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BILATERAL PRIMARY SIGNET RING CELL CARCINOMA OF THE OVARIES; A CASE REPORT AND REVIEW OF LITERATURE

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Abstract.

Background; Primary signet ring cell carcinoma (SRCC) of the ovary is rare, and the distinction between primary and metastatic SRCC of the ovary may be difficult.

Case; We herein present a case of bilateral primary SRCC of the ovary in a 37-year-old woman presenting with bilateral ovarian mass. A preoperative computed tomography (CT) scan of the abdomen and a postoperative positron emission tomography-CT scan did not reveal any suspicious extra-ovarian lesions. Total abdominal hysterectomy with bilateral salpingo-oophorectomy, partial omentectomy and incidental appendectomy were performed. Upon histological examination, a malignant tumor which is entirely composed predominantly of signet ring cells was observed in both ovaries.

Conclusion: Based on the histological and clinico-radiological and immunohistochemical examinations, this case was diagnosed as a primary ovarian SRCC.

Key Words: signet ring cell carcinoma; ovaries; bilateral

Introduction:

Mucinous carcinomas with predominant signet ring cells in the ovary are most commonly metastatic lesions from a primary malignancy. When such carcinoma of the ovary is composed predominantly of signet ring cells, it is referred to as signet ring cell carcinoma (SRCC), it is designated as a Krukenberg tumor, which is metastatic SRCC that may originate from many primaries; commonly the stomach.

Primary SRCC of the ovary is a rare tumor and differentiation between primary and metastatic ovarian SRCC has not been well described and may be confusing. To date there are only rare reported cases of primary SRCC of the ovary [**1-4].**

In the current case we have reported a rare case that is diagnosed with bilateral primary ovarian SRCC of the ovary by combination of clinical, radiological, histopathological and immunohistochemical investigations.

Case report:

The current case is a 37-year-old female patient that was admitted to General Surgery Department, Faculty of Medicine, Zagazig University Hospitals with abdominal pain and palpable hard bilateral pelvi-abdominal mass. The patient underwent an abdominal computed tomography (CT) scan, which revealed bilateral a ~20-cm solid mass arising from both ovaries and did not reveal any lesions in the gastrointestinal tract. The patient underwent total abdominal hysterectomy with bilateral salpingo-oophorectomy, partial omentectomy and incidental appendectomy (figure 1). Both removed ovaries exhibited a mass, ranged in size from 30x20x15 to 20.5x16.5x11.5 cm, and had an intact, lobulated and smooth external capsular surface. On sectioning, the mass contained lobulated solid components (Fig. 2). Sections from both ovaries were fixed in 10% neutral buffered formalin for 12 h at room temperature, and then at 45 °C for 44 min in an automated tissue processor.

H& E staining was performed using an automated staining system and was processed for 27 min at room temperature. The tissue was analyzed under a light microscope. The lateral side of the uterus, fallopian tubes, omentum and appendix appeared invaded by solid nodules on macroscopic examination.

Histologically ·

Both ovaries have the same histopathological features and revealed diffuse proliferation and infiltration by solid growth of sheets of signet ring cells which contain intracellular mucin that displaces nucleus to one side. There are pools of extracellular mucin are present. The sheets of cells are separated by bands of collagen fibers. The omental solid nodules, the appendix, the lateral sides of the uterus at origin of fallopian tubes and both tubes showed infiltration by solid growth of sheets of signet ring cells which resembles that which are present in both ovaries, but the cervix is not invaded by malignant cells. (figure 2).

A provisional diagnosis is reached as: High Grade Bilateral Signet Ring Cell Carcinoma of Both Ovaries with Positive Omental Nodules, Positive Spread to; both Fallopian tubes, Uterus and Appendix.

The tumor cells, including the signet ring cells, exhibited diffuse positivity for cytokeratin (CK)7, and focal scattered caudal type homeobox 2 (CDX2), positivity (Fig. 4). However, there was no expression of chromogranin, synaptophysin, CD56, estrogen receptor, progesterone receptor. (figure 3)

Postoperative positron emission tomography (PET-CT) revealed no residual malignancy and no alternative primary site. The cytology of the peritoneal fluid was positive for malignant cells. Based on these clinicoradiological and histopathological findings, this case was diagnosed as primary SRCC of the ovary.

As the patient is considered advanced stage so she is given 6 cycles of platinum/taxane combination regimens. One year after the surgery, a follow-up CT of the abdomen also revealed no evidence of recurrence or an alternative primary site. The patient remains alive and well. These investigations helped exclude other primary foci, and the tumor was definitively diagnosed as primary ovarian SRCC.

