Primary Pulmonary T-Cell Lymphoma Occurring Six Years after Breast Carcinoma: A Case Report and Literature Review

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Abstract

Primary pulmonary lymphoma (PPL) is a rare entity. PPL cases of T-cell origin represent a small, even less frequent subset. Only 19 such cases of T-cell PPL have been reported in literature, with none having a history of prior radiation or chemotherapy. Reported here, is a case of primary pulmonary peripheral T-cell lymphoma (PTCL) in a 63-year-old woman with a significant history of breast carcinoma six years prior, treated by wide local excision followed by standard adjuvant chemotherapy and radiation. Despite such rarity, PPL/PTCL should be included in the differential of pulmonary nodules, regardless of the clinical scenario or pretest probabilities. This case highlights the problems in diagnosing this entity, the historical epidemiologic relationship between breast cancer and lymphoma. It also highlights a distinct opportunity to examine errors in medical diagnoses and potential inclusions in future differential diagnoses algorithms.

INTRODUCTION

A distinct problem of diagnosing primary pulmonary T-cell lymphomas is the resemblance to many inflammatory or other neoplastic conditions as they have no clinically or radiologically distinguishable features. Even pathologic differentiation can be troublesome, since they mimic undifferentiated metastatic carcinomas by sharing the common characteristics of diffuse growth pattern, cytologic atypia, and are negative for many immunohistochemical stains. A useful consideration of this case presents opportunities to include rare entities in the differential work up clinically for the sake of reducing potentially missed diagnoses and improving patient outcomes.

CASE REPORT

Initial clinical, radiologic, and pathologic findings

A 63-year-old woman with a history of left breast carcinoma six years prior to encounter presented with shortness of breath. Her original breast tumor was a mucinous adenocarcinoma which was treated by wide excision and sentinel node biopsy. A metastatic workup was negative at that time. The surgical specimen showed a 2.0 cm invasive tumor, nuclear grade 2, with a close (0.1 cm) margin and extensive ductal carcinoma in-situ (DCIS) measuring 2.7 cm. There was vascular invasion, with a close (0.1 cm) margin and extensive ductal carcinoma in-situ (DCIS). By routine and in-situ immunohistochemical (IHC) staining. Estrogen receptor (ER) immunostaining of the invasive tumor showed 90% strong positivity, while the progesterone receptor (PR) and Her2 IHCs were negative. The final pathologic stage was pT1c N0 (sn) (i-). The patient received standard postoperative chemotherapy and local radiation.

When she returned with the presenting symptom of shortness of breath six years later, a computed tomography (CT) scan of the chest demonstrated multiple small bilateral multilobular pulmonary nodules, which were suspected to be metastatic breast carcinoma. No masses were present in the mediastinum. Multiple small subcutaneous nodules were also present in the left breast, adjacent to the post-surgical scar. No other metastases or tumors were identified beyond the lung or breast by further imaging studies, and the peripheral blood showed no hematologic abnormalities. No significant or appreciable lymphadenopathy was identified.

Wedge biopsies of the right middle and lower lobe lung nodules were performed and showed diffuse infiltrates of highly pleomorphic cells within the lung parenchyma. There were many mitotic figures, apoptotic cells, and focal accentuation around blood vessels without invasion or destruction of their walls (Figure 1). This was inconsistent with the original breast carcinoma morphology. Except for vimentin, all initial IHC stains were negative (AE-1/AE-3, TTF-1, GDCFP-15, ER, PR, CD20, S100, HMB45, CD15, PAX-5, ALK, CAM 5.2, CK903, EMA, CD34, CD45, CD56, desmin, myogenin, NSE, SMA, and SYN). Based on the morphology and IHC staining, these lung biopsies were interpreted as an "undifferentiated pleomorphic malignant neoplasm, consistent with metastatic tumor of uncertain primary site," or simply, a cancer of unknown primary (CUP) site.

