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Case Report

Carcinoid Crisis Precipitated by Chemotherapy in Metastatic Bronchial Neuroendocrine Tumor

Udit Joshi[1]*, Maria Elena Padilla Sorto[1#], Sagar Ranka[1], Harsh Rawal[2], and Benjamin[2]

[1]*Department of Internal Medicine, John H. Stroger Jr. Hospital of Cook County, USA*
[2]*Department of Internal Medicine, University of Illinois, USA*
[#]*The first two authors contributed equally to this work*

***Corresponding author**
Udit Joshi, 1969 Ogden Ave, Chicago, USA, Tel: 14703630598; E-mail: ujoshi@cookcountyhhs.org

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Abstract

Carcinoid Crisis has previously been reported to be precipitated by different kinds of interventions, most common being surgery and tumor manipulation. Serotonin and its metabolites have been frequently associated with carcinoid crisis. Here we report an index case of chemotherapy precipitating carcinoid crisis in a patient with atypical carcinoid syndrome; having borderline elevated 5- HIAA and chromogranin levels.

ABBREVIATIONS

NETs: Neuroendocrine Tumor; MICU: Medical Intensive Care Unit; SQ: Subcutaneous; 5-HIAA - 5- Hydroxy Indol Acetic Acid; AAAD- Aromatic Amino Acid Decarboxylase

INTRODUCTION

Carcinoid syndrome is a well-known clinical presentation of Neuroendocrine Tumors (NETs) and sometimes precipitates a carcinoid crisis with different interventions. Carcinoid crisis is a life-threatening complication associated with hemodynamic instability secondary to a vasoactive amine storm with a high mortality rate. To date, precipitation of carcinoid crisis secondary to chemotherapy has not been reported. Here we report a rare case of atypical carcinoid syndrome associated with lung NETs that developed carcinoid crisis with chemotherapy.

CASE PRESENTATION

Sixty three-year-old Caucasian woman with eighty pack year smoking history and hypertension, presented to the emergency department with complaints of moderate right flank pain for a day and productive cough for two weeks. She was hemodynamically stable with oxygen saturation of 98 percent on room air. Her physical examination was suggestive of bilateral wheezing and right upper quadrant abdominal pain. Her chest x-ray revealed a left suprahilar mass like opacity with additional nodular opacities in the right upper lobe suggestive of possible lung malignancy with metastasis (Figure 1). For diagnosis and staging, she got chest and abdominal CT scan and it confirmed a 11x 6 x 6 cm left suprahilar mass associated with mediastinal invasion, thoracic lymphadenopathy, right upper lobe lung lesions, left adrenal nodule and liver nodules suspicious for metastasis. The liver biopsy showed high-grade metastatic neuroendocrine tumor, with 30 mitosis per 10 high power fields (Figure 2). Ki67 staining was 100% with focal areas of necrosis. Immunohistochemistry was positive for immunostains CK7, synaptophysin and chromogranin. The primary tumor was presumed to be from the left upper lobe lesion and chemotherapy was planned as an outpatient.

Three weeks after the diagnosis, the patient was admitted with profuse, non-bloody watery diarrhea. It was associated with flushing, hoarseness of voice, shortness of breath and wheezing.

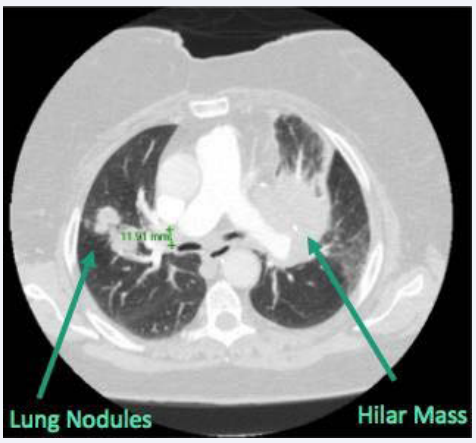

Figure 1 Left suprahilar mass with right upper lung nodules suggestive of metastasis.

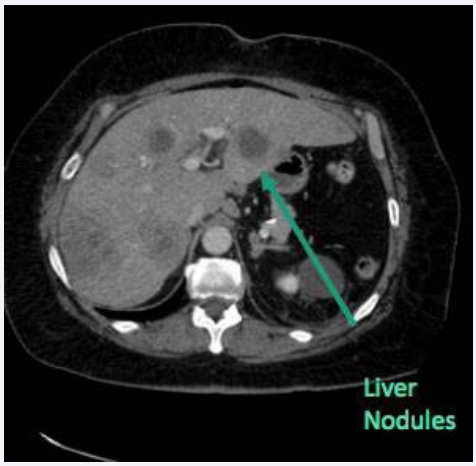

Figure 2 Metastasis in the liver.

Labs were suggestive of neutrophilic leukocytosis, however, infectious workup was negative including blood, urine, stool cultures and clostridium difficile PCR. She was started on dual nebs with some improvement in her wheezing. Hydroxy Indole Acetic Acid - 5 and chromogranin was mildly elevated at 7.1 mg/24h (normal: less or equal to 6.0) and 21ng/ml (normal is <15ng/ml) respectively. She was presumed to have carcinoid syndrome and was started on octreotide 50 mcg SQ Q 8 hrs. All her symptoms resolved in a couple of days on octreotide and this confirmed our presumption of carcinoid syndrome.

