Diagnostic Snapshot

Heart Failure in a Patient With Metastatic Well-Differentiated Neuroendocrine Tumor

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Authors' disclosures of conflicts of interest are found at the end of this article.

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Abstract

Patients with neuroendocrine malignancy with liver metastases are at risk for carcinoid heart disease which, if left unchecked, can lead to heart failure. This case study demonstrates a clinical situation in which an advanced practitioner performed a thorough workup consisting of lab work and imaging studies, including echocardiogram, cardiac MRI, and dotatate PET/CT, as well as outside record review and comprehensive physical exam. Early detection, intervention, and control of disease are paramount to prevent potentially life-limiting carcinoid heart disease.

HISTORY

Mrs. R is a 47-year-old Hispanic female with no significant past medical history who initially presented in Mexico with a 6-month duration of epigastric abdominal pain, abdominal bloating, watery diarrhea, and facial flushing. She underwent a CT of the chest/abdomen/pelvis with contrast in March 2019, which revealed diffuse, hypodense distribution of metastatic deposits in the liver with undetermined primary origin. She underwent a liver biopsy in April 2019, which confirmed grade 2 moderately differentiated neuroendocrine tumor ("atypical carcinoid") with probable intestinal origin. The diagnosis was confirmed by immunohistochemistry, positive for both chromogranin and synaptophysin. Liver function tests and complete blood count were within normal limits, as was carcinoembryonic antigen, alpha fetoprotein, and cancer antigen 125. There was no record of biochemical testing results (chromogranin A, 24-hour urine, or plasma 5-hydroxyindoleacetic acid [5-HIAA]) near the time of diagnosis, as unfortunately, medical records sent from Mexico were incomplete.

Approximately 3 months after diagnosis (July 2019), she was seen by an oncologist in Mexico and began long-acting octreotide acetate 20 mg intramuscularly monthly. She continued long-acting octreotide until May 2021 and stated that during the around 23 months that she received monthly injections, she had only mild improvement in her symptoms; in fact, she admitted to a 40-lb weight loss. She was last seen by her oncologist in Mexico in June 2021, at which time her chromogranin A level was 66,320 ng/mL.

PRESENTATION

Mrs. R then relocated to the US and presented to our institution's emergency department the following month with complaints of persistent

epigastric abdominal pain, watery, non-bloody diarrhea of 5 to 10 stools per day, abdominal bloating, and weight loss. She stated that her last long-acting octreotide injection was in May 2021 and since that time her watery diarrhea had worsened. She stated she was last told by her oncologist in Mexico that the cancer had damaged a valve in her heart. Mrs. R admitted to progressive dyspnea on exertion, bilateral lower extremity edema, intermittent chest discomfort with rest and exertion, and fatigue. A physical exam was consistent with a systolic ejection murmur, 2+ lower extremity edema, + jugular venous distention, and hepatomegaly extending four fingerbreadths below costal margin.

