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Case Report

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A Rare Presentation of a Malignant Melanoma Presenting as a Large Pulmonary Mass Causing Superior Vena Cava Obstruction

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Abstract

A 50-year-old otherwise well man with a 20-pack year smoking history was referred for a computed tomography pulmonary angiogram (CTPA) to investigate progressive dyspnea and cough over several weeks. A large 16 cm solitary mass was discovered in the right hemithorax causing encasement of the superior vena cava (SVC) with an intraluminal obstructing SVC tumor thrombus. Initial CT did not reveal any further sites of distant metastatic disease for a presumed primary lung malignancy. However, a core biopsy revealed the mass to be the solitary presentation of a primary BRAF V600E positive malignant melanoma. Urgent initiation of molecular targeted therapy with combination tyrosine kinase inhibitors (dabrafenib (BRAF) / trametinib (MEK) inhibition) led to significant tumor regression, including of the extensive tumor thrombus.

Keywords

Melanoma, Pulmonary, Lung, Molecular targeted therapy, Immunotherapy

Abbreviations

CT: Computed Tomography; CTPA: Computed Tomography Pulmonary Angiogram; SVC: Superior Vena Cava; CXR: Chest X-Ray

Case

A 50-year-old well man and current smoker was referred for a chest X-ray (CXR) and subsequent computed tomography pulmonary angiogram (CTPA) to investigate dyspnea and cough. On examination, he was tachypneic, had reduced breath sounds in the right chest and a positive Pemberton's sign but no other significant physical findings.

The CXR demonstrated almost complete opacification of the right hemithorax and mediastinal shift to the left (Figure 1). CTPA showed a large 16 cm x 16 cm x 15 cm solitary mass in the superior aspect of the right hemithorax, which encased and obstructed the superior vena cava with a small right pleural effusion (Figure 2). Urgent pleurocentesis demonstrated no malignant cells. Histopathology from CT guided percutaneous biopsy (Figure 3) revealed sheets of malignant cells in a perivascular distribution which were immunoreactive to SOX-10, HMB45 and Melan A immunostains, consistent with malignant melanoma (Figure 4), not a primary lung tumor.

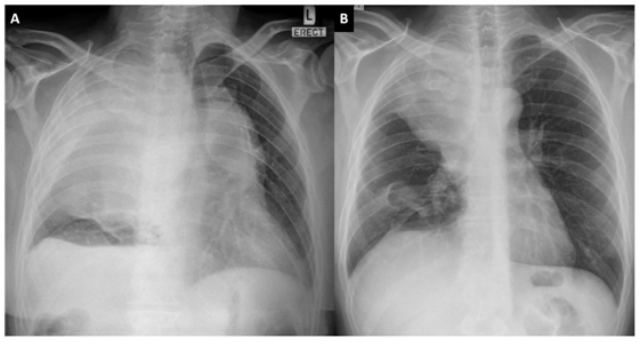

Figure 1: Initial CXR on diagnosis (A) demonstrates a large opacity in the right hemithorax. A serial CXR performed 3 weeks post-commencement of therapy (B) demonstrates marked reduction in the size of the opacity.

