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CASE REPORT

A case report of a patient with a primary ovarian carcinoid tumour who has right heart failure

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We present the case of a 57-year-old para 6 who was referred by a general practitioner to our tertiary level hospital with a pelvic abdominal mass as well as valvular heart disease and right heart failure. She had a subtotal hysterectomy, bilateral Salpingo-oophorectomy and an infracolic omentectomy. The histology revealed a primary ovarian carcinoid. She was free of carcinoid syndrome-related symptoms for a period of ten years. After this period of time, she unfortunately passed away from COVID-19 related complications (in July 2020).

Keywords: primary ovarian carcinoid, right heart failure, vasoactive substances, 5HIAA

Introduction

Carcinoid tumours of the ovary macroscopically appear as solid yellow, fibrous ovarian masses. Pure primary ovarian carcinoids are uncommon.[1] Only a third of these tumours are associated with carcinoid syndrome.[2]

Carcinoid syndrome is a paraneoplastic syndrome caused by the secretion of vasoactive substances such as serotonin (5HT), histamine, kallikrein, prostaglandins and tachykinins, which originate from well-differentiated neuroendocrine tumours.[3] These vasoactive substances are usually inactivated by liver enzymes, and the failure of this might lead to carcinoid heart disease.[4]

Signs and symptoms of carcinoid syndrome may include flushing, diarrhoea, abdominal pains, wheezing, valvular heart disease, telangiectasia, pellagra, mesenteric fibrosis, ureteral obstruction due to fibrosis, bowel obstruction and bowel ischaemia.[4] Diagnosis of carcinoid syndrome requires a combination of some of these signs and symptoms together with elevated levels of 5-hydroxyindoleacetic acid (5HIAA). 5HIAA is a metabolite of serotonin which can be measured from urine or blood.

The characteristics of a primary ovarian carcinoid tumour that distinguishes it from more common carcinoid tumours of small bowel origin is the development of right-sided carcinoid heart disease in the absence of liver metastasis. This happens in rarer primary ovarian carcinoid tumours because the first-pass effect of the liver does not occur, the venous drainage of the ovaries bypasses the portal circulation. The vasoactive amines secreted by carcinoid tumours arising from the gastrointestinal tract, lack direct access to the inferior vena cava and are infrequently reported to cause carcinoid heart disease, unless there is significant metastatic disease to the liver.[2]

Case presentation

The patient is a 57-year-old para 6 and a pensioner of sober habits. She presented to a general practitioner because she had abdominal pains, a sensation of a mass pressing in her abdomen, loss of appetite, loss of weight, palpitations and intermittent facial and leg swelling.

She had no respiratory symptoms. Furthermore, she was a type II diabetic, hypertensive and had dyslipidaemia for four years with no evidence of target organ damage. Three of her sisters had heart diseases; one sister died from ovarian cancer at 45 years of age and her brother had cancer of the prostate. She had no known allergies.

Clinical examination and ultrasonography revealed a highly vascular mass (10 cm x 7 cm x 10.5 cm) with cystic and solid components suspected to arise from the right ovary. There was no evidence of liver metastasis or para-aortic adenopathy. Both kidneys also looked normal.

The patient was sent to a tertiary level hospital for further management. On arrival at the tertiary unit, she was noted to be in right heart failure and was then sent for cardiac evaluation. She had an elevated jugular venous pressure (JVP), which was at the angle of her jaw, and a pansystolic murmur at the left sternal border was audible. She also had an early diastolic murmur more apparent at the pulmonary area, and a tender and congested hepatomegaly. A chest x-ray demonstrated a mild cardiomegaly, and an echocardiogram demonstrated mild mitral and aortic incompetence and severe tricuspid and pulmonary incompetence. The right ventricle and right atrium were both dilated. She was in right heart failure.