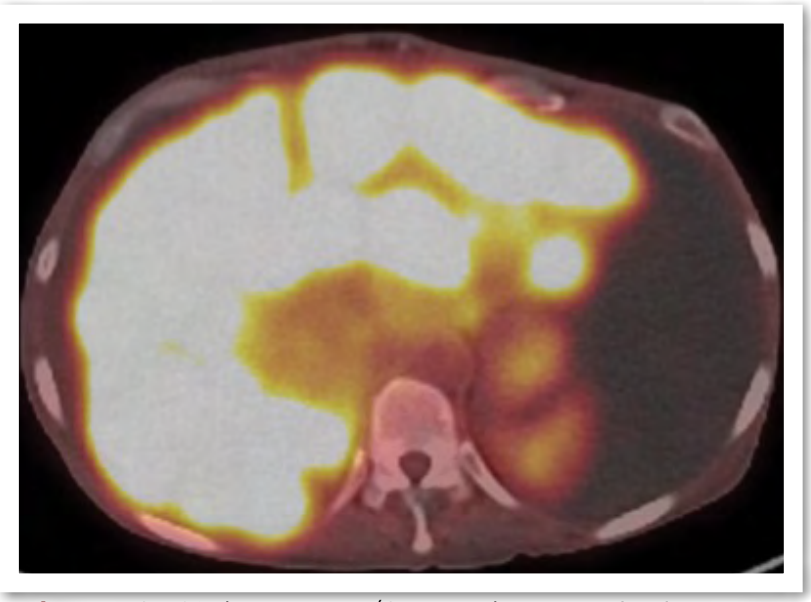

Figure 1. Ga-68 dotatate PET/CT scan demonstrating innumerable FDG-avid masses of the liver, consistent with Mrs. R's known history of metastatic neuroendocrine malignancy.

WORKUP

B-type natriuretic peptide (BNP) was 1,326 pg/mL. Imaging revealed near-complete replacement of the liver with soft-tissue masses consistent with metastatic disease and large-volume abdominopelvic ascites and anasarca (Figure 1).

A transthoracic echocardiography revealed a severely dilated right atrium, torrential tricuspid regurgitation due to incomplete coaptation and fixed open leaflets, and mild/moderate pulmonic stenosis. Left ventricular ejection fraction was 68%. Cardiology and cardiothoracic surgery teams were consulted for consideration of valve replacement. A cardiac MRI confirmed severe tricuspid regurgitation with regurgitant volume 89 mL/cycle with regurgitant fraction of 66% and dilation of the right atrium and right ventricle. The cardiology and cardiothoracic surgery team ultimately decided that her severe liver dysfunction precluded standard cardiac intervention, and she was referred to the interventional cardiology service for percutaneous options.

While inpatient, she was administered long-acting octreotide 30 mg intramuscularly, which only mildly improved her symptoms of watery diarrhea and facial flushing, so she was administered lanreotide 120 mg subcutaneously 2 weeks later. Mrs. R also underwent repeat liver biopsy, which confirmed well-differentiated neuroendocrine tumor.

DIFFERENTIAL DIAGNOSIS

WHAT IS THE CORRECT DIAGNOSIS FOR MRS. R?

- A ☐ Infiltrative cardiac metastasis
- B ☐ Infectious endocarditis
- C ☐ Carcinoid heart disease

SEE BACK FOR ANSWER ▶

WHAT IS THE CORRECT DIAGNOSIS FOR MRS. R?

A Infiltrative cardiac metastasis

B Infectious endocarditis

C Carcinoid heart disease (correct answer)

DISCUSSION

A Infiltrative cardiac metastasis. Cardiac metastasis from primary neuroendocrine tumors is exceedingly rare and usually found incidentally on dotatate imaging (also called octreoscan). The incidence of intracardiac metastasis is approximately 4% in all patients with metastatic carcinoid tumors (Kinney et al., 2020). Nonetheless, the advanced practitioner should rule out infiltrative cardiac metastasis by dotatate imaging as the cause of heart failure in this patient population. In this case, infiltrative cardiac metastasis was not supported by dotatate PET/CT and cardiac MRI.

B Infectious endocarditis. Infectious endocarditis is an inflammation of one or more valves of the heart usually caused by a bacterial infection or, more rarely, a fungal infection such as Candida (Vyas, 2020). Cancer patients are frequently at risk for infections due to central line insertions and immunosuppression from cancer-directed therapies. Mrs. R had no known history of endocarditis prior to her presentation at our institution, and blood cultures were subsequently negative. Echocardiogram did not support leaflet vegetation. Therefore, infectious endocarditis was ruled out as the cause of valvular dysfunction.

