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Case Report

Hypertension and Carcinoid Heart Disease as Initial Manifestations of Ovarian Carcinoid Tumor

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Abstract

Ovarian carcinoid tumors (OCTs) are rare and may cause carcinoid syndrome (CS) even in the absence of liver metastases. Carcinoid heart disease (CHD), which develops in up to 50% of patients with CS, substantially affects morbidity and mortality. While prognosis is generally favorable, maintaining clinical suspicion and early diagnosis is crucial to prevent the development of advanced heart failure or metastases. We present a case of a woman exhibiting asthenia, diarrhea, and de novo severe hypertension. Echocardiography revealed typical features of CHD. Elevated urinary levels of 5-hydroxyindoleacetic acid (5-HIAA) corroborated the diagnosis of CS. ^{68}Ga-DOTANOC positron emission tomography computed tomography identified a suspicious left pelvic mass, which was subsequently confirmed by magnetic resonance imaging. Surgical resection of the tumor was performed, followed by tricuspid valve replacement surgery, confirming the diagnosis of OCT associated with CS and CHD. Postoperative follow-up revealed considerable clinical improvement, and the patient has remained free of recurrence. This case underscores the complex cardiovascular involvement in CS, with secondary hypertension as the initial symptomatic manifestation, which improved following resection of OCT. Additionally, it highlights the role of CS in the pathogenesis of severe tricuspid valve dysfunction, which ultimately required cardiac surgery.

Key Words: neuroendocrine tumors, carcinoid tumor, carcinoid syndrome, carcinoid heart disease, ovarian neoplasms, hypertension

Abbreviations: 5-HIAA, 5-hydroxyindoleacetic acid; CgA, chromogranin A; CHD, carcinoid heart disease; CS, carcinoid syndrome; FIGO, International Federation of Gynecology and Obstetrics; HF, heart failure; MRI, magnetic resonance imaging; NETs, neuroendocrine tumors; OCT, ovarian carcinoid tumor; PET/CT, positron emission tomography/computed tomography.

Introduction

Neuroendocrine tumors (NETs) are heterogeneous tumors that predominantly arise from the gastrointestinal tract and lungs. Less frequently, these tumors can originate from other organs, including the ovaries [1, 2]. Ovarian carcinoid tumors (OCTs) are rare, accounting for less than 1.0% of all NETs [3], and less than 0.1% of all ovarian tumors [4]. Functioning OCTs have the particularity of inducing carcinoid syndrome (CS) in the absence of liver metastases. This occurs because the ovary drains directly into the systemic venous circulation, bypassing the liver's capacity to metabolize vasoactive hormones [4]. Approximately 20% to 50% of NETs with CS develop carcinoid heart disease (CHD), which typically affects the right heart valves, causing tricuspid and pulmonic regurgitation and stenosis [5]. This occurs because vasoactive substances, like serotonin, are enzymatically deactivated in the pulmonary vasculature, which prevents their transfer to the left heart [6]. Initially, cardiac involvement is well tolerated, making diagnosis challenging until the late presentation of symptomatic right heart failure (HF) [7].

Case Presentation

A 63-year-old woman presented with a 2-month history of asthenia, anorexia, and diarrhea (approximately 6 bowel movements per day). She denied abdominal pain, flushing, or weight loss. Physical examination revealed de novo severe hypertension, with a systolic blood pressure of 210 mm Hg and diastolic blood pressure of 125 mm Hg in all 4 limbs, raising the suspicion of secondary hypertension. Her medical history included excised melanoma and right total hip arthroplasty. There was no significant family history.

Diagnostic Assessment

A 24-hour ambulatory blood pressure monitoring was conducted, confirming the diagnosis of arterial hypertension. Transthoracic echocardiography revealed severe right atrial and ventricular dilation with preserved right ventricular contractility, tricuspid valve thickening with retraction of the valvular and subvalvular apparatus causing severe tricuspid valve regurgitation, and thickening of the pulmonary valve.

