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Back to the future: how to proceed in a patient with end-stage carcinoid heart disease of an unknown primary tumor?

Updates in carcinoid heart disease

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Abstract

BACKGROUND

+ADw-html+AD4APA-p+AD4-Gastroenteropancreatic neuroendocrine neoplasms (GEP-NENs) are rare tumors, and unfortunately often diagnosed in an advanced stage when curative treatment is no longer possible and exhausting symptoms related to vasoactive substance release by tumor cells affect patients' quality of life. Cardiovascular complications of GEP-NENs primarily in the form of tricuspid and pulmonary valve disease, and in particular right-sided heart failure, when present, are the leading cause of death, even in comparison to metastatic disease.+ADw-/p+AD4APA-/html+AD4-

CASE SUMMARY

+ADw-html+AD4APA-p+AD4-We present an interesting case of a 35 year old patient seen for progressive dyspnea, back pain, polyneuropathic leg pain and nocturnal diarrhea lasting for a decade, before a diagnose of neuroendocrine carcinoma of unknown primary with extensive liver metastases was reached. During the initial presentation serum biomarkers were not evaluated and patient received V cycles of doxorubicin, which he did not tolerate well so he refused further therapy and was for

years lost to follow-up. After ten years he presented to ER due to signs and symptoms of right-sided heart failure. Panneuroendocrine markers, serum chromogranin A and urinary 5-HIAA came back extremely elevated (900 ng/mL and 2178 umol/L), and transabdominal ultrasound confirmed hepatic metastases. On the CT scan, besides liver metastatic mases up to 6 cm in diameter, metastases were also noted in mesenteric lymph nodes and pelvis. In addition to mentioned, octreoscan was done and additional lesions were also found in the heart, thoracic spine, duodenum, and ascendent colon. Standard transthoracic echocardiogram confirmed typical findings for carcinoid heart disease. Patient was unfortunately not a candidate for valve replacement. He started the octreotide acetate treatment and the dose escalated to 80 mg sc monthly. Biochemical response and symptomatic improvement was noted, but unfortunately patient died.+ACY-nbsp+ADsAPA-/p+AD4APA-/html+AD4-

CONCLUSION

Carcinoid heart disease is a complication occurring in patients with carcinoid syndrome related to advanced NETs usually with liver metastases, which manifests as right-sided heart valve dysfunction leading to right-sided heart failure. When present, carcinoid heart disease, together with tumor burden, are major prognostic indicators of a reduced patient survival rate. Therefore, they must be actively sought by available biochemical markers and imaging techniques. Moreover, imaging techniques aiding tumor detection and staging, SSTR PET/CT and CT or MRI, should be performed at the time of diagnosis and then on a 3-to-6-month interval to determine tumor growth rate and assess the possibility of loco-regional therapy and/or palliative surgery, whereas valve replacement at the onset of symptoms or right ventricular dysfunction may be considered, while any delay can result in worsening of right sided ventricular failure.

Key Words: gastroenteropancreatic neuroendocrine neoplasms; carcinoid syndrome; carcinoid heart disease; diagnosis; treatment

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Core Tip: Cardiovascular complications of neuroendocrine neoplasms are the leading cause of patient death, even in comparison to metastatic disease. Early detection of right ventricular dysfunction, as well as all changes in the tricuspid valve are of crucial importance. Here being presented is a patient case of advanced carcinoid heart disease with a poor prognosis. In the light of current recommendations, it seems reasonable to search for subclinical right sided heart damage by determining NT-proBNP in patients with elevated biomarker values and neuroendocrine tumors with the aim of an earlier diagnosis and more timely treatment.

