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Case report

Low-grade serous carcinoma with extensive osseous metaplasia arising from ovarian serous cystadenofibroma

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1. Introduction

Instead of opposite ends on a continuum, the most current understanding of the dualistic model of carcinogenesis in ovarian serous neoplasia is that low-grade and high-grade serous carcinomas represent two distinct diseases with their own unique clinical, molecular, and morphological features (Malpica et al., 2004; Prat et al., 2018).

Low-grade serous carcinomas (LGSC) are relatively uncommon, accounting for less than 5% of ovarian carcinomas. They are thought to arise via step-wise progression from serous borderline tumors, with which they share mutually exclusive *KRAS*, *BRAF*, and *ERBB2* mutations (Prat et al., 2018; Ho et al., 2004; Mayr et al., 2006; Slomovitz et al., 2020).

In this context, mutations in KRAS and BRAF are more common, and appear to be mutually exclusive. They are thought to represent early events in carcinogenesis, as they are seen in both borderline tumors and adjacent benign cystadenomatous epithelium (Ho et al., 2004).

While distinct morphomolecular subgroups within LGSC are yet to be fully characterized, advanced stage tumors tend to harbor KRAS mutations more often than mutations in BRAF, with the latter being associated with the presence of cells with a "senescent" phenotype (Prat et al., 2018).

High-grade serous carcinomas (HGSC) are much more frequent, accounting for the vast majority of ovarian carcinomas. *TP53* mutation appears to be the earliest and fundamental genetic event in HGSC development, followed by *BRCA* inactivation, chromosomal instability, and copy number changes (Prat et al., 2018; Vang et al., 2016).

The discovery of serous tubal intraepithelial carcinoma (STIC) in the distal aspect of the fallopian tube led to a paradigm shift in the proposed model for HGSC carcinogenesis. Many cases of HGSC, however, do not appear to be associated with identifiable STIC, even with improved fallopian tube sampling protocols (Prat et al., 2018). There is also experimental evidence pointing towards a more complex "origin story" for HGSC (Kim et al., 2015; Kim et al., 2018).

While the dualistic model led to unquestionable progress in the field of ovarian serous carcinomas, there is room for further development. For example, a recent study by Zarei et al. (Zarei et al., 2020) has addressed the issue of serous carcinomas that defy classification into either LGSC or HGSC. It is possible that some of these cases arise from progression from low-grade to high-grade, as suggested by Murali et al. (Murali et al., 2019). Unusual clinical scenarios such as the aforementioned may prompt new questions and challenge our previously established concepts.

We herein report a case with the potential to raise questions regarding our pathogenesis models – low-grade serous carcinoma arising from a purely benign serous lesion, with no identifiable borderline or intermediate component. The low-grade serous carcinoma

