Case Reports in Oncology

Case Rep Oncol 2017;10:86–90

DOI: 10.1159/000455827
Published online: January 19, 2017

Case Report

Recurrent Malignant Melanoma Presenting as Isolated Pleural Metastases in a Patient with Chronic Lymphocytic Leukemia

Kartik Anand[a] Shashank Cingam[b] Prakash Peddi[c]

[a]Department of Hematology/Oncology, Methodist Hospital Cancer Center, Houston, TX, USA; [b]Department of Internal Medicine, LSU Health Sciences Center, Shreveport, LA, USA; [c]Department of Hematology/Oncology, Feist Weiller Cancer Center/LSU Health Sciences Center, Shreveport, LA, USA

Keywords
Chronic lymphocytic leukemia · Pleural metastases · Recurrent malignant melanoma

Abstract
Isolated pleural metastasis with pleural effusion is a rare occurrence in malignant melanoma. We report an unusual case of a patient with chronic lymphocytic leukemia (CLL) and recurrent pleural effusions. The pleural fluid cytology and immunohistochemistry profile were consistent with the diagnosis of CLL. However, chemotherapy with pentostatin, cyclophosphamide, and rituximab did not result in any meaningful clinical response. A video-assisted thoracoscopic surgery and biopsy of the affected nodular parietal layer of the pleura were consistent with malignant melanoma. Our case underlines the importance of having a suspicion for secondary causes of effusion in patients with CLL. We briefly discuss the mechanisms of an increased incidence of secondary cancers in CLL and the diagnosis of isolated pleural metastases in malignant melanoma.

Introduction

Malignant melanoma is an aggressive skin cancer accounting for about 4.5% of all new cancer cases and 1.7% of all cancer deaths in the United States [1]. Malignant melanoma can

KARGER

Prakash Peddi
Department of Hematology/Oncology
Feist Weiller Cancer Center/LSU Health Sciences Center
1501 Kings Highway, Shreveport, LA 71103 (USA)
E-Mail ppeddi@lsuhsc.edu

metastasize to various sites including, but not limited to, the brain, lung, and gastrointestinal tract. Intra-thoracic metastases in malignant melanoma most commonly present as multiple or solitary pulmonary nodules and rarely as isolated pleural effusions. Though there are few reported cases of recurrent malignant melanoma presenting with isolated pleural effusion, what makes our case intriguing, is its presentation in the context of coexisting chronic lymphocytic leukemia (CLL).

Case Presentation

A 65-year-old Caucasian woman presented in March 2007 with a 3-month history of painless left-sided cervical lymphadenopathy. She denied any associated fevers, chills, loss of weight, dyspnea, dysphagia, or any other symptoms. The patient's surgical history was pertinent for a completely resected stage IA melanoma over the left shoulder 16 years before this presentation. Physical exam revealed enlarged and non-tender cervical and axillary lymph nodes without splenomegaly. A skin survey did not reveal any new nevi or concerning lesions. A complete blood picture showed a white blood cell count of 14.7 × 103/μL, an absolute lymphocyte count of 7.35 × 103/μL, hemoglobin of 13.8 g/dL, a platelet count of 258 × 103/μL, and lactate dehydrogenase of 291 U/L. Flow cytometry of the peripheral blood demonstrated a monoclonal lymphocyte population expressing CD5, CD19, CD20, CD24, CD43, and CD52 with lambda light chain restriction and no increase in CD34-positive blasts. The cells were negative for CD38 and ZAP-70. Based on the above findings, the patient was diagnosed with Rai Stage I CLL and placed under observation.

Two years after her initial diagnosis, the patient presented with progressive dyspnea, associated with pleuritic chest pain and a 20 lbs weight loss over a period of 3 months. Physical examination revealed increased axillary and cervical lymphadenopathy and decreased breath sounds over the right lung. Chest X-ray revealed a large right-sided pleural effusion (Fig. 1a). White blood cell count was noted to be 53.4 × 103/μL, and she had an absolute lymphocyte count of 40.7 × 103/μL. The pleural fluid analysis was consistent with an exudative effusion, with increased atypical lymphocytes. Flow cytometry demonstrated a 12% clonal population consistent with the pleural involvement of CLL. The majority of the lymphocytes were CD4+ T-lymphocytes (CD4:CD8 in a ratio of 15:1), but polymerase chain reaction failed to show any clonal T-cell receptor-γ or T-cell receptor-β gene rearrangements.