Discussion:

Primary ovarian SRCCs of the ovary are extremely rare; most are metastatic neoplasms from gastrointestinal tract primary cancer [**5].** The current report is a case of high grade bilateral signet ring cell carcinoma of both ovaries with positive omental Nodules, Positive Spread to; both Fallopian tubes, Uterus and Appendix. Similarly **Kim et al., [1]** reported a case diagnosed with primary SRCC of the ovary and **Yazawa et al., [5]** reported a case of SRCC of the ovary which is removed with laparoscopic surgery. Only six cases could be identified in the international literature **[1,3,5,6].**

The presence of signet ring cells in an ovarian carcinoma is usually highly suspicious for a metastatic neoplasm, the primary site of which is most likely in the gastrointestinal tract, referred to as Krukenberg tumor [**2, 7**]. In addition to the signet ring cells, other characteristics suggesting a metastatic neoplasm like bilaterality, small size, a nodular element on macroscopic or microscopic examination, prominent histological variation among different areas, destructive invasion or individual cell stromal infiltration, microscopic surface tumor involvement (surface implantations), tumor cells floating in mucin pools, extraovarian extension and considerable lymphovascular invasion, particularly at the ovarian hilum [**2, 8]**. Although the presence of signet ring cells is a pathological characteristic which is highly favoring a metastatic rather than a primary neoplasm of the ovary, **Kim et al., [1]** case the neoplasm was considered to be a primary ovarian tumor due to the following findings: unilaterality, large size, malignant glands in a fibrous stroma, lack of surface implantations, lack of lymphovascular invasion and no extra-ovarian spread. Furthermore, the tumor displayed admixed components of benign mucinous cystadenoma and borderline mucinous tumor. The absence of several other characteristics of a metastatic neoplasm and the presence of admixed benign-appearing areas support that this was a primary ovarian neoplasm. Based on these findings, the diagnosis was primary ovarian SRCC. But in our case it was bilateral with presence of lymphovascular and extra-ovarian spread so we made many further investigations to excluded metastatic disease. Additionally, immunohistochemistry may be applied as an additional method to help distinguish between primary and metastatic mucinous carcinoma of the ovary. In particular, several primary ovarian mucinous neoplasms display intestinal differentiation and express enteric

markers, such as CK20, carbohydrate antigen 19-9, carcinoembryonic antigen and CDX2, at least partially, despite usually maintaining their diffuse CK7 expression **[9, 10].**

In our case the tumor cells, including the signet ring cells, exhibited diffuse positivity for cytokeratin (CK)7, and focal scattered caudal type homeobox 2 (CDX2), positivity (Fig. 4). However, there was no expression of chromogranin, synaptophysin, CD56, estrogen receptor, progesterone receptor. **In the Kim et al., [1]** case, the tumor was diffusely positive for CK20 and CK7, similar to primary ovarian mucinous carcinoma of the intestinal type [**10]**. However, these enteric markers are also variably positive in the majority of upper and lower gastrointestinal adenocarcinomas and pancreatobiliary adenocarcinoma **[9].** As the immunophenotypes of a primary ovarian mucinous tumor, particularly one containing abundant signet ring cells, and a metastatic mucinous tumor from the stomach, pancreatobiliary tract, appendix, or colorectum, may overlap, immunohistochemical studies may be of limited value in confirming the primary or a metastatic nature of ovarian mucinous tumors. Therefore, we depend more on clinical history and radiological findings also have to be carefully reviewed and integrated with thorough gross inspection and histopathological findings to ensure correct diagnosis and exclude the possibility of primary neoplasm. In the present case, diffuse CK7 positivity and focal scattered CDX2 positivity were helpful in excluding the possibility of colorectal or appendiceal primaries (1), whereas negativity for chromogranin, synaptophysin and CD56 help exclude other primary ovarian mucinous tumors that may comprise signet ring cells, such as goblet cell carcinoid. Possible primary lesions in the female genital tract, such as the cervix, and in the appendix were excluded following total abdominal hysterectomy, bilateral salpingo-oophorectomy and incidental appendectomy and examination of the resected specimens. No other lesions in the gastrointestinal tract were identified on abdominal CT. Consequently, primary ovarian SRCC was diagnosed. The remaining point of argument in this case is that a small occult primary neoplasm in other organs, most commonly in the stomach or appendix, may have been missed. However, postoperative PET-CT and follow-up CT 1 year after surgery showed no residual malignancy or alternative primary site. Taking into consideration the histopathological findings, these radiological evaluations support the exclusion of another primary focus, and the tumor was definitively confirmed as a primary ovarian neoplasm. Primary SRCCs of the ovary are extremely rare.