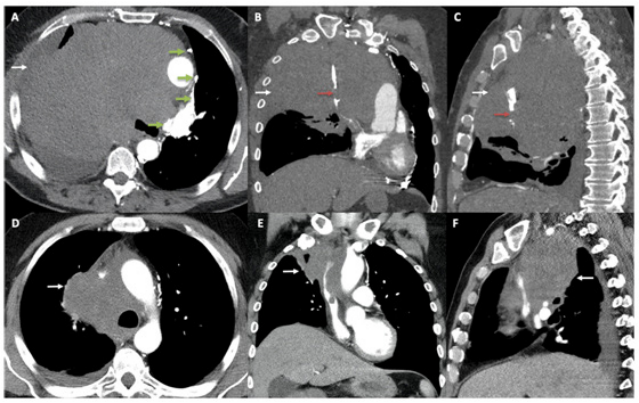

Figure 2: Initial axial (A), coronal (B) and sagittal (C) CTPA images demonstrate a large mass measuring 16 cm x 16 cm x 15 cm (white arrows) occupying the superior aspect of the right hemithorax with marked mediastinal shift to the left, encasing and obstructing the superior vena cava (brown arrows), with formation of numerous collateral veins (green arrows). 1-month follow-up axial (D), coronal (E) and sagittal (F) CT chest images confirm marked reduction in the size of the mass, measuring 7 cm x 6 cm x 7 cm (white arrows) and in the degree of superior vena cava obstruction.

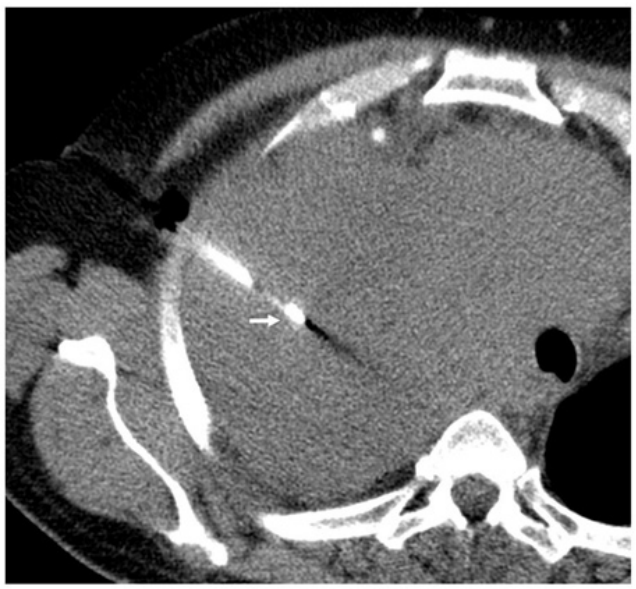

Figure 3: Axial CT establishing needle tip placement for percutaneous core biopsy of the mass (white arrow).

A thrombus in the superior vena cava (SVC) was also noted with extensive collateral vasculature, best demonstrated on the late portal venous phase of a computed tomography (CT) scan of the abdomen performed for staging (Figures 5 and 6). Bilateral adrenal masses likely represented further sites of metastases.

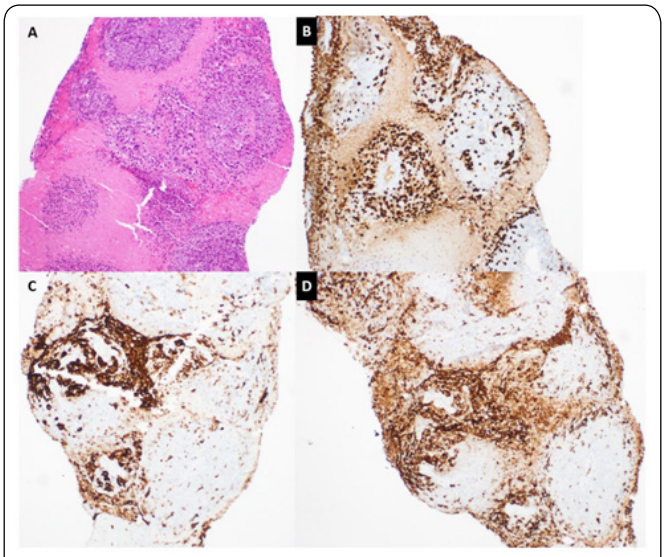

Figure 4: H&E X10 stain (A) demonstrates sheets of malignant cells with a perivascular distribution. The cells have moderate eosinophilic cytoplasm and hyperchromatic pleomorphic nuclei. Multiple mitoses are present, with no gland formation identified. The malignant cells stain positive on SOX-10 (B), HMB45 (C) and Melan A (D) immunostains. The overall morphology and immunoprofile is consistent with a malignant melanoma.

