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Case Report

Osseous Metaplasia in Low-grade Ovarian Serous Carcinoma With a BRAF Mutation: A Case Report

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Summary: A 44-yr-old woman presented with lower, painless abdominal discomfort and a vacuolated mass measuring 12 cm on the right-hand side of the pelvis. She subsequently underwent a bilateral salpingo-oophorectomy. An osseous lesion was identified in the left ovary, which was hard in consistency and was associated with a multicystic complex lesion. Microscopic examination of the left ovary showed clusters of serous cells with moderate atypia, surrounded by a desmoplastic stroma with large areas of bone matrix. To the best of our knowledge, this is the first reported case of low-grade serous carcinoma with osseous metaplasia and a *BRAF* mutation. **Key Words:** Low grade—Serous carcinoma—*BRAF*—Osseous—Metaplasia.

Osseous metaplasia is an extremely rare occurrence in ovarian tumors. The most common type of ovarian tumor containing osseous elements is a teratoma. Heterologous mixed mesodermal tumors of the ovary may also be associated with bone formation (1). Primary ovarian osteomas have also been described (2,3). Only 2 cases of high-grade serous carcinoma have been described in the literature. To the best of our knowledge, this is the first reported case where osseous metaplasia occurred in a low-grade serous ovarian carcinoma. This is also the first case where a

BRAF mutation is described in this particular context. Moreover, we believe that the psammoma bodies transitioned into osseous tissue in the patient. This observation is contrary to previous findings.

CASE REPORT

The patient was a 44-yr-old woman. She had previously undergone an abdominoplasty, a laparoscopy for a tubal ectopic pregnancy, and a cesarean section. The patient experienced menarche at the age of 15, gave birth to her first child at the age of 34, and had regular menstrual cycles. Her mother was diagnosed with breast carcinoma at the age of 58. The patient experienced lower, painless abdominal discomfort for a few weeks. An ultrasound showed a vacuolated mass measuring 12 cm on the right-hand side of the pelvis; however, the ovaries were not clearly observed (Fig. 1). The levels of serous markers were measured; CA125 levels were recorded as 67 kU/L (normal levels are < 35 kU/L), HE4 levels were recorded as 161 pmol/L (normal levels are < 76.2 pmol/L), and ROMA levels were recorded as 58.8% (normal levels in the reproductive period are < 11.4%). The patient did not receive neoadjuvant chemotherapy. A bilateral annexectomy

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The authors declare no conflict of interest.

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FIG. 1. Presence of an adnexal mass at the ultrasound.

was subsequently performed. The right ovary measured 12×12×7 cm, and exhibited a multicystic lesion and a hemorrhagic, yellow solid nodule. The left ovary measured 5×4×3 cm and presented with a multicystic lesion and an osseous lesion of 2.5 cm in diameter, which was hard in consistency (Fig. 2). The fallopian tubes and the ovarian capsules were unremarkable. There was no evidence of extraovarian disease.

A microscopic examination of the left ovary showed clusters of malignant cells, with moderate amounts of basophilic cytoplasm and an enlarged, hyperchromatic nuclei, surrounded by a dense fibrous stroma. Some



FIG. 2. Identification of a well-defined white nodule, which was hard in consistency.

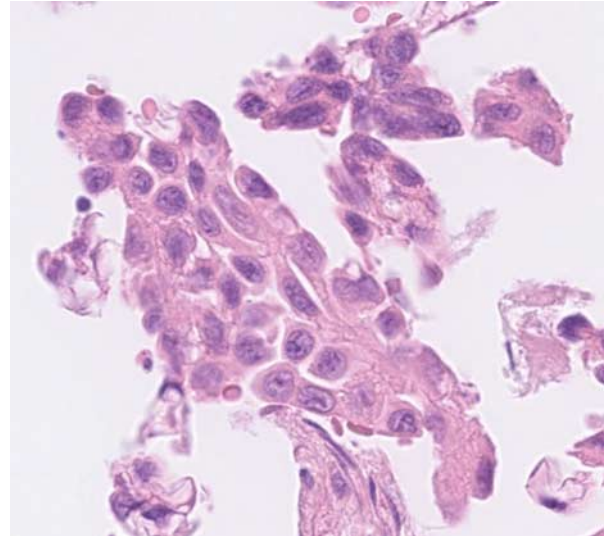


FIG. 3. Presence of exfoliated cells with a dense eosinophilic cytoplasm. Hematoxylin and eosin staining. Original magnification: ×20.

