A Case of Primary Insular Ovarian Carcinoid Tumor with Hyperandrogenism and Carcinoid Heart Disease

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Financial support: None declared
Conflict of interest: None declared

Patient: Female, 40-year-old
Final Diagnosis: Carcinoid heart disease • primary ovarian carcinoid tumor of insular type
Symptoms: Acne • diarrhea • heart murmur • hirsutism • secondary amenorrhea
Medication: —
Clinical Procedure: Total abdominal hysterectomy and bilateral salpingo-oophorectomy
Specialty: Endocrinology and Metabolic

Objective: Rare disease
Background: Carcinoid heart disease typically occurs in the presence of metastatic carcinoid tumor deposits in the liver, as vasoactive substances access the systemic circulation through the hepatic vein. Primary ovarian carcinoid tumors are rare neuroendocrine tumors, and can be associated with carcinoid syndrome and carcinoid heart disease.

Case Report: We describe the case of a 40-year-old woman who presented with secondary amenorrhea, acne, hirsutism, and diarrhea. She was found to have a heart murmur on exam in the absence of severe symptoms of heart failure. Her investigations demonstrated elevated urinary 5-hydroxyindoleacetic acid (5-HIAA), chromogranin A, and free testosterone. Abdominal computed tomography enterography showed a large and hypervascular pelvic mass. Octreotide scintigraphy confirmed the diagnosis of primary ovarian carcinoid tumor in the setting of an intensely octreotide-avid mass with no evidence of distant metastases. Transesophageal echocardiography showed severe tricuspid regurgitation with severe dilation of the right heart chambers. She underwent a total abdominal hysterectomy and bilateral salpingo-oophorectomy. The pathology demonstrated a 14-cm carcinoid tumor of ‘insular’ type confined to the ovary, pT1apNX, grade 1, positive for chromogranin and synaptophysin (neuroendocrine markers) and positive mib-1 (Ki-67). Postoperatively, clinical and biochemical parameters improved significantly but her cardiac function regressed over time, resulting in a tricuspid valve replacement 6 years later.

Conclusions: Primary ovarian carcinoid tumors can result in carcinoid heart disease, even in the absence of liver metastases. Early diagnosis and treatment contribute to favorable outcomes.

Keywords: Carcinoid Heart Disease • Carcinoid Tumor • Malignant Carcinoid Syndrome • Ovarian Neoplasms • Tricuspid Valve Insufficiency

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Background

Primary ovarian carcinoid tumors are rare [1,2]. They can be associated with carcinoid syndrome and carcinoid heart disease through systemic release of vasoactive substances without liver metastases [2,3]. Carcinoid heart disease generally involves the right-sided valves and chambers and can result in heart failure [4,5]. In this report, we present the case of a 40-year-old woman with primary ovarian carcinoid tumor of insular type presenting with hyperandrogenism and carcinoid heart disease.

Case Report

A 40-year-old woman presented with a 1-year history of secondary amenorrhea and hyperandrogenism including acne on her face, back and chest, hirsutism on her face and arms, and changes to her voice. She had also been experiencing daily flushing episodes for 5 years, diarrhea for 6 months, and occasional palpitations.

Diarrhea started 6 months prior to presentation, resulting in a large anal fissure as confirmed on colonoscopy, which also showed rectal polyps and aphthous ulcers in the rectum. A repeat colonoscopy 6 months later showed inflammation of the cecum with possible stricture of the terminal ileum. All biopsies at that time were negative. She began to notice recurrent night sweats, and developed weight loss of about 14 kg. She had dyspnea on exertion but not at rest. She did not report orthopnea or paroxysmal nocturnal dyspnea.

On physical exam, she had obvious hirsutism on her face and arms and facial acne. She had an elevated jugular venous pressure with prominent CV wave, a newly discovered systolic murmur that was loudest over the left sternal border, and pedal edema. She had a palpable, very large, firm mass in the lower right quadrant of the abdomen.

