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CASE REPORT

Primary ovarian neuroendocrine tumour arising in a benign mature cystic teratoma: a case report and literature review

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Abstract: Primary ovarian neuroendocrine tumours are very uncommon tumours. Herein, we describe a case of 27-year-old female who presented with abdominal pain and an ovarian mass, for which she underwent a right salpingo-oophorectomy. Histopathological evaluation confirmed a right-sided primary ovarian neuroendocrine tumour occurring in a benign mature cystic teratoma. The patient has not undergone any additional therapy and is currently well. This case illustrates the need for thorough clinicopathological correlation together with adequate sampling to ensure accurate diagnosis and timeous management of the patient.

Keywords: ovarian carcinoid, ovarian neuroendocrine tumour, primary ovarian neuroendocrine tumour, teratoma

Introduction

Neuroendocrine tumours, whilst having a propensity to develop within the gastrointestinal tract, may in fact arise in any organ, including the gynaecological tract.[1] Primary well-differentiated neuroendocrine tumours of the ovary are infrequently encountered and comprise roughly 0.1% of all ovarian tumours whilst ovarian benign mature cystic teratomas are commonly diagnosed.[1–4] Secondary spread of a neuroendocrine tumour to the ovary is relatively more frequently identified than a primary neuroendocrine tumour (NET).[5] Gynaecological NETs are histologically classified as low-grade (or carcinoid tumours in the ovary) to high-grade small- or large-cell neuroendocrine carcinomas.[5–7] The high-grade tumours are extremely aggressive tumours, whilst the carcinoid tumours are benign. Ovarian neuroendocrine tumours may arise in isolation or in conjunction with a teratoma.[2] We describe a neuroendocrine tumour arising within a benign mature cystic teratoma.

Informed consent was obtained from the patient, and ethical clearance was obtained from the University of the Witwatersrand Human Research Ethics Committee (Medical), clearance certificate number M180999.

Case report

A 27-year-old nulliparous female presented to her gynaecologist with abdominal distension and pelvic pain. Clinical examination revealed a right-sided pelvic mass which was tender to palpation. A computed tomography (CT) scan revealed an ovarian mass that was not suggestive of malignancy. She underwent elective surgery, at which time an enlarged right ovary was noted (Figure 1). There were no omental deposits identified and extra-ovarian spread was excluded. The fallopian tubes, left ovary and uterus were normal. The right ovary was excised and submitted for histopathological evaluation.

Macroscopically, the ovary weighed 192 g and measured 100 × 80 × 55 mm. The ovarian capsule was intact. On cut section, the ovary was multiloculated. Sebaceous material and hair were noted in one locule whilst the remainder of the ovary had a firm pink-yellow appearance. Areas of necrosis were not seen.

Microscopic examination confirmed a benign, mature cystic teratoma in which stratified squamous keratinising epithelium, sebaceous glands, hair shafts, adipose tissue and glandular gastrointestinal mucosa was identified. In addition, the adjacent ovarian stroma showed infiltration by a well-differentiated neuroendocrine tumour, which was arranged in solid nests, trabeculae and acini. These were composed of fairly uniform polygonal cells that had round to ovoid centrally placed nuclei with finely stippled chromatin. Mucinous (goblet cell) differentiation was not seen. Only one mitotic figure was identified in 10 high-powered fields and areas of necrosis were absent. The neuroendocrine tumour stained positively with a pancytokeratin (MNF116) immunohistochemical stain and showed dot-like accentuation. Cytokeratins 7 and 20 showed focal positivity of

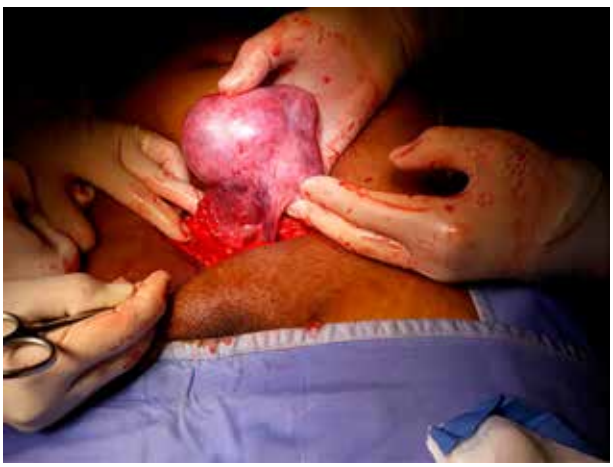

Figure 1: An intraoperative photograph of the ovarian tumour and the fallopian tube.