Her cancer antigen 125 (CA 125) was 12.5 U/ml, carcinoembryonic antigen (CEA) was 1.3 ng/ml, urinary 5HIAA was 384.7 mmol/l (10.4–41.6) and serum 5HIAA was 1 261.8 mmol/24 hrs (10.5–

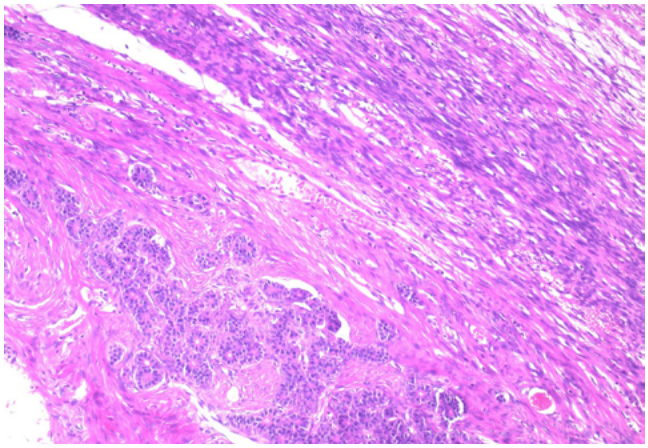

Figure 1: Histopathology of an ovarian carcinoid tumour of our patient

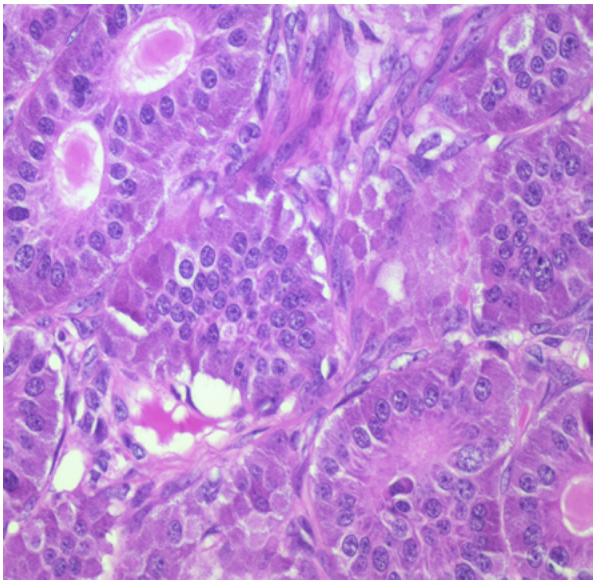

Figure 2: Nests of tumour cells with acinar structures lined by well-differentiated neuroendocrine cells

36.6). The cardiac findings and raised 5HIAA were consistent with carcinoid syndrome.

The patient was assessed to be fit for surgery with an Eastern Cooperative Oncology Group (ECOG) performance score of 2. ECOG scores range from 0–5 with a higher score indicating an increase in severity of the disability.

She was taken to the operating theatre after she gave consent for the surgery to be performed. Intraoperatively she was found to have severe peritoneal fibrosis, which rendered surgery extremely difficult. She had a subtotal hysterectomy, a bilateral Salpingo-oophorectomy and removal of the omentum. She had significant intraoperative blood loss and a blood transfusion as well as packing of the abdomen were required.

The blood products given in theatre entailed eight units of red blood cells, four fresh frozen plasma and one mega-unit of platelets. She required ICU admission post-surgery and abdominal packs were removed two days later.

Postoperatively, she was diagnosed with a urinary tract infection and liver dysfunction. She also developed depression while in hospital and required psychiatric intervention. We treated her for heart failure and she remained in hospital for two months, of which 29 days were spent in ICU, and we discharged her when her condition improved. We reviewed her six weeks after discharge.

Histology of the mass from the right ovary revealed an insular type carcinoid tumour predominantly comprising nests of tumour cells with acinar structures lined by well-differentiated neuroendocrine cells. The tumour cells have stippled ('salt-and-pepper') chromatin and 1 mitotic figure per 10 high power fields. Many of the tubular structures appear to contain eosinophilic secretions which did not contain thyroglobulin. There was no evidence of malignant transformation and there were no residual non-neuroendocrine teratomatous elements identified.

Sections of the omentum, uterus and left ovary were negative for malignancy, with histology of the uterus showing inactive endometrium and normal myometrium.

The following immunohistochemical stains were performed:

- Chromogranin A: Positive
- Synaptophysin: Positive
- Pankeratin: Positive
- CD56: Negative
- Thyroglobulin: Negative
- Ki67: Proliferation index is 1%

The patient continued with anti-heart failure treatment for a period of less than four years, after which the cardiologist was satisfied with her progress and stopped her treatment. She remained free of symptoms until 2020, 10 years later after the initial diagnosis. However, she sadly passed away from COVID-19 in 2020.