Her initial laboratory investigations showed the following (normal ranges shown in brackets): elevated am testosterone of 3.0 nmol/L (0.5-2.0 nmol/L), elevated free testosterone of 45 pmol/L (2.0-30 pmol/L), dehydroepiandrosterone (DHEAS) 2.5 umol/L (<11 umol/L), human chorionic gonadotropin (hCG) less than 5 units/L, estradiol 195 pmol/L, progesterone 7.3 nmol/L, follicle stimulating hormone (FSH) 5.6 U/L, LH 1.5 U/L, and alpha fetoprotein 2 ug/L with normal less than 9 ug/L. Prolactin level was normal at 9.6 ug/L (<25 ug/L). Cancer antigen CA-125 was 10 kU/L (<35 kU/L). Carcinoembryonic antigen CEA was 2 ug/L (<5 ug/L). A 24-hour urine 5-hydroxyindoleacetic acid (5-HIAA) was markedly elevated at 1245 umol/24 hours (<41 umol/24 hours). Vasoactive intestinal peptide level was normal at 32 pg/mL (<75 pg/mL).

She initially had a computed tomography (CT) enterography (Figure 1) showing a 10-cm hypervascular mass in the pelvis that measures 9.1×10.5×10.0 cm (maximal anteroposterior x transverse x cephalocaudal dimension), anterior to the uterus with atypical enhancement for fibroid (arrow).
cardiac source. An MRI of the abdomen and pelvis (Figure 2) showed a fibroid uterus and a large pelvic mass. There were 1 or 2 liver hemangiomas. There were also multiple areas of abnormal probable arteriovenous fistula. She then had an octreotide scan (Figure 3) that confirmed a large soft tissue mass in the anterior pelvis measuring 8.5×12.8×13.8 cm that was superior to the bladder and had intensive octreotide uptake. There was also evidence of a new right-sided pleural effusion. There were no other octreotide-avid lesions seen within the abdomen or pelvis.

In view of the presence of systolic murmur, lower extremity edema, and evidence of right atrial enlargement on CT scan, an echocardiography was performed and showed right ventricular volume overload and severe tricuspid regurgitation. Right ventricular systolic pressure (RVSP) was normal. A cardiac MRI was then performed and showed moderate to severe dilation of the right ventricle and severe dilation of the right atrium. There was severe tricuspid regurgitation with a regurgitant volume of 76%. She did not have a past medical history of heart disease or heart murmurs. The systolic murmur was discovered on physical exam at presentation. Cardiology assessment attributed the cardiac findings to the carcinoid tumor after ruling out other etiologies.

She has a past medical history of uterine fibroids with hysteroscopic myomectomy, adenocarcinoma in situ of the cervix, HSIL, and right axillary cystic hygroma. Her family history was significant for breast cancer in her maternal grandmother. She did not have any personal or family history of heart disease. She did not smoke, drink alcohol, or use any recreational drugs.
Carcinoid syndrome can occur in primary ovarian carcinoid tumors, occurring in less than 10% of the cases [4]. In terms of the mechanism, it is thought to be secondary to the direct venous drainage of the ovaries into the systemic circulation bypassing the portal venous circulation. This represents a unique characteristic of carcinoid heart disease in primary ovarian tumors. Carcinoid syndrome is typically associated with liver metastases in other carcinoid tumors, as vasoactive substances enter the systemic circulation through the hepatic vein [2,3].

Sauer et al first described the occurrence of a heart murmur in a case of primary ovarian carcinoid tumor [10]. This was thought to be caused by elevated serotonin levels, which can lead to fibrosis of the endocardium and can subsequently damage the valve [4]. It typically presents as right-sided valvular sclerosis and fibrosis that can cause tricuspid stenosis or regurgitation and pulmonary valve stenosis. Other rare presentations include myocardial dysfunction and pericardial thickening. Left ventricular heart failure is extremely rare [4,5]. Patients with carcinoid heart disease do not usually present with severe right heart failure symptoms despite severe valvular heart disease. They typically have New York Heart Association (NYHA) class III symptoms [11]. Similarly, our patient presented with minimal symptoms of dyspnea on exertion, a systolic murmur, and pedal edema, and was found to have severe tricuspid regurgitation on echocardiography.