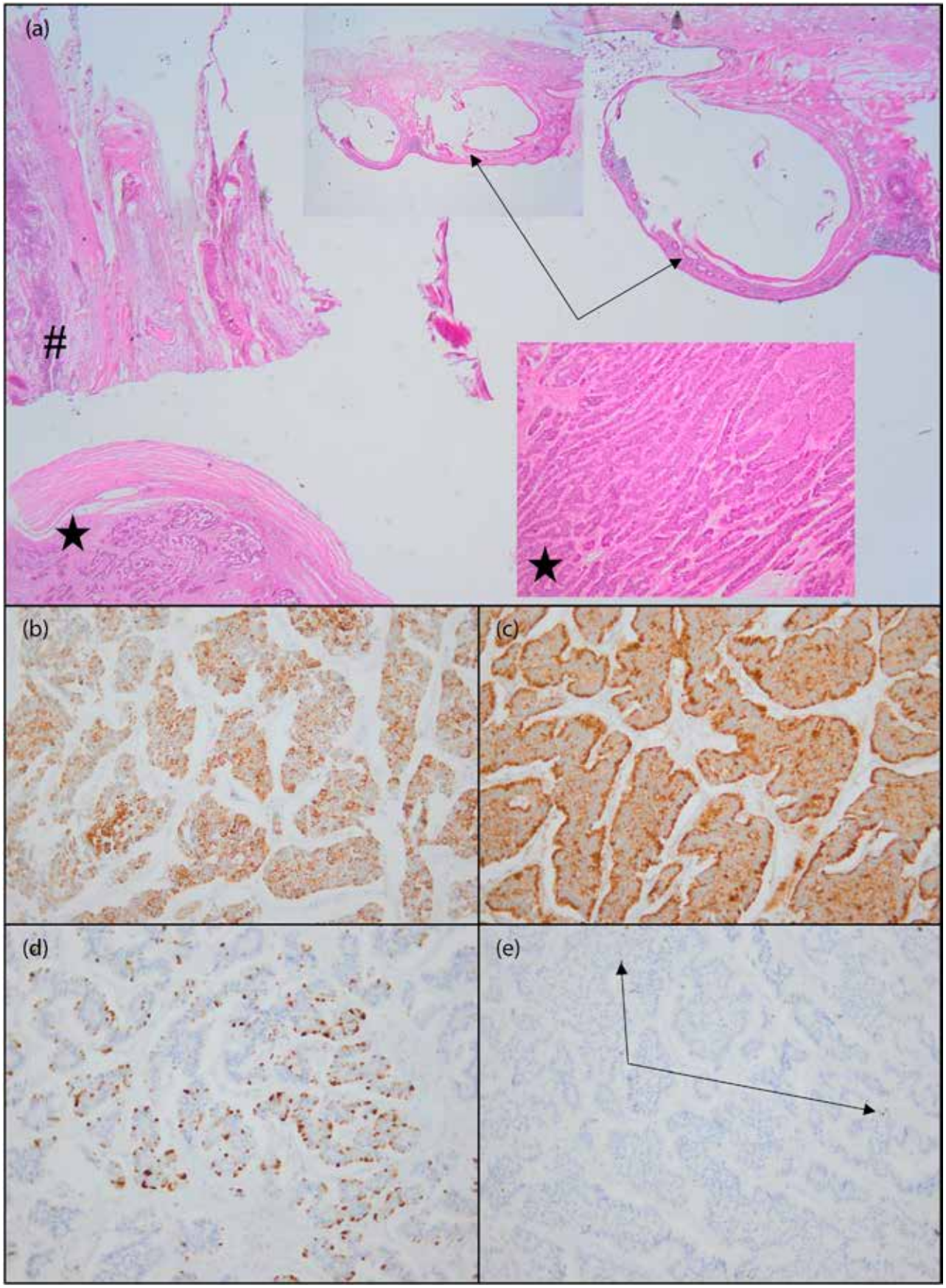

Figure 2: Photomicrographs of the tumour and relevant immunohistochemical stains. A: Haematoxylin and eosin stained section shows residual ovarian parenchyma (#) with the benign mature cystic teratoma (arrows) and the carcinoid tumour (stars) demonstrating characteristic neuroendocrine morphology. Original magnification 20x, inset of teratoma (arrow) 100x and inset of carcinoid (star) 200x. B: MNF116 immunohistochemistry stain showing positive dot-like staining in tumour cells. C: Synaptophysin immunohistochemical stain showing diffuse positive cytoplasmic staining of tumour cells. D: Chromogranin A stain showing scattered positive staining of tumour cells. E: Ki-67 immunohistochemical stain showing a low proliferation index with very few positive nuclear signals. Image A: Original magnification 20x, inset of teratoma (arrow) 100x and inset of carcinoid (star) 200x. Images B–E original magnification 200x.

neoplastic neuroendocrine cells. In addition, the tumour stained positively with the following neuroendocrine markers: Synaptophysin and Chromogranin A. A cluster of differentiation (CD) 56 immunohistochemical stain was negative. The Ki-67 proliferative index was < 1%. Scattered neuroendocrine tumour cells demonstrated positive nuclear staining with homeobox protein CDX2 and paired box 8 (PAX8) protein. The neoplasm was diagnosed according to the 2014 WHO classification under the category of a monodermal teratoma with a somatic-type tumour arising from a dermoid cyst. The neuroendocrine tumour, grade 1 (carcinoid tumour) represents the somatic component in this case (Figure 2).

