Synchronous pulmonary malignancies: atypical presentation of mantle cell lymphoma masking a lung malignancy

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Abstract

We present a case of a pleural space malignancy masked by an atypical presentation of mantle cell lymphoma. Our patient presented with a large pleural effusion and right sided pleural studding, initially attributed to a new diagnosis of mantle cell lymphoma. Rare atypical epithelial cells were also seen amongst the clonal population of lymphocytes. The patient lacked systemic manifestations of mantle cell lymphoma and did not improve with chemotherapy. A pleural biopsy ultimately revealed the presence of an undifferentiated carcinoma, favoring a lung primary. A discussion of synchronous pleural space malignancies involving lymphomas is given.

Introduction

Synchronous pleural space malignancies are rare (approximately 1% of all pulmonary malignancies) and pose a significant diagnostic and management challenge.1,2 We raise awareness of such occurrences by presenting a case where mantle cell lymphoma masked a clinically relevant second malignancy within the pleural space.

Case Report

A 70-year-old man presented for evaluation of six days of dyspnea and shoulder pain. He had no prior medical history and was a smoker of 75 pack-years. Tachypnea and dullness to percussion of the right lung were the only notable examination findings. A computed tomography (CT) scan showed a large right pleural effusion, with diffuse pleural thickening and nodularity confined to right side only. There was total collapse of the right lower lobe and portions of the right middle and right upper lobes (Figure 1). Lymphadenopathy was absent. Thoracentesis revealed an exudative pleural fluid (Table 1). A general laboratory evaluation was remarkable only for a mild polymorphonuclear predominant leukocytosis (Table 1). Whole body F-fluorodeoxyglucose positron emission tomography (FDG-PET) CT revealed intense uptake along the entirety of the right pleura (SUVmax 34), without uptake within the lung parenchyma (Figure 1). There was minimal uptake within the pleural effusion (SUVmax 1). No FDG uptake was noted throughout the rest of the body, including liver and spleen. Pleural fluid cultures were negative. Cytologic pleural fluid examination revealed a clonal population of CD5+, CD 20+, CD 10-, CD 23-, BCL-1 negative lymphocytes constituting greater than 60% of the B cell mass and consistent with mantle cell lymphoma (MCL). In addition, few atypical epithelial cells of undetermined origin were noted. Immunohistochemical staining could not further identify these cells due to their paucity, despite repeated analysis of large volume aliquots of the pleural fluid. Peripheral blood and pleural fluid flow cytometry were consistent with MCL. His subsequent bone marrow biopsy showed no evidence of MCL.

The collapsed lung did not expand despite adequate therapeutic thoracentesis and the effusion re-accumulated at a rate of greater than one liter per day requiring tunneled pleural catheter placement. Bronchoscopy did not reveal endobronchial lesions. Video assisted thoracoscopy revealed an erythematous, highly irritated pleura with a significant amount of adhesions, but without overt carcinomatosis.

He underwent treatment with rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP) for MCL. Only a transient reduction in pleural fluid production was observed after cycle 1. Due to a poor response to R-CHOP, a CT guided needle pleural biopsy was performed to assess for an additional pleural process. This revealed tissue positivity for CK, CK6, CK7, cyclin D1 and negative staining for LCA, calretinin, cytokeratin HMW, p63, CK20, CEA, BerEp and TTF-1 (Figure 2). These findings were suggestive of an undifferentiated carcinoma, favoring a lung primary. Unfortunately, the patient the patient continued to rapidly deteriorate due to aspiration pneumonia and severe sepsis. He opted for comfort care and expired shortly thereafter. An autopsy was declined.