Our case and **Kim et al., [1]** case have the same course that after one year after the surgery, a follow-up CT of the abdomen also revealed no evidence of recurrence or an alternative primary site. The patient remains alive and well. These investigations helped exclude other primary foci, and the tumor was definitively diagnosed as primary ovarian SRCC.

In **Yazawa et al., [5]** patient, the clinical course of SRCC progressed very rapidly, as evidenced by the extensive peritoneal dissemination. Although they were all very small lesions, they were formed or became obvious during the month between the two operations.

In conclusion, we herein described a rare case of primary ovarian SRCC. SRCCs of the ovary are very rare. They are mostly metastatic neoplasms, with the gastrointestinal tract as the most likely primary site. The oncologic surgeon must keep in mind the possibility of metastatic tumors and should examine the whole abdominal cavity, including the upper abdomen especially when tumors are solid or there are bilateral ovarian tumors.

The distinction between primary and metastatic ovarian signet ring cell carcinoma, has not been well delineated. All aspects of the pathological evaluation and clinical correlations are crucial for correct diagnosis. The aim of this case report was to remind pathologists to consider primary ovarian SRCC as a differential diagnosis when they encounter ovarian tumors with a major signet ring cell component.

Figures legends:

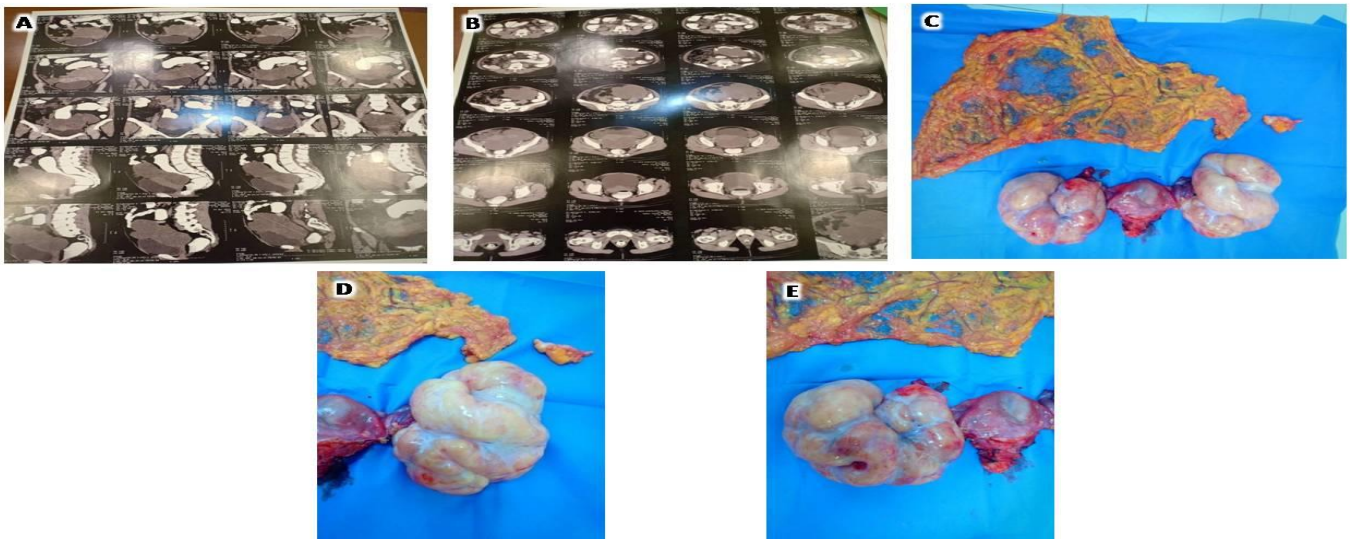

Figure1: Radiological (A & B) and postoperative findings (C- E) revealed: (A& B) computed tomography (CT) scan, which revealed bilateral a ~20-cm solid mass arising from both ovaries and did not reveal any lesions in the gastrointestinal tract. (C- E) Both removed ovaries exhibited a mass, ranged in size from 30x20x15 to 20.5x16.5x11.5 cm, and had an intact, lobulated and smooth external capsular surface.

