CASE REPORT

Ovarian carcinoid presenting with right heart failure

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SUMMARY

A 69-year-old woman presented with a pelvic mass as well as a 6-month history of progressive bilateral peripheral oedema with more recent breathlessness and abdominal distension. She was found to have significant right heart failure (RHF) which was extensively investigated. No significant lung disease or pulmonary embolism was identified to explain the findings. Severe tricuspid incompetence was thus thought to be secondary to the systemic effects of a carcinoid tumour, confirmed to be ovarian in origin (on positron emission tomography/CT scan and histopathology). Prior to major pelvic surgery for removal of the ovarian mass, she underwent tricuspid and pulmonary valve replacement surgery due to the deteriorating right heart function. She had an uneventful recovery after both operations and continues to be followed up closely with serial ovarian and carcinoid tumour markers.

BACKGROUND

Ovarian carcinoid tumours are rare neuroendocrine neoplasms, accounting for only 0.3% to 1.0% of all carcinoid tumours¹ and <0.1% of all ovarian tumours.² Accordingly, very few cases of ovarian carcinoid affecting the heart have been reported in the literature³ (table 1).

In relation to carcinoid tumours, however, carcinoid heart disease is a relatively common complication, arising in 11–66% of patients with carcinoid syndrome.⁹ Clinically, carcinoid syndrome presents with facial flushing, secretory diarrhoea, bronchospasm and hypotension¹⁰ caused by the tumour release of vasoactive substances (such as kinins and serotonin), generally in disseminated carcinoid disease. Intrinsic tricuspid and pulmonary valve disease is commonly (97% and 88%, respectively) involved in carcinoid heart disease, leading to significant morbidity and mortality as a result of RHF.¹¹

CASE PRESENTATION

A 69-year-old woman, weighing 66 kg, presented to a gynaecologic oncologist with a pelvic mass. She had seen her general practitioner (GP) because of increasing tiredness. The GP arranged a series of investigations which found that she had iron deficiency anaemia (with no obvious cause identified on upper and lower endoscopy). Also, a left ovarian mass was seen on a transvaginal ultrasound and confirmed by CT (figures 1–3), arranged after the woman subsequently reported left lower abdominal pain. The solid (~11×10×6 cm) left adnexal lesion (seen with evidence of significant ascites, small bilateral pleural effusions, an enlarged (~1.5 cm) left inguinal lymph node and no obvious metastatic lesions to the bladder/bowel/liver (fatty))

was suspicious for malignancy. Her medical history included that of type 2 diabetes mellitus (diet-controlled), hypertension (on perindopril and amlodipine), hyperlipidaemia (on atorvastatin), gastro-oesophageal reflux disease (on rabeprazole), irritable bowel syndrome (with increasing intermittent episodes of diarrhoea), a previous cerebral aneurysm (endovascular coiling), previous cholelithiasis (laparoscopic cholecystectomy), previous menorrhagia/uterine fibroid (laparotomy and total abdominal hysterectomy with ovarian conservation) and depression (on citalopram). She was also on aspirin (for thromboembolic prophylaxis), had no known drug allergies and was a non-smoker, with no family history of cardiac/lung disease or cancer. Her mother had renal failure (on dialysis) and died of a ruptured aortic aneurysm, and her father died of a cerebrovascular accident.

On gynaecological oncology review, the woman mentioned that over the past couple of weeks she was also experiencing increasing shortness of breath on exertion. She reported no history of chest pain, palpitations, orthopnoea or paroxysmal nocturnal dyspnoea. In addition to the pelvic mass (hard, irregular and craggy) on examination, she had marked lower limb pitting peripheral oedema extending onto her lower anterior abdominal wall and sacral region. She also had decreased air entry in her right lung base but no obvious inspiratory crackles, and an elevated jugular venous pressure. Symptoms and signs were suggestive of some degree of heart failure (right-sided). She was immediately admitted to hospital and referred to a general physician for urgent medical evaluation; with likely surgery for removal of the pelvic mass to be arranged for a later date.

Initial blood tests arranged by the general physician showed a raised brain natriuretic peptide (NT-proBNP 1351), negative troponin I and normal renal function (except for low potassium), which confirmed the diagnosis of heart failure without cardiac muscle damage (for which she was started on frusemide, spironolactone and potassium supplementation).