INTRODUCTION

Gastroenteropancreatic neuroendocrine neoplasms (GEP-NENs) are frequently being diagnosed in an advanced stage. This is mostly due to non-specific early symptoms and very often small, and easily unforeseen primary tumors, contributed by limited knowledge among most physicians of this relatively unknown subject[1]. Metastases of GEP-NENs are primarily in the liver, regional lymph nodes and bones, however hormones, amines and cytokines are released, and they can effect almost every organ and generate numerous exhausting symptoms. The carcinoid syndrome (CS), presenting with diarrhea, flushing and abdominal pain, caused by the systemic release of serotonin, is seen in up to 30% of patients as an initial tumor manifestation[2,3]. The cardiac manifestation of serotonin hyperproduction, carcinoid heart disease (CHD), develops in up to 70% of patients with CS due to right-sided valve, papillary muscle, and chordae tendineae fibrosis, initiated by the serotonin actions on receptors expressed on cardiac valves. When present, this negatively effects patient quality of life and survival[4,5].

Although now, there are diagnostic tools which are very effective in our armamentarium, it is still a great challenge to timely diagnose primary GEP-NENs and select patients at risk, for rare neuroendocrine tumor driven pathologies such as CHD[6,7]. In cases of CHD, surgical valve replacement (previously reserved only for severely symptomatic patients) is also now proposed for those who are mildly symptomatic, due to progression of heart failure and increase in overall mortality[8]. In addition, different tumor debulking procedures and cytoreductive surgery are considered in addition to pharmacotherapy in terms of symptom control and improvement of patient survival[9].

An interesting case to present, using current knowledge of GEP-NENs with CHD, is of a 35 year old patient seen for progressive dyspnea, back pain, polyneuropathic leg pain and nocturnal diarrhea lasting for a decade, before a correct diagnose was reached.

CASE PRESENTATION

Chief complaints

A young male patient was admitted through our emergency room (ER) in 2010 due to progressive dyspnea, back pain, polyneuropathic leg pain and nocturnal diarrhea. His medical history dates to the year 2000, when he initially complained of leg and lower back numbness. A transabdominal ultrasound was performed and metastases in the liver were detected. An abdominal computed tomography (CT) scan confirmed the liver metastases but omitted to detect the primary tumor. Fine needle aspiration (FNA) of a liver lesion was performed and the metastases of a neuroendocrine carcinoma was diagnosed. The common neuroendocrine markers were not evaluated at this time, and the patient refused further gastrointestinal endoscopic evaluation. He was referred to an oncologist and received five cycles of doxorubicin. Due to nausea and treatment intolerance, he refused further therapy and for years there was no medical follow-up. Meanwhile, he sought out treatments of bioenergy and unknown herbal substances.

History of present illness

At the time the patient first came to our attention, he was dyspneic, plethoric, and cyanotic with bluish red skin. The transabdominal ultrasound confirmed hepatic metastases so further imaging and laboratory tests were scheduled.

History of past illness

His medical history dates to the year 2000, when he initially complained of leg and lower back numbness. A transabdominal ultrasound was performed and metastases in the liver were detected. An abdominal computed tomography (CT) scan confirmed the liver metastases but omitted to detect the primary tumor. Fine needle aspiration (FNA) of a liver lesion was performed and the metastases of a neuroendocrine carcinoma was diagnosed. The common neuroendocrine markers were not evaluated at this time, and the patient refused further gastrointestinal endoscopic evaluation.

Personal and family history

He was referred to an oncologist and received five cycles of doxorubicin. Due to nausea and treatment intolerance, he refused further therapy and for years there was no medical follow-up. Meanwhile, he sought out treatments of bioenergy and unknown herbal substances.

Physical examination

A precordial systolic murmur II/VI was detected, and heart sounds were subtle. The liver was enlarged, and his legs swollen with trophic skin changes.

Laboratory examinations

Panneuroendocrine markers, serum chromogranin A (CgA) 900 ng/mL (normal range <90 ng/mL, and urinary 5-HIAA 2178 µmol/L (normal 78< µmol/L) came back

elevated. He was hypoglycemic with a blood glucose of 2.8 mmol/L, hypoalbuminemic, and anemic. His serum calcium levels, insulin and c-peptide levels were all normal.

