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Case report

Serous borderline tumor with micropapillary pattern of the right ovary that developed 6 recurrences over 30 years after primary surgery

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ABSTRACT

Serous borderline tumors (SBTs) are nonaggressive and have excellent prognosis. Furthermore, SBTs with micropapillary pattern (SBT-MP) are known to be associated with a higher recurrence rate, microinvasions and invasive implants compared to typical SBTs, and these characteristics have adverse effects on prognosis. Here, we report a case of SBT with micropapillary pattern (SBT-MP) that developed 6 recurrences over 30 years after primary surgery. The patient was a 70 year-old woman. At 41 years of the age she underwent total abdominal hysterectomy, bilateral salpingo-oophorectomy, partial omentectomy and pelvic lymphadenectomy and was found to have an SBT-MP involving the right ovary (International Federation of Gynecology and Obstetrics 2014, stage IC2). She was administered chemotherapy (cyclophosphamide, adriamicin, and cisplatin). She repeatedly developed recurrences 6 times after primary surgery. A left inguinal recurrence at age 55, a right inguinal recurrence at age 56, a right inguinal recurrence at age 64, an umbilical recurrence at age 65, a right inguinal recurrence at age 68 and left axillary recurrence at age 70. Histopathological examinations revealed that all recurrences were SBT-MP with noninvasive implants. Our case strongly justifies the belief that recurrent SBTs carry an excellent prognosis unless they develop significant malignant transformation.

1. Introduction

Ovarian serous borderline tumors (SBTs) are nonaggressive tumors. Even patients with SBT associated with extraovarian spread (advanced-stage disease) have excellent prognosis; 10-year survival rate is 94% (Kane et al., 2009). Some researchers reported the type of implant is one of the most reliable prognostic indicators. While Seidman and Kurman reported the overall survival rates of patients with noninvasive and invasive implants were respectively, 95% and 66% ($p < .0001$) (Seidman et al., 2000), Kane and Uzan reported 10-year recurrence-free interval of patients with noninvasive and invasive implants were similar; 61% and 69% (Kane et al., 2009). Silva et al. reported that a micropapillary pattern is another prognostic factor (Silva et al., 2006), however, Prat and De Nictolis reported SBT with micropapillary pattern (SBT-MP) are much closer in their biologic behavior to SBTs than to serous carcinomas (Prat and De Nictolis, 2002) and it is still controversial whether a micropapillary pattern itself could be an independent prognostic factor. Only a few cases have been followed for a long period, so that we present here a case of SBT-MP, which relapsed 6 times with noninvasive implants over 30 years after primary surgery.

2. Clinical summary

The patient is a 70-year-old woman (para 2, gravida 2). When she was 41 years old, she underwent total abdominal hysterectomy, bilateral salpingo-oophorectomy, partial omentectomy and pelvic lymphadenectomy for suspected cancer of the right ovary. Histopathological findings showed International Federation of Gynecological Oncology (FIGO) 2014 stage IC2 (T1aNxM0) SBT-MP and she received chemotherapy (Cyclophosphamide, Adriamycin, Carboplatin). After that, she repeatedly suffered from recurrent tumors 6 times; a left inguinal cystic tumor when 55 years old, A right inguinal cystic tumor at age 56, a right inguinal cystic tumor at age 65, an umbilical cystic tumor, that is, Mary-Joseph tumor, at age 66, right inguinal cystic tumor at age 67 and left axillary cystic tumor at age 70. Every recurrent tumor was resected completely and histopathologically revealed to be SBT-MP with noninvasive implants. Before the primary surgery her serum CA 125 level was markedly elevated (390 U/ml), but after the primary surgery it decreased to its normal level and did not increase again.

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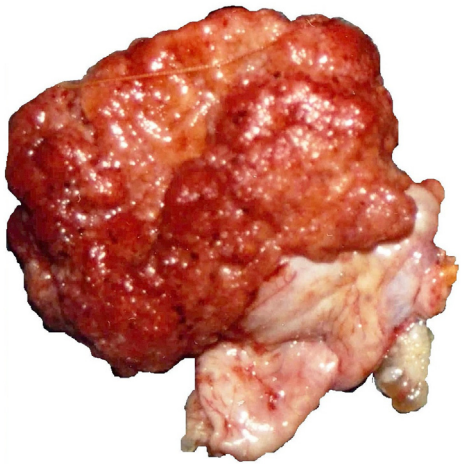

Fig. 1. The primary tumor of the right ovary was a polycystic tumor measuring 10 × 8 cm in size. It contained yellowish and clear serous fluid with a yellowish surface papillary structure.