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The left heart cavities, left ventricular systolic function, and aortic and mitral valves were normal. Transesophageal echocardiography further confirmed these findings. No evidence of bronchopulmonary disorders or pulmonary embolism was observed in the chest computed tomography (CT) angiography. Given the suspicion of CHD, a urinary 5-HIAA measurement was requested. Urinary 5-HIAA excretion was 130 mg/24 hours (4.75 µmol/d) (normal reference range, ≤15 mg/24 hours; 0.55 µmol/d), prompting further investigation with a ^{68}Ga-DOTANOC positron emission tomography (PET)/CT. It revealed an intense Ga-avid pelvic mass. Colonoscopy was normal. Additionally, a transvaginal ultrasound identified a suspicious adnexal mass measuring 12.6 × 11.6 × 8 cm. Abdominal-pelvic magnetic resonance imaging (MRI) confirmed the presence of a 13-cm heterogeneous ovarian mass with both cystic and solid components, devoid of fat or coarse calcifications, and no evidence of additional lesions, including lymphadenopathy or liver metastasis (Fig. 1A-1C). A subsequent analytical assessment showed a persistently elevated urinary 5-HIAA level of 87.3 mg (3.19 µmol/24 hours), and an elevated chromogranin A (CgA) value of 580.6 ng/mL (580.6 µg/L) (normal reference range, ≤102 ng/mL; ≤102 µg/L), while cancer antigen 125, carbohydrate antigen 19-9, and carcinoembryonic antigen were within normal reference ranges.

Treatment

New-onset hypertension prompted the initiation of carvedilol 25 mg twice daily. Despite this, the patient's hypertension persisted, requiring the addition of amlodipine 10 mg and perindopril 10 mg once daily. Triple therapy caused symptomatic hypotension, leading to carvedilol discontinuation. Her blood pressure was controlled with amlodipine 10 mg and perindopril 10 mg until her ovarian surgery.

Prior to the surgical procedure, octreotide LAR 20 mg every 28 days was initiated. An exploratory laparotomy was performed under octreotide perfusion, which ultimately resulted in a total hysterectomy and bilateral salpingo-oophorectomy. Macroscopic examination identified an ovarian mass measuring 12 × 7.8 × 7 cm, with a lobulated external surface and an intact capsule (Fig. 2). Histological examination was consistent with ovarian carcinoma, stromal type, with no evidence of invasion through the ovarian capsule or lymphovascular invasion. Immunohistochemical staining showed positivity for CK8/18, AE1/AE3, CgA, synaptophysin, and CD56, while it was negative for calretinin, WT1, CD99, α-inhibin, CK7, and CK20 (Fig. 3A-3C). The Ki67 index was 2%. The peritoneal washing cytology was negative for malignant cells. Therefore, the patient was diagnosed with OCT, classified as stage IA according to the International Federation of Gynecology and Obstetrics (FIGO) system.

Outcome and Follow-up

Postoperatively, the patient maintained surveillance with symptomatic improvement and normalization of urinary 5-HIAA and CgA levels. Her hypertension did not fully resolve following tumor resection; however, it showed substantial improvement. To address the CHD, a bioprosthetic valve replacement of tricuspid valve was performed. After 3 years of follow-up, the patient remains free of tumor recurrence and is currently being treated with ramipril 2.5 mg once daily.

Discussion

OCTs are rare neoplasms primarily affecting perimenopausal women, with a mean age of diagnosis of 50 years [8]. These tumors are often asymptomatic or present with nonspecific clinical features, leading to incidental detection during abdominal imaging studies [8]. Approximately 30% of patients with OCTs develop CS [4], which is clinically characterized by flushing, diarrhea, bronchospasm, and right-sided HF [5]. Unlike gastrointestinal NETs, the systemic venous drainage of the ovaries predisposes to the early manifestation of CS, even in the absence of liver metastases [4, 8]. Therefore, measurement of 5-HIAA should be performed in all cases of OCTs, regardless of stage [5].

