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Metastatic Singnet Ring Carcinoma of Unknown Primary Origin with Bilateral Chylothorax: A Case Report

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1. Abstract

Signet-ring cell carcinoma (SRCC) is defined as a poor prognosis carcinoma and it is not common. Despite the advancement of the technology, origins of about 3%–5% of metastatic tumors remain unknown. Furthermore, metastatic SRCC of unknown primary origin is very rare.

In this study, we will describe a rare case of metastatic SRCC with bilateral chylothorax that in spite of many work ups to find the primary site of tumor, its origin remained unknown. Therefore, our case was metastatic SRCC of unknown primary origin.

2. Introduction

Signet-ring cell carcinoma (SRCC) is defined as a poorly cohesive carcinoma which is for the most part made up of tumor cells with noticeable cytoplasmic mucin and a crescent-shaped nucleus that locates eccentric [1,2]. SRCC is very rare, poorly differentiated and has a poor prognosis [3,4]. SRCCs almost originate from gastrointestinal tract, specially stomach, breast or colon [3, 5]. From the emergence of treatment to eradicate Helicobacter Pylori, the prevalence of gastric adenocarcinoma has decreased. However, the prevalence of SRCC gets higher and SRCC is found in 8% to 30% of gastric cancers [6-8].

Finding the origin of tumors is very important and helpful for appropriate management specially for choosing chemotherapy regimens. So physicians use many methods to find the primary site of tumors. Despite the advancement of the technology, origins of about 3%–5% of metastatic tumors remain unknown [3]. The most unknown origin cancers reported in adenocarcinomas. SRCC is a poorly differentiated subtype of adenocarcinoma. Metastatic SRCC of unknown primary origin is very rare [4].

Superior Vena Cava (SVC) syndrome is made by raised venous pressure upstream caused by the SVC block, reduced venous return to the heart from the upper body (from the head to the upper extremities), and the evolution of venous shunts and collateral vessels to bypass the block. Patients present with swelling in face, neck and/or upper extremity, engorged neck veins, cough, dyspnea, orthopnea, distended anterior chest vein collaterals and conjunctival suffusion [9, 10]. The diagnosis is usually made clinically along with imaging, such as a CT of the chest that, along with the presence of collateral vessels, is sensitive and specific at 96% and 92%, respectively [11, 12]. Most of the SVC syndromes are caused by mediastinal malignancies, most of which are small cell bronchogenic carcinomas. The next most common cause is non-Hodgkin lymphoma followed by metastatic tumors. Further-

more, benign causes of SVC syndrome now consist of at least 40% of cases. SRCC is a rare etiology of SVC syndrome by formation of thrombus in the lumen of SVC caused by direct metastasis [10, 13].

Chylous effusion or accumulation of lymphatic fluid in the pleural space due to obstruction or leakage of the thoracic duct causes chylothorax. Chylous effusion contains high concentration of triglycerides. The etiology of chylothorax is categorized into non-traumatic and traumatic. Non-traumatic etiologies of the chylothorax are infection, neoplastic, superior vena cava thrombosis, sarcoidosis, amyloidosis, connective tissue disorders, and many other rare etiologies reported as case reports [14-16]. Although chylothorax due to malignancy is not rare and can be found in many types of neoplasms like metastatic carcinoma, but bilateral chylothorax is unusual [16, 17].

Hence, we will describe a rare case of metastatic SRCC that in spite of many work ups to find the primary site of tumor, its origin remained unknown. Therefore, our case was metastatic SRCC of unknown primary origin. Moreover, he presented with bilateral chylothorax. This manuscript adheres to the applicable EQUATOR guideline.

3. Case Description

The patient is a 53-year-old man who referred to the hospital with facial edema, upper extremities edema, and gradual onset dyspnea without chest pain and cough. There was also negative history of chills, fever, weight loss, loss of appetite, and night sweating. He had positive history of intermittent constipation for 5 years. Also, he had positive history of bilateral scrotal edema since four months before admission that was developed without pain and redness. The patient had a 30-pack year history of smoking and he was opium inhalation and methadone ingestion addict (10 mg/day). His family history was positive for esophageal cancer in his father. On admission, physical examination revealed a middle-aged man without respiratory distress and cyanosis with normal vital signs and elevated JVP. Cervical lymphadenopathy was detected in the neck. Heart examination showed normal S1, S2, with no murmur and muffle heart sound. In the lung examination, bilateral decreased sound, especially in the right side without any crackles, was found. The abdomen was soft with no hepatomegaly and no tenderness. No hair loss, clubbing or size difference were noted in his extremities. There was bilateral pitting edema in lower extremities with bilateral detectable pulses. He had normal neurologic examination. Bilateral scrotal swelling with no tenderness, hotness or redness and no testicular mass were noted in his examination. A chest X-ray revealed bilateral pleural effusion. Spiral chest and abdominal computed tomography scan with intra-venous contrast showed moderate bilateral pleural effusion, left brachiocephalic, and left subclavian veins were not visible; multiple collateral veins were detected in the soft tissue in favor of obstruction or thrombosis of the subclavian and brachiocephalic veins. Also, SVC obstruction due to SVC thrombosis was seen. Also, it showed cervical lymphadenopathy and some sub-centimeter retro-caval and aorto-pulmonary window lymph nodes (Figure 1). A thick wall stomach was also seen in the CT. The patient's lab data showed a normal Complete Blood Count [White Blood Cell: 5000/mm^3, Hemoglobin: 14.3 g/dl, Mean Corpuscular Volume: 84 fl, Platelet: 211000/mm^3] and Liver Function Test [Aspartate aminotransferase: 17 U/L, Alanine transaminase: 23U/L, Alkaline phosphatase: 189 U/L, total bilirubin: 3.4 mg/dl, direct bilirubin: 0.2 mg/dl, Albumin: 3.4 g/dl]. Other lab data included Blood Urea Nitrogen: 12 mg/dl, Creatinine: 1.1 mg/dl, Na: 140 meq/l, K: 4.6 meq/l. His urine analysis showed: alkaline pH, specific gravity: 1.016, blood: 1-2, protein: negative, RBC: 0-1, WBC: 0-1 and few amorphous phosphate crystals. A 24-hour urine analysis revealed volume: 2000 ml, protein: 40 g, urine Creatinine: 820 mg. His tumor marker analysis revealed CEA: 1 ng/ml (normal up to 5ng/ml), Beta HCG: 0.1 mIU/ml (normal up to 5 mIU/ml), CA-125: 734 U/ml (normal up to 35 U/ml), CA 19-9: 10.2 U/ml (normal up to 37 U/ml). The patient had a normal echocardiography with Ejection Fraction about 60%. A diagnostic thoracentesis was done which revealed findings consistent with a milky, white, opalescent fluid with exudative pattern [fluid protein: 4.9 g/dl, fluid LDH: 188 IU/L, fluid Triglyceride: 528 mg/dl, fluid Adenosine deaminase: 41 U/L (normal up to 35 U/L), plasma protein: 5.3 g/dl, plasma LDH: 347 IU/L]. Also, pleural fluid cell count showed total cell count: 260/mm^3, White Blood Cell: 100/mm^3, with 20% segment and 34% lymphocyte and mesothelial 46%. However, pleural cytology showed no malignant cell, and PCR for Tuberculosis was undetermined. Upper endoscopy was done and showed grade "A" esophagitis in gastroesophageal junction and superficial and deep biopsy from antrum was taken that showed mild chronic active gastritis. Also, colonoscopy was normal and biopsy from the terminal ileum was taken that was unremarkable. Finally, a biopsy from a supra-clavicular lymph node was taken that showed metastatic signet ring cell carcinoma (Figure 1).