A full blood picture (haemoglobin 105, mean corpuscular volume 81), subsequent iron studies (Fe 6, Ferritin 20) and normal folate and vitamin B₁₂ confirmed iron deficiency anaemia (for which she was given an iron infusion). Lactate dehydrogenase (LDH 359) was raised (and being a non-specific marker for anaemia, haemolysis, heart failure, hypothyroidism, lung/liver diseases and some tumours made it difficult to interpret in this setting). Haptoglobin (2.7) was raised (suggesting an acute-phase inflammatory response). Transglutaminase IgA (?coeliac disease), urinary haemosiderin (?chronic intravascular haemolysis), serum protein electrophoresis (?multiple myeloma) and Bence Jones protein (?multiple

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Table 1 Similar cases in the literature

Study	Patient age	Presentation	Primary carcinoid tumour	Heart involvement
Mordi and Bridges ³		Incidental finding on echo	Ovarian (→ excised 14 years prior)	Right valvular
Panayotova <i>et al</i> ⁴	65	Worsening heart failure	Pelvic	Severe TR with grossly abnormal, thickened and retracted tricuspid valve leaflets (→ considered feasible for valve replacement)
Levin and Flynn ⁵	39	Laparoscopic bilateral ovarian cystectomy	Right ovarian (→ completion salpingo-oophorectomy); with left dermoid cyst	Mild TR (→ no treatment)
Aggeli <i>et al</i> ⁶	60	Right heart failure	Ovarian (→ excised)	Severe TR and PR with thickened, immobile and retracted tricuspid/pulmonary valve leaflets (→ not considered feasible for valve replacement)
Bonaros <i>et al</i> ⁷	73	Increased dyspnoea and flushing	Left ovarian (→ excised)	Severe TR with thickened and akinetic tricuspid valve leaflets (→ valve replacement)
Nyktari <i>et al</i> ⁸	66	Right heart failure	Right ovarian (→ excised 6 months prior)	Severe TR and PR with thickened, retracted and fixed tricuspid/pulmonary valve leaflets (→ tricuspid valve replacement)

myeloma) were all normal. Urinary microalbumin (61) and the microalbumin/creatinine ratio (5.9) were also raised (suggesting an element of early kidney damage).

A raised thyroid-stimulating hormone (7.62) and normal T₄ suggested subclinical hypothyroidism (for which she was started on thyroxine). A normal carcinoembryonic antigen and raised cancer antigen (CA 125) (419) suggested the likelihood that the ovarian mass was a carcinoma. Liver function tests (Bilirubin 26, alkaline phosphatase 167, γ -glutamyl transpeptidase 48, albumin 28) were thought most likely to be in keeping with fatty liver disease; and a coagulation profile test was normal. Further testing showed a raised chromogranin A (360), suggesting the possibility of a carcinoid tumour (most likely thought to be gastrointestinal (GI) in origin), confirmed by a raised platelet serotonin (11.4). However, a 24 h urinary 5-hydroxyindoleacetic acid (5-HIAA 7) was normal.

An initial chest X-ray showed mild cardiomegaly and bibasal pleural effusions but no evidence of interstitial pulmonary oedema. A subsequent CT pulmonary angiogram excluded the presence of a pulmonary embolus (along with a ventilation-perfusion scan), but reflux of contrast into a distended inferior vena cava (IVC) and hepatic veins was seen supporting an

element of RHF. Lung function testing (forced vital capacity (FVC) 71%, forced expiratory volume in 1 s (FEV₁) 53%, FEV₁/FVC 60%) was consistent with an obstructive defect, with the postbronchodilator readings not showing significant improvement (for which she was started on fluticasone/salmeterol in order to optimise expiratory flow).

