Case report

Primary ovarian neuroendocrine tumor arising in association with a mature cystic teratoma: A case report

Nicolas M. Orsi a,b,⁎, Mini Menon a

a Department of Histopathology, Level 5, St James’s University Hospital, Leeds LS9 7TF, UK
b Women’s Health Research Group, Leeds Institute of Cancer & Pathology, Wellcome Trust Brenner Building, St James’s University Hospital, Leeds LS9 7TF, UK

Abstract

Primary ovarian carcinoid tumors are exceptionally rare entities accounting for approximately 0.1% of all ovarian neoplasms. This report describes a primary ovarian neuroendocrine tumor arising in association with a mature cystic teratoma in a 65 year-old woman. Macroscopically, the unilateral adnexal tumor was composed of cystic, solid and mucinous elements which resolved into a dual component lesion histologically. The majority of the tumor displayed an organoid architecture with mild to moderate pleomorphism and no discernible mitotic activity, while approximately 10% consisted of sheets and groups of cells with highly pleomorphic nuclei, necrosis and occasional mitoses. Features of a mature cystic teratoma were seen very focally. Immunohistochemistry revealed strong, diffuse positivity for CD56 and synaptophysin. Chromogranin immunonegativity was noted and there was an absence of nuclear β-catenin accumulation. Ki-67 index was 10–12%. Although there is no established diagnostic framework for primary ovarian carcinoid tumors, this case was diagnosed as a well-differentiated neuroendocrine tumor, Grade 2 (intermediate grade), arising in association with a mature cystic teratoma/dermoid cyst. This case highlights the need to develop ovarian diagnostic criteria in this area.

1. Introduction

Neuroendocrine tumors are a group of epithelial neoplasms with a predominantly neuroendocrine differentiation that can affect almost any organ system (Klimstra et al., 2010). Although these are typically associated with the gastrointestinal tract, pancreas and lung, gynecological cases have also been reported in the cervix, endometrium and ovaries (Fisseler-Eckhoff and Demes, 2012; Kupryjańczyk, 1997; Chun, 2015). Amongst these, primary ovarian carcinoid tumors are exceptionally rare, accounting for approximately 0.1% of all ovarian and 0.5% of all carcinoid neoplasms (Modlin and Sador, 1997; Modlin et al., 2003). Only 15% of these reportedly exist in pure form, with the remainder featuring teratomatous components such as struma ovarii or dermoid cysts (Fisseler-Eckhoff and Demes, 2012; Kupryjańczyk, 1997; Talerman, 1984). This report describes an unusual case of primary ovarian neuroendocrine tumor arising in association with a mature cystic teratoma, and highlights the diagnostic challenges posed by these neoplasms in the absence of a consensus ovarian classification system.

2. Case presentation

A 65-year-old Caucasian woman with a BMI of 28.8 kg/m² was referred as a fast-track patient for an abdominal mass and raised CA 125 following a three-week period of refractory diarrhea. Transvaginal ultrasound revealed a large, complex and predominantly vascular cystic mass extending from the pelvis to the umbilicus which was 14 × 14 × 9 cm in size. The uterus was retroverted with an endometrial thickness of 15 mm and no evidence of vascular enhancement. The kidneys were normal and there was a small amount of subphrenic ascites. A moderate right pleural effusion was noted. Subsequent CT abdomen and pelvis with contrast confirmed a large pelvic mass with a small volume of ascites but no convincing metastases. Her past medical history included carcinoid heart disease with moderate to severe left ventricular dysfunction and severe tricuspid regurgitation. Preoperative hematological profile was within normal limits; CA 125 was 248 units/ml and CEA 3.0 ng/ml. Urinary 5-hydroxyindoleacetic acid (5-HIAA) and chromogranin A were both raised at 771 mg/24 h and 338.6 μg/l, respectively. The patient underwent a total abdominal hysterectomy, bilateral salpingo-oophorectomy, pelvic and para-aortic lymphadenectomy and omentectomy for presumed carcinoid syndrome. Postoperative recovery was uneventful and she was discharged after 7 days with routine follow-up.

⁎ Corresponding author at: Department of Histopathology, Level 5, St James’s University Hospital, Leeds LS9 7TF, UK.
E-mail address: n.m.orsi@leeds.ac.uk (N.M. Orsi).

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3. Pathologic findings

Macroscopically, the right adnexa was enlarged, nodular and cystic, and measured 130 × 130 × 85 mm. It weighed 654 g and had a smooth, intact capsular surface incorporating the fimbrial end of the fallopian tube. Slicing of the specimen revealed cystic areas filled with hemorrhagic fluid, a tan colored solid component and mucinous elements. The allied uterus, cervix, left tube and ovary, and all lymph nodes were broadly unremarkable and of dimensions and appearances within normal limits, other than for the incidental finding of a fibroid in the anterior uterine wall.