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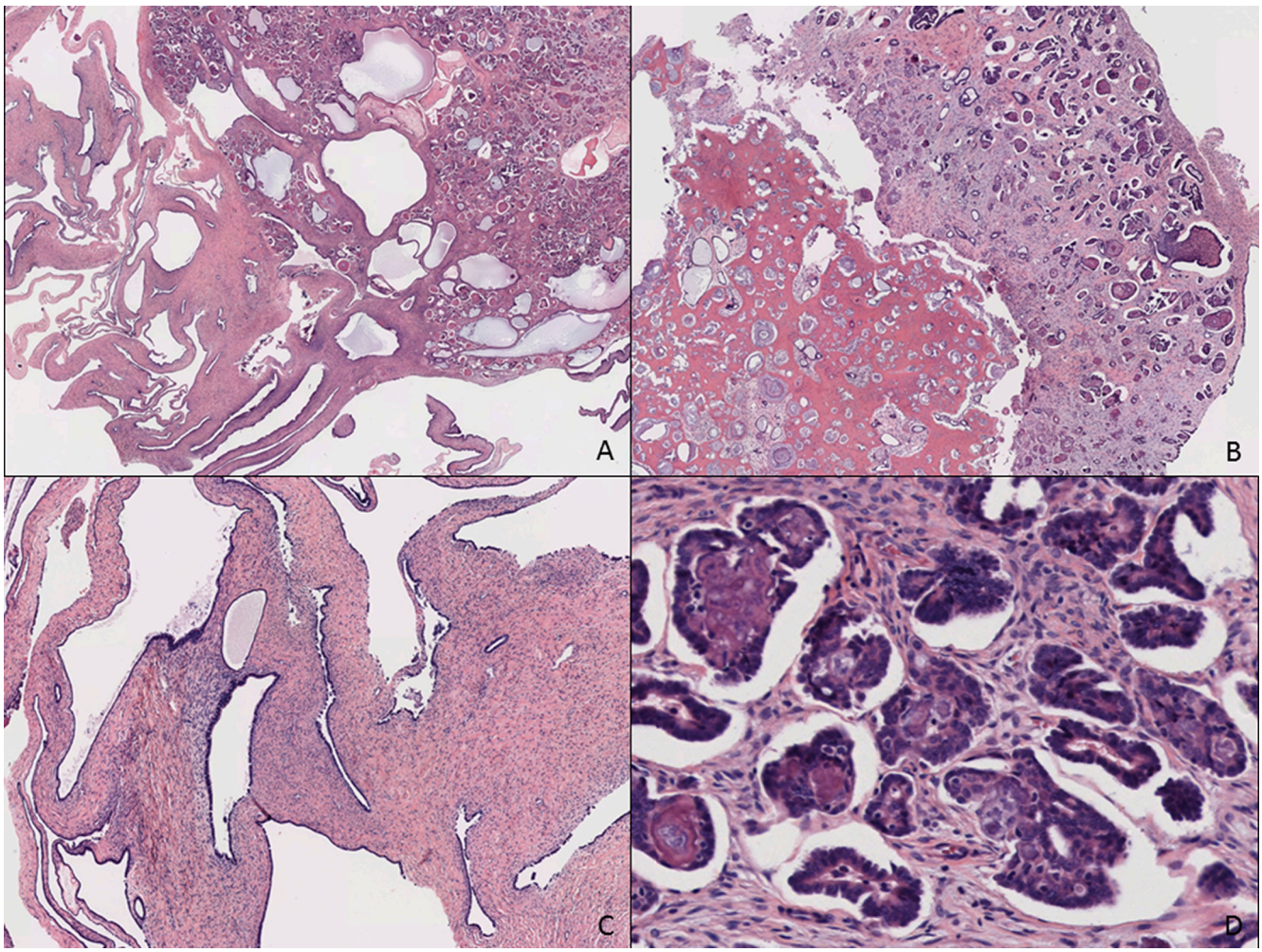

Fig. 1. Photomicrographs of the ovarian lesions. A. Low power view shows the interface between the cystadenofibroma and the low-grade serous carcinoma components. B. The low grade serous carcinoma showed extensive calcification and striking osseous metaplasia. C. Closer view of the cystadenofibroma component. No borderline elements were observed. D. Cytologic features of low grade serous carcinoma, with mild nuclear atypia and low mitotic activity.

reported in this study also displayed extensive metaplastic bone formation, an uncommon finding in non-teratomatous ovarian tumors.

2. CASE: Bilateral low-grade serous carcinoma with osseous metaplasia arising from cystadenofibromas

A 71-year old female presented with bilateral pelvic masses incidentally identified on a CT of the abdomen and pelvis in September 2019 ordered secondary to her history of numerous adenomatous colonic polyps by her gastroenterologist. At that time, a 5 cm right pelvic mass was noted. Pelvic ultrasound revealed a heterogeneous, partially calcified left adnexal mass measuring 5.5 × 5.0 × 6.8 cm that might represent either a calcified, pedunculated uterine fibroid versus an ovarian mass. Patient then underwent a pelvic MRI in October 2019 demonstrating a complex cystic and solid left adnexal mass measuring 5.0 × 4.2 × 4.7 cm. There was also abnormal morphology of the smaller right ovary that contained several small cysts. A loculated fluid collection versus large cystic component of these abnormal adnexal masses, posterior to both adnexal masses, was present and no abnormal lymphadenopathy was noted. The patient was planning to undergo surgery, however, she was not initially cleared by her pulmonologist for laparoscopic surgery due to the required Trendelenburg positioning. She underwent a repeat pelvic ultrasound in February 2020 which demonstrated the complex adnexal mass, slightly asymmetric to the left that measured 8.0 × 6.0 × 8.0 cm. Pre-operative tumor markers were within normal limits: CA 125 was 22.0 kU/L, CEA was 1.5 ng/ml. She then underwent laparoscopic bilateral salpingo-oophorectomy with pelvic washings. Intraoperative findings revealed a 10.0 cm cystic left ovarian mass, normal-appearing right ovary and bilateral fallopian tubes, small white flecks on the surface of small bowel, liver surface, and uterus were noted. The tissue was removed laparoscopically via a 15 mm “Endocatch bag” and submitted for intraoperative pathologic consultation. The right ovary was a disrupted predominantly hard cystic mass measuring 4.5 × 3.4 × 2.0 cm. The left ovary was a hard, solid-cystic mass measuring 8.0 × 6.5 × 3.0 cm. Diffuse calcifications and ossification were present in both lesions, impeding frozen section microscopic evaluation. The overall gross appearance was benign, and a gross diagnosis of bilateral cystadenofibromas was rendered.