Patients with CS, particularly those experiencing carcinoid crisis, may exhibit labile blood pressure, with episodes of hypotension and, less frequently, hypertension [9, 10]. It is hypothesized that this is influenced by varying concentrations of vasoactive substances interacting with the cardiovascular system, inducing vasodilation or vasoconstriction [10]. Serotonin is thought to be the primary vasoactive mediator in CS with hypertension and can trigger hypertensive crises resistant to conventional treatments, similar to what is observed in serotonin syndrome [7, 10, 11]. Functioning OCTs may be an underrecognized cause of secondary hypertension in women [9].

OCTs can be classified as either primary or metastatic, with the majority of metastatic cases originating from the gastrointestinal tract [1, 8]. Histologically, primary OCTs are further categorized into insular, stromal, trabecular, and mucinous subtypes, with the insular type being the most common and the mucinous subtype the rarest [8, 12]. The differentiation between primary OCTs and metastatic tumors can be particularly challenging due to the overlap in their microscopic features [13]. Given the rarity of primary OCTs, it is critical to exclude the possibility of a primary gastrointestinal NET [1, 2].

CS is exceedingly rare in stromal OCTs. In a retrospective analysis of 119 cases, only 1 patient was found to have CS [14]. In our patient, the concurrent presentation of diarrhea, de novo severe hypertension, and right-sided cardiac involvement strongly suggested the diagnosis of CS, which was confirmed by an elevated 5-HIAA level. Instead of the more common sites associated with CS, a stromal carcinoid tumor was found in the ovary. The diagnosis of a non metastatic primary OCT was confirmed, as the patient presented with a unilateral ovarian lesion, with no evidence of additional lesions on preoperative imaging studies and colonoscopy. Furthermore, postoperative follow-up demonstrated symptomatic improvement and normalization of 5-HIAA and CgA levels.

Preoperative diagnosis of OCT requires the use of multiple imaging modalities. Ultrasound and cross-sectional imaging are useful for locating the tumor, although they cannot definitively confirm if the lesion is a NET. MRI is considered the preferred imaging technique for local assessment, as it provides crucial information for surgical planning and evaluation of operability [15]. OCTs typically express somatostatin receptors, making ^{68}Ga-DOTA-peptides PET/CT crucial for confirming the diagnosis, detecting metastases, and determining the disease stage [1, 13].

Among patients with OCTs and concomitant CS, up to 29% may develop CHD [8, 13]. As CHD can present with minimal symptoms despite substantial cardiac involvement, maintaining a high index of suspicion is crucial [7]. N-terminal-proBNP is considered the most valuable adjunct biomarker

