Gynecologic Oncology Reports 31 (2020) 100522

Contents lists available at ScienceDirect

Gynecologic Oncology Reports

journal homepage: www.elsevier.com/locate/gynor

Case report

Primary signet ring cell carcinoma with neuroendocrine differentiation arising in mucinous borderline tumor of the ovary

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ARTICLE INFO

Keywords:
Ovary
Signet ring cell carcinoma
Mucinous borderline tumor
Neuroendocrine differentiation
Krukenberg tumor

1. Introduction

The presence of signet ring cells in ovarian tumor is a highly suggestive feature for metastatic tumor (Krukenberg tumor) (Lee and Young, 2003; Kiyokawa et al., 2006; McCluggage and Young, 2008). Signet ring cells may arise in association with primary ovarian neoplasms, either Mullerian tumors (McCluggage and Young, 2008; Scully et al., 1996) or non- Mullerian tumors (Scully et al., 1996) such as mucinous carcinoid, Sertoli-Leydig cell tumor with heterologous elements, and small cell carcinoma of hypercalcemic type (Scully et al., 1996). Primary signet ring cell carcinoma of ovary rarely occurs (McCluggage and Young, 2008; Scully et al., 1996). To our knowledge, there are relatively few studies of primary signet ring cell carcinoma in ovarian mucinous tumors, with only seven reported cases (McCluggage and Young, 2008; El-Safadi et al., 2010; Ong and Ostor, 2002; Jaya Ganesh et al., 2014; Kim et al., 2018).

Herein we present a case of primary ovarian signet ring cell carcinoma with neuroendocrine differentiation that arises in the background of a mucinous borderline tumor.

2. Case presentation

A 59-year-old, gravida 2 para 2, postmenopausal woman presented with an abdominal mass for six months. She had a history of a previous hysterectomy due to uterine leiomyoma and appendectomy 23 years before. The pelvic examination showed a pelvic mass. The serum CA19-9 level was elevated at 156.9 U/mL (normal < 39 U/mL). The serum CA-125 and Carcinoembryonic antigen (CEA) were 37.6 U/mL (normal < 35 U/mL) and 2.46 U/mL (normal < 5 U/mL), respectively. A whole abdominal computed tomography (CT) scan showed a multicystic ovarian tumor (26 × 21 × 12 cm) with few mural nodules. No other intra-abdominal lesion was identified.

The patient underwent bilateral salpingo-oophorectomy with omental biopsy and peritoneal washing. Intraoperatively, a 25 cm ovarian tumor with leakage was found. Intraabdominal organs including pelvic nodes appeared normal.

Macroscopically, the left ovarian mass measured 24 × 19.5 × 7 cm showing a previous rupture. Sectioned surface revealed multiple cystic locules with watery mucinous content. There were two pale tan solid nodules measuring 3 and 0.5 cm in diameter. Microscopically, the tumor was composed of variable-sized cysts that lined by benign-appearing, flat to cuboidal mucinous epithelial cells, alternating with papillary structures lined by stratified epithelial cells with mild to moderate nuclear atypia (Fig. 1A, B). The mural nodules were sharply demarcated from the adjacent mucinous epithelium (Fig. 1C) and showed numerous signet ring cells. The adjacent mucinous epithelium contained rare neuroendocrine cells. The signet ring cells revealed moderate to marked nuclear atypia and these cells were arranged in nests of variable size or single individual cells in cellular fibrous stroma (Fig. 1D, E). There was no evidence of multinodular growth pattern, lymphovascular tumor emboli, hilar tissue invasion, or surface deposits of mucin or neoplastic cells. Teratomatous component or endometriosis was not identified.

