Carcinoid Tumour of the Ovary: A Diagnostic Puzzle

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Abstract

A case of bilateral carcinoid tumour of the ovary, with benign cystic teratoma in one ovary, in a 38 year old woman is presented. She had total abdominal hysterectomy, bilateral salpingoophorectomy, infracolic omentectomy and appendectomy. There was no macroscopic tumour in the vermiform appendix and the rest of the gastrointestinal tract, although microscopically, there were malignant carcinoid cells in the appendix, omentum, fallopian tubes and the uterus. Available evidence suggested that the carcinoid tumour was primarily ovarian a rare ovarian malignancy.

Key Words: Carcinoid Tumour, Ovary, Primary.

Introduction

Carcinoid, a term first applied to hormonally active tumours by Oberndorfer in 1907, are carcinoma-like tumours that follow a more insidious clinical course than most other malignancies[1,2]. They are neuroendocrine tumours and are generally rare[2]. When they do occur, they tend to be hidden, unthought-of because they are rarely seen, except there is a carcinoid syndrome which betrays their presence[1,2]. Carcinoid tumours most often originate in the lungs and the entero-chromaffin cells of the gastrointestinal system where the vermiform appendix is the most common site[3]. Less commonly, carcinoid tumours occur in the ovary where they may be primary or metastatic[4]. Primary carcinoid tumour of the ovary is uncommon and represents less than 0.1% of ovarian malignancy[4,5]. The majority of primary ovarian carcinoids occur in association with mature cystic teratoma, but a considerable number presents in the pure form[4]. They are more often unilateral and vary from microscopic to large tumours.[4,5] On the other hand, metastatic carcinoid tumours of the ovary are nearly always bilateral[4]. The index case was bilateral ovarian carcinoid tumour with a benign cystic teratoma in one of the ovaries. There was microscopic involvement of the fallopian tubes, uterus and the appendix.

Case Summary

Mrs. R.O. was a 38 year old civil servant. She was Para 3^{+0}, 3 alive. She presented in our outpatient department with a five month history of generalized, painless and progressive abdominal swelling. She started vomiting about 2 months before presentation. The vomitus was greenish, not projectile and mostly in the morning. There was malaise, weight loss and poor appetite. There was no fever, diarrhoea or constipation. The last menstrual period was a week before presentation. The menstrual cycle was regular and the flow was normal. All her deliveries were spontaneous vertex with no significant complication during pregnancies, labours and puerperia. The last delivery was 2 years before presentation.

Physical examination revealed a chronically ill looking woman with evidence of weight loss. She was not pale, afebrile, anicteric and not dehydrated. There was no significant peripheral lymph node enlargement or pedal oedema. The pulse rate was 100 beats per minute, regular and of good volume. Blood pressure was 120/80mmHg. The heart sounds were normal. Respiratory rate was 20 cycles per minute. The breath sounds were normal. The abdomen was uniformly distended and moved with respiration. There was mild tenderness in the suprapubic region. There was no mass palpable per abdomen. The liver and spleen were not palpably enlarged. There was ascites demonstrated by fluid thrill. Bowel sounds were normal. Pelvic examination revealed normal vulva and vagina. The cervix was of smooth surface, pink with no mass or bleeding. The uterus was of normal size and anteverted. There was a deep-seated, irregular, hard mass, about 8cm x 6cm x 7cm, in the pouch of Douglas. It was tender and not mobile. Rectal examination revealed no abnormality except the above mass that was felt through the anterior rectal wall in the pouch of Douglas. Based on the clinical findings, provisional diagnosis of malignant ovarian tumour was made.

Full blood count, electrolyte and urea, urinalysis, urine microscopy, culture and sensitivity revealed no abnormality. Abdomino-pelvic ultrasound revealed a complex mass measuring 7.9cm x 3.5cm in the right adnexium. There was generalized ascites with abdominal orga floating in it. Other intra-abdominal organs were sonographically normal. Intravenous

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urography revealed no abnormality and chest x-ray was normal.
Mrs. R.O. had exploratory laparotomy, total abdominal hysterectomy, bilateral salpingoophorectomy, infracolic omentectomy, pelvic and para-aortic lymph node sampling and appendectomy. At surgery, there was 3 liters of serous ascitic fluid. The peritoneal surfaces were smooth and grossly normal. There were bilateral ovarian tumours. The right ovarian tumour was cystic, freely mobile and measured 5cm x 5cm x 3cm. The left ovarian tumour was entirely solid and buried in the pouch of Douglas to which it was adhered. It measured 6cm x 6cm x 5cm. The surface was irregular and the capsule was breached. The stomach, intestines, appendix and omentum were grossly normal. The liver, gall bladder and spleen were also grossly normal. The pelvic and para-aortic lymph nodes were not enlarged. Ascitic fluid was sent for cytology and AFB staining. Surgical

specimens were sent for histology. Ascitic fluid was negative for AFB.

A re-accumulation of ascitic fluid was noticed at the end of the first week after surgery. This was associated with bilateral pitting pedal oedema. She also vomited intermittently, lacked appetite with a further gradual loss of weight. Full blood count, electrolyte and urea and liver function test were repeated. There was hypoalbuminaemia and a Pack Cell volume of 27%. Other parameters were normal. Relatives however requested for treatment overseas.