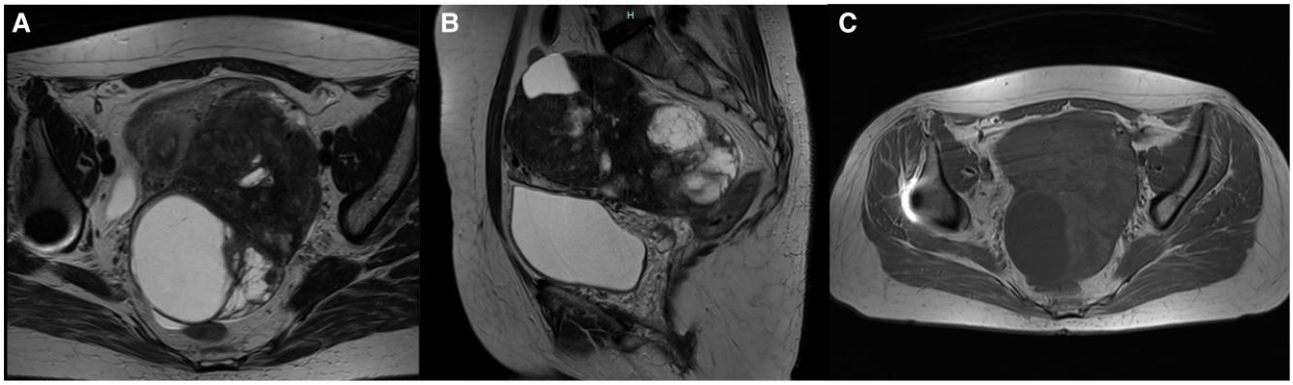

Figure 1. Magnetic resonance imaging results. A, T2-weighted sequence, axial plane, showing a heterogeneous pelvic mass displacing the uterus anteriorly and to the right. The mass exhibits a cystic component with multiple septations and a solid component. B, T2-weighted sequence, sagittal plane, showing a pelvic mass compressing the rectum posteriorly. C, T1-weighted sequence, axial plane, with no evidence of calcifications or macroscopic fat in the pelvic mass, ruling out the possibility of a teratoma.

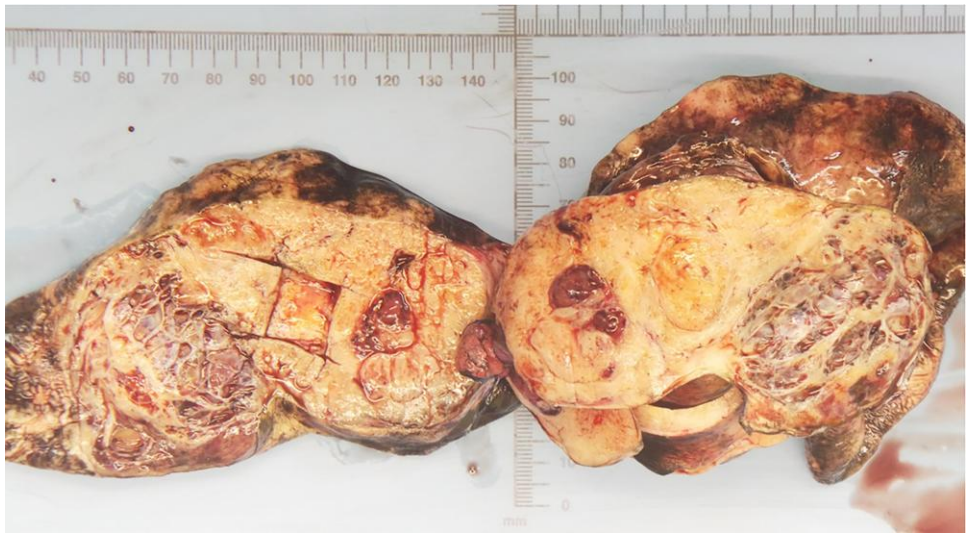

Figure 2. Macroscopic examination of the adnexectomy specimen revealed a tumoral ovarian mass measuring 12 cm at its largest diameter. The tumor was predominantly solid, consisting of whitish, firm tissue, with yellowish, soft-elastic areas, and some cavitated regions visible.

to echocardiography for the screening and monitoring of CHD, as its median levels are significantly higher in patients with CHD compared to those without. It is recommended that NT-proBNP levels be measured in all patients exhibiting elevated urinary 5-HIAA and/or presenting with suspicious symptoms, both at baseline and during follow-up [5].

The therapeutic management of OCTs with CS involves the use of somatostatin analogues, which alleviate symptoms by inhibiting serotonin secretion. This approach not only provides symptomatic relief but also enables the safe resection of the ovarian tumor, the only potentially curative treatment, while minimizing the risk of triggering a carcinoid crisis [5, 15]. The standard surgical treatment generally involves total hysterectomy with bilateral salpingo-oophorectomy, along with surgical debulking of any extraovarian spread or metastases when indicated. In premenopausal women with tumors confined to the ovary, fertility-sparing surgery may be considered, given the typically unilateral nature of these tumors and their generally favorable prognosis. However, the safety of fertility-preserving approaches is not well established, as only a few cases have been reported, with limited follow-up data available [8, 15]. Adjuvant therapy is not recommended for early-stage ovarian carcinoid tumors, as there is no demonstrated benefit [8, 16].

