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Case Report

A very rare case of synchronous carcinomas of the endometrium and ovary with peritoneal keratin granulomatous involvement☆,☆☆

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Introduction

Keratin granulomas encompass eosinophilic laminated keratin within multinucleated giant cells, histiocytes, lymphocytes and plasma cells (van der Horst and Evans, 2008). Keratin is associated with ghost squamous or shadow cells, whereupon the nucleus is absent due to karyolysis (Nakayama et al., 1997). When peritoneal granulomatous inflammation develops, the condition may coincide with fungal or bacterial infections, a ruptured dermoid cyst or an assortment of irritants (Kim and Scully, 1990; Uehara et al., 2011; Chen et al., 1978).

Peritoneal keratin granulomas, albeit rarely, have been reported in association with endometrioid adenocarcinoma, ovarian carcinoma and an atypical polypoid adenomyoma (Kim and Scully, 1990; Uehara et al., 2011; van der Horst and Evans, 2008). In uterine cancer, one theory propounds that keratin is refluxed into the peritoneum via the fallopian tubes following endometrial curettage (Uehara et al., 2011; Chen et al., 1978; Wotherspoon et al., 1989). Alternatively, the tumor cells may infiltrate the peritoneal cavity and undergo keratinization, which potentiates granulomatous development (Kim and Scully, 1990).

Peritoneal keratin granulomas infrequently manifest themselves in conjunction with endometrial adenocarcinoma of squamous differentiation (van der Horst and Evans, 2008) and are rarely identified in ovarian cancer (Scully et al., 1998; Russell et al., 2002; Wu et al., 2006). Consequently, the presence of keratin granulomas coinciding with the synchronous involvement of the aforesaid primary tumors is quite exceptional (Kim and Scully, 1990). Initially, we conducted a PubMed search that comprised the terms synchronous, ovarian and endometrial cancers, and peritoneal keratin granulomas; we were unable to ascertain any previous cases. Thus, to the best of our knowledge, this is the first reported case in the past 20 years involving a patient diagnosed and treated for coexistent ovarian and endometrial carcinomas with keratin granulomatous involvement.

Case

A 57 year-old, nulligravid, woman was originally referred to our clinic in June 2012 with abdominal pain and distension in conjunction with a large pelvic mass that was identified on a CT of the abdomen and pelvis; further evaluation revealed bilateral lower extremity edema and extensive deep venous thrombosis, for which she received anticoagulation therapy. The patient's presenting CA-125 serum level was 925 U/mL. Her medical history was significant for anemia and ankle surgery in 1992.

The patient initially underwent a diagnostic laparoscopy that revealed placement of the right adnexa within a 17 cm mass; there were miliary implants identified on the serosa of the bladder and ascites pervading the right upper quadrant. Consequently, the procedure was converted to an open procedure, which comprised a laparotomy, abdominal hysterectomy, bilateral salpingo-oophorectomy, infracolic omentectomy and tumor debulking procedure.

At the time of laparotomy, the ovarian mass was loosely adherent to the cul-de-sac and the peritoneal side wall. There was also a separate tumor implant involving the cecal mesentery and a portion of the cecum, measuring 4×2 cm; there was miliary disease involving the cul-de-sac and select areas of the distal ileum. An infracolic omentectomy was first performed; the right ovarian mass was then bluntly dissected away from the cul-de-sac and right pelvic sidewall peritoneum and elevated; the utero-ovarian and infundibulopelvic ligaments were then divided. The mass was sent for frozen section evaluation.

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Pathologic findings

Final pathology revealed a stage Ic, grade 1 endometrioid adenocarcinoma of the ovary with extensive squamous differentiation; there were also surface ovarian adhesions with keratin granulomas. A serosal leiomyoma, endometriosis and both left tubo-ovarian and periovarian adhesions with keratin granulomas were identified (Fig. 1a–b). In addition, a deeply invasive, grade I endometrioid adenocarcinoma of the uterus was detected; interestingly, the uterine tumor did not show appreciable squamous differentiation (Fig. 2). The cecal and small bowel implants also contained fibrovascular and granulation tissue (Fig. 3a–d). The omentum and cul-de-sac nodules were negative for malignancy.

The remaining specimen, encompassing the uterus, cervix and the left adnexa, was resected. Henceforth, only the cecal disease and scant miliary disease on the distal ileum were present; the areas thereof were excised and submitted separately. Once the procedure was concluded, the patient was considered to be optimally debulked. She tolerated the procedure well and was admitted to the Recovery Room in stable condition. Following the patient's recovery, she commenced six cycles of adjuvant weekly paclitaxel (80 mg/m^2) and monthly carboplatin (AUC = 6) chemotherapy; the patient has done well with 3 months of follow-up.

Discussion

The presence of keratin in the peritoneum has been well described in the literature (Kim and Scully, 1990; van der Horst and Evans, 2008; Wu et al., 2006). In gynecologic cancer, the most common location of these granulomas is the ovarian and serosal surfaces of the fallopian tube (Uehara et al., 2011). Additionally, peritoneal keratin granulomas have been reported in cases of endometrioid adenocarcinoma with squamous differentiation and atypical polypoid adenomyoma (van der Horst and Evans, 2008; Wu et al., 2006).