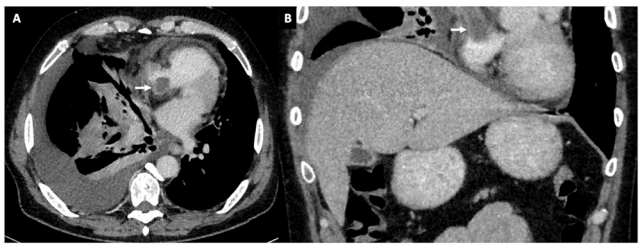

Figure 5: Axial (A) and coronal (B) late portal venous phase CT of the abdomen demonstrates a non-enhancing filling defect within the proximal partially imaged superior vena cava, likely representing a thrombus (white arrows).

Urgent treatment was arranged due to the size of the tumor, compression of vital structures and impending respiratory arrest. Based on the diagnosis of metastatic melanoma, VE1 positive by immunohistochemistry, he was commenced on molecular targeted therapy with combination tyrosine kinase (BRAF / MEK) inhibitor therapy (dabrafenib and trametinib) and subcutaneous enoxaparin for anticoagulation. Serial CXR performed following 3 weeks of treatment demonstrated significant reduction in the size of the mass (Figure 1), with further regression of the tumor on a follow-up chest CT performed 1-month after initiation of molecular targeted therapy (Figure 2) and ongoing response to therapy in his 3rd month of follow-up.

Discussion

Large intrapulmonary mass lesions are most commonly due to primary lung malignancy (most commonly non-

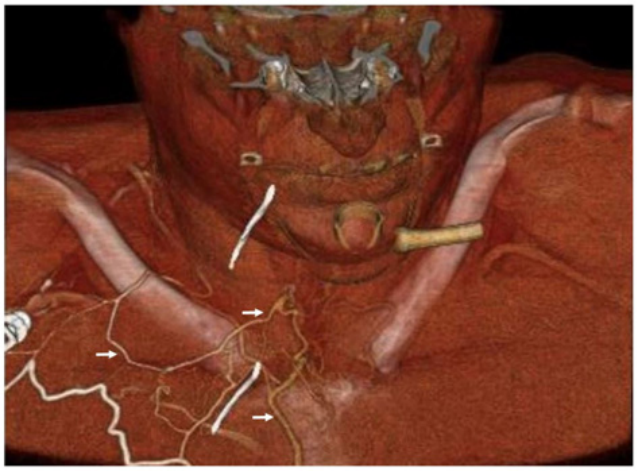

Figure 6: Volume rendered 3D reconstructed CT demonstrating swollen collateral veins in the anterior chest wall, in keeping with superior vena cava syndrome as a result of obstruction of the superior vena cava from the tumor and thrombus (white arrows).

small cell lung adenocarcinomas [1]), particularly in the absence of other suspicious lesions elsewhere in the body. However, a differential possibility includes solitary pulmonary metastases from occult tumors such as melanoma without an obvious primary [2]. Biopsy of these lesions remains crucial in treatment decision making, particularly in the era of molecular targeted therapy and immunotherapy which have demonstrated remarkable improvements in cancer survival.

Primary pulmonary malignant melanomas are extremely rare and account for roughly 0.05% of primary lung tumors, with limited case reports in the literature [3]. 5% of metastatic melanomas have an unknown primary origin [4] and it is presumed that pulmonary malignant melanoma is nearly always metastatic [5].

The metastatic pulmonary malignant melanoma in our patient was large enough to cause obstruction of the superior vena cava, resulting in thrombus formation proximally and numerous collateral veins in the mediastinum and anterior chest wall. This is in keeping with superior vena cava (SVC) syndrome. Our patient presented with dyspnea, which is the most frequently reported symptom in SVC obstruction [6]. Most SVC syndromes are secondary to malignant diseases which cause an extrinsic mass effect or invasion of the venous intima, with lung, breast and mediastinal neoplasms being the most common causes [7], leading to retrograde blood flow, venous engorgement and subsequently, edema [8].