The mucicarmine stain confirmed the presence of intracytoplasmic

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https://doi.org/10.1016/j.gore.2019.100522
Received 13 September 2019; Received in revised form 15 November 2019; Accepted 24 November 2019
Available online 27 November 2019

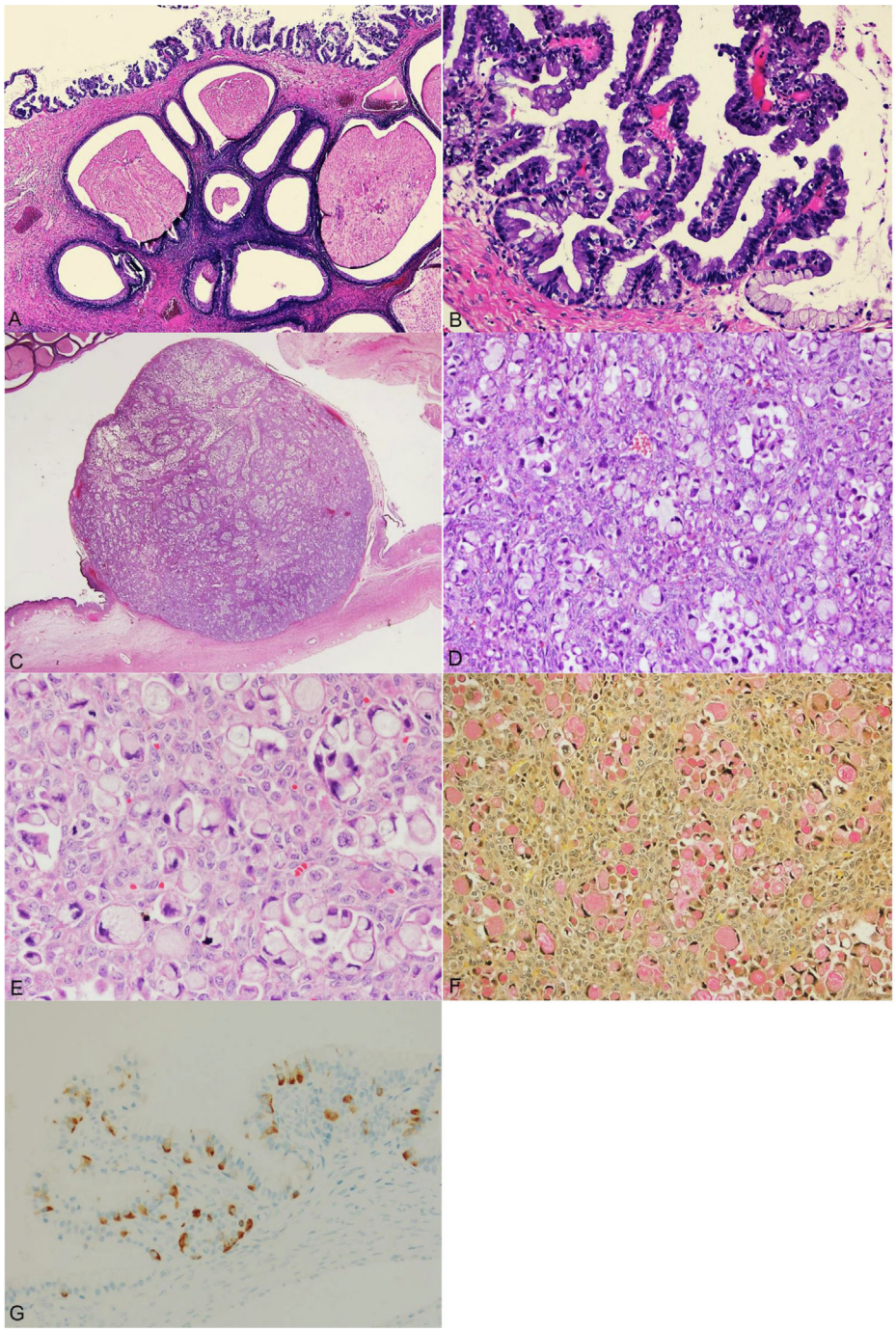

Fig. 1. Primary signet ring cell carcinoma in mucinous borderline ovarian tumor (A) Multiple locules of variable size that lined by mucinous epithelium. Note the papillary structure on cystic lining (Hematoxylin and Eosin stain, 4×). (B) The mucinous epithelium ranged from flat cuboidal cells (at the right side) to stratified epithelium with papillary growth (Hematoxylin and Eosin stain, 20×). (C) A well-circumscribed mural nodule of signet ring cell carcinoma (Hematoxylin and Eosin stain, 1.25×). (D) Numerous variable-sized groups of signet ring cells in cellular fibrous stroma (Hematoxylin and Eosin stain, 20×). (E) Small groups and individual signet ring cells with moderate to marked nuclear atypia (Hematoxylin and Eosin stain, 40×). (F) Intracytoplasmic mucin in signet ring cells (Mucicarmine stain, 20×). (G) Scattered neuroendocrine cells in mucinous epithelium highlighted by synaptophysin immunostain (20×).