Imaging examinations

The transabdominal ultrasound confirmed hepatic metastases so further imaging were scheduled.

On the CT scan, involvement of the liver with hypervascular metastatic masses up to 6 cm in diameter were noted, as well as ascites and metastases to mesenteric lymph nodes and pelvic bones. The pancreas and suprarenal glands were normal, and the primary tumor location could not be identified.

A whole-body scintigraphy and thoracic and abdominal single-photon emission computerized tomography (SPECT)imaging 4 and 24 h after intravenous injection of 111 MBq 111In-pentetreotide were performed. Diffusely intense accumulations of the radiopharmaceutical (RF) were found in the heart, and several lesions in the thoracic spine. Multiple lesions with increased accumulation of RF were found in the enlarged liver, intestine (as this could be the site of the primary tumor), the duodenum and ascendent colon (similar finding on both days of imaging), paraaortic lymph nodes, and one focal lesion within the pelvis. All lesions were seen better on the 24 hr scan- planar and SPECT (Figure 1).

The upper gastrointestinal (GI) tract endoscopy was indicative of chronic H. Pylori negative gastritis, and a complete colonoscopy was normal. A capsule endoscopy revealed long and diffuse segments of erythematous and edematous ileal mucosa, with a granular appearance, villous denudation, one erosion and patchy areas of edematous "remaining" villi. No mucosal (flat or protruding), or submucosal lesions were visualized, as well as no signs of stenosis or intraluminal bleeding (Figure 2). An enteroscopy was planned for obtaining histology specimens, but the patient refused the examination. Due to progressive dyspnea, and suspected carcinoid heart involvement, a

standard transthoracic echocardiogram was performed. It revealed typical manifestations of CHD. The right-atrium and ventricle were dilated with typical thickening and retraction of immobile tricuspid valve leaflets, associated with severe tricuspid regurgitation. Signs of mild tricuspid stenosis (area of 2.2 cm^2) were observed. Coexisting pulmonary valve disease, with predominant stenosis of a gradient up to 33 mmHg was also noted. The pericardium was thickened with a small pericardial effusion and signs of diastolic filling impairment with paradoxical movement of the interventricular septum. The inferior vena cava was dilated, as well as hepatic veins, without any inspiratory variations. The unexpected and unusual finding was an apical displacement of the tricuspid valve (24 mm above mitral ring) as seen in type 1 Ebstein's anomaly (Figure 3).

FINAL DIAGNOSIS

The patient was diagnosed with carcinoid heart disease with right-sided heart failure due to metastatic neuroendocrine neoplasm of unknown primary site.

TREATMENT

The patient was started with intramuscular octreotide acetate (Sandostatin LAR) 20 mg in monthly intervals, but without significant improvement initially (biochemical or clinical). The dose was increased to 80 mg over 12 months and he was followed-up. The drug was well tolerated even at a high dose, and laboratory findings had regressive dynamics (CgA at 3, 6, 9, and 12 months were 800, 650, 500 and 350 ng/mL respectively; 5-HIAA at 3, 6, 9 and 12 months 2005, 1880, 1650 and 950 μmol/L, respectively). Although cardiac symptomatology persisted, it did not progress any further. The patient was not a good candidate for valve replacement due to his right sided heart dysfunction, and he refused ablative procedures for the liver metastases. He did not want chemotherapy to be reinitiated and refused irradiation of bone metastases.

OUTCOME AND FOLLOW-UP

The patient died in 2014.