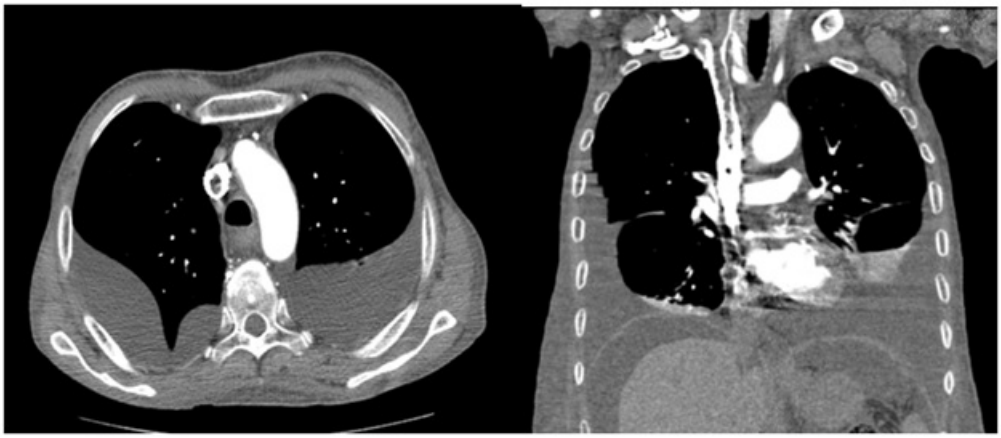

Figure 1: Superior Vena Cava thrombosis and bilateral pleural effusion

4. Discussion

The case of this study presented with facial and upper extremities edema and dyspnea. Chest CT revealed thrombosis in the superior vena cava (SVC) and subclavian and showed bilateral pleural effusion. These chest CT findings can justify his presentation symptoms and can cause SVC syndrome. The appearance of the pleural effusion was milky. It had exudative pattern with lymphocyte dominancy and high triglyceride concentration. Also, two cervical malignant looking lymph nodes were found in the neck CT. The cervical lymph node biopsy was consistent with metastatic adenocarcinoma with signet ring feature. SRCC is rare, poorly differentiated aggressive subtype of adenocarcinoma that most commonly arises from gastrointestinal tract. The breast and lung have been reported as other potential primary organs. In the present case, careful examination and workup including serial endoscopy and colonoscopy with superficial and deep biopsies, CT scan, bronchoscopy and pleural effusion cytology failed to detect the primary site until death. Although, todays' diagnostic equipment is very advanced, but primary origin of 3–5% of the metastatic tumors is not discovered [3, 5].

Clinical presentation of SVC syndrome varies, including facial and upper extremities edema, increased intracranial pressure, pleural effusion, chylothorax. SVC obstruction is presenting symptom of previously undiagnosed tumor in up to 60%. It is estimated that lung cancer and non- hogkin lymphoma are responsible for approximately 95 percent of the cases of SVC syndrome that are caused by malignancy. Any disruption or dysfunction of the flow of chyle through the thoracic duct can cause chylothorax. Thus, there are several etiologies of chlothorax that can be broadly categorized as non-traumatic and traumatic [2,10,15,16,18]. Non-traumatic chylothorax can be caused by malignant and non-malignant condition. Malignancy is the leading cause of non-traumatic chylothorax. Common malignancy include lymphoma with 11 to 37 percent, lung cancer, mediastinal cancer, chronic lymphocytic leukemia, kaposi sarcoma, multiple myeloma, metastatic cancer, etc [16, 19].

In summary, although the SRCC of unknown primary origin is extremely rare, the disease could exhibit a variety of common clinical features like SVC syndrome and chylothorax. Feature clinical experience and studies are, therefore, required to determine the clinical and pathological characteristics in SRCC of unknown primary origin.

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