Discussion

Carcinoid syndrome refers to a group of symptoms caused by the systemic release of various kinds of humoral factors like polypeptides, biogenic amines and prostaglandins which are secreted by carcinoid tumours. Carcinoid tumours are slow-growing neuroendocrine tumours derived from enterochromaffin cells. These often arise within a cystic teratoma or dermoid tumour. Only a third are associated with carcinoid syndrome. In the ovary, the terminology preferred by the World Health Organization (WHO) for these tumours is ovarian carcinoid (if unassociated with struma ovarii) or struma carcinoid (if associated with thyroid follicles). This is in contrast to the gastrointestinal tract (GIT) and pancreas, where the term well-differentiated tumour is recommended. Also, in contrast to neuro-endocrine tumours in the body, "ovarian carcinoids are considered to be mono-dermal teratomas that arise from neuro-endocrine cells within intestinal-type epithelium of a mature cystic teratoma".[5]

Ovarian carcinoid tumours may be either primary or metastatic in origin. Metastasis to the ovaries usually originate from the GIT. To differentiate whether the tumour is primary or due to metastasis is usually difficult, but bilaterality of tumour, peritoneal deposits, absence of teratomatous elements and

presence of lymphovascular space invasion are features of metastatic disease.[6]

Pathogenesis of carcinoid heart disease involves deposition of plaque-like thickenings, which are composed of smooth muscle and collagen fibres that are deposited on to the intimal layer of the right ventricle, the tricuspid valve and the pulmonary valve.[7] The left side of the heart is spared by the inactivation of serotonin and bradykinin by monoamine oxidase (MAO), found in the pulmonary vascular endothelium, as the blood flows through the lungs. However, left sided heart disease can occur when there is incomplete inactivation of mediators like in a pulmonary carcinoid or a patent foramen ovale with right-to-left flow.

Carcinoids from the GIT are most commonly found in the ileum and appendix. Vasoactive amines, arising from a GIT primary, lack direct access to the inferior vena cava. These biogenic amines are first metabolised by the liver, resulting in hepatic metastatic deposits. Carcinoid heart disease is seldom found in bowel carcinoid tumours unless there is a significant metastatic disease to the liver.

It is not clear which of the bioactive products causes carcinoid syndrome, but there is clinical correlation between plasma serotonin (5HT) and urinary 5HIAA, which is a serotonin metabolite, and severity of right sided heart lesions.[8] The subsequent fibrosis of the intima on the inside surfaces of the cardiac chambers and valvular leaflets mainly in the right ventricle, the tricuspid and pulmonary valves, result in decreased right cardiac function and subsequent heart failure.

There are four main histological variants, namely insular, trabecular, stromal and mucinous, in addition to a mixed variant. The reported incidence of ovarian tumour-related carcinoid syndrome depends on the histological type, but ranges from 7.8% to 39%, the insular type being the most common and frequently associated with carcinoid syndrome.[9]

Histological variants of carcinoid tumours

Insular carcinoid

This is the most common histologic subtype and accounts for 50% of ovarian carcinoids. Carcinoid syndrome is described in 43% of these cases and is related to the size of the tumour. Approximately 60% of insular teratomas are admixed with mature cystic teratomas. Only 40% are pure insular ovarian carcinoids.[2] Histologically, the tumour is composed of solid nests that often form acinar, glandular or tubular structures. The differential diagnoses include granulosa cell tumour, Sertoli-Leydig cell tumour, benign Brenner tumour and metastatic carcinoid.[5]

Strumal carcinoid

Approximately 40% of ovarian carcinoids are strumal carcinoids, characterised by nests and columns of neuroendocrine cells admixed with thyroid follicles. Strumal carcinoid is unique to the ovary and has been diagnosed as malignant 'struma ovarii' in the past. Both ovarian carcinoids and ovarian struma are rare, with ovarian carcinoids accounting for approximately 1% of ovarian tumours and ovarian struma accounting for 0.3–1.0% of all ovarian tumours.[5]

Trabecular carcinoid

These carcinoids are very rare, slow-growing tumours with a low-grade malignant potential. These tumours are also less likely to be associated with carcinoid symptoms and often diagnosed with stage 1 disease.[9] Histologically, the tumour is composed of cells that form parallel ribbons, cords or columns.