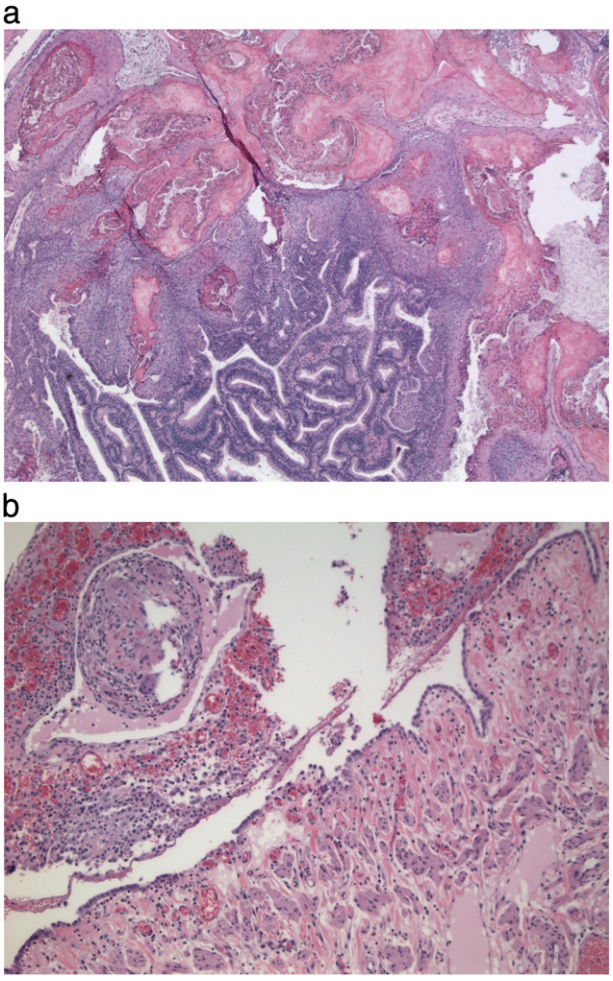

Fig. 1. a–b. Images of the ovarian tumor showing grade 1 endometrioid adenocarcinoma associated with extensive squamous differentiation (a: H&E 40×), in contrast to the endometrial tumor. The left tubo-ovarian tissue showed keratin granulomas (b: H&E 100×).

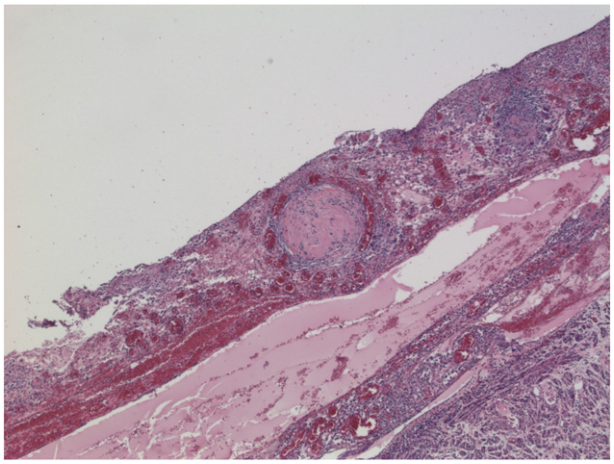

Fig. 2. The endometrial tumor was infiltrating the outer myometrium and did not exhibit appreciable squamous differentiation, in contrast with the ovarian tumor. The endometrial serosa contained keratin granulomas (H&E 40×).

Keratin granulomas coinciding with endometrioid adenocarcinoma of the uterine corpus resemble a dissemination of tumor cells, both macro- and microscopically; the squamous differentiation component potentially exhibits extensive keratinization, calcification and a foreign body giant cell reaction (Scully et al., 1998; Wu et al., 2006). However, the presence of degenerated squamous cells, irrespective of viable neoplastic cells, is more frequently associated with endometrial cancer; in contrast, keratin granulomas coinciding with ovarian cancer are quite unusual (Scully et al., 1998; Russell et al., 2002).

In the current study, we document a very rare case involving a patient who presented with coexistent ovarian and uterine carcinomas containing extensive keratin granulomas. Interestingly, the ovary had extensive squamous differentiation whereas the endometrial tumor did not; we suspect that the keratin granulomas are attributed to the ovarian tumor. To our knowledge, there have only been four reported cases of keratin granulomas coinciding with these concurrent gynecologic neoplasms; however, there has been none since 1990 (Kim and Scully, 1990).

In an extensive series of keratin granulomas of the peritoneum associated with endometrial and/or ovary cancer, Kim & Scully identified 4 patients with synchronous ovarian and endometrial cancers (Kim and Scully, 1990); two patients had a stage Ia endometrial cancer and a stage Ia ovarian tumor; one patient had a stage Ib endometrial cancer and a stage Ic ovarian tumor; the fourth had a stage IIIa endometrial cancer with a stage Ia ovarian tumor.