Secondary to rapid reaccumulation of pleural fluid, increasing lymphadenopathy, and rapid doubling time of lymphocyte count, the decision to treat symptomatic CLL was made. Chemotherapy with pentostatin, cyclophosphamide, and rituximab did not result in any meaningful clinical response. As the patient's pleural effusion was refractory to CLL treatment, video-assisted thoracoscopic surgery was performed, which demonstrated diffuse nodular thickening of both visceral and parietal layers of the pleura (Fig. 1b). A biopsy of these lesions revealed enlarged cells with an increased nuclear-cytoplasmic ratio and pleomorphic nuclei with occasional cherry red nucleoli (Fig. 1d). Immunohistochemistry studies demonstrated positive staining with HMB-45 (Fig. 1c) and S-100 protein. Electron microscopy revealed type II melanosomes with cross-striated lattice in an enclosed membrane (Fig. 1e), type III melanosomes with increased deposition of electron-dense melanin, and type IV melanosomes with highly electron-dense melanin (Fig. 1f). Based on the above findings, a diagnosis of malignant melanoma was made. Computed tomography of the chest revealed extensive lobulated tumor lining the entirety of the right parietal pleural surface without any

evidence of parenchymal involvement. The patient's medical condition rapidly declined, and she ultimately succumbed to death before initiation of any therapy.

Discussion

CLL is a low-grade lymphoproliferative state characterized by the accumulation of functionally incompetent monoclonal B-lymphocytes [2]. Immunosuppression in CLL is hypothesized to be a result of immunosuppressive factors released by the neoplastic B cells that downregulate T-cell function [3]. Loss of ζ chain and costimulatory molecule CD28 on T-cell lymphocytes [4] along with reduced IL-4 and IFN-γ expression by CD4+ T cells in patients with CLL [5] also seem to play a role in the T-cell dysfunction in CLL. The immune system plays a crucial role in immunosurveillance against malignant transformation and tumor propagation [6] and, hence, T-cell dysregulation and dysfunction in CLL patients increase their risk of recurrent or secondary malignancies. In several retrospective studies involving patients with CLL, increased incidence of secondary cancers like Kaposi sarcoma, head and neck cancer, lung cancer, and malignant melanoma was noted [7, 8]. Royle et al. [9] reported that the overall risk of any second-incident cancer in CLL patients was higher than in the general population (second-incident cancer: 2.17, 95% CI 2.07–2.27), and the risk of melanoma was found to be 7.74 times that of the general population (95% CI 6.85–8.72). CLL is also associated with decreased survival in patients with malignant melanoma [10]. Hence, prompt detection and treatment of the malignant melanoma are crucial in patients with CLL.

Metastases to various viscera have been known to occur even after the resection of the original tumor. However, isolated pleural metastasis with pleural effusion as a metastatic recurrence is very rare. In a series of 130 patients with malignant melanoma and thoracic complications, 15% were found to have pleural effusions, and less than 3% had isolated and unilateral pleural effusion [11]. Only a handful of cases with recurrent isolated metastatic pleural involvement presenting after a prolonged period after resection of the primary lesion were reported, with the longest reported progression-free survival being 14 years [12, 13]. In our patient, isolated pleural metastases were noted 16 years from the complete resection of the skin lesion.

Computed tomography of the chest may aid in the diagnosis of pleural metastasis by demonstrating thickened pleura and parenchymal involvement. Positron emission tomography may also aid in the detection of FDG-avid pleural metastasis.

Thoracentesis, unless contraindicated, should be considered in all cases of suspected malignant pleural effusions. Cytology of the effusion may reveal malignant melanocytes in some cases. Effusions in malignant melanoma are relatively richer in CD8+ than in CD4+ T-lymphocytes [14]. In our case, the majority of the cells in the pleural effusion expressed CD4+, and only 12% of the lymphocytes expressed the markers expressed by tumor cells. The latter can be explained by the deficient migratory capacity of the B-CLL cells, which might have led to a relative enrichment of reactive T cells [15]. Video-assisted thoracoscopic surgery and pleural biopsy may be useful for diagnosis and to perform molecular studies.