Histologically, the ovarian tumor exhibited two components. Approximately 90% of the main tumor was composed of an insular pattern resembling a carcinoid tumor with nested areas, together with foci of tumor cells arranged in groups and trabeculae (Fig. 1) within an unremarkable fibrovascular stroma. The nuclei in these areas exhibited mild to moderate pleomorphism and no mitotic figures were identified. The remaining 10% of the tumor consisted of sheets and groups of cells with highly pleomorphic and bizarre nuclei within a vascular stroma. This component also contained foci of coagulative tumor cell necrosis and contained 2–3 mitoses per 10 high power fields. Other focal elements of the tumor were reminiscent of a mature cystic teratoma (dermoid cyst), featuring cyst-like spaces, variably lined by cuboidal cells, and areas showing duct-like structures resembling skin appendages. Some of these cystic spaces were also lined by histiocytes and foreign body-type giant cells. Occasional foci exhibiting neural differentiation were also noted.

Immunohistochemistry was performed for chromogranin, synaptophysin and CD56 given that these have previously been shown to be expressed in ovarian neuroendocrine tumors (Chun et al., 2015; Rindi et al., 2006; Rindi et al., 2007; Bosman et al., 2010). Further staining was conducted for β-catenin and Ki-67 (Kim et al., 2015; Rindi et al., 2006; Rindi et al., 2007; Bosman et al., 2010). Staining revealed strong, diffuse positivity for CD56 and synaptophysin (Fig. 2). By contrast, chromogranin was negative in the tumor cells. No nuclear accumulation of β-catenin was noted. The Ki-67 index was 10–12% in the areas characterized by highly pleomorphic nuclei.

4. Discussion

The organoid arrangements of tumor cells identified were consistent with the neuroendocrine differentiation growth patterns described for these lesions (Klimstra et al., 2010), and the staining patterns were similarly supportive. According to the WHO classification of pulmonary and thymic lesions (Klimstra et al., 2010; Travis, 2004), low to intermediate grade lesions can be classified into typical and atypical subtypes (with high grade lesions being either small or large cell carcinomas). The former should have fewer than 2 mitoses per 10 high power fields (HPFs) and no necrosis. Their atypical counterparts instead feature 2–10 mitoses/10 HPFs or the presence of necrosis. However, as underscored by a previous case report (Kim et al., 2015), there is a dilemma when attempting to apply this distinction to ovarian carcinoid tumors. Given their rarity, there are currently no widely accepted diagnostic criteria to cover their subclassification or sufficient patient outcome data to relate to atypical or aggressive histological appearance. Nevertheless, based on the presence of >2 mitotic figures/10 HPFs and the presence of necrotic foci, this tumor fell into the category of atypical (intermediate grade) carcinoid by applying the criteria set for pulmonary/thymic lesions. Importantly, necrosis per se is not diagnostic of neuroendocrine carcinoma; rather, a Ki-67 index of >20% is diagnostic (Rindi et al., 2006; Rindi et al., 2007; Bosman et al., 2010), which is in excess of what was recorded for this lesion. In the gastrointestinal tract, a neuroendocrine tumor with features such as those described for this lesion would be considered to be a well-differentiated neuroendocrine tumor, Grade 2 (intermediate grade). On balance, we elected to favor this classification system, resulting in a final diagnosis of well-differentiated neuroendocrine tumor, Grade 2 (intermediate grade), arising in association with a mature cystic teratoma/dermoid cyst.

A previous case report of a similar lesion noted strong nuclear immunoreactivity for β-catenin (Kim et al., 2015), an aberrant staining pattern of aggressive histology associated with both pulmonary neuroendocrine carcinomas and atypical carcinoid tumors (Pelosi et al., 2005). Moreover, this is also described to be an independent predictor of lymph node spread in patients with atypical pulmonary carcinoid.

Fig. 1. Histology displaying (A) pleomorphic area with bizarre nuclei, (B) areas of necrosis (C) carcinoid-type areas, and (D) adjacent carcinoid and pleomorphic areas.
tumors. In the present case, there was no nuclear β-catenin accumulation and all four identified lymph nodes were negative for tumor. Although primary ovarian carcinoid tumors’ surgical management reportedly has a good outcome for organ-confined disease (Davis et al., 1996), these remain poorly studied entities (Gardner et al., 2011) and as such, attentive follow up was recommended and the case was referred to the neuroendocrine multidisciplinary team. Importantly, clinicoradiological correlation was recommended to exclude the possibility of any other primary site given the obvious impact of metastatic disease on prognosis (Chun, 2015). The patient continues to be monitored biochemically.

In summary, this case highlights the diagnostic challenges posed by ovarian carcinoid tumors due to the lack of established diagnostic criteria available for these rare entities and the need to develop a unified system to which ovarian neuroendocrine tumors can be aligned. Further cases and the accumulation of additional clinical outcome data would further contribute to improving the accuracy of future prognostic prediction.

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