Internal Medicine
The Japanese Society of Internal Medicine
doi: 10.2169/internalmedicine.5693-20
Intern Med 60: 247-250, 2021
http://internmed.jp

【 CASE REPORT 】

# Extremely Late Recurrence of Ovarian Carcinoma Diagnosed by an Endoscopic Ultrasound-guided Fine-needle Biopsy

Mitsuru Chiba, Takashi Goto, Wataru Sato, Tomomi Shibuya, Kenichi Takahashi, Shinichiro Minami, Hisanori Matsuzawa, Yuki Sato and Katsunori Iijima

**Abstract:**
We herein report a case of recurrence of epithelial ovarian carcinoma 41 years after the primary surgery that was diagnosed by an endoscopic ultrasound-guided fine-needle biopsy (EUS-FNB). The differential diagnosis based on the imaging findings was difficult. We performed an EUS-FNB and compared the EUS-FNB specimen to the surgical specimen that had been resected in the primary surgery for ovarian carcinoma 41 years earlier, including immunohistochemical staining. Finally, we made a definitive diagnosis of extremely late recurrence of ovarian carcinoma of the retroperitoneum. An EUS-FNB enables an accurate histological diagnosis by obtaining a sample that is large enough to perform immunohistochemical staining.

**Key words:** recurrence, ovarian carcinoma, ultrasound-guided fine needle biopsy

**(Intern Med 60: 247-250, 2021)**
**(DOI: 10.2169/internalmedicine.5693-20)**

## Introduction

In almost all recurrent cases of epithelial ovarian carcinoma, recurrence occurs within eight years (1). Late recurrence at more than 20 years after primary surgery is a very rare event. Furthermore, few cases of recurrent ovarian carcinoma have been diagnosed by an endoscopic ultrasound-guided fine-needle biopsy (EUS-FNB).

We herein report a case of extremely late recurrence of ovarian carcinoma that was diagnosed by an EUS-FNB.

## Case Report

The patient was a 79-year-old woman who had undergone total hysterectomy, bilateral salpingo-oophorectomy, omentectomy, and adjuvant chemoradiation for stage IC of ovarian carcinoma at 38 years of age. She had no family history of breast or ovarian cancer. She was scrutinized at our hospital because of continuing abdominal discomfort. Laboratory tests revealed that the patient's sialylated carbohydrate antigen (Krebs von den Lungen-6 antigen; KL-6), thyroid stimulating hormone (TSH), and carbohydrate antigen (CA 125) levels were elevated, and her C-reactive protein (CRP) level was slightly elevated. Other laboratory findings, including her tumor marker levels, were within normal ranges.

On abdominal multi-detector computed tomography (MD-CT), a large tumor measuring 80 mm in diameter with internal necrosis was observed on the dorsal side of the pancreas (Fig. 1a). In addition, a tumor measuring 10 mm in diameter protruding from the outside on the surface of the liver was observed (Fig. 1b). The lesion on the dorsal side of the pancreas showed heterogenous enhancement and deeply invaded the surrounding blood vessels.

As an additional examination, we performed EUS using a forward oblique viewing echoendoscope (GF-UCT260®; Olympus Medical System, Tokyo, Japan). On EUS, a large hypoechoic mass on the dorsal side of the pancreas was observed, and the border of the mass to the pancreas was clear (Fig. 1c). After EUS, we performed EUS-FNB to obtain a specimen of the lesion through the gastric wall using a 22-G Franseen needle (Acquire®; Boston Scientific, Natick, USA). A histopathological analysis of the EUS-FNB specimens with Hematoxylin and Eosin (H&E) staining showed papil-

Department of Gastroenterology, Akita University Graduate School of Medicine, Japan
Received: June 25, 2020; Accepted: July 20, 2020; Advance Publication by J-STAGE: September 12, 2020
Correspondence to Dr. Mitsuru Chiba, chiba617@med.akita-u.ac.jp