Laboratory Findings

Cytology Report

Ascitic fluid smear showed clusters and nests of malignant cells with hyperchromatic nuclei and variable cytoplasms. Some lymphocytes were also seen.

Histopathology Report

The uterus, fallopian tubes, appendix and omentum were macroscopically unremarkable. The capsule of the right ovarian cyst was translucent and the cut surface showed multilocular cysts measuring 1.5 to 2.5cm in diameter. They were filled with serous fluid with 2 yellowish, solid areas. The cut surface of the left ovarian cyst showed a mixture of sebaceous material, fat and Negroid hair.
Sections of the right ovarian tissue were composed of cysts lined by compressed epithelia. The walls of the cysts were composed of fibrocollagenous stroma and corpora albicantes. The walls were also haphazardly infiltrated by nests and clusters of malignant cells with hyperchromatic nuclei and variable cytoplasm. There was a clearing zone surrounding the cells. Sections of the left ovarian tissue were composed of cysts lined by epidermal type keratinizing squamous epithelia. The sub-epithelial tissue was composed of sebaceous glands, sweat glands and adipocytes. There were islands of nests and clusters of malignant cells with hyperchromatic nuclei, prominent nucleoli in some, and variable cytoplasms. There were foci of central necrosis and surrounding clear zones. Keratin whorls were seen in the cystic areas.

Similar clusters and nests of malignant cells with surrounding clearing zones were found in the lamina propria and fibromuscular wall of the fallopian tubes, in the myometrium, within the cervical stroma and the omentum. The appendix also showed haphazard panmural presence of nests, clusters and trabecules of malignant cells with surrounding clearing zones. There was variable loss of glands in the lamina propria and numerous lymphoid follicles especially in the submucosa. There were no other remarkable features in all these organs. There were no malignant cells in the lymph nodes biopsied.

Diagnosis (Surgico-pathological): Right follicular cyst, left benign cystic teratoma and bilateral carcinoid tumour of the ovary, stage 3A.

Discussion

The presence of clusters and nests of malignant cells with surrounding clearing zones is typical of carcinoid tumours. One of the ovaries had these cells in an otherwise benign cystic teratoma. There was microscopic involvement of the uterus and the appendix. The puzzle was whether the tumour in the ovary was primary or metastatic. There was no gross evidence of a primary tumour elsewhere after careful examination of the intra-abdominal structures at surgery The vermiform appendix and the gastrointestinal tract were all grossly normal.

Carcinoid tumours tend to be hidden because of their slow growing and indolent nature[1,2]. Symptoms are usually vague and early diagnosis may be difficult[1-3,6]. Averagely, carcinoid tumours are present for more than 8 years before they are diagnosed[1-3,6]. Therefore, most patients have metastasis at the time of presentation. Even though the index case reported symptoms for only 5 months, the disease, most likely, had been in progress prior to when she noticed the symptoms.

The tumours arise from neuroendocrine tissues and the most predominant sites of occurrence are the gastrointestinal tract and the lungs[1-3,6]. In the ovary, they tend to occur as a component of a teratoma in their primary form as found in our case[4,5,7]. Primary ovarian carcinoids are thought to arise from the intestinal epithelium in a teratoma and are divided into insular, trabecular, strumal and mucinous types[4,5,7,8]. They are

mostly unilateral, vary from microscopic to large tumours and of low malignant potential[4]. They could form a solid nodule within a cystic teratoma, or when pure, a solid yellow-grey mass replacing the ovary. Metastasis occurs only occasionally and is usually to the contralateral ovary and pelvic and para-aortic lymph nodes[4]. On the other hand, secondary (metastatic) ovarian carcinoids are usually bilateral and the primary sites are usually in the gastrointestinal tract[4]. However, ovarian involvement from gastrointestinal carcinoid is rare in the absence of widespread hepatic and peritoneal seedlings[3,6]. These were absent in the case presented.

The appendix is the most common site in gastrointestinal carcinoid[3,9]. Appendiceal carcinoids appear as bulbous swelling at the terminal end in about 70% of cases[9]. Metastasis is rare and mostly by local infiltration[9]. Intestinal carcinoids are usually small, often less than 10mm in diameter, yellowish (because of rich fat content) and usually asymptomatic[1,3]. Multiple lesions are fairly common, and therefore, a thorough examination of the small bowel should be performed at laparotomy. Distant metastasis is commoner than in the appendix and usually to the liver and the peritoneum[3,9]. In the index case, the appendix and the intestines were grossly normal.