In a review of the literature over 15 years by Georgescu et al [12], 99 cases of primary ovarian carcinoid tumors were reported. The average age was 53 years old. Our patient was younger, aged 40 years at the time of diagnosis. About one-third of the patients were found to have carcinoid heart disease on presentation, as seen in our case [12]. It was reported that the severity of cardiac involvement is proportionally related to the degree of elevation of serum 5-HIAA [13].

Some reviews have observed that carcinoid heart disease in primary ovarian tumors is associated with overall poor outcome, with a 3-year survival rate of 31% [13]. While some authors noted resolution of cardiac symptoms after surgical resection of the primary ovarian carcinoid [5,14,15], others found that cardiac disease persisted postoperatively [16]. Valvular heart lesions do not regress spontaneously and require surgical intervention with valve replacement once present [13]. Our patient had progression of her cardiac symptoms after her tumor resection and required a tricuspid valve replacement 4 years later.

Discussion

Ovarian carcinoid tumors, which are considered a rare form of neuroendocrine tumors, were first described by Stewart et al over 80 years ago [1]. They account for less than 0.1% of all ovarian cancers and about 0.3% of carcinoid tumors [2]. The types of primary ovarian carcinoid tumors include insular, trabecular, stromal, and mucinous carcinoids. The insular type, which derives from the midgut, is considered the most common variant. Ovarian carcinoid tumors can also present as mixed endocrine/exocrine primary tumors resulting from a combination of 2 or more types [3,6-9].

Carcinoid syndrome can occur in primary ovarian carcinoid tumors, and has been identified in the insular variants in about one-third of the cases, but was not found to be associated with other histologic types [3]. The variant found in our case is in concordance with the literature. Cardiac disease is common in carcinoid tumors despite their rarity. Previous studies showed that 20% of patients who present with carcinoid syndrome had heart disease at diagnosis. However, it is considered a rare complication in primary ovarian carcinoid tumors, occurring in less than 10% of the cases [4]. In terms of the mechanism, it is thought to be secondary to the direct venous drainage of the ovaries into the systemic circulation bypassing the portal venous circulation. This represents a unique characteristic of carcinoid heart disease in primary ovarian tumors.

In light of these findings, she underwent extensive surgical resection including a total abdominal hysterectomy, bilateral salpingo-oophorectomy, and resection of a 14×18 cm mass (Figure 4). She was treated with octreotide 100 μg subcutaneously 3 times daily for 5 days preoperatively.

The pathology came back positive for a carcinoid tumor of ‘insular’ type confined to the ovary. On immunohistochemical analysis, the tumor cells were confirmed to be positive for neuroendocrine markers chromogranin and synaptophysin. There were very rare tumor cells positive for Ki-67 (<1%), in agreement with the very rare mitotic figures seen. Pathologic staging was pT1apNX, grade 1.

Postoperatively, her symptoms improved significantly. Biochemical markers improved as well, with 5-HIAA normalizing to 11 μmol per day. Chromogranin A was 112 ng/mL, and free testosterone was 2.2 pmol/L. There was no evidence of recurrence on repeat imaging studies. Her carcinoid heart disease was initially monitored closely by Cardiology until she underwent a tricuspid valve replacement and closure of patent foramen ovale 4 years later due to progression of her cardiac symptoms.

Figure 4. Photographs of the ovarian mass weighing 780 g and was 14×14×8 cm.
Conclusions

In summary, carcinoid heart disease can be a presenting symptom of primary ovarian carcinoid tumors, even in the absence of liver metastases. Early diagnosis and treatment are crucial and contribute to favorable outcomes.

Acknowledgements

Dr. Daniel Schiller: Associate professor, Department of Surgery, Division of General Surgery.

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