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Low grade serous neoplasms of the ovary with transformation to high grade carcinomas: Report of 3 cases

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Abstract

Ovarian borderline tumors usually occur in young patients and are associated with good clinical outcomes. A proportion of these tumors, particularly those with micropapillary features, may progress to low grade serous carcinomas. Evolution of low grade serous neoplasms to high grade carcinomas is rare and infrequently reported. In this case report, we describe 3 cases of serous borderline tumor that progressed to high grade carcinoma. Patient ages were 22, 35 and 47 years. Two patients were initially diagnosed with ovarian serous borderline tumor, and recurred in the pelvis 3 years and 10 years later with sarcomatoid carcinoma. The third patient presented with low grade serous carcinoma arising in a micropapillary serous borderline tumor, and recurred with a carcinosarcoma 3 years later. All three patients had an aggressive clinical course: 2 died of disease and 1 patient has disease progression on chemotherapy. Occasional low grade serous tumors of the ovary may transform to high grade carcinomas, which can occur many years after initial diagnosis. The presence of a high grade component significantly worsens patient outcomes.

Introduction

Ovarian neoplasms are divided into types I and II. Type I carcinomas are low grade tumors that develop from identifiable precursor lesions such as borderline tumors, and include mucinous, endometrioid and low grade serous carcinomas.¹ Low grade serous carcinomas often arise in a background of serous borderline tumors, particularly those with micropapillary features, and may show BRAF, KRAS and ERBB2 mutations. Type II carcinomas are high grade neoplasms that frequently show p53 mutations, the prototype being high grade serous carcinoma. These are usually not associated with precursor borderline neoplasms and do not show the mutations observed in low grade serous tumors.^{1, 2} There are important prognostic and therapeutic differences between low grade and high grade serous carcinomas. Patients with low grade serous carcinomas typically develop multiple recurrences over time and patient death can occur many years after the initial diagnosis. These tumors do not respond to conventional platinum based chemotherapy used for ovarian tumors. High grade serous carcinomas of the ovary, on the other hand, usually respond to platinum based chemotherapy, and the median survival is much shorter.³

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This proposed model of ovarian tumorigenesis effectively segregates ovarian serous neoplasms into two types with distinct morphologies, pathogenesis, molecular abnormalities and clinical characteristics. In most cases, there is no overlap between these two types. Low grade serous carcinomas, at recurrence, typically retain their original low grade appearance. However, occasional cases of transformation or progression of low grade serous tumors to high grade carcinoma have been reported, but this is a rare phenomenon and current literature exists in the form of sporadic case reports.

These include cases of high grade serous carcinomas associated with low grade serous tumors diagnosed at initial presentation. Malpica et al found one case of high grade serous carcinoma in association with a serous borderline tumor, representing 2% of their 50 high grade serous carcinomas.⁴ Dehari et al reviewed 210 ovarian high grade serous carcinomas and found 6 tumors associated with low grade serous neoplasms (2.8%), 3 with serous borderline tumors and 3 with invasive low grade serous carcinomas.⁵ Quddus, et al also reported a case of high grade serous carcinoma arising in association with serous borderline tumor and low grade serous carcinoma.⁶

In some cases, a low grade serous tumor recurred as high grade carcinoma. Parker et al reported 2 cases of ovarian serous borderline tumor with early recurrences as high grade carcinoma in axillary lymph nodes and hernia sac, 18 months and 2 years respectively, after initial diagnosis.⁷ One tumor recurred as high grade serous carcinoma while the other recurrence consisted of poorly differentiated carcinoma with sarcomatoid areas.

There are also four reported cases of “sarcoma like mural nodules” in association with serous borderline tumors.^{8–11} In all of these cases, the high grade component consisted of sarcomatoid carcinoma.

In this report, we describe three additional cases of low grade serous tumors that recurred as high grade malignant neoplasms.

Patient 1

This patient initially presented at age 22 years with bilateral ovarian serous borderline tumors with non invasive implants. She recurred twice within 3 years as serous borderline tumor and non invasive implants. She presented with a pelvic recurrence 7 years later which was diagnosed as low grade serous carcinoma with invasive implants, and received 6 cycles of chemotherapy. She then presented 1 year later at our institution with radiologic evidence of pelvic recurrence. She received multiple cycles of chemotherapy (combinations of doxorubicin, bevacizumab and paclitaxel) with questionable response. She then presented with small bowel obstruction, and underwent palliative surgery with peritoneal biopsies. She died of disease one month later.