The majority of OCTs are confined to the ovary and are diagnosed at an early stage, specifically FIGO stage I [1]. Despite this, OCTs can exhibit aggressive behavior and may metastasize, with metastatic OCTs having a poor 5-year survival rate [1, 3]. For stage I tumors, the prognosis is generally favorable, with a 5-year survival rate exceeding 90% [4, 15, 16]. However, the presence of cardiac involvement adversely affects morbidity and mortality, resulting in a markedly poorer prognosis in the absence of treatment [5].

The management of CHD requires a multidisciplinary approach. Medical treatment focuses on controlling the tumor and managing the release of vasoactive substances, primarily through the use of somatostatin analogues [5]. Even after successful tumor resection, cardiac symptoms may persist. In cases of severe symptomatic CHD with an anticipated postoperative survival of at least 12 months related to the NET, surgical valve replacement can provide considerable symptomatic relief and improve long-term survival outcomes, with the majority of patients being reclassified to NYHA class I following the procedure [5, 7].

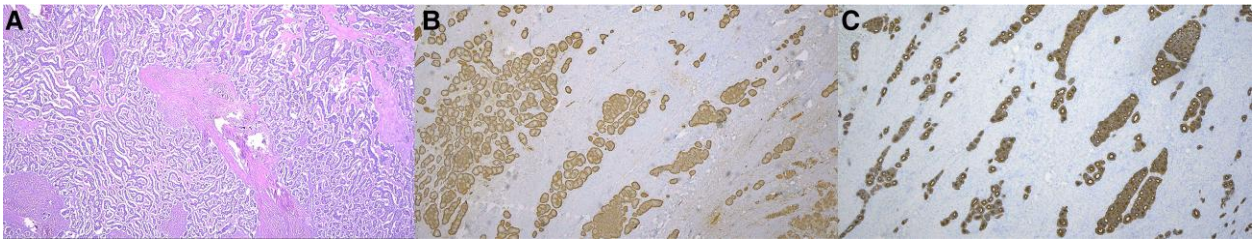

Figure 3. Histological results. A, Magnification at 2× of a hematoxylin and eosin stain showing a tumor with trabecular and acinar patterns, often featuring solid masses arranged in a fibromatous stroma. B and C, Magnification at 4× with immunohistochemical staining for chromogranin A and AE1/AE3, respectively.

In conclusion, this case highlights the importance of maintaining a high clinical index of suspicion for the early diagnosis of CS and CHD. Although OCTs are rare, they should be included in the differential diagnosis of CS-related symptoms, particularly in middle-aged women. An effective management strategy requires a multidisciplinary approach, with a focus on preventing tumor progression, metastasis, and the development of advanced HF.

Learning Points

- CS can occur in the absence of liver metastasis in rare cases, such as OCTs, in which vasoactive substances are released directly into the systemic circulation, bypassing the liver's ability to metabolize them.
- A high clinical suspicion is crucial for the early diagnosis of CS, and the measurement of 5-HIAA should be performed in all cases of ovarian NETs, irrespective of disease stage.
- Functioning OCTs may be an underrecognized cause of secondary hypertension; therefore, in women with new-onset hypertension and clinical features suggestive of CS, OCTs should be considered in the differential diagnosis.
- Early detection of CHD through NT-proBNP and/or echocardiography, coupled with prompt therapeutic intervention, is essential to preventing irreversible cardiac damage and progression to advanced HF.
- In cases of severe symptomatic CHD, surgical valve replacement can provide considerable symptomatic relief and improve long-term survival outcomes.

Contributors

All authors made individual contributions to authorship. A.M.F. drafted the manuscript. S.R., C.N., D.P., P.A., and R.G.M. were involved in patient care and critical review of the manuscript. S.R. was involved in histopathology section and preparation of histology images.

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Disclosures

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Informed Patient Consent for Publication

Signed informed consent obtained directly from the patient.

Data Availability Statement

Data sharing is not applicable to this article as no data sets were generated or analyzed during the present study.

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