exfoliated cells had a dense eosinophilic cytoplasm (Fig. 3), which has been previously described in cases with *BRAF* mutations (4). The desmoplastic stroma had large areas of bone matrix containing osteoblastic and osteoclastic cells. Both tumor cells and psammoma bodies were incorporated into the haversian spaces. In addition, psammoma body clusters were identified which may to have transformed into bone matrix (Fig. 4). This tumor did not have a serous borderline component.

A histologic examination of the right ovary showed the same cluster of malignant cells present in the left ovary, with moderate cellular atypia. Papillary formation was also observed in a number of areas, and psammoma bodies were abundant. Osseous metaplasia was not observed.

These features were consistent with the diagnosis of a bilateral low-grade serous carcinoma, with osseous metaplasia of the left ovary. The ovaries were thoroughly examined to exclude the possibility of an underlying teratoma; however, no teratomatous tissue was found. Immunohistochemical analysis showed the presence of wild-type p53 protein. The lesion was sequenced via next-generation sequencing (Ion Torrent/PGM sequencing) and a mutation of the *BRAF* gene was identified (exon 11, p.G469A).

DISCUSSION

In 1956, De Brux et al. (5) provided the first description of osteogenesis within the genital tract (6). The presence of osseous tissue is a rare phenomenon in the gynecologic