Discussion

The notion of multiple synchronous primary thoracic tumors is best discussed in the primary lung cancer literature, as lung cancer is by far the most common thoracic tumor. Martini and Melamed first classified such tumors as synchronous (detected simultaneously) or metachronous (detected after identification and treatment of a primary lesion).3 As per their criteria, tumors must be physically distinct and separate. They may be histologically identical if they arise from carcinoma in situ in different lung segments at minimum, and if there is no identification of lymphatic, lymphangitic, or extra-pulmonary spread at the time of diagnoses (for metachronous tumors, there is also a requirement of a greater than two year interval between lesion identification). Antaki et al added DNA ploidy testing to these criteria to further aid in differentiating metastatic lesions from synchronous and metachronous lesions.2 Defining the histology of synchronous tumors is paramount to cancer care, as simultaneous tumors may have markedly different treatment strategies and prognoses. In regards to pleural tumors (by definition lesions that arise exclusively from the parietal and visceral pleura,4 with 90% of these lesions representing malignant mesothelioma), they are thought to represent 0.3-3.5% of all thoracic tumors and are quite rare overall with approximately 3600 cases per year in the United States, as opposed to...
approximately 225,000 cases of primary lung cancer per year in the United States.5

There is no reliable data on the co-existence of pleural tumors with other thoracic tumors. At this time, incidence rate extrapolations (as well as some case series) of the much more common primary lung cancer put synchronous discovery of such primary lung malignancies at approximately 1% of all lung cancer malignancies.1,2 The synchronous involvement of a primary pleural tumor with any thoracic malignancy is likely much rarer.

Mantle cell lymphoma is an uncommon B cell lymphoma overall representing 3-10% of all non-Hodgkin lymphomas. It has the genetic hallmark of a chromosomal translocation of t(11;14)(q13;q32) which causes deregulation of the BCL-1 proto-oncogene and ultimately lymphoproliferation.4 MCL generally presents with advanced disease.8 Eighty percent of patients have diffuse lymphadenopathy at discovery and sixty percent may have splenomegaly. Predominantly extra-nodal disease can be the initial presentation in up to 25% of cases,7 usually as gastrointestinal polyposis. Pleural disease may be the primary site of involvement.7 However, our literature review shows this to be an extremely rare event as only two identifiable case reports of pleural involvement of MCL without concurrent lymphadenopathy could be found.5,8 The former involved a patient who presented with a persistent apical pneumothorax, whereupon examination of the resected tissue there was involvement of the pleura by a lung adenocarcinoma as well as newly-identified MCL. The latter described an 80 year old man who presented with pleuritis and pleural effusions without any detectable lymphadenopathy on imaging. His MCL was detectable in the pleural fluid, peripheral blood, and bone marrow. This patient also exhibited findings attributable to his MCL in the form of a systemic vasculitis, manifesting as transient hemiparesis and a membranoproliferative glomerulonephritis.6 Furthermore, there are only three reported cases of mantle cell lymphoma co-existing with any primary lung malignancy.3,9,11 In all of these cases, the patients received chemotherapy directed at both malignancies.

Table 1. Pleural fluid chemistry and complete blood count.

| Parameters                    | Value          |
|-------------------------------|----------------|
| Serum complete blood count    |                |
| White blood cells             | 13.34 k/cmm    |
| Hemoglobin                    | 14.0 g/dL      |
| Hematocrit                    | 40.5%          |
| Mean corpuscular volume       | 90.4 fL        |
| Platelets                     | 402 k/cmm      |
| Red blood cells               | 29,000         |
| Neutrophils, %                | 63.8           |
| Lymphocytes, %                | 19.2           |
| Monocytes, %                  | 12.0           |
| Pleural fluid cell count with chemistries | | 7.5 |
| pH                            | 836 U/L        |
| lactate dehydrogenases        | 3.7 g/dL       |
| Protein                       | 19 mg/dL       |
| Glucose                       | Red            |
| Color                         | 3541           |
| Nucleated cells               | 34             |
| Red blood cells               | 29,000         |
| Lymphocytes, %                | 13             |
| Segs, %                       | 45             |
| Macrophages, %                |                |

Figure 1. Imaging of the chest. A) Positron emission tomography-computed tomography (PET-CT) whole body; B) non-contrast CT chest; C) PET CT chest.
Treatment for MCL involves chemotherapy, with or without autologous stem cell transplantation. Chemotherapy alone in general is not curative, but may control symptoms with overall response rates for induction chemotherapy with R-CHOP approaching 90%. Whilst MCL is an aggressive lymphoma with a median survival of two to five years, with treatment, low risk patients (up to 44% of all MCL patients) may remain stable for even longer. These individuals tend to have low MCL international prognostic index scores. Furthermore, a portion of this population may represent in situ MCL, nomenclature specifically referring to the pathologic discovery of a MCL cells restricted to the mantle zone in some reactive lymph nodes. Often this lesion is discovered during evaluation for another process (e.g. acute appendicitis). In situ MCL may progress to overt disease, but often remains asymptomatic and stable for decades without treatment, even in the presence of peripherally circulating MCL cells.