mucin in signet ring cells (Fig. 1F). The tumor cells including signet ring cells revealed diffuse and strong positivity for cytokeratin 7 (CK7) (Fig. 2A). CDX-2 was positive with variable intensity in 60% of tumor cells (Fig. 2B). The signet ring cells showed moderate to strong expression of synaptophysin and chromogranin-A in 50% and 30% of cells, respectively (Fig. 2C, D). The adjacent mucinous epithelium was also positive for synaptophysin and chromogranin-A with moderate to strong intensity in 30% and 40%, respectively (Fig. 1G). Cytokeratin 20 (CK20) was negative.

Meticulous clinical investigations including esophagogastroscopy, colonoscopy, and mammography did not identify any primary cancer. The diagnosis of primary ovarian signet ring cell carcinoma with neuroendocrine differentiation arising in mucinous borderline tumor – FIGO stage IC2 was made. The postoperative abdominal CT scan at 6 months after surgery revealed no evidence of tumor recurrence or new intra-abdominal lesion. The patient received Paclitaxel and Carboplatin chemotherapy and she was well without recurrence or metastasis at 11 months postoperatively.

3. Discussion

The coexistence of primary signet ring cell carcinoma and the ovarian mucinous tumor is rarely documented (Scully et al., 1996). A review of the previously reported cases including the present case is shown in Table 1. The patient age ranges from 20 to 60 years (mean age 47 years). The appearance of signet ring cell carcinoma component is variable, ranging from microscopic foci (McCluggage and Young, 2008) to grossly visible solid component (Kim et al., 2018) or mural nodule arising in the cyst wall (up to 5 cm in size) (Ong and Ostor, 2002; Jaya Ganesh et al., 2014). The morphological spectrum of associated

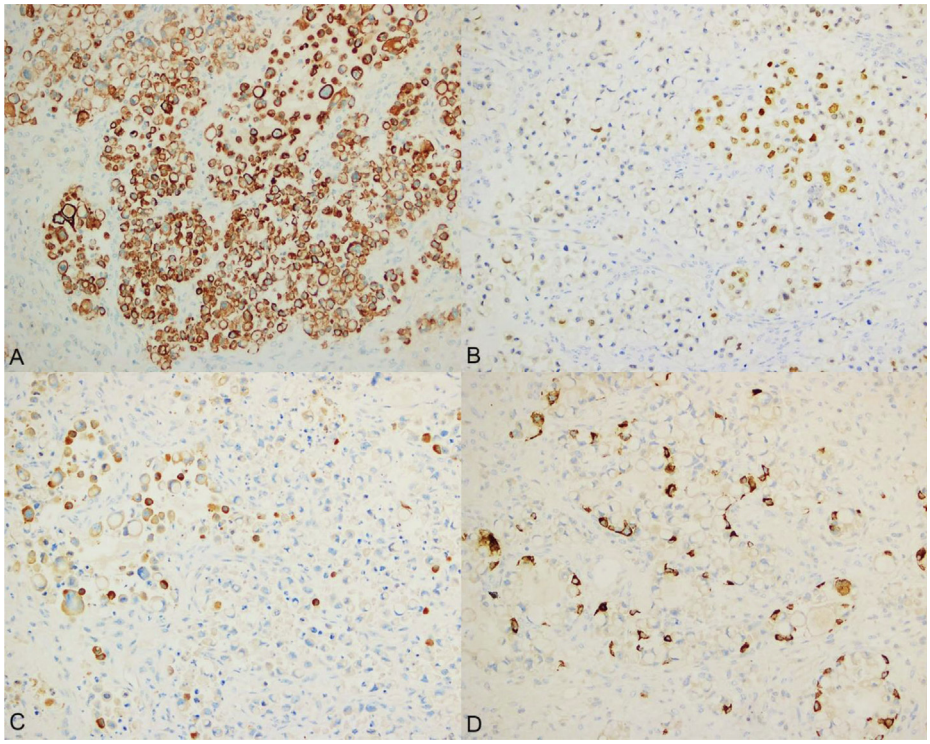

Fig. 2. Immunohistochemical stains of signet ring cell carcinoma (A) Diffuse and strong positivity for cytokeratin 7 (20×). (B) Positivity for CDX-2 with variable intensity (20×). (C) Positivity for synaptophysin with moderate to strong intensity (20×). (D) Positivity for chromogranin-A with moderate to strong intensity (20×).

