

Carcinoid Heart Disease in a Primary Ovarian Carcinoid

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Ovarian carcinoids are very rare, and only their insular form is associated with carcinoid syndrome. We herein describe a case report of an elderly woman who presented with typical carcinoid syndrome, which is routinely characterized by right-sided heart failure, diarrhoea, flushes, and other common manifestations. Further examination and biochemical testing of the patient confirmed suspected carcinoid tumor. However, the tumor was surprisingly localized in the left ovary. The presence of the patient's severe combined tricuspid valve disease would create impossible surgical management conditions, so we decided to first perform cardio-surgery with tricuspid valve replacement. After tumor removal, levels of hydroxyindolacetic acid did not normalize and although the patient was asymptomatic, a small lesion was detected by tectrotyd scan paravertebrally. Treatment with lanreotide led to complete remission with negative biochemical and imaging signs of tumor. Thus, to summarize, carcinoid tumor even in an atypical localization (ovary) should be considered in elderly female patients with severe combined tricuspid valve disease due to carcinoid syndrome.

Key Words: Carcinoid syndrome • Ovarian carcinoid • Tricuspid valve

INTRODUCTION

Carcinoid tumors are relatively uncommon, although they are one of the most frequently seen neuro-endocrine tumors (NET) with an estimated incidence of 1.5-2 per 100,000.¹ They typically occur in the gastrointestinal tract and lungs, whereas their other localizations (such as the ovary) are very rare. Primary ovarian carcinoid tumors constitute only about 1% of all carcinoid tumors and < 0.1% of all ovarian carcinomas;^{2,3} they are divided into trabecular, strumal, mucinous and insular types, the

latter being the most common and the only one associated with carcinoid syndrome. Ovarian carcinoids manifest primarily in postmenopausal women and are customarily unilateral. The metastatic carcinoids are nearly always bilateral and scattered tumor deposits are present throughout both ovaries. Primary ovarian carcinoids metastasize only occasionally, and should be treated as ovarian tumors with low malignancy potential.⁴

Carcinoid syndrome that can accompany carcinoid tumor (mostly carcinoids with liver metastasis or primary lung carcinoids) is often characterized by diarrhoea, vasomotor changes (flushing, erythema and cyanosis), dyspnoea, bronchospasm and symptoms of carcinoid heart disease, which affects approximately half of the patients with carcinoid tumors. Carcinoid heart disease with typical endocardial plaques of fibrous tissue occurs in 1/3 to 1/2 of the patients with carcinoid syndrome,¹ with tricuspid or pulmonary regurgitation being the most common valves affected (97%, 88%, respectively), however, its occurrence in patients with ovarian carcinoid is anecdotal.⁵⁻⁸ Right-sided heart valve

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dysfunction occurs due to the venous drainage of a vasoactive substance serotonin which escapes liver metabolism. Correspondingly, left-sided valve dysfunction, which is usually accompanied by coronary vasospasm, is present as the result of a patent foramen ovale found in less than 10% of individuals with carcinoid heart disease.^{9,10}

CASE REPORT

We present a 77-year-old female patient who was hospitalized at the department of cardiology because of weight gain (up to 10 kg), dizziness, shortness of breath, edema of lower limbs, paroxysmal flushing of the face and diarrhea in January 2013. All these symptoms have been progressing within a couple of months. Previously, she had been treated for hypertension (metoprolol ZOK 50 mg daily) and hypothyroidism (levothyroxin 50 µg daily). She did not have any allergies and was retired (originally worked as a nurse). She has been menopausal since the age of 51 years, had two deliveries and did not take any hormonal replacement therapy. Her last gynecological preventive check-up occurred 2 years ago with normal finding.

Upon admission, the patient's weight was 83 kg, height 164 cm, blood pressure 145/80 mmHg, heart rate regular 90/min. She had plethoric face, tachypnoeic (24 breathes/minute), and rough systolic murmur was heard above the mitral (intensity 3/6) and tricuspid (intensity 4/6) valves, and diastolic murmur (intensity 1/6) above tricuspid valve and sporadic crackles in the basal parts of the lungs. The filling of jugular veins was enlarged, hepatomegaly (+ 3 cm) was palpable and edemas were present in the lower extremities to the knees.

