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CASE REPORT

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A rare case of metastatic small cell neuroendocrine carcinoma of the lung presenting as isolated thrombocytopenia

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ABSTRACT

Small cell neuroendocrine carcinoma (SNEC) is a high grade and poorly differentiated neuroendocrine tumor which typically presents as a primary pulmonary neoplasm near the bronchial region. Due to the aggressive nature of the tumor, there are many ways it can initially present, mostly involving the lungs. We present a case of a 68-year-old male patient who initially presented with new-onset of severe thrombocytopenia with superimposed pneumonia. It was late in the progression of the disease that histopathology from the bone marrow confirmed SNEC, which presented only after it metastasized to the bone marrow by way of a rare paraneoplastic syndrome. Furthermore, the bone marrow biopsy revealed atypical markers not commonly seen in SNEC. Since this was such an atypical presentation of SNEC, management was limited to stabilization of the patient. The patient expired two weeks later.

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1. Introduction

The 2004 WHO classification recognizes four major types of lung neuroendocrine tumors: typical carcinoid, atypical carcinoid, large cell neuroendocrine carcinoma, and small cell lung cancer. Neuroendocrine tumors make up 25% of primary lung carcinomas with the most common of these being small cell carcinoma. Primary site of involvement in the lung should be considered in any organ metastasis since more than 95% of small cell carcinomas arise from the lung [1].

Our patient presented to the emergency room with a chief complaint of dizziness, weakness, and progressive weight loss over the past six months. Patients may present with a paraneoplastic syndrome, which is a byproduct of the malignancy but unrelated to the invasion of the primary tumor. Examples pertaining to small cell lung carcinoma are the following: cushing syndrome, SIADH, eaton-lambert syndrome, and in extremely rare cases like our patient, microangiopathic hemolytic anemia (MAHA). MAHA is a non-immune hematologic process characterized by the destruction of red blood cells which can be seen hemolytic uremic syndrome (HUS), disseminated intravascular coagulation (DIC), and thrombotic thrombocytopenic purpura (TTP), and also malignancy. Cancer-related microangiopathic hemolytic anemia (CR-MAHA) is considered to have a prevalence of <6% in paraneoplastic syndrome in which thrombocytopenia and schistocytes on peripheral smear may be the only presenting clinical features of an underlying non-hematologic malignancy that has metastasized to the bone marrow, as in this particular case [2–4].

The classic adult tumors to metastasize are lymphomas and carcinomas of the prostate, breast, and lung [1]. CR-MAHA, although rare, indicates a metastasized malignancy to the bone marrow and requires further investigation with bone marrow aspiration and biopsy. Classic findings in patients presenting with microangiopathic hemolytic anemia (MAHA) include a negative coombs test, thrombocytopenia, schistocytes on peripheral smear, and an elevated LDH. The importance behind acquiring additional tests for further evaluation of systemic processes causing MAHA is well documented but often commonly overlooked. We present to you a case report of a patient who initially presented with new-onset severe thrombocytopenia and pneumonia, where a bone marrow biopsy diagnosed a small cell neuroendocrine carcinoma that had metastasized from the lungs.

2. Case report

A 68-year-old male with a past medical history of inflammatory bowel disease, alcoholism, smoking (cigars) for over 30 years, and COPD presented to the emergency department with shortness of breath, dizziness, poor appetite, and progressive weight loss of 30 lbs over a six-month period. He attributed his poor oral intake due to his dental extraction one month prior. The physical examination showed diffuse skin ecchymosis otherwise unremarkable at the

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time. Significant laboratory findings showed hemoglobin 12.5g/dl, platelets of 17,000 k/ul, white blood count 21,000 k/ul, potassium 2.6 mmol/L, lactic acid 10.9 mmol/L, lactate dehydrogenase 8,256 u/l and a negative flow cytometry. Peripheral smear displayed schistocytes without clumping. Blood cultures were positive for staphylococcus aureus in two culture bottles. Iron studies, b12, folate were all normal. He was negative for hepatitis, cytomegalovirus, Lyme disease, babesia, and HIV. The patient's platelet count was 402 k/ul approximately two years ago.

Computerized tomography (CT) scan demonstrated right-sided aspiration pneumonia and necrotic lymph nodes in the mediastinum. Induced sputum testing was negative three times for acid-fast staining in order to rule out tuberculosis. Echocardiogram was normal. He was treated with intravenous vancomycin and piperacillin-tazobactam but his condition began to deteriorate rapidly with new-onset atrial fibrillation, encephalopathy, decline in hemoglobin with melena, and worsening respiratory distress now requiring non-invasive positive airway pressure support. Due to his poor respiratory status, a bronchoscopy with biopsy could not be performed. The patient began treatment for TTP. He was transferred to the ICU for plasmapheresis with transfusions of platelets and administration of high dose steroids. His hemoglobin dropped to as low as 4.9 g/dl requiring multiple blood transfusions to maintain hemodynamic stability. The platelets continued to range between 5,000 u/l and 26,000 u/l. A bone marrow biopsy was done and intravenous immunoglobulin was administered. CD 25, natural killer cells, ADAMS13, and antiplatelet antibody were all normal.