An ECG showed sinus rhythm and right bundle branch block. A subsequent transthoracic echocardiogram showed normal left ventricular size and systolic function, mildly dilated left atrium, significantly dilated right atrium and ventricle with borderline systolic function, markedly abnormal and incompetent tricuspid valve with severe tricuspid regurgitation, mild mitral and aortic regurgitation and mild pulmonary hypertension (suggesting a normal left heart but isolated severe tricuspid regurgitation). The tricuspid valve appearances (focally thickened with markedly retracted leaflets and no systolic coaptation) were thought to be most consistent with primary tricuspid valve disease. A transoesophageal echocardiogram confirmed similar findings with no evidence of an intra-cardiac shunt or valvular vegetation, normal pulmonary venous drainage and mild descending aorta atheroma. Cardiac catheterisation showed normal coronary arteries with no significant

Figure 1 CT coronal. **Figure 2** CT sagittal.

Figure 3 CT axial.

pulmonary hypertension. An outpatient cardiac MRI showed changes in keeping with carcinoid cardiomyopathy (structurally normal tricuspid valve, tricuspid caudal tendon shortening, malcoaptation, severely dilated right atrium/right ventricle).

Also after discharge, an outpatient positron emission tomography/CT scan (figure 4) showed that the pelvic mass had

significant moderate to intense gallium octreotate uptake (with no evidence to indicate metastatic disease), thus suggesting an ovarian carcinoid tumour. A gastroenterology review also surmised that this primary ovarian carcinoid tumour could give rise to severe tricuspid valve disease in the absence of liver disease.

By the time she was discharged, her weight was down by approximately 10 kg.

DIFFERENTIAL DIAGNOSIS

Right ventricular infarction, inferior myocardial infarction, left ventricular failure, coronary artery disease, left-to-right cardiac shunts (atrial/ventricular septal defect), pulmonary embolus, pulmonary hypertension (chronic obstructive pulmonary disease, obstructive sleep apnoea, drugs) and diseases that directly affect the tricuspid valve (congenital dysplasia, infective endocarditis, carcinoid syndrome) were all considered in consultation with a haematologist, respiratory physician and cardiologist.

Carcinoid syndrome was considered possible given the circulating biomarkers, the appearance of the tricuspid valve and in view of her chronic diarrhoea. This was subsequently found to be ovarian in origin.

TREATMENT

The patient was admitted to hospital for preoperative assessment in preparation for her surgery to remove the ovarian mass. A

Figure 4 Positron emission tomography scan.

repeat transthoracic echocardiogram showed further deterioration in her right ventricular function, and a closer inspection of the pulmonary valve suggested that it was also significantly diseased with at least moderate regurgitation (which was not detected on the initial echocardiogram or cardiac MRI). She had also redeveloped progressive peripheral oedema despite increasing diuretic dosages. In view of these findings, she was transferred to a coronary care unit to receive intravenous levosimendan (to improve right ventricular function preoperatively) prior to undergoing valve replacement surgery (bioprosthetic tricuspid and pulmonary valve replacements with postoperative warfarin for 3 months).

A couple of months after her cardiothoracic surgery, she underwent surgery for removal of her ovarian mass (laparotomy, pelvic washings, bilateral salpingo-oophorectomy, omentectomy, bowel and rectal serosal biopsies where the ovarian mass had been adherent to, and appendicectomy). Histopathology confirmed the diagnosis of a left ovarian carcinoid tumour (13×9×7 cm solid nodule, low grade, tumour confined to the ovary with an intact capsule, no other teratomatous elements were present, positive for the immunohistochemical stains CAM 5.2, chromogranin, synaptophysin and CD56). No carcinoid tumour was demonstrated in any of the other specimens.

Surgical resection alone was considered the appropriate therapeutic strategy.

OUTCOME AND FOLLOW-UP

The patient continues to be followed up by a medical oncologist with three monthly blood tests (CA 125, chromogranin A and neuron-specific enolase). Her chronic diarrhoea and fatigue have resolved.

DISCUSSION

In RHF, the right ventricle loses its pumping function, and blood may back up into other areas of the body, producing congestion. Congestion affects the liver (hepatomegaly), the gastrointestinal tract (ascites) and the limbs (peripheral oedema). In addition, the right ventricle may be unable to pump blood efficiently to the lungs and to the left ventricle (pulmonary oedema). Valvular heart disease is one of the causes of RHF. In carcinoid heart disease, the endocardium of valvular cusps and leaflets of the right side of the heart¹⁰ are more commonly affected as inactivation of tumour vasoactive substances (particularly serotonin) by pulmonary metabolism protects the left-sided heart valves. The affected cardiac valves have a white appearance, thick leaflets and chordal structures, with microscopy demonstrating plaque-like fibrous tissue deposits (composed of smooth muscle cells, myofibroblasts and collagen). Retraction and fixation of tricuspid/pulmonary valve leaflets leads to reduced motion and deficient central coaptation.¹² Severe tricuspid/pulmonary regurgitation characteristically ensues; and less frequently, tricuspid/pulmonary stenosis.