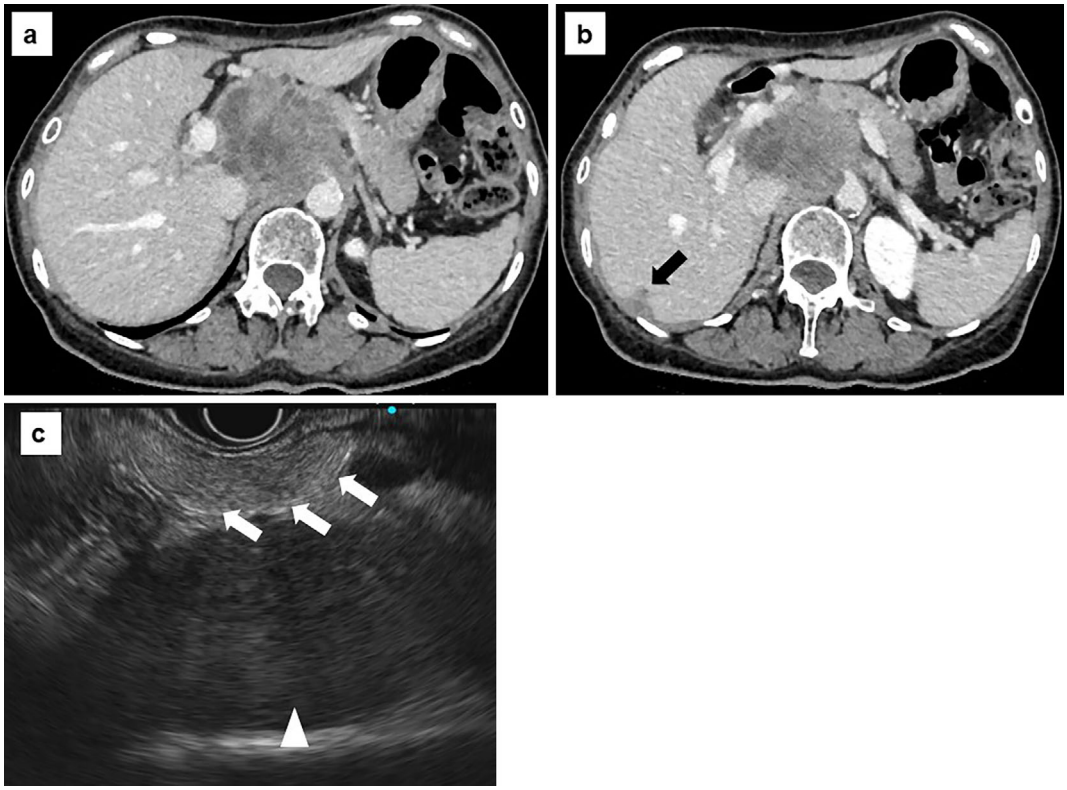


**Figure 1.** **(a) On abdominal multi-detector computed tomography (MD-CT), a large tumor measuring 80 mm in diameter with internal necrosis on the dorsal side of the pancreas was observed. This tumor showed heterogenous enhancement and deeply invaded the surrounding blood vessels. (b) On MDCT, a tumor measuring 10 mm in diameter protruding from the outside on the surface of the liver was observed (black arrow). (c) On endoscopic ultrasound (EUS), a large hypoechoic mass on the dorsal side of pancreas was observed, and the border of the mass with the pancreas was clear (white arrows: pancreas, arrowheads: tumor).**

lary tubular adenocarcinoma (Fig. 2a). The differential diagnosis between the primary pancreatic tumor and the metastatic retroperitoneal tumor was difficult based on this histopathological result.

Immunohistochemical staining was performed, which revealed that the tissue was positive for cytokeratin 7 (CK7), carbohydrate antigen 125 (CA125), and estrogen receptor (ER), and negative for cytokeratin 20 (CK20), carcinoembryonic antigen (CEA), progesterone receptor (PGR), carbohydrate antigen 19-9 (CA19-9), and hepatocyte nuclear factor 1β (HNF1B). In addition, weak positivity was noted only in the focal part for p53, and the Ki-67 index was 15%. The tumor was considered to be derived from ovarian carcinoma. We therefore compared the EUS-FNB specimen to the ovarian carcinoma specimen that had been surgically resected 41 years previously (Fig. 2b-g). We made a definitive diagnosis of late recurrence of ovarian carcinoma in the retroperitoneum because the immunohistochemical findings of the EUS-FNB specimen were identical with those of the surgical specimen. Chemotherapy was initiated for the treatment of epithelial ovarian carcinoma.

