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Primary high grade serous carcinoma of the appendix: a diagnostic dilemma

To the Editor,

High grade serous carcinoma (HGSC) constitutes the major subtype of surface epithelial gynaecological cancer. The ovaries/fallopian tubes are the usual likely primary organs; however, the uterus, cervix, and peritoneum have also been reported as other primary sites. Rarely, it has been reported in extraperitoneal locations such as retroperitoneum, broad

ligament, endocervix, and pelvic and retroperitoneal lymph nodes. The 2019 World Health Organization (WHO) classification of digestive system tumours does not list Müllerian type serous carcinoma as an entity in the digestive system. It does discuss a malignant transformation in a pancreatic cystadenoma (serous cystadenocarcinoma),¹ which has morphology and immunophenotype quite unlike the Müllerian type serous carcinoma, which is one of the most common tumours of the female genital tract.^{2,3}

Exhaustive literature search by various keyword combinations via Google Scholar and PubMed failed to produce a single case report of any primary gastrointestinal serous carcinoma of the Müllerian type. Even case reports of non-gastrointestinal serous carcinoma mimicking a gastrointestinal primary are a rarity. One report described a peritoneal primary⁴ and another was a metastasis from a microscopic primary in the fimbria.⁵

We report a patient presenting with HGSC involving solely the lower gastrointestinal tract without a trace of a primary elsewhere and with no history of chemotherapy before her debulking surgery.

A middle-aged female presented at an outside medical centre with pain in the abdomen which was clinically diagnosed as appendicitis. Laparoscopic appendectomy was done which was reported as a Grade 3 neuroendocrine tumour in a peripheral laboratory without immunohistochemistry. The histopathology report of the appendix was reviewed at our centre and it was reported as a HGSC. The tumour appeared as a whitish irregular growth involving the wall of the appendix with base involved; the proper anatomy of the specimen was not ascertained as per the outside report. Lymphovascular invasion was seen. Immunohistochemistry (IHC) was strongly positive for PAX-8 and WT1; p16 showed block-like positivity; synaptophysin was negative; and p53 was strongly and diffusely positive (mutated phenotype) (Fig. 1). The immunophenotype suggested an ovarian/tubal/peritoneal primary, therefore gynaecological consultation was recommended.

Her serum CA-125 was subsequently found to be elevated at 191.0 U/mL while CEA was normal (3.62 ng/mL). Positron emission tomography-computed tomography scan, done outside and reviewed in-house, showed that there was no peritoneal disease but there was significant nodal disease along the retro peritoneum and pelvis. The disease appeared to be resectable and the patient was taken up for primary debulking surgery.

Intraoperatively, there was a large tumour of size 10 cm at the mesentery near the ileo-caecal junction, which was suspicious for an enlarged lymph nodal mass. The base of the appendix was also indurated. The rest of the small bowel and mesentery were free from disease. The porta hepatis and root of mesentery were palpated and were found to be free from infiltrative disease. The large bowel was free from gross disease. All quadrants of the abdomen (as per Sugarbaker's PCI score) were assessed and the disease was deemed resectable to less than 1 cm residual disease. Incision was extended and cytoreductive procedures started. The patient underwent total omentectomy, hysterectomy with bilateral salpingo-oophorectomy, right hemicolectomy and ileo-colic anastomosis, removal of parietal peritoneum deposit, and peritoneal lavage.

Surgical specimens were processed and examined in house. The uterus, cervix, and bilateral adnexal were free of

Fig. 1 High grade serous carcinoma involving the appendix. (A,B) H&E, (C) PAX-8 positive, (D) WT-1 positive, (E) p53 positive, mutated overexpression.

tumour (entire endometrium was submitted and bilateral adnexa submitted entirely as per SEE-FIM protocol).⁶ The tumour involved mainly the mucosal aspect of the distal terminal ileum (Fig. 2). The tumour infiltrated the bowel mucosa, lamina propria, muscularis propria, and per-intestinal adipose tissue; however, the serosal lining was free of tumour (exhaustively sampled). The serosal lining of a brownish area of the caecum (prior surgical site of appendectomy) was also free of any residual tumour. The remainder of the peritoneal surface of the viscera was thoroughly examined and was free of any potential lesion. Extensive lymphovascular emboli and extensive regional nodal metastasis were present. Immunohistochemistry, repeated on the tumour in the intestine, showed PAX-8, WT-1, and p53 (mutated pattern of staining) to be positive, and was morphologically and immunophenotypically identical to the one in the appendix.