One of the two patients with stage Ia endometrial cancer and stage Ia ovarian cancer received adjuvant radiotherapy and the other received surgery alone; they had no evidence of disease at 5.6 and 7.3 years, respectively. The patient with stage Ib endometrial cancer and a stage Ic ovarian tumor was treated with surgery alone and the patient with stage IIIa endometrial cancer and stage Ia ovarian tumor had surgery and adjuvant radiotherapy; the first patient expired from an unrelated cause after 21 years and the latter patient had no evidence of disease with 6.8 years of follow-up (Kim and Scully, 1990).

The data on adjuvant therapy for the treatment of keratin granulomas infiltrating gynecologic disease are limited, particularly since radiotherapy and chemotherapy can influence the natural course of this

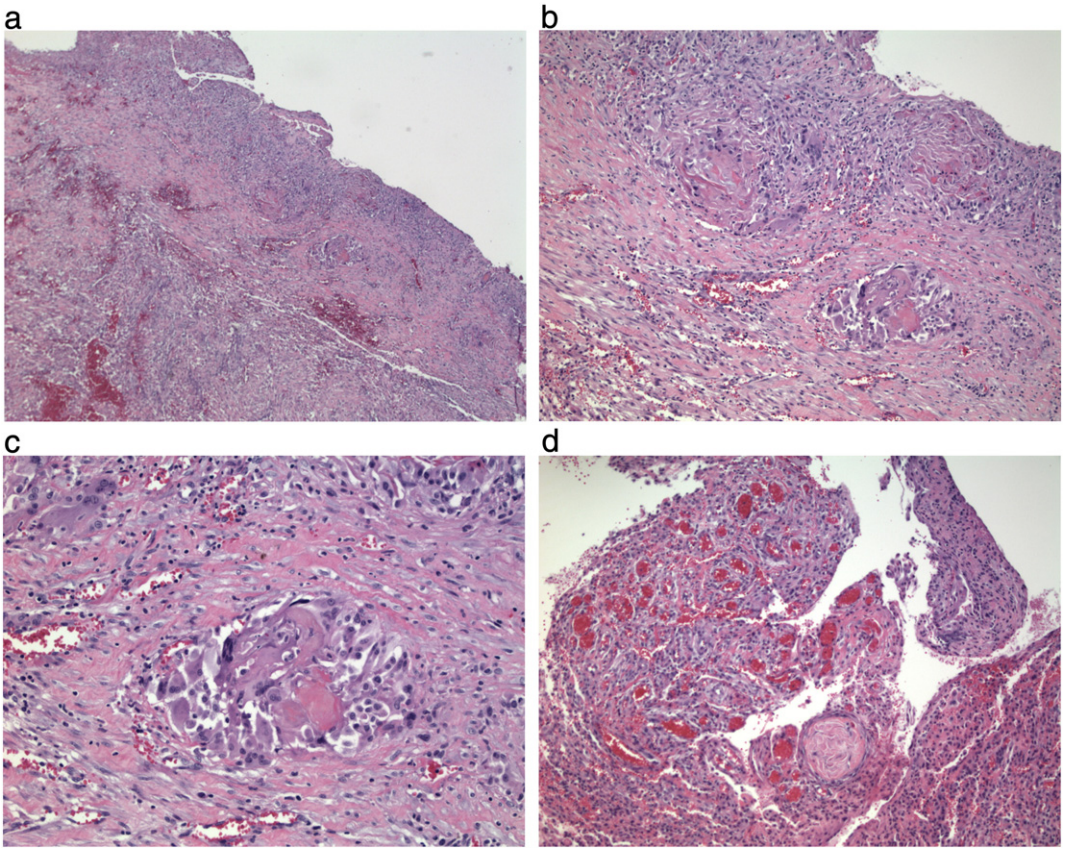

Fig. 3. a–d. Sections from cecal (a: H&E 40×; b: H&E 100×; c: H&E 200×) and small bowel (d: H&E 100×) implants exhibiting keratin granulomas with associated reactive tissue.

disease (Nakayama et al., 1997). Moreover, the prognostic significance of keratin granulomas is difficult to ascertain because of the scant, published case reports and limited patient follow-up (van der Horst and Evans, 2008). Consequently, we elected to employ adjuvant taxane and platinum chemotherapy therapy, emphasizing the more serious (i.e., ovarian cancer) diagnosis.

When initially evaluating a patient diagnosed with a peritoneal keratin granuloma, one may consider that these lesions resemble metastatic carcinoma or another granulomatous lesion macroscopically (van der Horst and Evans, 2008). Therefore, peritoneal washing cytology may be essential to distinguish between reactive mesothelial cells and tumor cells. Clinically, however, keratin granulomas without viable cancer cells do not appear to proffer any significant prognostic influence, vis-á-vis disease staging. Thus, extensive pathologic sampling for clonality studies (e.g., P53) (Wu et al., 2006) to determine the granulomas' provenance may be highly informative and potentially instrumental in discerning the disease's pathogenesis.

Conflict of interest statement
The authors have no conflicts of interest to declare.

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