## Discussion

In almost all cases, recurrence of epithelial ovarian carcinoma occurs within eight years after primary therapy (1). Late recurrence after more than 20 years is a very rare event, with only a few cases reported (2-6) (Table). Late recurrence is considered to occur as a result of regrowth of ovarian cancer. Buller et al. hypothesized that recurrent ovarian cancers are distinguishable on the basis of a molecular genetic fingerprint and that some are actually new primary cancers of the peritoneum, rather than recurrent ovarian cancer (7). In this case, even though it was difficult to determine whether the lesion was recurrent or a primary cancer, recurrence was suspected based on the results of immunohistochemical staining. Very late recurrence is considered to relate to tumor malignancy and cell proliferation. Kurman et al. divided ovarian cancer into two groups of type I and type II (8). Type I tumors are slow-growing, whereas type II tumors are rapid-growing and characterized by a mutation in TP53 and a high level of genetic instability. In the present case, immunohistochemical staining of the EUS-FNB specimen showed that the tissue was weakly positive only in the focal part for p53, and the Ki-67 index

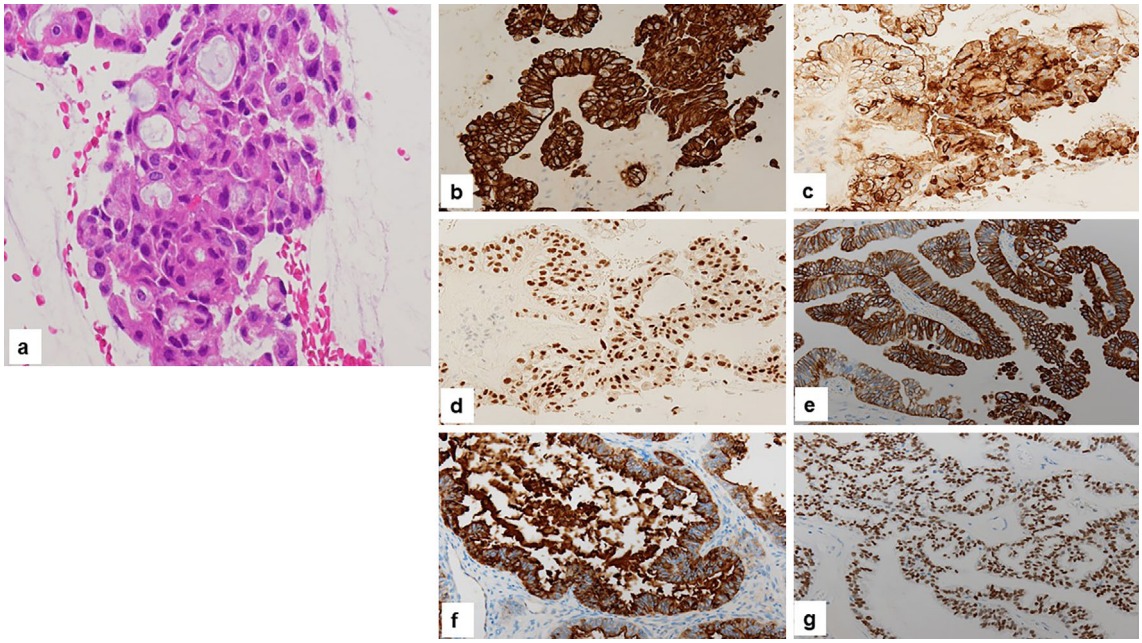


**Figure 2.** **(a) The histopathological findings of an endoscopic ultrasound-guided fine needle biopsy (EUS-FNB) specimens on Hematoxylin and Eosin staining showed papillary tubular adenocarcinoma. (b)-(g) Immunohistochemical staining of the EUS-FNB specimen and the surgical specimen. The tissue was positive for CK7 (b), CA125 (c), and estrogen receptor (d) on the EUS-FNB. The tissue was positive for CK7 (e), CA125 (f), and estrogen receptor (g) on the surgical specimen.**