The diagnosis of bilateral ovarian serous borderline tumors with non invasive implants was confirmed. Only representative slides were submitted from bilateral ovaries for our review, and although focal micropapillary features were noted in one ovary, the findings did not meet the criteria of >5 mm micropapillary growth for an outright diagnosis of micropapillary borderline tumor.¹² However, this evaluation was limited by our ability to examine only

selected slides. Slides from the invasive implants and low grade serous carcinoma were not available for our review.

Biopsies of the pelvic recurrence performed at our institution from the small bowel and abdomen showed a high grade undifferentiated spindle cell malignant neoplasm, involving small bowel serosa and abdominal biopsies (Figures 1a and 1b). There was no evidence of a low grade serous component. Tumor cells were spindled and high grade and the differential diagnosis included high grade anaplastic carcinoma and sarcoma. By immunohistochemistry, the tumor cells displayed patchy staining for epithelial markers (cytokeratins and EMA). All other stains, to exclude angiosarcoma, dedifferentiated liposarcoma and mesothelioma, were negative. The tumor did not show abnormal expression of p53 by IHC. Based on the morphology and immunohistochemical profile, a diagnosis of sarcomatoid carcinoma was favored. The tumor was negative for BRAF and KRAS mutations.

Patient 2

Patient was a 47 year old woman who presented with abdominal symptoms and was found to have bilateral ovarian serous borderline tumors. She then presented 3 years later with a pelvic mass. She also had a history of lung adenocarcinoma, with brain metastasis. Patient died of disease 6 months later.

Slides from the initial surgery showed bilateral ovarian serous borderline tumors with surface involvement. The ovarian tumors were well sampled, and there was no evidence of micropapillary features. Slides from the pelvic recurrence showed a high grade spindled and epithelioid malignant neoplasm, without any evidence of a low grade serous component (figures 2a and 2b). Immunohistochemistry showed that tumor cells were negative for multiple epithelial markers and sarcoma specific markers. P53 stain could not be performed due to lack of material. The tumor was diagnosed as high grade undifferentiated malignant neoplasm, sarcomatoid carcinoma was favored. The pelvic tumor was morphologically and immunophenotypically distinct from the lung primary.

Patient 3

This patient presented at age 35 years with abdominal symptoms and was diagnosed with right ovarian micropapillary low grade serous carcinoma, stage IIIC. She received IV and IP chemotherapy. She then presented 2 years later with rising CA-125 and underwent splenectomy and pancreatectomy. She presented within one year with right axillary lymph node metastasis and underwent right axillary lymph node dissection. She subsequently received radiation and chemotherapy, but had evidence of disease progression on therapy.

Sections from the right ovary showed a low grade serous carcinoma arising in a background of micropapillary serous borderline tumor (figures 3a and 3b). Tumor in extra-ovarian sites, including cul-de-sac and diaphragm showed higher grade areas, with more cytologic atypia and mitoses. However, these foci did not meet criteria for a diagnosis of high grade serous carcinoma and were diagnosed as grade 2 serous carcinoma (by application of the Shimizu-Silverberg criteria).¹³ The splenectomy showed a poorly differentiated tumor with spindled

and epithelioid appearance involving the splenic parenchyma and hilum (figure 3c). Immunohistochemistry for p53 on the splenic tumor was reportedly not abnormal. KRAS mutational analysis was also performed on the ovarian and splenic tumors, and both were negative. Finally, sections from the axillary lymph node metastasis showed overt features of carcinosarcoma (MMMT) with high grade carcinoma and sarcoma components (figure 3d). A p53 stain in this tumor showed strong and diffuse overexpression.

Discussion

Progression in ovarian serous borderline tumors typically occurs in the form of low grade serous carcinoma. This transformation is typically associated with increased disease tempo and poor prognosis. However, low grade serous carcinomas tend to retain their low grade histology at recurrent/metastatic sites.¹⁴ Evolution of borderline neoplasms or low grade serous carcinoma to high grade carcinoma is unusual, and described in sporadic case reports. In this case report, we described 3 additional cases of high grade tumors arising in association with ovarian low grade serous neoplasms. Table 1 summarizes all such reported cases in the English literature, including the current cases (table 1).

The high grade carcinoma component may be seen at initial presentation, or in a subsequent recurrence. In all our cases, the high grade component was evident only at the time of recurrence. The time period between initial diagnosis of low grade serous tumor and progression to high grade carcinoma is variable and ranges from 18 months to as long as 10 years in reported cases. The morphology of the high grade component can also vary, 2 of 3 cases in our series recurred as sarcomatoid carcinoma and 1 as carcinosarcoma. High grade serous carcinoma constituted the high grade component in many reported cases. Some cases of serous borderline tumor with sarcomatoid carcinoma have been described as having mural like nodules.⁸⁻¹⁰ While mural nodules are well described in mucinous cystic tumors of the ovary, they are rare in serous borderline tumors.¹⁵

