management strategies for PTCL include response-guided therapy, which entails conducting a positron emission tomography (PET) scan after three cycles of induction chemotherapy (PET3). This benefit is

that refractory disease can be identified more promptly, enabling earlier implementation of appropriate care. [14]. Reported management also included a CD30-positive induction regimen involving brentuximab vedotin (BV), an antibody-drug conjugate targeting CD30 [14]. CD30 pessimistic induction is another regimen where CD30 expression is minimal or absent; standard induction therapy comprises anthracycline-based chemotherapy [14]. Consolidation therapies are considered in patients who achieve a complete or partial response to induction therapy. Since the disease control achieved during induction therapy is often not sustained long-term, post-induction management is individualized based on disease presentation, age, and overall fitness [14]. After therapy completion, patients are regularly monitored for relapse and potential adverse effects related to treatment [14].

For subtypes of PTCL, the treatment regime consists of CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) chemotherapy, or EPOCH (etoposide added to CHOP) chemotherapy [3]. CHOP provides 60% complete remission and a 30-50% five-year survival rate [5]. Temporary management includes systemic corticosteroids to stabilize the patient to undergo surgical biopsy. There is a possible chance of a cure if the tumor is localized for surgical resection [9]. Patients with PTCL generally have a worse prognosis due to life-threatening complications, including infections, hypercalcemia, and tumor progression. [5] The prognosis is determined by various models, including the International Prognostic Index, Prognostic Index for PTCL, and the International Peripheral T cell Lymphoma Project score [7].

Primary pulmonary peripheral T-cell lymphoma is an uncommon condition, typically has nonspecific clinical and radiographic symptoms. Consequently, it's imperative to identify and diagnose as soon as feasible. These lymphomas generally have a poor prognosis; more severe treatment regimens may be recommended for recurring bilateral illness. We are presenting this case to highlight the significance of primary peripheral pulmonary T-cell lymphoma in the differential diagnosis of lung tumors. With continuing investigation, we seek to improve patient outcomes by increasing awareness of this malignancy and advancing the development of safe, effective detection and treatment options.

Human subjects: Ethical review and approval were not required for the study on human participants following the local legislation and institutional requirements. The paper has been sufficiently anonymized to keep the patient's confidentiality.

Conflicts of interest: In compliance with the ICMJE uniform disclosure form, all authors declare the following:

Payment/services info: All authors have declared that no financial support was received from any organization for the submitted work.

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Other relationships: All authors have declared that no other relationships or activities could appear to have influenced the submitted work.

Patient's consent: Patients was lost to follow-up, and all attempts to reach the patient or family member were unsuccessful. Therefore, the paper has been sufficiently anonymized to maintain patient confidentiality.

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