The patient had an uneventful immediate postoperative course. She did not have any clinical symptoms of carcinoid syndrome and she had not undergone any additional therapy. She is currently well with no evidence of recurrence.

Discussion

Ovarian teratomas are common tumours that often present as enlarging adnexal masses or may be incidental findings.[8] Most primary ovarian carcinoids occur in a wide age range with most arising in peri-or postmenopausal females.[2,9] The majority develop within mature cystic teratomas, and most are unilateral tumours that are small and are microscopically detected within teratomas.[6] They may, however, be identifiable as yellow foci at the time of macroscopic dissection. The carcinoid syndrome, with classic clinical features of flushes, carcinoid cardiac effects, diarrhoea and bronchoconstriction, is an uncommon finding in patients with a primary ovarian carcinoid.[6,8,10]

The age of the patient described in the current case report (27 years old) is far younger than the mean age reported in a review by Dias *et al.* of 55 (17–83) years old.[2] Our patient presented with an adnexal mass but had no clinical features of carcinoid syndrome.

There are currently four recognised histological subtypes of ovarian carcinoid, which include: insular, trabecular, mucinous and strumal.[6] Insular carcinoids are the most common subtype, which demonstrate diffuse positivity with neuroendocrine immunohistochemical stains Synaptophysin, Chromogranin and CD56. Similarly, trabecular carcinoids display the same immunohistochemical profile but may lack chromogranin staining. Both insular and trabecular variants stain positively with cytokeratin (CK) 7, whilst insular and mucinous variants may display CDX2 positivity. CK20 may demonstrate variable staining as it is usually negative in insular and trabecular subtypes but positive in the mucinous variant. The Ki-67 proliferation index in primary ovarian carcinoids is low ($\leq$ 1%).[6]

The microscopic features and immunohistochemical profile of the present case are in keeping with most previous case reports that included immunohistochemistry results. Our case demonstrated insular and trabecular carcinoid but was devoid of mucinous and strumal variants. In most instances, a definitive diagnosis of a primary ovarian carcinoid can only be made following histopathological evaluation and underscores the need for judicious sampling at the time of macroscopic specimen dissection.

Secondary ovarian carcinoid neoplasms tend to develop in patients who have grades 1 or 2 neuroendocrine tumours of the gastrointestinal tract, usually of midgut origin. In the absence of an ovarian teratoma, the presence of spread beyond the ovary, identification of tumour on both ovaries, bilateral ovarian involvement and nodules of tumour within ovarian parenchyma in addition to lymphovascular infiltration are pointers toward metastatic ovarian involvement.

In general, primary ovarian carcinoids of insular, strumal and trabecular variants behave in a benign, indolent manner. In contrast, mucinous carcinoids may be aggressive with spread beyond the ovaries.

Fertility-sparing surgery is preferred in patients of reproductive age, who tend to have disease confined to a single ovary.[8,11] However, as always, thorough intraoperative assessment of extra-ovarian involvement is advised. Peri- and premenopausal patients may be offered total abdominal hysterectomy and bilateral salpingo-oophorectomy. In patients with mucinous variant of primary ovarian carcinoid, omentectomy and paraaortic lymph node dissection may be indicated. There is currently no evidence for use of adjuvant therapy.[10]

Patients affected by the carcinoid syndrome pose an anaesthetic risk due to their amplified biological responses to stimuli. As such, in an attempt to prevent a carcinoid crisis, use of sympathomimetics and catecholamines should be avoided.[8] Patients with carcinoid syndrome should have long-term follow-up.[12]

Conclusion

Primary ovarian carcinoids are uncommon tumours that tend to arise in association with benign mature cystic teratoma. Intraoperative examination for possible extra-ovarian involvement is suggested. Histopathological documentation of the neuroendocrine tumour arising in a teratoma requires thorough tissue sampling. The diagnosis is confirmed by identification of typical neuroendocrine features of the tumour, low mitotic activity and Ki-67 proliferation index, in addition to positive staining with neuroendocrine immunohistochemical markers. In general, these tumours have a good clinical outcome and may be treated with surgical excision, the extent of which may depend on age and fertility-preservation wishes of the patient.

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