mucinous tumor includes benign (either cystadenoma or adenofibroma), borderline tumor, intraepithelial carcinoma, and adenocarcinoma (McCluggage and Young, 2008; El-Safadi et al., 2010; Ong and Ostor, 2002; Jaya Ganesh et al., 2014; Kim et al., 2018). To our knowledge, the present case is the first case of primary ovarian signet ring cell carcinoma which showed neuroendocrine differentiation by immunohistochemical stains (synaptophysin and chromogranin-A).

Metastatic tumor (Krukenberg tumor) is the most important differential diagnosis. Signet ring cell carcinoma most frequently originates from the gastrointestinal tract, particularly the stomach, but may be found in many organs such as pancreaticobiliary tract, breast, urinary bladder, cervix, and renal pelvis (Kiyokawa et al., 2006; McCluggage and Young, 2008; Scully et al., 1996). The immunoreactivity for CK7 and negativity for CK20 in the present case supports a non-colorectal origin of the tumor, but the immunostain is of limited value in distinguishing between primary ovarian tumor and metastases from non-colorectal origin, since many of tumors originating in stomach, pancreaticobiliary tract, and breast also exhibit a CK7-positive/CK20 or CDX-2-negative or focally positive immunophenotype (McCluggage and Young, 2008). Therefore, the distinction of primary ovarian tumor from metastatic tumors to the ovary requires thorough clinicoradiologic investigation and meticulous pathologic examination including the judicious use of immunostains (Kiyokawa et al., 2006).

In the present case, another primary cancer cannot be identified after thorough clinical investigation and we have not found any pathological evidence of metastasis including bilaterality, small tumor size, multinodular appearance, surface implant, lymphovascular or hilar invasion (McCluggage and Young, 2008). As described earlier, we think the possibility of metastasis is less likely. The ovarian tumor in this case probably represents primary signet ring cell carcinoma arising within the background of mucinous borderline tumor. Although the presence of borderline tumor may be one of the pathological clues to support the primary nature of this tumor (Lee and Young, 2003; McCluggage and Young, 2008), it must be borne in mind that metastatic mucinous carcinoma may contain areas resembling borderline or even benign mucinous tumor of the ovary (Lee and Young, 2003). This has been referred to as a maturation phenomenon and can be potentially mimic a primary ovarian tumor and the presence of benign or

Table 1
Primary signet ring cell carcinoma arising in ovarian mucinous tumor.

Authors	Age (years)	FIGO stage	Mucinous component	Size (cm)		Adjuvant treatment	Follow-up duration (months)	Patient outcomes	Autopsy
				Tumor mass	Signet component				
McCluggage and Young (2008)	27	IA	Cystadenoma	9	1	No	36	NED	–
	60	IA	Adenofibroma	9	Microscopic foci	No	N/A	N/A	N/A
	55	IA	Intraepithelial carcinoma in borderline tumor	27	N/A	No	8	NED	–
El-Safadi et al. (2010)	24	IIIC	Borderline tumor	25	N/A	CMT	5	DOC	None
Ong and Ostor (2002)	60	At least IIIB	Adenocarcinoma	15	5	CMT	N/A	N/A	N/A
Jaya Ganesh et al. (2014)	38	IC	Adenocarcinoma	20	3	N/A	N/A	N/A	N/A
Kim et al. (2018)	54	IA	Adenocarcinoma	20.5	N/A	No	12	NED	–
Current case	59	IC2	Borderline tumor	24	3	CMT	11	NED	–

N/A, not available; CMT, chemotherapy; NED, no evidence of disease; DOC, dead of other causes.

borderline-appearing areas alone cannot be used as definitive criteria for diagnosing primary ovarian tumor (Lee and Young, 2003).