Fine needle aspiration of breast nodules, and additional immunohistochemistry

A subsequent fine needle aspiration (FNA) of the subcutaneous pericicatricial nodules in the left breast, performed two weeks...
after the lung surgery, revealed malignant cells morphologically consistent with recurrent or metastatic breast carcinoma, and were very different from the pleomorphic malignant cells of the lung tumors. No cell block was available from the FNA material to perform IHC stains, but the additional review provided by the FNA prompted the performance of additional IHC stains on the lung biopsy material. The malignant cells in the lung stained positively for the T-cell markers CD3 and FL-1 (Figures 2a, 2b). Although not specific by itself, FL-1 stains represent a theoretical percentage of PTCL cases most consistent PTCL diagnoses not otherwise specified (PTCL-NOS); a CD30 IHC stain was positive. Consultation notes included that “the submitted lung biopsy (contained) atypical hematolymphoid infiltrates. Large cells were noted with moderate and abundant pale cytoplasm and large pleomorphic nuclei with coarse chromatin and prominent eosinophilic nucleoli, mitotic figures and apoptotic debris were abundant.”

Although the tumors showed some angiocentric features reminiscent of anaplastic large cell lymphoma (ALCL), a subtype of peripheral T-cell lymphoma which can be ALK (-), it was not favored because most ALCLs are EMA positive (this case was negative); moreover, no “hallmark” or horseshoe-type bizarre cells typical of ALCL were identified, and ALCLs which are ALK (-) are usually present in higher stages [1]. However, there are some overlapping molecular features between the two entities, as described in the discussion portion below. A CD31 IHC stain highlighted many small cells which may be consistent with reactive NK cells within the malignant T-cell aggregates (Figure 3).

The pulmonary tissue slides were sent out for consultation to an internationally-recognized hematopathologist who agreed with the amended diagnosis of CD30-positive, PTCL-NOS. The patient received CHOP chemotherapy (cyclophosphamide, doxorubicin, vincristine and prednisone) and refused autologous bone marrow transplantation; she was free of disease after three and a half years of clinical follow-up. Further sub categorization as a primary pulmonary T-cell lymphoma is possible since there was no mediastinal mass, no extrathoracic involvement, and no leukemic features, thereby satisfying the criteria necessary to make this clinical diagnosis [2,3].

**DISCUSSION**

The original IHC testing included a four-panel stain to distinguish tumors with no clear lineage differentiation (broad-spectrum cytokeratin, S100, CD45, and vimentin), with only vimentin staining positive [4]. Additional staining for a pan-T cell marker, such as CD3, is recommended when confronted with these results, but this was not done during the first round of IHC staining. As a result, the case was signed out erroneously as an undifferentiated malignant neoplasm/CUP. Lymphoma was ruled out by error because the CD45 stain was negative, but CD45 can occasionally be negative in PTCLs as well as in some diffuse large B-cell lymphomas, plasmablastic lymphomas, and anaplastic lymphomas [4]. Some lymphomas in the PTCL-NOS category may not even express pan T-cell markers, or can aberrantly express B-cell markers CD79a and CD20 [5,6]. More aggressive workup in some cases may offer insight into tailored therapies; molecular investigation can reveal specific therapeutic targets that can very often be discovered [7-9]. CUP is a relatively common default diagnosis, accounting for approximately 4-5% of all invasive cancer diagnoses. 20 to 25 percent of CUPs are poorly differentiated and cannot be precisely characterized by histologic examination. About 80 percent of these poorly differentiated tumors have features of carcinoma and are termed “poorly differentiated carcinoma” after initial pathologic examination [10-12]. This diagnosis is often a result of limited diagnostic information and requires further pathologic investigation.
Primary lymphomas of the lung of any subtype are rare and represent only a small portion of all primary pulmonary malignancies. The most common primary lymphoma of the lung is marginal zone lymphoma arising from mucosa-associated lymphoid tissue (MALT) of the bronchus, accounting for approximately 70% of cases (“MALTomas”). PPLs of T-cell origin are the least represented, with only 19 cases reported [13,14]. While most peripheral T-cell lymphomas have been categorized into defined subtypes, those that cannot be separated by well-defined characteristics are placed by default into the subtype of peripheral T-cell lymphomas known as “not otherwise specified” (PTCL-NOS). PTCLs of all subtypes represent approximately 10% to 15% of all non-Hodgkin lymphomas in North America. Lymphomas in the PTCL-NOS category comprise approximately one-quarter of all PTCLs and show extreme cytological and phenotypic heterogeneity [15]. The median age at presentation is 60 years, with a male predominance. 70% of the cases present in advanced stage, with generalized lymphadenopathy, and extranodal spread when present is usually to the skin, gastrointestinal tract, liver, spleen or marrow [16,17]. The report from the WHO 2016 Classification of Lymphoid Neoplasms notes that “subsets [of PTCL-NOS] based on phenotype and molecular abnormalities are being recognized that may have clinical implications but are mostly not a part of routine practice at this time”. Gene expression profiling studies have identified subtypes of PTCL-NOS with differing clinical behavior and response to therapy [1,18]. Iqbal et al., demonstrated that there are at least three subtypes, including two major molecular subgroups which are characterized by high expression of either GATA3 or TBX21, associated with 5-year overall survival of 19% and 38% respectively [15]. That study also showed multiple gene expression overlap of ALK (-) ALCL with CD30(+) PTCL-NOS. CD30 expression alone might also define two biologically distinct PTCL-NOS subgroups. In one study, those lymphomas which were negative for CD30 tended to have an inferior clinical outcome compared to those which were positive for CD30 [19]. The lymphomatous cells in this case were positive for CD30; no molecular testing or IHC staining for GATA3 or TBX21 was performed. PTCLs typically have a rich microenvironment [20] typified in this case by the presence of numerous CD31(+) cells consistent with reactive NK cells, which may partially explain why the patient had such a durable remission, since the presence of NK cells-in solid tumors has been associated with better prognosis [21].