Upon microscopic examination, both lesions were predominantly characterized by serous cystadenofibromas. In the largely calcified areas we identified low-grade serous carcinoma with a predominantly micropapillary pattern, with small groups of malignant cells surrounded by retraction artifact. Nuclear atypia was mild, and the mitotic rate was low. Amidst the low-grade serous carcinoma cells there were abundant psammomatous calcifications and also striking heterologous osseous metaplasia (Fig. 1). Immunostaining for p53, p16 and ki67 supported this diagnosis (Fig. 2). The tumor cells were also positive for estrogen receptor (90%, strong) and progesterone receptor (50%, strong).

The entire specimen was submitted to histologic examination, but there was no identifiable intermediate borderline component in either

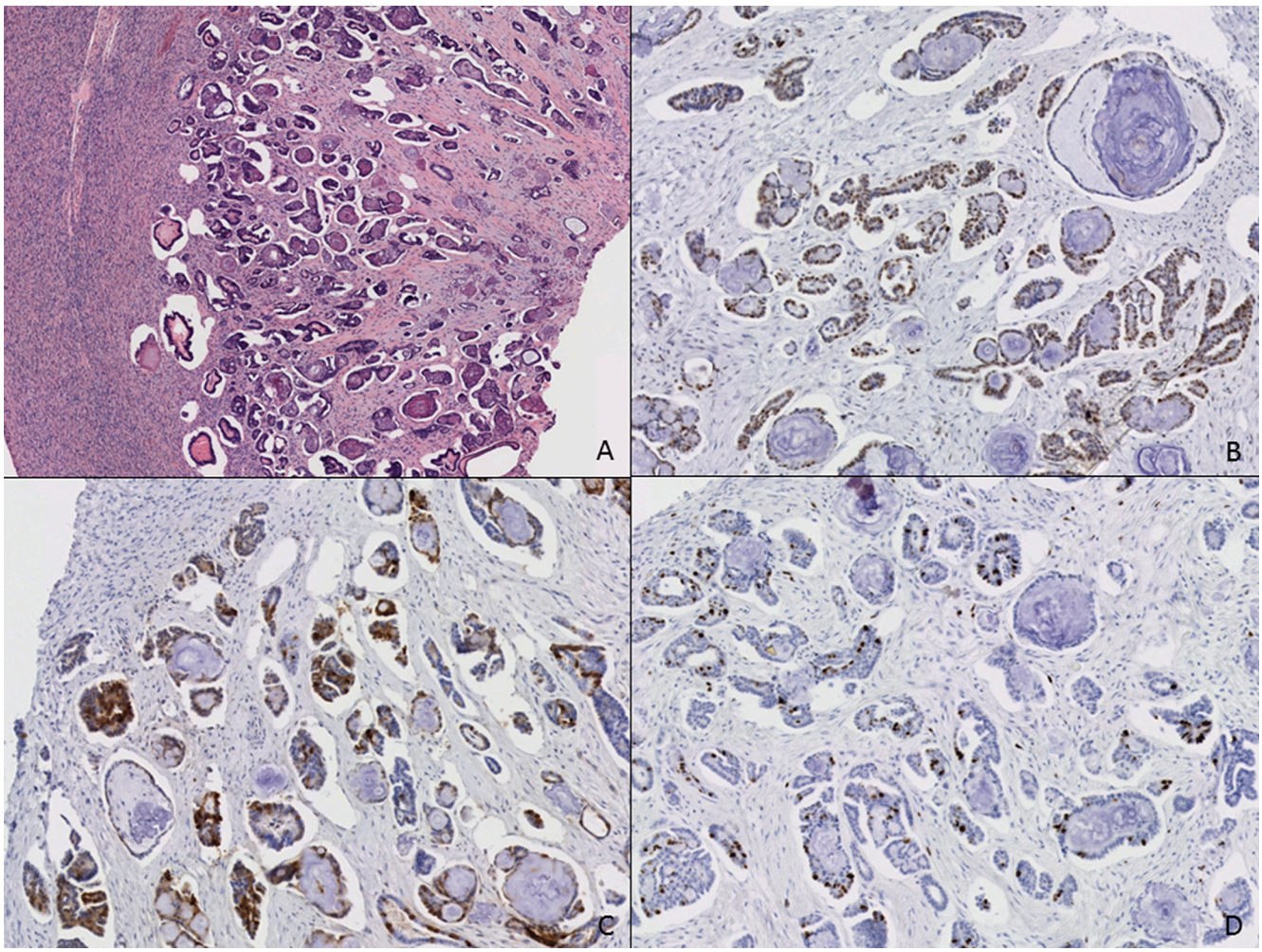

Fig. 2. Both ovarian lesions displayed a similar immunoprofile. A. Low power view of low-grade serous carcinoma infiltrating residual ovarian stroma. B. Wild-type p53 expression. C. Patchy p16 staining. D. Low index of proliferation labeling with ki67 (MIB1).

ovarian mass. In the bilateral residual ovarian stroma there were foci of endosalpingiosis and proliferative endosalpingiosis. There was also a microscopic Brenner tumorlet in the right ovary. No abnormalities were found in the fallopian tubes. Peritoneal washings submitted with the bilateral salpingo-oophorectomy were positive for neoplastic cells.

An attempt to perform mutational analysis on paraffin embedded tissue blocks was made, but the decalcification process hindered results.

After discussing the final pathology with the patient, recommendation was made for staging procedure. She returned to the operating room for exploratory laparotomy, total abdominal hysterectomy, infra-gastric omentectomy, and bilateral pelvic and para-aortic lymph node dissection. Final pathology revealed no additional malignancy. Given the positive peritoneal washings at the time of bilateral salpingo-oophorectomy, the patient's final pathologic stage was IC3.

The patient returned to the clinic post-operatively. Per National Comprehensive Cancer Network guidelines (Nccn.org. 2020), adjuvant chemotherapy using carboplatin and paclitaxel versus observation was discussed. Ultimately, the patient opted for adjuvant treatment given the positive pelvic washings. Maintenance endocrine therapy should be considered in stage II-IV LGSC as approximately 95% will have estrogen receptor expression and more than 50% will also express progesterone receptor.

3. Discussion