Given that the tumour appeared to arise from the ovary, this can explain how the patient had evidence of significant carcinoid valve disease in the absence of liver disease (and with negative urinary 5-HIAA, a serotonin metabolite). This is believed to be due to the direct venous drainage of vasoactive substances into the systemic circulation via the IVC (right ovary) or renal vein (left ovary), bypassing the portal system (ie, without being inactivated by first-pass metabolism in the liver).

Carcinoid syndrome can also lead to small airway fibrosis as a consequence of the secretory vasoactive amines which might account for the changes of chronic airflow limitation that were found on lung function testing.

Ovarian carcinoid tumours are generally classified as a histological subtype of ovarian germ cell tumours, that of monodermal highly specialised teratomas (in itself a subset of teratomas). Primary ovarian carcinoid tumours are divided into four main types: insular (most common, ~40% associated with the carcinoid syndrome¹³), trabecular, mucinous and mixed. They are usually seen in perimenopausal/postmenopausal women, are unilateral, localised to the ovary and composed of a solid nodule of GI or respiratory epithelium within a mature cystic teratoma (~60%), or simply a pure solid hypervascular nodule (~40%). These tumours tend to be well differentiated and lack nuclear atypia, mitotic figures and necrosis. Given their degree of differentiation, their disease course is thought to be indolent; however, the rarity of this tumour type limits data available on their clinical outcomes.⁹ The prognosis is excellent for women who present with a Federation of Gynaecology and Obstetrics (FIGO) stage I ovarian carcinoid tumour, with a greater than 90% 5-year survival rate.¹⁴

Metastatic carcinoid tumours (most commonly from the small intestine) to the ovary tend to be bilateral, of insular type and have scattered tumour deposits throughout both ovaries. The prognosis is poor, with a less than 50% 5-year survival rate.¹³

Treatment options are complex. Consideration must be given to simultaneous treatment of the systemic disease (ovarian mass, carcinoid syndrome and any metastases) and the cardiac disease. Somatostatin analogues (octreotide acetate subcutaneous/intramuscular depot) can provide relief of carcinoid syndrome symptoms. Surgical resection of the ovarian tumour (fertility-sparing to radical debulking) seems to be the mainstay of management, with the aim of attaining negative tumour margins.⁹ Liver metastases should be considered for surgical resection, cryotherapy, radiofrequency ablation or regional embolisation. Bone metastases should be considered for localised radiotherapy with/out bisphosphonates. There is no evidence to support adjuvant therapy (hormonal, chemotherapy or radiation). Cytotoxic chemotherapy (doxorubicin, 5-fluorouracil, dacarbazine and interferon α) is reserved for patients with advanced-stage or recurrent disease.⁹ The choices for medical treatment of RHF related to carcinoid heart disease are limited (mainly with diuretics). Valve replacement surgery should be considered early and is an effective therapeutic option if indicated (for symptoms of RHF with progressive fatigue, significantly impaired exercise capacity, progressive right ventricular dilation or decline in right ventricular systolic function).

Learning points

- ▶ Primary ovarian carcinoid tumour is rare; metastatic carcinoid tumour to the ovary is even rarer.
- ▶ It is important to rule out a metastatic gastrointestinal primary as this bears clinical significance for management and prognosis.
- ▶ Carcinoid syndrome/heart disease can be observed in non-metastatic ovarian tumours which can release hormones directly into the systemic circulation.
- ▶ Carcinoid heart disease typically presents with symptoms of right heart failure (RHF).
- ▶ Consider a baseline echocardiogram in all patients with carcinoid syndrome, and in those who develop clinical features of RHF, to aid evaluation for possible future valve replacement surgery.
- ▶ A multidisciplinary specialist approach is required to provide optimal patient care in management of ovarian and cardiac carcinoid disease.

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