DISCUSSION

This patient was an unfortunate typical example of a neglected/uncared for GEP-NEN patient, even though newer treatment options provide a relatively good prognosis[10,11].Carcinoid heart involvement is characteristic for 40-50% of patients with full-blown picture of CS and when present it is more likely to be the cause of death, rather than metastatic disease. It typically effects the right side of the heart, with tricuspid and pulmonary valve involvement as a universal finding[12]. In the pathogenesis of right sided heart fibrosis, growth factors such as transforming growth factor- β (TGF-β) and serotonin seem to play a crucial role. Several studies have shown that 5-HIAA, a serotonin metabolite, levels are higher in urine of patients with fully developed CHD or those who are at a higher risk for heart involvement. In a specific, prospective follow-up of 252 patients with CS, after a median of 29 months, showed that urinary 5-HIAA level ≥ 300 μmol/24 h is an independent predictor of the development of CHD[13].

In addition, a significant parameter differing between patients with poor (average of 6 months) or long (average of 50 months) survival following diagnosis of CHD is the time following the initial GEP-NEN diagnosis[14]. An asymptomatic or subclinical CHD could be present during CS with a negative impact on the disease progression and clinical deterioration. Therefore, it is recommended to have a baseline evaluation of NT-proBNP at the time of the diagnosis of CS[15]. Monitoring of NT-proBNP followed by echocardiography in patients with CS, especially in the case of high urinary 5-HIAA levels, could emerge as a new screening and follow-up recommendation[15,16]. Once detected, elevated levels of NT-proNP, should facilitate echocardiography and other imaging modalities (such as cardiac CT and MRI) to detect early cardiac damage and valvular disease. Unfortunately, in this case during the initial patient evaluation, routine NT-proBNP measurements were not available, and a proper risk stratification

was not possible. To date, the European Neuroendocrine Tumor Society (ENETS) recommends tumor markers (chromogranin A, 5-HIAA) as well as NT-proBNP to be evaluated annually or semiannually in GEP-NEN patients[17, 18]. Once diagnosed, CHD calls for a more proactive attitude. Although the optimal timing of surgery, in relation to the severity of valve dysfunction and symptoms, has not yet been defined, based on newer data, valve replacement surgery at the onset of symptoms or right ventricular dysfunction may be considered, while any delay can result in worsening of right sided ventricular failure[19].

In addition, side-effects of pharmacological treatment, especially chemotherapy, in case of metastatic NEC, must be considered in patients with CS[20-23]. Although doxorubicin has a high potential for cardiotoxicity, in the case of this patient its significance was not clear. The left sided heart function of this patient was preserved, so it is not entirely clear whether prior treatment with this drug facilitated or accelerated the deterioration of the right sided heart function.

In order to optimize the surgical outcome and reduce complications, it is important to control the circulating vasoactive carcinoid tumor substances before heart valve replacement[24,25] is performed. With respect to the aforementioned, the European Society for Medical Oncology (ESMO) recommends somatostatin analogue therapy as a standard first-line option in patients with CS as it diminishes tumor progression[26]. Unfortunately, in this case, a somatostatin analogue was not introduced as an initial therapy, but rather a late, nonetheless achieving biochemical and symptomatic improvement. Further pharmacological treatment, especially in a case of refractory CS, remains a matter of debate. The data on chemotherapy are historic and usually demonstrating reduction of urinary 5-HIAA levels. On the other hand, evidence of its usefulness in carcinoid syndrome-related outcomes, including CHD, is lacking and inconsistent[20].

In addition, it is of the utmost importance to properly stage the tumor, and if possible to find the primary site, while different extents of surgical treatment, even for disease spread, are possible and a reduction in tumor load can result in a better biochemical control and be favorable for patient survival[18]. Until precise evidence-based recommendations become available, the order by which surgery should be approached (surgery based on tumor operability/metastatic type with valve replacement surgery) in patients with carcinoid heart involvement is still a matter of debate and should be decided individually, focusing on the severity and symptoms of CHD. According to current, mainly retrospectively collected evidence, valve replacement might be considered prior to cytoreductive surgery in patients with progressive CHD, while the evidence supporting the role of performing hepatic resection first to improve prognosis of patients with CHD is scarce[27].