In view of the negative findings in the total abdominal hysterectomy with bilateral salpingo-oophorectomy with absence of peritoneal nodularity, an ovarian/tubal/peritoneal primary was ruled out. A possibility of a primary ileal/colonic/appendiceal high grade serous carcinoma was considered since the tumour was seen involving the mucosal lining without any obvious serosal involvement, grossly (Fig. 2B,C), or on microscopy (Fig. 2D,E). Moreover, the patient had not had any prior anti-cancer therapy, ruling out a regressed primary.

The case was discussed in a multidisciplinary tumour board meeting and the decision for chemotherapy was made. The clinical team proceeded with adjuvant chemotherapy with paclitaxel and carboplatin, based on the diagnosis of a high grade serous carcinoma. To date, she has received five cycles and continues to be under close observation.

The WHO classification suggests that extrauterine HGSC with serous tubal intraepithelial carcinoma or fallopian tube involvement is considered to be fallopian tube primary.

Similarly, extrauterine HGSC without any tubal intra-epithelial and invasive lesion is considered to be primarily ovarian only after the confirmation of ovarian involvement. Pelvic HGSC with no histologically proven adnexal lesions is considered to be a peritoneal primary tumour.⁷ However, our case is unique as this high grade serous carcinoma does not have a uterine, cervical, adnexal or primary peritoneal origin. Therefore, the case raises the possibility of a primary high grade serous carcinoma arising out of the ileum, caecum, or appendix, which has not previously been reported in the English literature to the best of our knowledge.

The mucosal location of the tumour, the site of the lymph nodes involved, and the pattern of invasion of the tumour are all in favour of a gastrointestinal tract primary. On the contrary, if we were to assume that the tumour was from an occult peritoneal site invading into the intestinal mucosa/submucosal area, the route of its spread would be unclear. The possibility of a lymphovascular embolus from an occult peritoneal primary (omental or periappendicular) reaching the ileal-caecal tumour site would also require extreme serendipity as the flow of lymph would be against the normal direction of motion of lymph in this region. Even a distinct peritoneal primary arising on the ileo-caecal serosa would need to breach through the serosa and invade into the bowel from outside. The pattern of growth of the tumour in this specimen is more like a tumour coming out of rather than going into the intestine, and therefore almost rules out the possibility of a peritoneal primary. Therefore, histogenesis of such a tumour remains an enigma. The possible potential sources of this tumour could include intestinal epithelium, Müllerian inclusions or other primitive stem cells that were residing dormant in the area.

More work needs to be done to ascertain the precise histogenetic mechanism of the tumour but it certainly throws up the possibility of a primary high grade serous

Fig. 2 High grade serous carcinoma (HGSC) of the lower gastrointestinal tract. (A) Gross unfixed image of tumour area in the terminal ileum. (B) Gross post-fixation image of tumour in the terminal ileum showing involvement of the intestinal mucosa in a pattern that is suggestive of a primary in intestine. (C) Gross image of tumour in the terminal ileum and adjacent soft tissue. (D) H&E: corresponding to microscopy of section in Fig. 2B. (E) H&E: HGSC involving the ileo-caecal valve region with involvement of the intestinal mucosa in a pattern that is compatible with egress of a primary. (F) PAX-8 positive. (G) WT-1 positive.

carcinoma of the appendix/ileum/caecum which can direct future research.

This case highlights the importance of a meticulous histological, radiological, and intraoperative examination in unearthing a hitherto unheard of high grade serous carcinoma of the gastrointestinal tract. All case reports of mimics that we found could be resolved, except this. Although more work still needs to be done regarding the histogenesis of the tumour, this case hopefully will open up research in this field.

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