3. Pathological findings

Ovarian and recurrent tumors were fixed in 10% formalin and embedded in paraffin. Sections (4-μm thick) were cut from each blocks and stained with hematoxylin and eosin. Immunohistochemical analysis was performed using antibodies against Ki-67 (mouse monoclonal anti-human, clone: MIB-1, 1:50 dilution, Dako, Tokyo, Japan) and p53 (mouse monoclonal, clone: DO-7, 1:50 dilution, Novocastra, Newcastle upon Tyne, United Kingdom).

Diagnosis of noninvasive implants was based on the criteria proposed by Gershenson and Silva (Singer et al., 2005). Briefly, noninvasive implants are characterized by glandular and/or papillary structures lined by serous epithelium with epithelial proliferation and cellular detachments within spaces lined by epithelial cells and tracked along the lobules of adipose tissue, which appear to be trapped within the tissue as a result of adhesions but without invasion of underlying normal tissue.

The primary tumor of the right ovary was a polycystic tumor measuring 10 × 8 cm in size. It contained yellowish and clear serous fluid with a yellowish surface papillary structure (Fig. 1). Microscopically, mildly atypical cells appeared to have proliferated without microinvasion of the basement membrane. A filigree pattern of small, uniform, elongated, stroma-poor or stroma-free papillae lined the cyst walls. These findings revealed that the tumor was SBT-MP (Fig. 2). Almost no mitosis was observed (MIB-1 index was very low, < 5 in 1000 cells were stained by ki-67). Almost no cells were stained by p53.

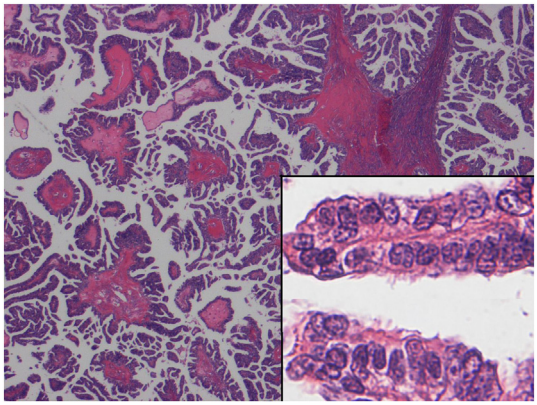

Fig. 2. Microscopically, mildly atypical cells appeared to have proliferated without microinvasion of the basement membrane. A filigree pattern of small, uniform, elongated, stroma-poor or stroma-free papillae lined the cyst walls.

All the recurrent cystic tumors were evaluated by a gynecological pathologist and revealed to be SBT-MP with a noninvasive implants. From the primary tumor to the latest recurrence, no increase in nuclear atypia, MIB-1 index, or positive rate for p53 was observed.

4. Discussion

SBTs, accounting for 5%–30% of ovarian serous tumors, are non-aggressive and have an excellent prognosis even in advanced-stage cases associated with extraovarian spread. Extraovarian spread is referred to as implants instead of metastases and classified into two types; invasive implants and non-invasive implants. SBTs with invasive implants resembles low-grade serous carcinoma (LGSC) and have a significantly worse prognosis. As Seidman et al. reported that in the review of 245 studies the survival of patients with noninvasive implants was 95.3%, as compared with 66% for invasive implants ($p < .0001$) after 7.4 years of follow-up (Seidman et al., 2000). However, this seems to be because noninvasive recurrences commonly develop over many years. To investigate this issue, Silva et al. identified 80 cases of advanced-stage SBT with noninvasive implants; the minimum follow-up period for these cases was 5 years or until the deaths of the patient (median of 15 years). They reported that 35 patients (44%) developed recurrences. Only 10% of the patients had a recurrence in < 5 years, however, 19% between 5 and 10 years, and 10% between 10 and 15 years. Regarding overall survival rates, 25% of the patients died of disease in their series (Seidman et al., 2000). Considering these results, invasive implants appear to be mainly associated with short-term recurrence, i.e., within 5 years from primary surgery, while the recurrence rate of SBTs with noninvasive implants slowly increases with time.