Review of the patient's electrocardiogram indicated sinus tachycardia and negative T waves in III lead, but otherwise normal finding. Because of the presence of predominant right-sided heart failure and suspected valve disease, echocardiography was performed which revealed normal function of the left ventricle with mild mitral regurgitation, but also severe combined tricuspid valve disease, both stenosis and regurgitation. The tricuspid leaflets were thickened and stiffened. There was also severe tricuspid stenosis (maximal/mean pressure gradient 20.2/10.0 mmHg) and regurgitation (with wide

jet to 2/3 of right atrium, Figure 1A and B). Echocardiography also revealed mild pulmonary regurgitation, dilated right ventricle (proximal diameter 32 mm and basal diameter 42 mm), thick right ventricle (wall thickness 6 mm) and adequate right ventricular function (tricuspid annular plane systolic excursion 19 mm). The echocardiographer suspected foramen ovale patens (PFO), and carcinoid heart disease.

After admission the patient was clinically stabilized with diuretics (furosemide intravenously, then orally, and spironolactone 25 mg orally). Thereafter, transesophageal echocardiography (TEE) and bilateral heart catheterisation were performed. TEE confirmed combined severe tricuspid valve disease and PFO. During bilateral heart catheterisation (which was performed at heart rate of 70 beats/minute) there was a normal coronary angiogram. The patient's hemodynamic examination showed right atrial pressure 15/22 (21) mmHg, right ven-

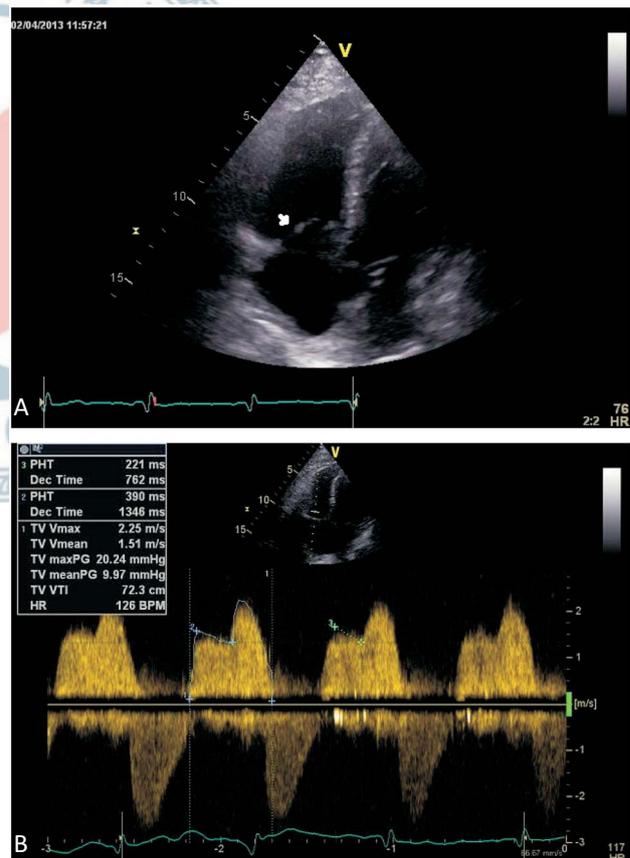


Figure 1. (A) Right ventricular apical 5-chamber view showing thickening of tricuspid valve (marked with white arrow). (B) Continuous wave Doppler recording through the tricuspid valve. Note the elevated peak diastolic velocity of 2.25 m/s and mean pressure gradient 9.97 mmHg.

tricuspid pressure 33/11 mmHg, pulmonary artery pressure 33/12 (20) mmHg, pulmonary capillary wedge pressure 9/14 (10) mmHg, pulmonary artery resistance 349 (normal < 250 dyn.s/cm⁵) and tricuspid valve area 0.60 cm². The pressures were 145/12 mmHg in left ventricle, 145/76 (105) mmHg in aorta. Oxymetry showed 10% right-left shunt and 14% left-right shunt, and cardiac output was 3.1 l/min.

Despite the suspected presence of patent foramen ovale, our patient has not developed left valve disease. Based on these findings, tricuspid valve replacement with PFO suture was indicated as well as endocrinological examination to exclude carcinoid.