The current pathogenesis model for low-grade serous carcinoma of the ovary is a step-wise progression from benign serous lesions to some form of atypical proliferative (borderline) tumor and subsequent carcinoma, driven by *KRAS*, *BRAF*, and *ERBB2* mutations (Prat et al., 2018; Ho et al., 2004; Mayr et al., 2006). These findings have been recently supported by paired analysis of subsequent serous carcinomas in patients with a prior borderline tumor (Murali et al., 2019; Chui et al., 2019).

To the best of our knowledge, this is a rare instance in which low-grade serous carcinoma is seen arising from pure serous cystadenofibroma, with no identifiable atypical proliferative/borderline component. The entire specimen was submitted to histologic examination for both adnexa, minimizing the risk of sampling bias.

One possible explanation is that a previously existing borderline component had, at the time of surgery, already been largely replaced by LGSC. On the other hand, one has to entertain the possibility that steps in low-grade serous carcinogenesis could be "skipped" or "added," leading to divergent behavior in a smaller subset of cases.

The presence of extensive heterologous bone formation, or osseous metaplasia, was also striking. While the presence of psammomatous calcifications is relatively common, osseous metaplasia in non-teratomatous ovarian tumors have only been reported in 10 other cases, including a benign serous cystadenoma (Miliaras et al., 2007) and two cases classified as "papillary serous cystadenocarcinomas." (Bosscher et al., 1990; Mukonoweshuro and Oriowolo, 2005).

The case reported by Bosscher in the 1990s (Bosscher et al., 1990) was very similar to the case currently being discussed, with prominent

psammomatous calcifications coexisting with heterologous bone. The original diagnosis of "well differentiated papillary serous carcinoma" may presumably correspond to a more modern low-grade serous carcinoma.

Pathological examination is the analysis of "still photographs" taken from dynamic disease processes. Due to this characteristic, there will be inherent limitations in any attempts to translate tumor progression into a model. Photography is all about timing. A perfectly timed image is sometimes able to convey the essence of a moment. The same can be said for pathology - the only way we can increase our chances of capturing the essence of human disease is to take more pictures.

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CRediT authorship contribution statement

Renan Ribeiro e Ribeiro: Writing - original draft, Writing - review & editing, Conceptualization, Investigation. **Ashley Valenzuela:** Writing - review & editing, Investigation. **Lindsey Beffa:** Supervision. **C. James Sung:** Supervision. **M. Ruhul Quddus:** Writing - review & editing, Supervision, Conceptualization, Project administration.

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.

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