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A Case Report of Primary Ovarian Squamous Cell Carcinoma: Pathways (And Pitfalls) To A Difficult Diagnosis

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1. Abstract

A 50 year old female was admitted to a major tertiary hospital with abdominal pain and fever and was treated as presumed diverticulitis with a tubo-ovarian abscess later identified. Following antibiotic treatment for both diverticulitis and pelvic inflammatory disease, a prolonged admission and two laparotomies, histopathology returned an unexpected diagnosis of primary ovarian Squamous Cell Carcinoma (SCC). This showed no sign of having arisen from a teratoma, endometriosis or Brenner's tumour. The SCC was found to be locally advanced and only palliative treatment was able to be offered. This case is important in part due to its rarity and contribution to a small pool of literature on this disease. It also serves as a reminder to not take undue reassurance from normal tumour markers or the absence of traditional risk factors for malignancy. It is also an important reminder that when the clinical picture does not fit the presumed diagnosis, there are rarer causes to be considered.

2. Background

Ovarian squamous cell carcinomas are very rare tumours that most commonly originate from mature cystic teratomas [1], endometriosis [2] or Brenner tumours [1].

Primary squamous cell carcinomas arising de novo from the epithelium are extremely rare with only approximately thirty cases recorded within the literature [3].There have thus far been several purported associations; the most common of which is cervical dysplasia, occurring concurrently with primary ovarian SCC in three of eleven cases in the largest and most cited primary ovarian SCC study [4].

The reporting of these cases is important as ovarian SCC is currently not well understood by clinicians. Metastatic spread differs from other common ovarian tumours in that the mode of spread is transmural with extensive local invasion [5] as opposed to being primarily disseminated within the peritoneal cavity with only superficial invasion [6]. These factors are crucial in terms of identification of disease, staging and prognosis as well as determining appropriate clinical pathways for treatment. This is particularly important because given the rarity of this condition, established treatment protocols have not yet been established [1, 5]. There have been only three reported cases of response to adjuvant chemotherapy; a single reported case of resulting in recurrence-free survival at five years reported by Yazawa et al. A patient with FIGO stage IIIc pure primary ovarian SCC and two further cases of survival at 18 and 19 months [7].

3. Case Presentation

A 50 year old female, with a previous history of open ovarian cystectomy and perforated sigmoid diverticulitis, presented to a major tertiary hospital with fevers and abdominal pain. She had elevated inflammatory markers and an initial presumptive diagnosis of diverticulitis was made.

A detailed history revealed that the patient was G2P1 having had one normal vaginal delivery. She experienced menopause aged 40yrs, had never used HRT and pap smears were up to date and normal. She was sexually active, with no new partners or previous diagnoses of STIs or PID. She smoked 10 cigarettes and consumed 3-4 alcoholic drinks per day. There was no family history of gynecological cancers. She was seen in the gynecology clinic one month prior to presentation for an ultrasound finding of thickened endometrium (7mm) and complex left ovarian cyst (4.3cm). The initial ultrasound request was for new onset left upper leg and groin pain with neuropathic features. Tumor markers (CEA and Ca-125) were both normal. She was booked for laparoscopic bilateral salpingectomy, oophorectomy and a hysteroscopy with dilatation and curettage. At this stage, her risk of malignancy index [8] was noted to be <200 and gynecological malignancy was considered unlikely.

Upon presentation to the emergency department, CT abdomen/pelvis showed a large complex structure (68mm x 37mm) apparently arising from the left ovary and/or fallopian tube. The structure was lobulated with solid and cystic areas and there was associ-

ated left hydronephrosis and hydroureter. There was also poor perfusion to the left kidney. Diverticulosis was noted as was possible mild colitis, but no clear signs of diverticulitis were demonstrated. There was no evidence of organ perforation. The presumed diagnosis at this time was tubo-ovarian abscess and the possibility of malignancy was considered unlikely in the context of this patient's history and examination.

The patient showed no improvement on IV antibiotics and a subsequent ultrasound showed a 7.6cm ovarian mass. Antibiotics were escalated to give more broad-spectrum and the mass was drained under CT-guidance resulting in 5ml of purulent material. Microscopy, histopathology and culture for mycobacterium, fungi, chlamydia and gonorrhea all returned negative results. Repeat imaging showed psoas and iliac abscesses which were later seen to extend to the bifurcation of the aorta. An attempt was made at further CT-guided drainage but when this failed, the decision was made for operative investigation and management.

Ten days into her admission, the patient underwent a laparotomy, hysteroscopy and dilatation and curettage. Substantial adhesions required assistance from general surgeons to access the left pelvic collection. A small amount of fluid was drained and sent for microscopy, culture and sensitivities but not for cytology. The left ovary was not visualized and the right ovary and fallopian tube both appeared normal. The planned bilateral salpingo-oophorectomy was not able to be safely performed at this time due to risk of inadvertent injury.

Post-operatively, the patient remained febrile and IV antibiotics were escalated to meropenem in consultation with both infectious diseases and immunology. A repeat CT scan showed further pelvic collections and persistent hydronephrosis but no evidence of malignancy. Further septic screening returned negative results; transthoracic echo showed no evidence of infective endocarditic. HIV serology was negative. A colonoscopy was attempted but the scope was unable to be advanced past the recto sigmoid junction.