Irrespective of morphology, presence of a high grade component significantly worsens patient outcomes. Two of the 3 patients in this report died of disease within one year of diagnosis, while the 3rd patient had evidence of disease progression while on chemotherapy. Unfavorable clinical outcomes were also seen in all such reported cases, most patients being dead of disease or alive with disease (table 1). Patients with ovarian serous borderline tumor generally have a good prognosis with overall survival and disease free survival of 98% and 87% for stage 1, and 91% and 65%, respectively, for patients who present at higher stages.¹⁴ Reported 5 year survival rates range from 40% to 56% for low grade serous carcinomas, and 9% to 34% for high grade serous carcinomas.^{4, 16}

The mechanism of this transformation is not certain. Low grade serous tumors show mutations in BRAF/KRAS/ERBB2, while high grade serous carcinomas arise as a result of Tp53 mutations. BRAF and/or KRAS mutational analysis was performed in two of our cases and both were negative. Dehari et al found identical KRAS mutations in the low and high grade components in 2 of their 6 combined high and low grade serous carcinomas, indicative of a clonal relationship. However, they did not find p53 mutations in any of the high grade components of the 6 tumors. This raises the possibility that unlike conventional high grade

serous carcinomas, those that arise in this setting may not be associated with p53 mutations. However, Quddus et al reported the presence of strong and diffuse p53 staining (an immunohistochemical staining pattern that correlates with Tp53 mutation) in the high grade component of their combined low and high grade serous carcinoma.¹⁷ Therefore, the role of Tp53 mutation in this progression is not certain. Our cases also showed variable p53 staining results. The high grade tumor from patient 1 did not show p53 overexpression. The carcinosarcoma from patient 3 showed p53 overexpression, while the preceding splenic tumor was reportedly p53 negative; suggesting that p53 mutation was acquired during transformation to high grade carcinoma. Staining for p53 could not be performed in one case.

Conclusions

Progression of ovarian serous borderline tumor and low grade serous carcinoma to high grade carcinoma is unusual, but can sometimes occur. The high grade component may be seen at presentation or in a recurrence many years after the initial diagnosis. The high grade component may be composed of high grade serous carcinoma, sarcomatoid carcinoma or carcinosarcoma. The presence of this component is associated with aggressive behavior and poor clinical outcomes. The mechanism of this transformation/progression is not clear.

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Figure 1. Biopsies of the pelvic recurrence from patient 1 a high grade undifferentiated spindle cell malignant neoplasm, involving small bowel serosa and abdominal biopsies (Figures 1a). On higher magnification, there is marked cytologic atypia and numerous mitotic figures (figure 1b).

Figure 2.

The pelvic recurrence from patient 2 consisted of a high grade spindled and epithelioid malignant neoplasm diffusely involving colon (figure 2 a). The tumor showed anaplasia and brisk mitotic activity (figure 2b).

Figure 3.

The ovarian neoplasm from patient 3 showed a micropapillary serous borderline tumor (figure 3a). Other areas showed invasion, consistent with low grade serous carcinoma (figure 3b). The recurrence in the spleen showed a poorly differentiated tumor with spindled and epithelioid appearance (figure 3c). Tumor from the axillary lymph node metastasis showed a malignant biphasic tumor consistent with carcinosarcoma (MMMT) (figure 3d).

Table 1

Reported cases of high grade carcinomas in association with ovarian low grade serous neoplasms

	Number of cases	Diagnosis	Age (years)	Time to progression	Patient status
Parker, et al ⁷	2	-SBT* with progression to high grade carcinoma	50–61	18–27 months	1 DOD [¶] 1 AWD [€]
Dehari, et al ⁵	6	-3 SBT* to high grade serous carcinoma -3 low grade serous to high grade serous carcinoma	31–67	At presentation	Not reported
Quddus, et al ⁶	1	-SBT with high grade serous carcinoma	23	At presentation	AWD [€]
Andrews, et al ⁹	1	-SBT with sarcomatoid carcinoma	49	At presentation	DOD [¶] (32 months)
DeRosa, et al ¹¹	1	-SBT with sarcomatoid carcinoma	41	At presentation	DOD [¶] (6 months)
McCullough J, et al ¹⁰	2	-SBT with sarcomatoid carcinoma	49–72	At presentation	DOD [¶] (8 days and 5 months)
Garg K, et al	3	-2 SBTs with progression to high grade malignant neoplasms -1 SBT with low grade serous carcinoma with progression to carcinosarcoma	22–47	3 years – 10 years	-2 DOD [¶] (6 months and 12 months) -1 AWD [€]

* SBT: Serous borderline tumor,

[¶]DOD: Dead of disease,

[€]AWD: Alive with disease