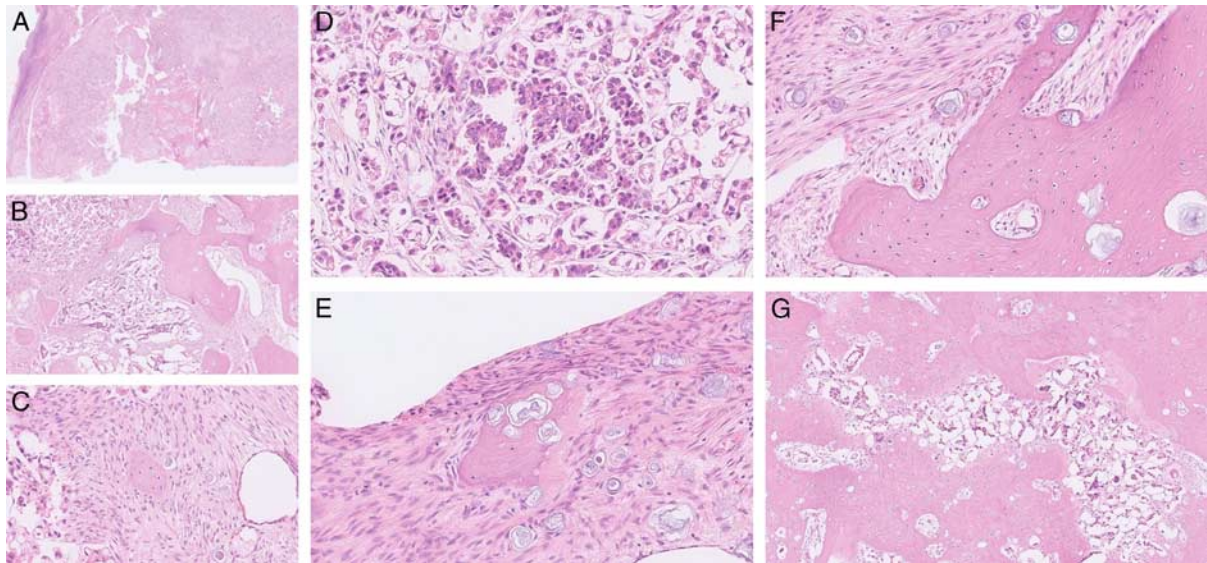


FIG. 4. (A) Low power view of the osseous nodule. Hematoxylin and eosin staining. Original magnification: $\times 4$. (B, C, and G) Presence of clusters of malignant cells in the desmoplastic stroma, which was composed of large areas of bone matrix and psammoma bodies. Hematoxylin and eosin staining, original magnification: $\times 10$. (D) Clusters of tumoral cells with moderate atypia, moderate amounts of basophilic cytoplasm, and enlarged, hyperchromatic nuclei. Hematoxylin and eosin staining, original magnification: $\times 20$. (E and F) Association and possible transition between psammoma bodies and bone matrix/haversian spaces. Hematoxylin and eosin staining, original magnification: (E) $\times 10$, (F) $\times 20$.

logical tract. This phenomenon was described in benign conditions, such as endocervical polyps, isolated vaginal and endometrial osseous metaplasia, endometriosis, endosalpingiosis, infections, ischemia, retained fetal bones in the endometrium, and endometrial hyperplasia, in addition to in neoplastic lesions, including serous adenofibroma, high-grade serous carcinoma (2 reported cases), mucinous cystadenoma (3 reported cases), ovarian endometrioid adenocarcinoma, malignant mixed Mullerian tumors, calcifying Sertoli cell tumors, and luteinized thecoma (3,7–18). Ossification is more frequently observed in cases of teratoma, heterologous mixed mesodermal tumors, osteomas, or osteosarcomas (7,9,19).

Because it is so rare, the histogenesis of osseous metaplasia in ovarian serous carcinoma is largely unknown. Osseous metaplasia has been described in other gynecologic tissues, such as the endometrium, cervix, and the vulva. One proposed explanation is the initiation of bone formation by the extension of preexistent psammoma bodies in the serous tumor. Psammoma bodies are made up of microcrystals highly similar to the calcium phosphate crystals of the bone (9). An area of calcification similar to the bone matrix could be formed between psammoma bodies and the stroma. One argument against this theory is that no transition from psammoma bodies to bone elements has ever been identified. In addition, psammoma bodies are a common finding in ovarian serous carcinoma, but

evidence of bone formation is extremely rare, suggesting that such an association between psammoma bodies and bone formation does not exist. However, in our case, it seems that there is a transition from psammoma bodies to the bone. Another explanation for the discovery of bone in a serous carcinoma is to assume that the original tumor was an ovarian teratoma composed of predominantly 2 cell lines, in which the epithelial component underwent a malignant transformation. The most plausible explanation for bone formation in an ovarian serous carcinoma is the metaplastic process of multipotential stromal cells (10,20). The physiopathology of the osseous metaplastic process could be due to the release of superoxide radicals, tumor necrosis factor, transforming growth factor β -1 (TGF- β 1), growth differentiation factor-5 (GDF-5), and bone morphogenic protein-7 (BMP-7). All these proteins are increased in areas of osseous metaplasia, suggesting their important role (21,22). Endometrial ossification may be associated with acute or chronic inflammation (6). A possible mechanism of this metaplasia is that dystrophic calcification is a response to chronic inflammation, which then drives bone formation. This metaplastic change could be viewed as an adaptive transformation of cells in an adverse environment. Another mechanism for osseous metaplasia is that it may have mullerian origins (23). However, no conclusions can be made from such a limited number of reported cases regarding the

prognostic significance of the presence of bone in an ovarian serous carcinoma. In tumors such as this, the aggressiveness will most likely be determined by the carcinoma grade, and not the benign osseous component (10,20). Previous studies have illustrated the phenomenon of bone metaplasia, but not in the presence of *NRAS* and *BRAF* mutations (24). In the literature, no association was found between the presence of a *BRAF* mutation and the presence of osseous metaplasia. Therefore, further studies are required to improve our understanding of the physiopathology of this rare phenomenon in ovarian carcinomas.

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