Ovarian carcinoids are known to be associated with carcinoid syndrome especially when they are large[4,8]. This results from secretion of physiologically active compounds into the circulation. These substances include serotonin, histamine, kinins, indoles and prostaglandins[1,2,10] Measurement of the serotonin metabolite 5-hydroxyindoleacetic acid (5-HIAA) in a 24-hour urine collection may be useful in biochemical diagnosis of carcinoid tumours[1,6]. However, unlike intestinal carcinoids, involvement of the liver is not necessary for ovarian carcinoids to produce carcinoid syndrome as the tumours secrete the biochemical substances directly into the systemic circulation and bypasses hepatic inactivation[4,7,8]. Ovarian carcinoids are therefore more frequently associated with carcinoid syndrome than intestinal carcinoids[4,7,8]. Despite this, only a third of primary carcinoid tumours of the ovary are associated with carcinoid syndrome[4,7,8]. The larger the tumour, the more the chance of the patient developing carcinoid syndrome[4,5,8]. The clinical syndrome itself consists of reddish blue cyanosis, flushing attacks often precipitated by ingestion of alcohol, diarrhoea or constipation, borborgymi, bronchoconstriction and right heart valvular disease[1]seedling was lacking. [,2]. These were all absent in our index case.

Surgical resection is the standard therapeutic modality[6,11]. Tumour size and presence of metastasis are of essence with regard to the extent of surgery[6,11]. The surgical modality in the index case was tailored in line with the extent of surgery in the management of ovarian tumours. Attempts should be made at optimum debulking. All patients with advanced-stage carcinoid tumors should be evaluated for possible multimodal surgical therapy because surgery is the best form of paliation[11]. Response rates to chemotherapy are variable but rarely exceed 30%[1,2]. Results are usually short-lived. 5-Fluorouracil and streptozocin based regimens are commonly used in patients with metastatic carcinoid tumors[1,2]. The value of using newer agents (eg, platinum based compounds, taxanes, gemcitabine, irinotecan) remains unproven[6,12]. Chemotherapeutic regimens are only for palliative purposes with some reduction in symptoms. However, tumour reduction is rarely observed[2,3,6]. When reductions occur, they are only transient. Patients with problematic diarrhoea usually find benefit from antidiarrhoeal medication[6].

Survival is dependent on the primary site, the size of the tumour and presence of metastasis[1,2]. Generally speaking, the prognosis of ovarian carcinoid is poorer than in intestinal carcinoid because of increased association with the carcinoid syndrome[4,8]. Tumour behaviour is largely unpredictable. The presence of necrosis and mitosis predict aggressive behaviour and metastasis is the absolute indication of a malignant process[1,2]. It is therefore clinically wise to regard every case of carcinoid tumour as malignant because of the latent potential for metastasis. All patients, except for those with lesions smaller than 1 cm, need conscientious follow-up care[2]. The 5-year survival rate from the time of diagnosis of metastatic disease is about 67%[1]. No therapy to date has been shown in any randomized clinical trial to prolong survival for patients with metastatic carcinoid tumors, and therapy remains palliative. [1,2,3]

In conclusion, diagnosing carcinoid tumours offers some challenges in the setting of multiple organ involvement. Our index case suggests a primary ovarian carcinoid. In spite of the presence of tumour deposits in different organs, the largest mass was seen in the ovary, there was no obvious intestinal or appendiceal mass during surgery and peritoneal

References

1. Kulke MH, Mayer RJ. Carcinoid tumours. *N Engl J Med* 1999; 340: 858-868.
2. Modlin IM, Lye KD, Kidd M. A 5-decade analysis of 13,715 carcinoid tumours. *Cancer* 2003; 97: 934- 959.
3. Marshall JB, Bodnarchuk G: Carcinoid tumours of the gut. Our experience over three decades and review of the literature. *J Clin Gastroenterol.* 993; 16: 123-129.
4. Talerman A: Carcinoid Tumours of the Ovary. *J Cancer*

Research Clin Oncol, 1984; 107: 125-135.
5. Kuscu E, Eroglu D, Ozdemir BH, Secme S, Haberal A. Primary carcinoid tumour of the ovary: a case report. *Eu J Gynaecol. Oncol.* 2003; 24: 574-576.
6. Oberg K: Carcinoid tumours: current concepts in diagnosis and treatment. *Oncologist* 1998; 3: 339-345.
7. Davis KP, Hartmann LK, Keeney GL, Shapiro H. Primary ovarian carcinoid tumours. *Gynecol Oncol* 1996; 61: 259-265.
8. Matsuda K, Maehama T, Kanazawa K: Strumal carcinoi tumour of the ovary: a case exhibiting severe constipation associated with PYY. *Gynecol Oncol.* 2002; 87(1): 143-145
9. Deans GT, Spence RA. Neoplastic lesions of the appendix. *Br J Surg* 1995; 82: 299-306.
10. Kema IP, de Vries EG, Slooff MJ, Biesma B, Muskiet FA. Serotonin, catecholamines, histamine, and their metabolites in urine, platelets, and tumour tissue of patients with carcinoid tumours. *Clin Chem*. 1994; 40: 86-95
11. Boudreaux JP, Putty B, Frey DJ, *et al*: Surgical treatment of advanced-stage carcinoid tumours: lessons learned. *Ann Surg* 2005 Jun; 241: 839-846.
12. Moertel CG, Kvols LK, O'Connell MJ, Rubin J. Treatment of neuroendocrine carcinomas with combined etoposide and cisplatin. evidence of major therapeutic activity in the anaplastic variants of these neoplasms. *Cancer,* 1991; 68: 227-232