Symptoms and signs include dyspnea, cough and swelling of the face and neck, with formation of collateral veins which aim to bypass the obstruction. Indeed, the severity of symptoms from SVC obstruction relates to the rate at which complete SVC obstruction occurs in comparison to the rate of recruitment of venous collaterals [9], which may account for the gradual onset of this patient's symptoms. Severe SVC obstruction is an emergency because of the risk of sudden respiratory failure and death.

Roughly 50% of melanomas have BRAF mutations (most commonly BRAF V600E), most commonly seen in cutaneous melanomas in skin intermittently exposed to the sun, and rare in melanomas in areas which are never or seldom exposed to the sun such as on acral skin or mucosal membranes [10, 11]. Metastatic BRAF melanomas are commonly treated with combination therapy with BRAF (e.g. dabrafenib) and MEK (e.g. trametinib) inhibitors, which have been shown to demonstrate high response rates (70%) and rapid response induction corresponding to symptom control [12]. For BRAF negative metastatic melanomas, immunotherapy with checkpoint inhibitors are the standard first-line systemic therapy. In recent years, tumor mutational burden has emerged as a prognostication tool in identifying patients who would benefit from immunotherapy; generally better response rates, progression-free survival and overall survival have been demonstrated in patients with a high mutation load [13].

A pulmonary malignant melanoma presenting as a large solitary pulmonary mass of this size (16 cm) causing SVC obstruction is unique and unseen previously. To date, only three cases of SVC obstruction secondary to melanoma in the mediastinum have been reported in the English literature [14-16], measuring up to 7 cm in a report by Mesko et al [15]. One was treated with the BRAF inhibitor vemurafenib [15], another with chemotherapy and radiotherapy [16], while the third received endovascular stenting to the SVC [14]. Three other non-English reports of mediastinal melanoma causing SVC obstruction were also noted in our literature search, [17-19], with one report presenting a lesion measuring 7 cm [19].

In our patient, while clinical examination did not yield an obvious primary site, the consensus was that it should be treated as a metastatic pulmonary malignant BRAF V600E positive melanoma, with an unknown primary. The severity of the patient's symptoms did not allow for a more exhaustive screen such as a dermatology, ophthalmology or gastroenterology review (for consideration of endoscopic screening) to identify a primary site. Following careful consideration of the risks of delaying treatment, a joint decision was made with the patient to proceed with urgent systemic therapy as identification of a covert primary would not have significantly altered management. It should also be noted that combination BRAF / MEK inhibitor therapy in our patient was commenced on the basis of the BRAF VE1 positivity on immunohistochemistry (although the BRAF V600E mutation was later proven on molecular testing, which is the gold standard), again due to the impending onset of a medical emergency.

Conclusion

Pulmonary malignant melanoma is a recognized rare entity, usually presenting as numerous bilateral pulmonary nodules which demonstrate histopathological features of melanoma. In some of these cases, the primary site of the melanoma is never found. This case presents a solitary 16 cm mass lesion causing significant mass effect and SVC syndrome, the size of which is unprecedented in the literature as well as serves to underline that melanoma can present in an insidious and dramatic fashion, mimicking a primary lung lesion. Similar to our case report with BRAF V600E mutation,

molecular targeted therapy is often used in the first line setting for rapid tumor regression. The advent of systemic treatment options for stage 4 melanoma has significantly improved the long-term prognosis in such patients, explicitly exemplified in our patient who demonstrated a rapid response to tyrosine kinase inhibitor therapy (BRAF/MEK inhibitor combination therapy) with dabrafenib and trametinib.

Conflict of Interest

The authors declare no conflict of interest or acknowledgements.

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