**Table.** **Very Late Recurrence of Ovarian Carcinoma.**

| References | Stage | Time to recurrence (year) | Histological type |
|---|---|---|---|
| (2) | I | 25 | Serous |
| (3) | IC | 21 | Serous |
| | IIIC | 21 | Serous |
| | IIIC | 26 | Serous |
| (4) | III | 23 | Serous |
| (5) | IIIB | 28 | Serous |
| (6) | III | 29 | Serous |
| This case | IC | 41 | Serous |

was 15%. Based on these results, the tumor was considered low-grade serous ovarian cancer, which is type I, so it was conceivable that it took 41 years to relapse. However, we cannot completely deny the possibility that new ovarian cancer occurred after surgery for ovarian cancer. There may have been some genetic mutation, such as hereditary breast and ovarian cancer (HBOC). A BRCA1 or BRCA2 mutation carries a high risk of ovarian cancer, and the mean cumulative cancer risks for mutation carriers at 70 years old are 40% for BRCA1 and 18% for BRCA2 mutation carriers (9). However, there are few reports describing the association between BRCA1/2 mutations and the late recurrence of ovarian cancer. We did not analyze any gene mutations, but mutations in genes such as BRCA1 and BRCA2 should have been evaluated in order to elucidate the mechanism underlying the late recurrence despite this case having no family history of breast or ovarian cancer.

There are no previous reports of recurrence at more than 40 years after primary surgery. Usually, in the absence of recurrence, clinical follow-up is ended at 5 to 10 years after resection of a malignant tumor. Thus, very late recurrence may not be included in the differential diagnosis for such patients. For that reason, late recurrence should be kept in mind, no matter how many years pass. An accurate diagnosis of late recurrence enables us to carry out appropriate treatments, such as chemotherapy or radiation therapy.

The diagnosis of late recurrence of ovarian carcinoma is made based on surgical resection of recurrent lesions, such as metastatic lymph nodes (5). It is highly invasive to diagnose recurrence based on surgical resection. A biopsy guided by US or CT has been proposed as a less invasive method (10, 11). However, it is difficult to obtain specimens from deep lesions in the abdomen or pelvis using these methods. Thus far, the usefulness of endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) for the diagnosis of abdominal lymphadenopathy has been reported (12, 13). EUS-FNA has also been used to diagnose recurrence of gynecological tumors, including ovarian carcinoma (14). Recently, in EUS-FNA of pancreatic tumor, a 22-G Franseen needle for EUS-FNB was developed to allow larger tissue specimens to be obtained, and some reports have described the usefulness and safety of EUS-FNB (15, 16). Obtaining a larger amount of tissue led to an accurate histopathological diagnosis in the present case.

In this case, we initially suspected a pancreatic tumor and

metastatic retroperitoneal tumor based on the MD-CT and EUS findings and performed an EUS-FNB with a 22-G Franseen needle. Although a primary pancreatic tumor and metastatic retroperitoneal tumor were suspected based on the pathological findings of H&E staining, a definitive diagnosis was not reached. Additional immunohistochemical staining revealed that the specimen was positive for CK7, CA125, and ER; thus, ovarian carcinoma was suspected to be the primary lesion. Similarly to the EUS-FNB sample, the primary ovarian carcinoma that had been resected 40 years earlier was also immunohistochemically positive for CK7, CA125, and ER, and we were able to reach a definitive diagnosis of extremely late recurrence of ovarian carcinoma.

Larger tissue samples are required to make an accurate histological diagnosis, especially for immunohistochemical staining. There have been no reports showing the usefulness of an EUS-FNB using a Franseen needle for immunohistochemical staining to detect metastatic recurrence; however, El Chafic et al. reported that an EUS-FNB using another type of needle improved the diagnosis of gastrointestinal stromal tumors by immunohistochemistry (17).

Even in cases of late recurrence of diseases such as ovarian carcinoma, an EUS-FNB using a Franseen needle enables an accurate histological diagnosis to be made by obtaining a sample that is large enough to perform immunohistochemical staining, which ultimately enables the primary lesion to be accurately treated.