We were not able to confirm the presence of an in situ lesion in this case, but speculate its possible existence here based on the patient’s clinical course. The patient’s poor response to R-CHOP suggests that the driving factor for his refractory effusion and progressive clinical decline was likely the undifferentiated carcinoma. In addition, given the lack of clearly attributable symptoms to MCL, the absence of lymphadenopathy, and his relatively normal CBC and BM biopsy, it is reasonable to consider that our patient’s MCL was detected in a subclinical stage. This case is notable as pleural biopsies and pleural tumors exist- tant malignant cell line (albeit with otherwise atypical behavior of that cell line), a direct biopsy was delayed. Furthermore, earlier identification of the bronchogenic carcinoma may have led to inclusion of chemotherapy agents targeting epithelial lesions. Further study is needed regarding pleural presentations of MCL as well as in situ MCL as such presentations may complicate the evaluation of other ongoing processes.

Conclusions

In summary, we report a case of MCL recovered from the pleural space masking the existence of a clinically relevant carcinoma. A high index of suspicion for secondary processes is warranted for patients who present with pleural effusions attributed to MCL as this presentation is atypical, and may mask an underlying, clinically relevant secondary process.

References

1. Shen K, Meyers BF, Larner JM, et al. Special treatment issues in lung cancer: ACCP evidence-based clinical practice guidelines (2nd Edition). Chest 2007;132:290S-305S.
2. Antaki T, Schaefer RF, Rutherford JE, et al. Second primary lung cancer. Ann Thorac Surg 1995;59:863-6.
3. Martini N, Melamed MR. Multiple primary lung cancers. J Thorac Cardiovasc Surg 1975;70:606-12.
4. Erb CT, Johnson KM, Kim AW. Rare pleural tumors. Clin Chest Med 2013;34:113-36.
5. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. CA Cancer J Clin 2015;65:5.
6. Carvajal-Cuenca A, Sua LF, Silva NM, et al. In situ mantle cell lymphoma: clinical implications of an incidental finding with indolent clinical behavior. Haematologica 2012;97:270-8.
7. Argatoff LH, Connors JM, Klasa RJ, et al. Mantle cell lymphoma: a clinicopathologic study of 80 cases. Blood 1997;89:2067-78.
8. Hatzibougias D, Bobos M, Karayannopoulos G, et al. A rare tumoral combination, synchronous lung adenocarcinoma and mantle cell lymphoma of the pleura. World J Surg Oncol 2008;6:137.
9. Hill P, Somerville C. An 80-year-old man with renal insufficiency, proteinuria, hematuria, hemiparesis, and pleuritis. Am J Kidney Dis 2004;44:1121-5.
10. Kampalath B, Abed N, Chitambar CR, et al. Mantle cell lymphoma in lymph nodes with metastatic small cell carcinoma of lung: a diagnostic and treatment dilemma. Leuk Lymphoma 2004;45:409-14.
11. Sun Y, Shi YF, Zhou LX, et al. Synchronous pulmonary squamous cell carcinoma and mantle cell lymphoma of the lymph node. Case Rep Genet 2011;2011:1-5.
12. Flinn IW, van der Jagt R, Kahl BS, et al. Randomized trial of bendamustine-rituximab or R-CHOP/R-CVP in first-line treatment of indolent NHL or MCL: the BRIGHT study. Blood 2014;123:2944-52.
13. Hoster E, Dreyling M, Klapper W, et al. A new prognostic index (MIPI) for patients with advanced-stage mantle cell lymphoma. Blood 2008;111:558-65.