Hematopoietic malignancies following chemoradiation (CRT) for breast carcinoma are rare; one Italian study of 5,248 patients with breast carcinoma who were treated by CRT reported only 8 patients (0.15%) who had leukemia and 4 patients (0.07%) who had non-Hodgkin lymphoma (NHL), based on a follow-up of five or more years [22]. While it cannot be determined if chemoradiation was related in any way to the development of the patient’s lymphoma, there is a statistically significant increased incidence of NHL in breast cancer patients, suggesting a relationship unrelated to therapy for either neoplasm [23-25]. In one report, it was shown that 90% of 87 patients with both malignancies had their breast cancer diagnosed first or concurrently with non-Hodgkin lymphoma [26-28].

A beta-retrovirus mouse mammary tumor virus in inbred strains of mice could possibly be one of the causes of both breast cancer and lymphoma in humans. Since John Bittner’s discovery in 1936 that an infectious filterable agent, now “mouse mammary tumor virus” (MMTV), was present in the milk of cancer-prone mice and could cause breast cancer in the offspring who nursed on this milk. Although initially quite controversial, enough animal and epidemiologic evidence has now accumulated to believe that a causative relationship between human breast cancer and MMTV is very likely [29,30]. In another study, 6 of 12 patients with both breast cancer and NHL of both T- and B-cell types were shown to have MMTV viral sequences in each malignancy [31].

The chest imaging features of a primary pulmonary T-cell lymphoma have not been well defined but range from large prominent masses, to pneumonic-type infiltrates, to bilateral nodules, the latter being seen in this case [32,33]. The best-practice of using an up-to-date algorithm for IHC staining of an undifferentiated malignant neoplasm, as well as incorporating molecular testing as needed, is demonstrated in this case. Other lessons from the case include understanding the limitations of any one immunohistochemical marker, such as CD45, whose misinterpretation affected premature closure in the interpretative phase of diagnosis. Further research into the genetic and epigenetic profiles of PTCL-NOS will undoubtedly allow better characterization of these lymphomas. More data on specific therapeutic targets may yield insight into improved prognoses and treatments. Additional studies are also warranted to investigate the link between breast carcinoma and lymphoma considering their documented viral connection. Physiologically, this patient’s presentation of shortness of breath has a very wide differential. Understanding the mechanisms through which malignancy can disturb native tissue architecture can offer insight into potential targets for future epigenetic evaluations and treatments.

A weakness of this case is that all desired IHC stains could not be performed to better characterize the cells, using cytotoxic markers such as TIA-1, granzyme b, or perforin. Molecular characterization of the lymphoma would obviously have been helpful. The diagnosis was however strengthened by an internationally-renowned hematopathologist’s consultation. Despite the specific weaknesses, it is worthwhile to report misdiagnosed rare events
in medicine, even if not all the descriptive elements are present. Medical error and misdiagnoses are inevitable occurrences. If one broadens the scope of a particular differential as highlighted in this case, then this should reduce error and, ergo, improve outcomes. While the aforementioned pathology in PPL is rare, differentials of presenting symptoms should address serious "no miss" diagnoses including malignancy for effective treatment and outcomes. While the populations involved in this etiology are a small subset of T-cell malignancies, no less attention should be given to this critical potential diagnosis.

REFERENCES

Cite this article