Mucinous carcinoid

Primary ovarian mucinous carcinoid tumours are very rare. Most cases are metastatic bowel tumours, particularly from the appendix. Some discerning features may include the additional presence in the specimen of teratomatous or an ovarian surface epithelial tumour, an absence of lymphovascular space invasion, as well as involvement of one ovary. Metastatic mucinous carcinoids are usually bilateral. Approximately 88% of patients present with stage 1 disease. Advanced stage presentation appears to be associated with poorer outcomes.[8]

Histologically, the tumour is composed of small glands or acini within pools of mucin. These glands are lined by goblet cells as well as columnar cells with neuroendocrine differentiation. Mucinous carcinoids may be atypical, characterised by crowded glands that may show confluence or have a cribriform pattern.[5] Carcinoma arising in mucinous carcinoid have also been reported and are characterised by nodules of severely atypical cells or cords of signet ring type cells infiltrating a fibrous stroma. Mucinous carcinoids are typically CK20 positive, whereas other types are CK7 positive, CK20 negative.[10]

Mixed types

Mixed ovarian carcinoids with a variable combination of goblet cells, struma, insular carcinoid and trabecular carcinoid have been described. Certain combinations, such as mixed mucinous and struma carcinoids are very rare and the clinical behaviour for such combination is not well defined.[11]

Management pitfalls

The available data regarding carcinoids are limited. Much of the literature focuses on single case reports, previously dismissed as a totally benign disorder. Therefore, long-term considerations and evidence-based management guidelines are lacking.[9]

The majority of these tumours are well-differentiated having a low mitotic activity and low proliferation, mostly with a Ki67 index of < 2%; while others are intermediate or poorly differentiated, with an increased mitotic rate and higher proliferation with Ki67 index of 10–40%.[8]

Our patient demonstrated a classical picture of primary ovarian carcinoid syndrome, with a Ki67 proliferative index of 1%, insular type with no teratomatous components and had right sided carcinoid heart disease. This is consistent with the study done by Pellikka et al.[11], in which they looked at 132 patients who had carcinoid syndrome, and 74 participants (54%) had carcinoid heart disease (CHD). They concluded that cardiac disease may be the initial manifestation of the carcinoid syndrome with more than 50% of all patients with carcinoid syndrome showing evidence of right sided heart valve involvement.[11]

Cardiac manifestations that develop in patients with carcinoid syndrome include valvular regurgitation and/or stenosis, usually with right heart failure. Biomarkers (5HIAA) and cardiac imaging (echocardiography) are tools used in screening and diagnosis of carcinoid heart disease in patients with carcinoid syndrome. Management of these patients entails both medical attention to control symptoms as well as surgery to remove the tumour.

Attentive examination of and comment on the small bowel and appendix is recommended, should the diagnosis be suspected. For cases where the diagnosis is made retrospectively, as is usually the case in these rare tumours, completion surgery is not indicated.

A significant cause of morbidity in these patients is the additional burden of cardiac impairment produced by fibrotic valvular changes caused by the vasoactive agents.[12]

These complex patients should be managed by an experienced multidisciplinary team that includes endocrinologists, cardiologists, oncologists and pathologists. This is the approach that was employed in the management of our patient.

Patients with primary ovarian carcinoids have a better survival rate compared to patients with secondary tumours.[13]

Our patient's presenting symptoms were classical of carcinoid syndrome: she presented with diarrhoea, abdominal pains as well as symptoms of right heart failure due to valvular lesions which were detected on echocardiogram as well as swelling of the lower limbs. Her 24-hour urinary 5HIAA was also markedly elevated.

Misdiagnosis of carcinoid syndrome places the patient at a high risk of developing carcinoid crisis which has some deleterious effects such as significant drop in blood pressure, tachycardia, elevated serum glucose, severe bronchospasm with subsequent loss of life.[14]

Modlin and Sandor[15] assessed 8 305 observations and noted a 5-year survival rate of up to 95% of patients diagnosed with ovarian carcinoids compared to 64.9% of those with small bowel carcinoids and 85% with bronchopulmonary locations.[15]

Our patient passed away 10 years later, from a condition not related to carcinoid syndrome.

Conclusion

Although carcinoid ovarian tumours are rare, it should be considered as a differential diagnosis in patients who present with signs and symptoms suggestive of neuro-endocrine disease and have a pelviabdominal mass. If managed appropriately, their long-term overall survival can be good.

Conflict of interest

The authors declare no conflict of interest.

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Ethical approval

This study was approved by the Ethics Committee of The University of Cape Town (HREC REF: 579/2021).

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