METASTATIC CARCINOID TUMOR- ATYPICAL PRESENTATION

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METASTATIC CARCINOID TUMOR - ATYPICAL PRESENTATION (Abstract): Carcinoid tumor is a slow-growing type of neuroendocrine tumor, originating in the enterochromaffin cells and secreting mainly serotonin. Neuroendocrine tumors (NETs) are found throughout the intestinal tract, the appendix and terminal ileum being the most common locations, and are classified by site of origin and by degree of differentiation, with well-differentiated lesions representing those tumors formerly referred to as carcinoid tumors. The clinical symptoms are characterized by flushing, diarrhea, abdominal pain, and/or bronchial constriction and occur almost exclusively in patients with liver metastases due to the release of bioactive peptides and amines directly into the systemic circulation. We report the clinical, serological and histological diagnosis of a 67-year-old male patient with congestive heart failure secondary to carcinoid heart disease in the context of liver metastases of an ileum carcinoid tumor. Keywords: CARCINOID SYNDROME, HEART DISEASE, METASTATIC LIVER DISEASE, SEROTONIN.

Neuroendocrine tumors (NETs) are a very heterogeneous group arising from the neuroendocrine cells, and include carcinoid, non-carcinoid gastroenteropancreatic tumors, catecholamine-secreting tumors (pheochromocytomas, ganglioneuroblastomas, paragangliomas, and neuroblastoma), medullary carcinoma of the thyroid, chromophobe pituitary tumors, small cell lung cancer and Merkel cell tumors. The different NETs may be divided into functioning and non-functioning tumors (1).

The carcinoid syndrome occurs in approximately 10% of NETs and becomes manifest when vasoactive substances from the tumors, such as serotonin as well as several other chemicals, enter the systemic circulation escaping hepatic degradation (2, 3).

This particular type of syndrome is often encountered when metastatic lesions are found spread throughout the liver or they develop from the bronchi. The clinical properties are characterized by flushing (63%–94%), diarrhea (68%–84%), abdominal pain (10%–55%), telangiectasia (25%) and bronchial constriction (3%–19%) (4, 5). High levels of vasoactive substances released from hepatic metastases can cause, in 10-20% of patients with carcinoid syndrome, the appearance of lesions that compromise the integrity and functionality of the endothelium and cardiac valves causing heart failure (6, 7).

CASE PRESENTATION
A 67-year-old man was admitted for
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Watery diarrhea, abdominal discomfort and shortness of breath. He had been having loose stools for 5 years, with 3 to 4 bowel movements per day, progressing over the previous 2 months to 4-5 large volume watery stools daily, including nocturnal stools. Abdominal cramps preceded these episodes and were partially relieved by bowel movements. He noted no blood or oil in the stool.

On examination, the patient was alert and oriented. His body mass index was 17. The temperature was 37.2°C, blood pressure 95/65 mm Hg, pulse up to 100 beats per minute and regular, respiratory rate 19 breaths per minute, and oxygen saturation 99% while he was breathing ambient air. The scleras were anicteric, and the oropharynx had no ulcers or lesions. The neck was supple and without jugular venous distention.

Further clinical examination revealed a diffuse rash characterized by fixed pink patches on his scalp, trunk and limbs that became red and pruritic when scratched or exposed to sun and heat and facial flushing, brought on by exertion or strong emotion.

The abdomen was slightly distended, depressible and diffusely painful with a painless, firm, nodular hepatomegaly of 6 finger-widths. Splenomegaly was not noted. Brown stool was negative for occult blood. The neurologic examination was unremarkable.

Apparently, he was diagnosed 20 years ago with idiopathic liver disease and multiple hepatic nodular areas spread throughout the liver which were recorded and measured periodically to see any signs of growth. They maintained relatively stable in size over the last few years.

Six months prior to admission the patient underwent major cardiac surgery to replace the aortic and mitral valve, because of severe aortic stenosis and mitral regurgitation with favorable postsurgical outcome. After surgery, he was encouraged to seek gastroenterological advice for liver distress and intestinal discomfort.

On admission, the patient recalls he had had multiple similar episodes during the previous 5 years, with flushing, hypotension and mild diarrhea, but he managed to avoid seeking medical care. The symptoms, which were usually provoked by physical exertion, mental stress, or intense emotion, lasted up to 2 hours.

The ultrasound performed in our clinic confirmed the presence of numerous nodular areas spread throughout the liver which were suggestive of metastatic liver disease (fig. 1).

![Liver ultrasound: multiple hyperechoic nodules](image)

Fig. 1. Liver ultrasound: multiple hyperechoic nodules
Abdominal CT scan showed multiple hepatic masses, the largest was 10 cm in diameter and another mass located in the mesenteric region approximately 40 mm in diameter relatively well defined which needed additional tests to establish its nature.

Endoscopic video capsule was performed and it showed multiple irregular masses located in the proximal jejunum and ileum protrusive in the lumen and covered by normal looking mucosa, with visible vascular pattern but with no obstructive potential (fig. 2).

Adding all the pieces of the puzzle, the clinical presentation (flush, diarrhea, low blood pressure), metastatic liver disease, intestinal tumor and heart disease the diagnosis of carcinoid tumor became obvious.

Serological tests including urinary levels of 5-hydroxyindoleacetic acid (5HIAA), serotonin (Ser) levels and chromogranin A concentration (Cg A) were performed and high levels of these parameters confirmed the diagnosis (tab. I).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
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<tbody>
<tr>
<td>Chromogranin A</td>
<td>22064 µg/L</td>
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<tr>
<td>Urinary excretion of 5-HIAA</td>
<td>148.5 mg/24h</td>
</tr>
<tr>
<td>Serotonin</td>
<td>450 µg/L</td>
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</table>
The patient was discharged on his own free will and returned to Modena, Italy. There he performed additional investigations.