For staging purposes this patient had a CT scan which could not identify the primary tumor site. Given the clear superiority of an MRI for examination of the liver and pancreas, one could argue in concordance with recent ESMO clinical practice guidelines, that if this patient in 2010 was additionally evaluated with an MRI perhaps the primary GEP-NEN would be localized. Endoscopic ultrasound (EUS), with FNA or fine needle biopsy (FNB), currently are the best methods for visualization of a small pancreatic neuroendocrine tumors (Pan-NETs); this patient was not evaluated with either these methods. The diagnosis of GEP-NEN in this patient was achieved with FNA cytology review of the liver metastases. The contrast enhanced ultrasound (CEUS) with biopsy for histology in 2023 gives added benefit to split the heterogeneous G3 GEP-NENs into well-differentiated NET G3 and poorly differentiated NEC G3 according to the 2019 World Health Organization classification. These two diverse classes of GEP-NENs have clear prognostic differences and could affect surgical approach (debulking surgery/palliative resection?) and/or locoregional treatments[28].

During diagnostic and follow-ups, patients with NEC with unknown primary sites should undergo functional imaging. Historically, scintigraphy using 111In-pentetreotide (Ostreoscan), was most important and useful for identifying and staging tumors containing somatostatin receptor subtypes 2 and 5. It is a highly sensitive and specific method for carcinoid tumors, both functioning and non-functioning. In patients with asymptomatic gastrointestinal neuroendocrine tumors the diagnostic sensitivity is 80-90%, and in those with symptoms of carcinoid syndrome more than 90%[29]. Unfortunately, Octreoscan can miss a primary tumor in a significant proportion of patients with metastatic disease, which was also the case in our patient[30,31].

Compared to Ostreoscan, ^{68}Ga-DOTATATE can identify more lesions and therefore aid in management of GEP-NEN patients. Furthermore, positron emission tomography (PET)/MRI with ^{68}Ga-DOTATOC may be superior to PET/CT in guiding the management of GEP-NENs, especially in terms of precise evaluation of hepatic tumor load[32]. A 2017 study of 40 patients with metastatic GEP-NENs who had undergone CT or MRI but still had an unknown primary tumor location showed that ^{68}Ga-DOTATOC PET/CT could effectively localize the primary tumor to facilitate treatment[33].

In cases of metastatic carcinoid tumors, primary lesions are usually located in the jejuno/ileal region and endoscopic procedures are of the utmost importance, while they offer tissue biopsy and patohistological assessment. In this case, the patient had an interesting capsule finding, which prompted further enteroscopy. This was, like the measurements of specific tumor markers, unfortunately initially omitted, but one might speculate that reduction of tumor burden and/or removal of the primary tumor would have had beneficial effects in terms of symptom relief, as well as attenuation of the disease progression.

CONCLUSION

CHD is a complication occurring in patients with CS related to advanced NETs usually with liver metastases, which manifests as right-sided heart valve dysfunction leading to right-sided heart failure. When present, CHD, together with tumor burden, are major prognostic indicators of a reduced patient survival rate. Therefore, they must be actively sought by available biochemical markers and imaging techniques in patients with CS, even though not present from the beginning of the disease or at the time of diagnosis, or clinically significant. The most useful marker is urinary 5-HIAA and its rise above ≥ 300 µmol/24 h, together with NT-proBNP > 260 pg mL–1, necessitates the need for further echocardiography evaluation. Moreover, imaging techniques aiding tumor detection and staging, SSTR PET/CT and CT or MRI, should be performed at the time of diagnosis and then on a 3-to-6-month interval to determine tumor growth rate and assess the possibility of loco-regional therapy and/or palliative surgery. Cytoreductive surgery might be prudent and to follow with valve replacement surgery, especially in case of more severe forms of CHD. First line pharmacotherapy includes somatostatin analogues with a dose escalation until symptom relief is achieved. In cases of refractory CS, defined by persisting symptoms and increasing or persistently high urinary 5-HIAA levels despite the use of maximum labelled doses of somatostatin analogues, optimal subsequent treatment options still need to be determined.

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