The patient failed to improve and a repeat laparotomy was performed by obstetrics and gynecology in conjunction with both the gynecological oncology team and the colorectal team. The surgery was difficult due to multiple adhesions but identified a 50mm lesion filled with caseating material eroding pelvic sidewall which was thought to contain the left ovary and fallopian tube. Serosal tears were repaired, a ureteric stent was inserted and inadvertent enterotomies necessitated a distal small bowel resection. Tissue culture grew vancomycin-resistant enterococcus and linezolid was added to the antibiotic regimen.

The resected specimen consisted of a complex tubo-ovarian mass measuring 60mm in maximum dimension with the cut surface showing a mostly solid appearance with areas of necrosis and cystic change. Microscopically, there were classical features of a well to moderately differentiated keratinizing squamous cell carcinoma, with nests and cords of moderately pleomorphic squamous cells. Areas of lymph vascular space invasion were noted in the tumour but no perineural invasion was seen. Elsewhere the ovarian stroma contained dense lymphohistiocytic in filtrate with collections of xanthoma cells and numerous keratin granulomas. The fallopian tube showed active chronic salpingitis. Complete examination of the specimen did not reveal any teratomatous components. Immunohistochemically, the tumour cells strongly expressed p16 and was also positive for HPV ish. The tumour was locally advanced with infiltration into the pelvic sidewall which was confirmed on histopathological examination.

Though the mass was resected, there was known residual disease and adjuvant therapy could not be offered due to ongoing active infections. The patient had multiple subsequent admissions with pain and fever associated with the remaining pelvic collections. New lesions were noted on PET scans and her care was transferred to the palliative care team. She passed away four months after her diagnosis.

4. Discussion and Conclusions

This case describes a further rare example of this phenomenon and is important not only because of its rarity but also its value as a cautionary tale. There were no features of a pre-existing or coexistent teratoma, no endometriosis or primary tumor elsewhere in the body and there was no evidence of lower genital tract disease.

Pure primary ovarian SCC is a diagnosis that is easily missed. In the above described case, commonly utilized ovarian cancer markers (CA-125 and CEA) both returned normal results. However, this would also be the case for many early ovarian cancers. Often in a clinic setting, these findings provide reassurance and can influence the timeframe before a definitive tissue diagnosis is made. In this case, the patient presented shortly after her initial review in the gynecology clinic due to abdominal pain and fevers and her malignancy was already advanced. However, in early cases, there may be no symptoms and these factors could result in delays that significantly affect prognosis. Further, this case illustrates the important dictum that when the patient fails to improve with appropriate treatment, even the diagnosis itself needs to be carefully reconsidered.

On presentation to the emergency department and in multiple imaging modalities, a tubo-ovarian abscess was described. Again, the patient had very little in the way of risk factors for this disease process (post-menopausal, no new sexual partners, no history of STIs/PID). As Jackson and Soper [4] suggest "Behavioral, physiologic, and anatomic alterations that occur with advancing age offer barriers to the usual means of developing PID". Hence, whilst tubo-ovarian abscess is most commonly a late sequelae of PID there are other rarer causes, and indeed alternative diagnoses to be con-

sidered [9]. With this in mind, the initial diagnosis of diverticulitis is not unreasonable given that this is the most common non-neoplastic GI cause of postmenopausal tubo-ovarian abscess [7, 4] and the patient's history of diverticulitis. However, she did not improve with treatment suggesting that this presentation was unlikely to be complicated diverticulitis alone.

In the case described herein, delays to diagnosis are unlikely to have changed this patient's outcome. However, it is our hope that with such a rare presentation, case reports such as this, when pooled from multiple sites globally will provide clinicians with information to make faster and more accurate diagnoses and in time enable treatment to be optimized for patients in our care. Further, there are some very important learning points illustrated by this case, including the need for careful planning of exploratory laparotomies including consideration of what expertise may be needed and which biopsy specimens are to be taken. If biopsies had been taken in the first laparotomy, the time to diagnosis would likely have decreased.

In summary, we have described a rare case of a primary ovarian SCC which on extensive examination was not seen to be associated with a teratoma, endometriosis, or another tumor elsewhere. Interestingly this tumour was also HPV 16 associated. Whilst very rare, this tumor provides another differential when considering causes of tubo ovarian abscess or abdominal pain particularly in postmenopausal women and particularly in the setting of a complex ovarian cyst on imaging.

5. Learning Points

- Reassuring serological markers do not rule out ovarian malignancy and should not be seen to provide false reassurance to clinicians.
- In postmenopausal women, who are at low risk of PID, uncommon causes need to be considered in the differential for patients with suspected tubo-ovarian abscesses.
- SCC is an uncommon but important cause of ovarian cancer and behaves differently from other ovarian cancers.
- When rationalized and aggressive antibiotic treatment is ineffective in presumed diverticulitis or presumed PID, particularly with negative septic screens, malignancy should be considered.
- Biopsy and histopathology are essential for the diagnosis of malignancy and should be carried out at the earliest possible opportunity.

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