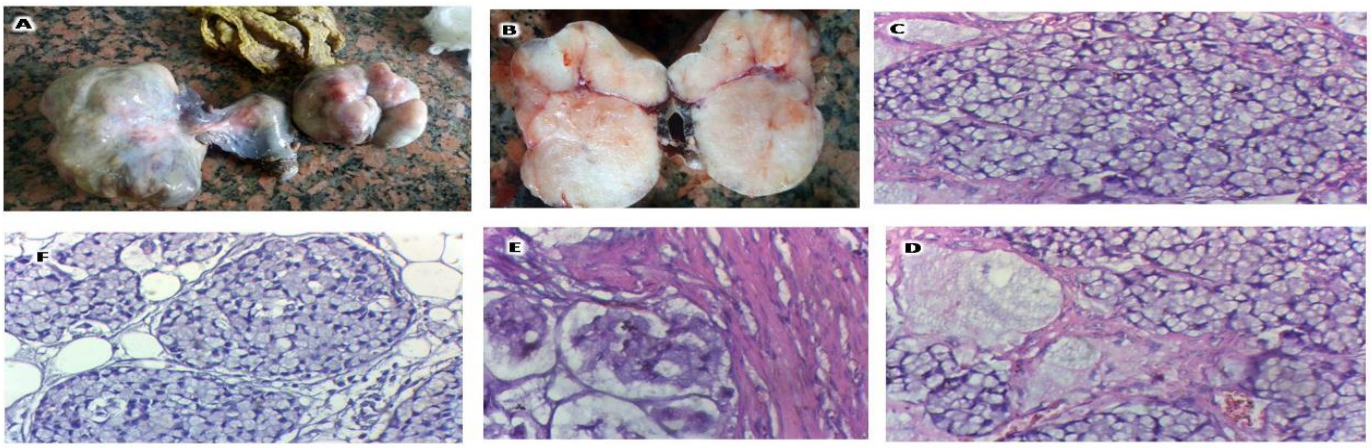

Figure2: Morphological findings (A& B) Gross examination of the excised mass X400 (C & D); Histopathlogical examination of sections prepared from both ovaries revealed that ovaries have the same histopathological features and revealed diffuse proliferation and infiltration by solid growth of sheets of signet ring cells which contain intracellular mucin that displaces nucleus to one sidex400. There are pools of extracellular mucin are present. The sheets of cells are separated by bands of collagen fibers; cells have hyperchromatic nuclei x400 (E) Invasion of uterus by solid growth of sheets of malignant signet ring cells x400(F) Omentum invasion by solid growth of sheets of malignant signet ring cells x400.

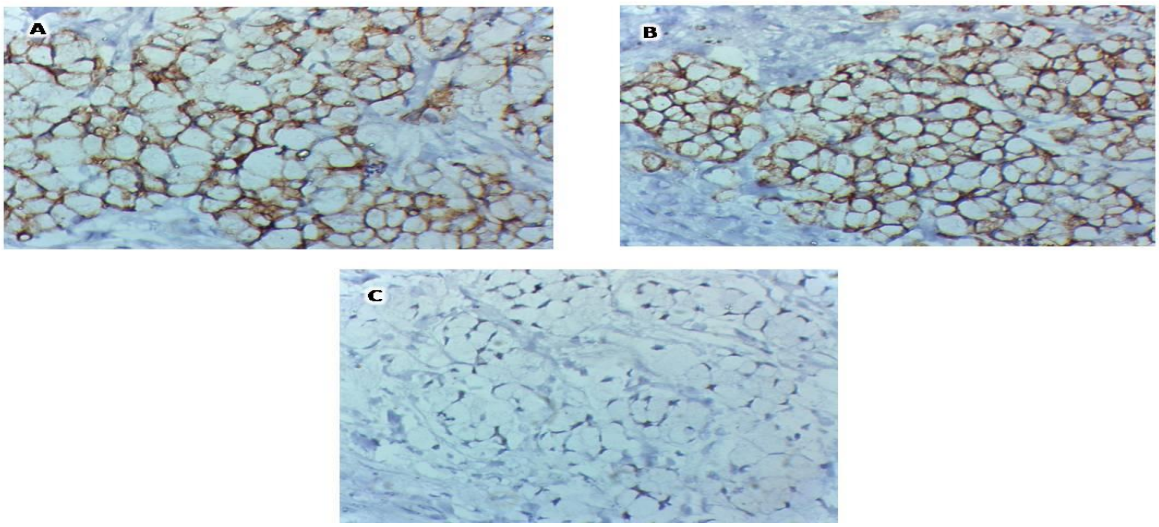

Figure 3: Immunohistochemistry results; (A& B) Positive CK 7 the tumor cells x400 (C) Scattered focal CDX 2 positivity x400

Authors' contribution:

The first 3 authors share in making the surgical operation for the patient the 4th author prepare the samples and made the histopathological diagnosis and immunohistochemical tests the last 3 authors were responsible for the treatment and follow-up of the patient. And all authors share in writing and revision of the case report and agree for publication.

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Ethics approval and consent to participate

Written informed consent was obtained from the patient prior to surgery.

Patient consent for publication

Written informed consent was obtained from the patient regarding the publication of the case details and associated images.

Conflicts of interests

The authors declared no conflicting interests

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