Bone marrow biopsy results were positive for e-cadherin, cytokeratin CAM 5.2, CD117, and CD56 consistent with small cell infiltration of the bone marrow. He was started on imatinib, but at this point, he was no longer a candidate for chemotherapy. On hospital day 12, he became hypotensive resulting in multi-organ failure requiring high doses of norepinephrine. Later during the night, he began to exsanguinate from all of his orificesrequiring more blood transfusions. Laboratory results at this point showed an LDH of 14,000 u/l, Bun 109 mg/dl, Creatinine 3.1 mg/dl, PT 54 H, INR 5.83H, aPTT 42.6 H, AST 1597 u/l, and ALT 341u/l. The patient expired 15 days after presentation.

3. Discussion

Small cell neuroendocrine carcinomas of the lung are high grade poorly differentiated malignancies that are known to be highly aggressive with an extremely poor prognosis since when it is diagnosed it has already metastasized from the primary site. The mean age at presentation is 65 years, mostly in heavy cigarette smokers [1]. However, our patient only smoked cigars. This goes to show the importance behind the consideration of malignancy even when the history and presentation are atypical.

To aid in the discovery of and management of metastasized SNEC, biopsy of the bone marrow can carry a significant prognostic value and can change the course of therapy. In this case report, we did not suspect a carcinogenic process in the initial stages of presentation. Our patient presented atypically with new-onset severe thrombocytopenia and pneumonia. Once we ruled out common hematologic possibilities, it was then the histopathology from the bone marrow biopsy that detected the underlying malignancy. SNEC is indicated when chromogranin, synaptophysin, or CD56 are positive. The bone marrow biopsy demonstrated metastatic carcinoma expressing CD56 and CD117, suggesting a carcinoma with neuroendocrine differentiation. However, in our patient, the malignant cells were positive for e-cadherin, cytokeratin CAM5.2, CD117, and CD56, but negative for TTF-1, chromogranin A, and synaptophysin. So the only positive markers that pointed towards SCLC with neuroendocrine differentiation were the CD56 and CD117, which makes this in itself a rare occurrence.

It is well documented that small cell lung carcinoma (SCLC) classically spreads to the brain in 50–80% of patients after it presents itself in the lungs. In our patient the head CT was negative and the chest CT showed hypodense foci in the mediastinum suggestive of necrotic lymph nodes. The next clinical step would have been to biopsy these nodes via bronchoscopy but due to the patient's complicated pneumonia with acute respiratory distress, our main concern was to stabilize the patient.

CR-MAHA is a rare phenomenon that can be easily overlooked and misdiagnosed. Patients presenting to the hospital with a new-onset of severe thrombocytopenia and schistocytes on peripheral smear require expedited labatory investigations to confirm the underlying cause of hemolysis thus allowing for an early and appropriate intervention. This step is crucial in order to rule out TTP, isolated thrombocytopenia, hemolytic uremic syndrome, and disseminated intravascular coagulation. This can be accomplished by ordering ADAMTS 13 antibodies, anti-platelet antibodies, a complete blood count with peripheral smear, and complete metabolic count. Once MAHA is confirmed and systemic disorders are being evaluated, it may be beneficial to acquire additional tests to rule out malignancies (chest radiographs, bone marrow biopsies) [5].

An elevated LDH can easily be overlooked but is also known as a prognostic indicator, although poor, for overall survival in cancer patients. In a retrospective study of 311 cancer patients with metastatic disease

who had an LDH >1000 IU/L, the median overall survival was 1.7 months [6]. This patient's LDH ranged from 3,000 to 14,000 IU/L throughout his hospital course, which in retrospect could have been used to consider malignancy as an earlier differential.

4. Conclusion

In conclusion, new-onset severe thrombocytopenia and schistocytes on peripheral smear should raise concerns for malignancy as a differential in diagnosis and should be investigated further. Chest CT and bone marrow biopsy were pivotal in the eventual diagnosis of SNEC that had infiltrated the bone marrow. It is uncertain if early chemotherapy and radiation would have improved overall mortality, but early diagnosis of CR-MAHA could start patients on appropriate treatment and could improve median survival, and clinical outcome [2].

Disclosure statement

No potential conflict of interest was reported by the authors.

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