Micropapillary patterns in SBTs are also reported as one of the possible prognostic indicators in 1996 by Burks et al. (1996) and Seidman and Kurman (1996). These tumors are characterized by a filigree pattern of small, uniform, elongated, stroma-poor or stroma-free papillae, are at least 5 times as long as wide, and emerge directly in a nonhierarchical manner from large papillary stalks or from cyst walls. SBTs-MP account for approximately 20% of SBTs (Burks et al., 1996; Seidman and Kurman, 1996). Compared with typical SBTs, SBTs-MP are characterized by the following features; bilateral tendency, younger patients (mean age: 36–41 years vs. 45–50 years), frequent advanced stages, frequent microinvasion, frequent lymph node association, high CA125 serum levels, and frequent association with implants (Burks et al., 1996; Seidman and Kurman, 1996). While the majority of investigators including Uzan, Fauvet and Park reported that a micropapillary pattern is not associated with and adverse outcome (Fauvet et al., 2011; Park et al., 2011; Uzan et al., 2011), Silva et al. reported that the presence of a micropapillary pattern is statistically significant feature associated with recurrence in their long-tern follow-up series (Silva et al., 2006). Though Prat and De Nictolis reported SBT with micropapillary pattern (SBT-MP) are much closer in their biologic behavior to SBTs than to serous carcinomas, it is still controversial whether a micropapillary pattern itself could be an independent prognostic factor because of the lack of long-tern follow-up studies. Prat and De Nictolis studied 137 SBTs and identified 18 cases of SBT-MP, including only the one patient with invasive implants who had an unfavorable outcome. Compared with typical SBTs, SBT-MP seemed to be much closer in their biologic behavior to SBTs than to serous carcinomas. They concluded the micropapillary pattern alone does not imply an unfavorable prognosis, but only micropapillary tumors associated with invasive implants behave aggressively (Prat and De Nictolis, 2002).

It has been suggested that ovarian serous carcinoma should be divided into two groups, designated type I and type II, based on their tumorigenesis pathways. Type II tumors including high-grade serous carcinomas (HGSCs) do not develop from established precursor lesions, but rather are highly aggressive and rapidly grow in *de novo* (Kurman and Shih, 2008; Dehari et al., 2007). This model cannot completely

account for ovarian tumor pathogenesis because it has been reported that HGSC may emerge from SBTs in rare cases (Dehari et al., 2007), but now it is known that most of HGSC develops from serous tubal intraepithelial carcinoma (STIC) (Kurman and Shih, 2008). Type I tumors are slow growing and generally develop from borderline tumors as well as established precursor lesions by the so-called adenoma-carcinoma sequence. They include LGSCs which are characterized by numerous genetic mutations including KRAS, BRAF, PTEN and β-catenin. Singer et al. reported that p53 over expression and mutations are infrequent SBTs and LGSC but occur in as many as 50% to 80% of HGSC and suggested a common lineage for SBTs and LGSC (Singer et al., 2005). May et al. reported that the SBT-MP gene expression profile is similar to LGSC, but yet distinct from typical SBTs, indicating their more aggressive clinical behavior (May et al., 2010). It is risky to minimize the importance of recurrence, and conservative treatment should aggressively be pursued only in limited cases, such as in young women who want to preserve their fertility potential (Kane et al., 2009; Laurent et al., 2008). A long-term careful follow-up is much more important for patients with SBT-MP or with implants because of their tendency to frequently develop recurrences, which can transform into low-grade serous carcinomas.

In conclusion, SBT-MP patients require a long-term follow-up period because they generally develop recurrences, even more than three decades after primary surgery. If a recurrent lesion is a SBT-MP, it still carries excellent prognosis; however, if it has developed a LGSC by malignant transformation, it carries a worse prognosis. In our study, during 30 years after the primary surgery, all 6 recurrences were SBT-MP with noninvasive implants showing the same histopathological features as the primary tumor. It is important to perform a surgical resection to conduct pathological examinations, if a new recurrence is detected.

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Conflict of interest statement

The authors declare they have no conflict of interest.

Author contribution

Mari Minagawa, Mamoru Maeda and Shinichi Teshima designed the study. All authors collected the data and contributed to the analysis of the results. Mari Minagawa wrote the paper with input from all authors.

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