Endocrinological examination included analysis of urine for 5-hydroxyindolacetic acid (HIAA) and serum chromogranin A levels. Both parameters were significantly elevated (Table 1): 5-HIAA 480 µmol/day (normal level up to 41.8 µmol/day) and chromogranin A 1252 U/l (normal level up to 84.7 U/l). Computerized tomography (CT) enteroclysis and CT of the lungs did not detect the tumor, thus tectrotyd scan was performed which revealed abnormal activity of the radionuclide in the left ovary (Figure 2), where the tumor was confirmed by gynecologic examination (including ultrasonography) and CT of the small pelvis. The timing of indicated operations was as follows: first, the patient was indicated for cardio-surgical tricuspid valve replacement together with closure of PFO (March 2013). Second, radical hysterectomy was then indicated. Before cardio-surgical operation the patient was stabilized by somatostatin 100 µg/hour i.v. starting 2 hours before anaesthesia and continuing 8 hours after the surgery. The patient's tricuspid valve was replaced with a Carpentier-Edwards Perimount Magna Ease Aortic Heart Valve 23 mm, and PFO was closed. Following the operation, the patient was recovering adequately.

The pathologist described severe thickening of valvular and parietal endocardium with a large layer of cel-

lular connective tissue. Echocardiography performed after surgery confirmed good function of the replaced tricuspid valve (Vmax 1.2 m/s; pressure gradient max/mean 5.7/2.87 mmHg, pressure half time 76 ms, no regurgitation) and complete closure of PFO.

Radical hysterectomy was performed two months later. The definitive histological finding was insular carcinoid with minor tubular and solid structure in the size of 60 × 50 × 45 mm. The patient was discharged from the hospital within 2 weeks in good clinical condition.

However, at the 3-month routine endocrinological check-up, although the patient's clinical condition remained very good without any symptoms of carcinoid syndrome or heart failure, her HIAA and chromogranin



Figure 2. Tektrotyd scan. Pathologic accumulation of radiopharmakon in left ovary is marked with a black arrow.

Table 1. Levels of hydroxyindolacetic acid and chromogranin A

	February 2013	July 2013	July 2014
Hydroxyindolacetic acid (µmol/day)	480	71	30
Normal range: 10.5-41.8			
Chromogranin A (U/l)	1252	243	227
Normal range: 0-84.7			

levels were again elevated [71 $\mu\text{mol/day}$ and 243 U/l (Table 1), respectively]. The second tectrotyd examination was performed which showed a discrete lesion (1-1.5 cm) paravertebrally near the 7th thoracic vertebra.

The patient began a treatment regimen with lanreotide, 120 mg once monthly. After the treatment was initiated, levels of HIAA normalized (30 $\mu\text{mol/day}$), whereas levels of chromogranin A nearly normalized (227 U/l) (Table 1), and tectrotyd examination 12 months later showed physiological distribution of radionuclide without any pathological lesion. To date, the patient continues her medication regimen of lanreotide 120 mg each month.

DISCUSSION

Carcinoid tumors are very uncommon, an unusual clinical condition rarely seen in our facility. We were presented with an elderly woman with typical carcinoid syndrome with predominant, severe tricuspid valve involvement leading to progressed right-sided heart failure. However, to our surprise, carcinoid tumor was not detected in the typical localizations associated with carcinoid syndrome,² but was localized in the left ovary. The patient was postmenopausal and was regularly checked-up by her gynecologist, who last underwent a preventative check-up two years ago. Thus, we can only speculate whether the tumor was present at that time, though not observed and otherwise diagnosed.

There have been published case reports involving ovarian carcinoid (however rare) occurring in elderly postmenopausal women,⁵⁻⁸ and patient prognosis was generally promising except in one reported case.⁵ The noted therapy of choice has been complete surgical removal, and in cases with carcinoid syndrome standard treatment with somatostatin analogues should be introduced.⁴ However, in our case, due to extensive and severe debilitating cardiac involvement, cardio-surgery was indicated initially, followed by surgical removal of the tumor (radical hysterectomy) after recovery; this strategy was later proven to be successful.

Curiously, although our patient had noted foramen ovale, we did not observe any left heart valve involvement, which has been previously described in carcinoid patients who presented with this defect.^{9,10}

After primary surgery, the patient's hormonal activity remained positive with organic correlate of a small lesion detected by second tectrotyd scan. However, this small lesion disappeared altogether with near normalization of hormonal activity and tumor marker levels (chromogranin A) after successful treatment with somatostatin analogue lanreotide.

In conclusion, ovarian carcinoid with carcinoid syndrome causing severe combined tricuspid valve disease represents a very rare diagnosis, which should be considered in case of an elderly female patient with isolated right-sided valve disease comprising carcinoid syndrome with negative localization of tumor in gastrointestinal tract or lungs. Ultimately, primary surgical treatment with accompanying therapy of somatostatin analogue can lead to the remission of the disease.

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