She was started on chemotherapy and received one cycle of carboplatin and etoposide during her stay in hospital. Two days later she developed severe flushing and became tachycardic to 150-160s (sinus tachycardia) with fluctuating blood pressure. Initially, blood pressure was in 190s/80s range, however, later dropped to 90/50s, and subsequently dropped further. She was also tachypneic and wheezing with feeling of a chocking sensation. Her chest x-ray was unchanged and she was saturating 98% on room air. Tumor lysis syndrome was a consideration, however she never met the criteria for the same. She was never hyperkalemic with potassium ~ 4.7, calcium ~ 9 mg/dl, phosphate ~ 3.3 mg/dl and uric acid ~13-14 mg/dl (has been steady at this level even after chemo). She was presumed to be in carcinoid crisis due to wide blood pressure fluctuations and typical symptoms and was transferred to MICU for further management.

She was started on octreotide; an intravenous bolus followed by drip, however, she remained hypotensive and vasopressor agents were introduced. She also received hydrocortisone 100 mg every 8 hrs for 3 doses in MICU with no clinical improvement. Unfortunately her clinical course was complicated by the development of sepsis. She was later placed on multiple vasopressive agents including methylene blue without any recovery and expired couple of days later.

DISCUSSION

Carcinoid syndrome is defined as a constellation of symptoms mediated by the humoral factors released by well-differentiated neuroendocrine tumors of the digestive tract and lung. The symptoms include episodic flushing, diarrhea, bronchospasm and rarely fibrotic valvular disease [1]. 34-62% of the patients have diarrhea and 40-53% of the patients have flushing; these symptoms have been associated with poor quality of life in patients with NET [2,3]. Most frequently observed primary site for the NETs include small bowel, respiratory organs and colon or rectum [4]. As per a population-based study, frequency of carcinoid syndrome with localized disease was 8% and with distant metastasis was 15% [4].

Biological active amines responsible for the carcinoid syndrome include serotonin (most common), histamine, tachykinins, kallikrein, and prostaglandins. Measurement of 5- HydroxyIndol Acetic Acid (5- HIAA) levels in a 24 hr urine sample has almost 100% specificity and 73% sensitivity for diagnosing carcinoid syndrome [5]. Foregut NETs often lack aromatic amino acid decarboxylase (AAAD) and cannot make serotonin and its metabolites [5-HIAA] hence they can be normal. Chromogranin A level also has significant sensitivity and specificity for differentiating patients without neoplasia from patients with endocrine tumors, with the cutoff range of 31 to 32 U/L (sensitivity, 75.3%; specificity, 84.2%) [6]. Since in our patient 5-HIAA and chromogranin was borderline elevated, symptoms from carcinoid syndrome were presumed to be from other amines, particularly histamine as is often seen in atypical carcinoid syndrome. Foregut tumors (including lung) have been described to release histamine, which is responsible for severe flushing, sweating, sometimes also cutaneous edema, broncho constriction and cardiovascular instability mainly manifested as hypotension [7,8]. Our patient had all these symptoms and hence was managed with octreotide with significant improvement until she received chemotherapy precipitating carcinoid crisis.

Carcinoid crisis is a life-threatening form of the carcinoid syndrome that results from the release of an overwhelming amount of biologically active compounds from the tumor. It may be precipitated by surge ry, anesthesia or any other type of intervention including arterial embolization, radiofrequency ablation, endoscopic procedures, diagnostic procedures or treatment with peptide receptor radionuclide therapy [9-14]. Predominant symptoms in carcinoid crisis include wide blood pressure fluctuations with a predominance of hypotension and severe flushing with bronchospasm, which were all evident in our patient. There are no specific recommendations validated in randomized controlled trials regarding the use of pre intervention octreotide. Patients in whom prophylactic octreotide has been used still have a 60% chance of having intraoperative complications [15,16]. There has been no case reported till date per our literature review in which carcinoid crisis was precipitated by receiving chemotherapy. For treatment of carcinoid crisis, our patient was started on octreotide with a bolus of 500 mcg followed by drip gradually up titrated from 5 mcg/hr to 200 mcg/hr. However, she remained hemodynamically unstable and vasopressor agents were introduced even though we knew there was a possibility of provoking further release of vasoactive mediators. However, she subsequently developed bacteremia a few days later and was eventually on four vasopressors but unfortunately expired in a couple of days after the development of sepsis.

Hence, it is very important for the physician to be cognizant of possible precipitation of carcinoid crisis from interventions

including chemotherapy, even if 5 HIAA and chromogranin levels are just mildly elevated. This could be precipitated from amines other than serotonin such as histamine which is most commonly released in atypical carcinoid syndrome from lung NETs. As there is no specific recommendation regarding prevention or treatment of carcinoid crisis, further studies are warranted.

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