C Carcinoid heart disease (correct answer). Mrs. R's presentation and workup were most consistent with carcinoid heart disease (CHD). She had extensive liver metastatic disease, an elevated BNP, and her echocardiogram revealed tricuspid regurgitation, fixed/open leaflets, and mild/moderate pulmonary valve stenosis. Carcinoid heart disease occurs almost exclusively in the presence of extensive liver metastasis (Ram et al., 2019). Liver dysfunction from metastatic tumor burden affects the breakdown of serotonin metabolites in the circulation. It is this excessive exposure of serotonin that causes plaque formation on cardiac valves (Grozinsky-Glasberg et al., 2015). Carcinoid heart disease most commonly affects right-sided heart valves (tricuspid and pulmonic; Bober et al., 2020). Due to inactivation of serotonin in the lung vasculature by pulmonary monoamine oxidase, left-sided heart valves are spared exposure to excessive serotonin while the right-sided heart valves are not (Figure 2; Jin et al., 2020).

CLINICAL OUTCOME

Due to significant tumor burden and substantial delays in obtaining adequate funding, it was determined that cardiac intervention would be deferred, and systemic chemotherapy was initiated with the plan to reevaluate for response after four cycles and re-refer to interventional cardiology for percutaneous valve replacement if she had an adequate response to treatment. She began carboplatin dosed at area under the curve 6 administered on day 1 followed by etoposide 100 mg/m^2

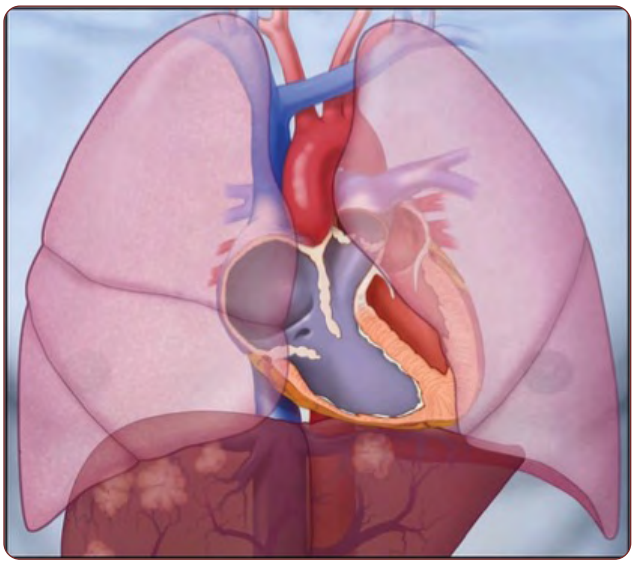

Figure 2. This illustration is consistent with carcinoid heart disease. Note the metastatic tumors in the liver, endocardial plaques within the right ventricle, and thickening of tricuspid and pulmonary valves (Mayo Clinic, 2015). Used with permission from the Mayo Foundation for Medical Education and Research. All rights reserved.

on days 1 to 3 every 21 days. The pre-treatment chromogranin level was 97,420 ng/mL. She was then discharged home after cycle 1 with close oncologic and cardiac follow-up. Mrs. R went on to receive a total of three cycles of systemic therapy with carboplatin/etoposide, which she tolerated well with minimal toxicity.

Mrs. R presented to the emergency department in September 2021 with complaints of worsening abdominal pain, nausea without vomiting, progressive weakness, and diminished oral intake. She was cachectic with lower extremity edema, and the abdomen was distended and diffusely tender. Lactate was 13 mmol/L and BNP 20,093 pg/mL. On the following day, Mrs. R became acutely unresponsive with fixed, dilated pupils. Orders for do not resuscitate/do not intubate were obtained, and she passed away after cardiac arrest.

CONCLUSION

While the correct diagnosis was likely the most obvious, it is essential that the advanced practitioner pursue a thorough workup to include baseline lab assessment (BNP, chromogranin A, and urine 5-HIAA) in addition to imaging studies with a transthoracic echocardiogram, cardiac MRI, and dotatate PET/CT. Carcinoid heart disease is more common in patients with metastatic liver disease who exhibit symptoms of carcinoid syndrome and have a high 5-HIAA and serotonin metabolites. If liver metastases are identified, serial BNPs and echocardiograms are warranted to evaluate for the development of CHD. Proper evaluation and early recognition are essential to circumvent the manifestations of heart failure in patients with metastatic neuroendocrine tumors. ●

Disclosure

The authors have no conflicts of interest to disclose.

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