**The authors state that they have no Conflict of Interest (COI).**

## *References*


1. Dembo AJ. Controversy over combination chemotherapy in advanced ovarian cancer: what we learn from reports of matured data. J Clin Oncol **4**: 1573-1576, 1986.
2. Otsuka I, Shoji K. Paraaortic node recurrence 25 years after removal of epithelial ovarian carcinoma. J Obstet Gynaecol Res **42**: 1609-1612, 2016.
3. Zylberberg B, Dormont D, Madelenat P, Daraï E. Relapse after more than 20 years of follow-up for epithelial ovarian carcinoma. Obstet Gynecol **103**: 1082-1084, 2004.
4. Testelmans D, Van Raemdonck D, Amant F, De Wever W, Verbeken E, Nackaerts K. Late recurrent ovarian carcinoma metastatic to the thoracic wall. Acta Clin Belg **65**: 354-356, 2010.
5. Menczer J, Schreiber L, Peled O, Levy T. Very late recurrence (after more than 20 years) of epithelial ovarian carcinoma: case report and literature review. Arch Gynecol Obstet **291**: 1199-1203, 2015.
6. Inoue E, Yotsumoto T, Inoue Y, et al. Mediastinal metastasis from ovarian serous carcinoma 29 years after initial treatment. Respir Med Case Rep **29**: Article ID 101003, 2020.
7. Buller RE, Skilling JS, Sood AK, Plaxe S, Baergen RN, Lager DJ. Field cancerization: why late "Recurrent" ovarian cancer is not recurrent. Am J Obstet Gynecol **178**: 641-649, 1998.
8. Kurman RJ, Visvanathan K, Roden R, Wu TC, Shih IeM. Early detection and treatment of ovarian cancer: shifting from early stage to minimal volume of disease based on a new model of carcinogenesis. Am J Obstet Gynecol **198**: 351-356, 2008.
9. Chen S, Parmigiani G. Meta-analysis of BRCA1 and BRCA2 penetrance. J Clin Oncol **25**: 1329-1333, 2007.
10. Zikan M, Fischerova D, Pinkavova I, Dundr P, Cibula D. Ultrasound-guided tru-cut biopsy of abdominal and pelvic tumors in gynecology. Ultrasound Obstet Gynecol **36**: 767-772, 2010.
11. De Filippo M, Saba L, Azzali E, et al. CT-guided fine-needle aspiration of abdominal and retroperitoneal small lesions with the coaxial technique using MPR images. Acta Biomed **87**: 57-62, 2016.
12. Nakahara O, Yamao K, Bhatia V, et al. Usefulness of endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) for undiagnosed intra-abdominal lymphadenopathy. J Gastroenterol **44**: 562-567, 2009.
13. Tanisaka Y, Ryozawa S, Kobayashi M, et al. Usefulness of endoscopic ultrasound-guided fine needle aspiration for lymphadenopathy. Oncol Lett **15**: 4759-4766, 2018.
14. Subtil JC, Alcázar JL, Betes MT, et al. Gastrointestinal endoscopic ultrasound-guided fine-needle aspiration for assessing suspected deep pelvic or abdominal recurrence in gynecologic cancer: a feasibility study. J Ultrasound Med **38**: 761-765, 2019.
15. Mukai S, Itoi T, Yamaguchi H, et al. A retrospective histological comparison of EUS-guided fine-needle biopsy using a novel franseen needle and a conventional end-cut type needle. Endosc Ultrasound **8**: 50-57, 2019.
16. Bang JY, Hebert-Magee S, Hasan MK, Navaneethan U, Hawes R, Varadarajulu S. Endoscopic ultrasonography-guided biopsy using a franseen needle design: initial assessment. Dig Endosc **29**: 338-346, 2017.
17. El Chafic AH, Loren D, Siddiqui A, Mounzer R, Cosgrove N, Kowalski T. Comparison of FNA and fine-needle biopsy for EUS-guided sampling of suspected GI stromal tumors. Gastrointest Endosc **86**: 510-515, 2017.