Whole-body scintigraphy and single photon emission computed tomography (SPECT) after intravenous injection of indium-111-octreotide showed hepatomegaly highlighting a large and high uptake halo that occupied almost the entire right hepatic lobe with other several liver focal accumulations. Also, a focal uptake localized in the small intestine, femoral neck, sternum and right shoulder were detected.

Liver biopsy was performed and the histology report showed a well differentiated neuroendocrine tumor with no necrosis or mitotic activity. Chemotherapy was initiated. Chemotherapy sessions were marked by severe granulocytopenia which needed growth factor correction and temporization of chemotherapeutic drugs.

A recent assessment (December 2013) showed clinical and biological improvement, with a stationary size of the hepatic lesions and decrease in size of the intestinal and bone tumors. In June 2014 liver ultrasound showed neoplastic hepatomegaly with multiple large nodular areas which increased in size compared to the previous examination, but with relative good clinical tolerance (fig. 3).

**DISCUSSION**

When liver metastasis occurs, the heart is exposed to intermittently high levels of vasoactive substances, which is believed to result in damage to the endocardium.

Carcinoid heart disease occurs in up to 60% of patients with carcinoid syndrome (8). Left-sided cardiac involvement can also occur in <10% of patients (2, 3, 10). The left side of the heart is relatively protected as the lungs filter the vasoactive peptides, inactivating them in the pulmonary circulation before they reach the left atrium (11). Therefore left sided disease is seen only in patients with bronchial carcinoid or patent foramen ovale or in those with poorly controlled severe carcinoid syndrome that overwhelms the degradation capacity of the lung (12, 13, 14).

Tumor size is an unreliable predictor of metastatic disease, and metastases have been reported even from tumors measuring less than 0.5 cm in diameter. Long-term survival correlates closely with the stage of
the disease at presentation (1). With regard to the clinical course of cardiac involvement, high urinary 5HIAA levels are a predictor of progression of carcinoid heart disease (10). This finding was corroborated by Bhattacharyya et al (11) who demonstrated that a urinary 5HIAA level greater than 300μmol/24 h and more than 3 flushing episodes per day are independent predictors of the development or progression of carcinoid heart disease.

The case presented is unique because the disease had a long and mostly mild progression, with the onset of left cardiac complications and liver metastasis prior to carcinoid syndrome manifestation. In our patient, carcinoid heart disease involved all 4 cardiac valves: the aortic valve to a higher extent than the pulmonary valve and the mitral valve to a worse extent than the tricuspid valve. It is hard to estimate if the severe left cardiac involvement is the sole result of carcinoid stress or the combined outcome of both degenerative and carcinoid disease.

CONCLUSIONS

The case presented had a peculiar development with silent liver metastases and left cardiac involvement, long disease progression and relatively favorable outcome. The primary goal of treatment in patients with NETs is curative, with symptom control and the limitation of tumor progression. However, as most patients with NETs are diagnosed once metastases have occurred, curative surgery is generally not possible. Octreotide decreases the secretion of serotonin by the tumor and can improve the symptoms of carcinoid syndrome and stabilize tumor growth in many patients. Unfortunately, there are no specific guidelines and no opportunity to accurately assess prognosis. Disease progression and overall survival are case dependent, as illustrated by the case here presented.

REFERENCES

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### NEWS

**EVALUATION OF ADJUNCTIVE SYSTEMIC DOXYCYCLINE WITH NON-SURGICAL PERIODONTAL THERAPY WITHIN TYPE 2 DIABETIC PATIENTS**

The aim of a study realized by a group of researchers from King Abdulaziz University, King Saud University, Riyadh, Kingdom of Saudi Arabia was to evaluate the effects of systemic doxycycline on clinical and microbiological parameters of diabetic subjects with chronic periodontitis. The 9-month multi-center, randomized, parallel, single-blinded study was conducted from different hospitals in Riyadh, Saudi Arabia between April 2010 - December 2010. A total of 76 diabetic subjects with chronic periodontitis were randomized into 2 groups: control group (CG) received only scaling and root planing (SRP), and the treatment group (TG) receiving systemic doxycycline during the reevaluation visit 45 days after the completion of SRP. Probing pocket depth, clinical attachment level, gingival index, plaque index, and bleeding on probing were collected at baseline, 45 days after SRP, and one, 3, and 6 months after the use of systemic doxycycline. Microbiological analysis comprised the detection of *Tannerella forsythia* (Tf), *Aggregatibacter actinomycetemcomitans* (Aa), *Porphyromonas gingivalis* (Pg), and *Prevotella intermedia* (Pi) by polymerase chain reaction method. Sixty-eight (33 CG and 35 TG) subjects completed the study. Greater reduction in the population of Tf, Pg, and Pi were observed in TG compared with CG in the first month after the administration of systemic doxycycline. The TG showed a significant improvement in gingival index scores compared with the CG by the end of the first and 6 months after the administration of doxycycline. The conclusion of the study was that the adjunct systemic doxycycline can be associated with a reduction of Tf, Pg, and Pi in the first month after the administration of doxycycline with an improvement in the GI. (Al-Nowaiser AM, Al-Zoman H, Baskanadoss JK, Robert AA, Al-Zoman KH, Al-Sohail AM, Al-Suwayed AS, Ciancio SG, Al-Mubarak SA. Evaluation of adjunctive systemic doxycycline with non-surgical periodontal therapy within type 2 diabetic patients. *Saudi Med J* 2014; 35(10):1203-1209)

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