Conclusion

Concomitant history of CLL, pleural fluid studies suggestive of CLL, and a distant history of malignant melanoma made the diagnosis challenging in our patient. We speculate that

immune dysregulation associated with CLL could have led to recurrence of melanoma in our case. Our case underlines the importance of having a suspicion for malignant melanoma in patients presenting with isolated pleural effusion, especially in the setting of an underlying lymphoproliferative disorder and a previous history of melanoma.

Statement of Ethics

The authors have no ethical conflicts to disclose.

Disclosure Statement

The authors have no conflicts of interest to declare.

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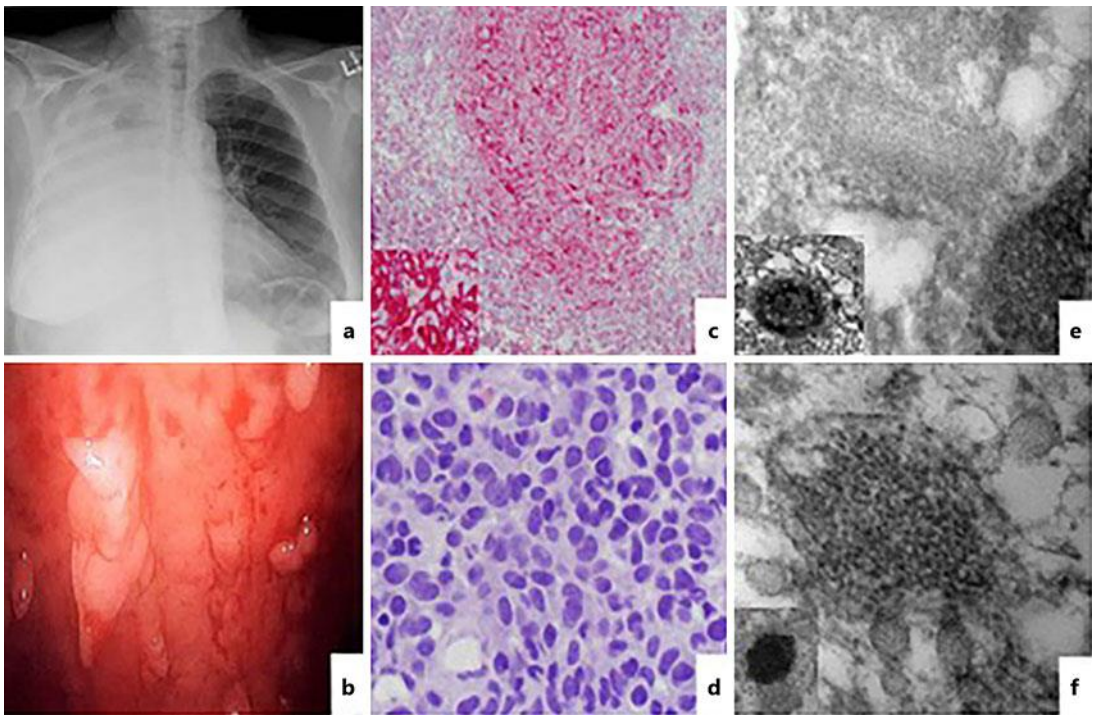

Fig. 1. **a** Chest X-ray showing opacification of the right hemithorax. **b** Video-assisted thoracoscopic surgery images showing diffuse pleural thickening. **c** HMB-45 antibody staining of melanoma cells (×10). **d** HE stain showing large melanoma cells with pleomorphic nuclei and occasional cherry red nucleoli (×40). **e** Type II melanosome with cross-striated lattice in an enclosed membrane. **Inset** Type III melanosome with increased deposition of electron-dense melanin. **f** Type III melanosomes superimposed on lattice. **Inset** Type IV melanosomes with increased deposition of highly electron-dense melanin.