Most reported cases of primary ovarian signet ring cell carcinoma in mucinous tumor had a rather short follow-up with duration ranging from 8 to 36 months (McCluggage and Young, 2008; El-Safadi et al., 2010; Ong and Ostor, 2002; Jaya Ganesh et al., 2014; Kim et al., 2018). In the studies by McCluggage and Young (2008) and Kim et al. (2018), the pathological features of ovarian tumor, as well as the absence of an identifiable primary tumor in other sites, were considered as sufficient to support the ovarian origin (McCluggage and Young, 2008; Kim et al., 2018). We acknowledge the limitation of follow-up duration in this case, but we have not found any evidence of non-ovarian malignancy despite thorough clinical and pathological evaluation. However, the follow-up period could be extended up to ten years to exclude the possibility of occult cancer that may be initially undetected (Kiyokawa et al., 2006; Scully et al., 1996), particularly in stomach and breast (Kiyokawa et al., 2006). Another exceeding rare possibility could be a collision tumor that the metastatic tumor spreads to primary ovarian mucinous tumor and exhibits a similar appearance to the primary tumor with mural nodule (Lee and Young, 2003).

Mucinous tumors of the ovary, particularly borderline tumor and adenocarcinoma categories, may be associated with mural nodules, either benign or malignant (Scully et al., 1996). The gross appearance of the present case is rather similar to those in the studies by Ong and Ostor (2002) and Jaya Ganesh et al. (2014)) that reported the mural nodule of signet ring cell carcinoma within multicystic mucinous tumor (Ong and Ostor, 2002; Jaya Ganesh et al., 2014).

Primary mucinous carcinoid tumor of ovary should be included in the differential diagnosis as this entity may contain signet ring cells (McCluggage and Young, 2008). The diagnosis of mucinous carcinoid, by definition, requires at least focal areas of distinctive morphology of neuroendocrine tumor such as small round to oval glands or solid nests of neuroendocrine cells (McCluggage and Young, 2008). In the present case, we have not identified these morphologic features including the associated teratomatous component. Despite the immunoreactivity for neuroendocrine markers in this case, we believe the expression of these markers could be explained by neuroendocrine differentiation in signet ring cell carcinoma. Neuroendocrine differentiation has been reported in almost 40% of gastric signet ring cell carcinoma without neuroendocrine morphology (Bakkelund et al., 2006; Fujiyoshi and Eimoto, 2008). It was suggested that these cancer cells possibly derived from enterochromaffin-like cells that were normally confined to the gastric epithelium (Bakkelund et al., 2006). The neuroendocrine cells generally reside within an ovarian mucinous tumor of intestinal type, particularly in borderline tumor (Scully et al., 1996). In this case, the existing of neuroendocrine cells in adjacent mucinous epithelium is confirmed by the expression of neuroendocrine markers. Interestingly, the mural nodules of signet ring cell carcinoma with neuroendocrine differentiation may possibly arise from these neuroendocrine cells in the mucinous epithelial lining.

The prognosis of primary signet ring cell carcinoma in ovarian mucinous tumor is still unknown at this time due to the rarity of cases (McCluggage and Young, 2008). The previously reported cases showed a favorable outcome without evidence of recurrence or metastasis in three cases with stage IA (see Table 1). The background of mucinous tumor of these cases ranged from benign to intraepithelial carcinoma and adenocarcinoma. The size of signet ring cell carcinoma was mentioned in one case that it was only 1 cm. As previously described by McCluggage and Young (2008), we thought that the patients with early stage tumor and small size of primary signet ring cell carcinoma may tend to have a favorable outcome. Also, due to the rarity of this tumor, there was no existing evidence-based guideline regarding the type of postoperative chemotherapy. For this patient, the standard paclitaxel and carboplatin combination was chosen although others might prefer different chemotherapy regimens especially those that are more specific to gastrointestinal malignancies due to the aggressiveness and poor survival outcomes of this particular cell type discovered in other primary organs.

In conclusion, the pathologist should be aware of this rare entity and consider it in the differential diagnosis of signet ring cell carcinoma involving the ovary. The integrated assessment from entire clinical data with careful pathological evaluation is absolutely necessary to distinguish between primary ovarian signet ring cell carcinoma and metastatic tumor.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

This study was supported by (1) the National Research UniversityProject, under Thailand's office of the Higher Education Commission; and (2) the Faculty of Medicine, Chiang Mai University.

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