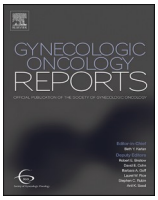
Gynecologic Oncology Reports 48 (2023) 101248

Contents lists available at ScienceDirect

Gynecologic Oncology Reports

journal homepage: www.elsevier.com/locate/gynor



High-grade endometrial stromal sarcoma with *YWHAE-NUTM2B* fusion gene abnormality identified after 10 years of recurrent pulmonary metastases: A case report

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1. Introduction

Endometrial stromal sarcoma (ESS) is the second most common type of uterine sarcoma, accounting for 1% and 15% of all uterine malignancies and malignant mesenchymal uterine tumors, respectively (Micci et al., 2021). ESS has undergone modifications since its 1996 proposal by Norris and Taylor resulting in its current classification. The World Health Organization (WHO) classifies ESS into low-grade ESS (LG-ESS), high-grade ESS (HG-ESS), and undifferentiated uterine sarcomas (WHO Classification of Tumours Editorial Board, 2020).

Heterogeneous mixtures of morphological and genetic features of LG-ESS and HG-ESS are distinct histopathological entities, and LG-ESS is more common than HG-ESS. Among these, LG-ESS is frequently diagnosed after hysterectomy (Sampath and Gaffney, 2011), has a slow recurrence course, and is typically treated with multidrug therapy. Particularly, hormonal therapy is effective as it generally expresses estrogen receptors (ERs) and progesterone receptors (PRs) (Reich and Regauer, 2007).

In contrast, HG-ESS has a poor prognosis, with a median overall survival (OS) and a 5-year OS rate of 19.9 months and only 32.6%, respectively, according to the National Cancer Database (Seagle et al., 2017). It is generally detected at an advanced stage, and effective adjuvant therapy has not yet been established.

Knowledge regarding tumors with unique genetic abnormalities has rapidly accumulated recently, and the disease concept of sarcoma has become more organized. HG-ESS, which was previously categorized under undifferentiated stromal sarcoma in the 2003 WHO classification, was re-classified in 2014 after the identification of the fusion YWHAE-NUTM2A/B t (10;17) (q22;p13). Additionally, HG-ESS is clinically aggressive, frequently associated with extrauterine disease, and reportedly has a median progression-free survival and an OS of 7–11 and 11–23 months, respectively (Pautier et al., 2014).

Patients with HG-ESS usually present with abnormal uterine bleeding, which is possibly associated with an enlarged uterus or pelvic mass with pain. These masses are histologically characterized by confluent permeative and destructive deep myometrial invasion, frequent necrosis, lymphovascular invasion, significant nuclear atypia, and mitotic activity of >10 cells per 10 high-power fields. Additionally, they consist primarily of high-grade rounded cells in sheets and irregular nests, with a minor low-grade fibromyxoid spindle cell component (WHO Classification of Tumours Editorial Board, 2020).

Complexes of *YWHAE-NUTM2* with both *BRAF/RAF1* and *YAP/TAZ* in HG-ESS are functionally relevant. Furthermore, these findings established that *YWHAE-NUTM2* regulates cyclin D1 expression and cell proliferation by dysregulating RAF/MEK/MAPK and Hippo/YAP-TAZ signaling pathways (Ou et al., 2021).

CD10, ER, PR, and cyclin D1 are the most suitable immunohistochemical markers for diagnosing these tumors (Hoang et al., 2017; Lee et al., 2012). Additionally, the rounded tumor cells may be variably intermixed with a minor low-grade fibromyxoid spindle cell component.

Although HG-ESS caused by *YWHAE-NUTM2A/B* gene fusion is generally reported to be progressive with poor prognosis, it may have a clinical course similar to LG-ESS. Here, we report an atypical case where a *YWHAE* gene abnormality was detected in a patient with a 10-year

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https://doi.org/10.1016/j.gore.2023.101248
Received 9 June 2023; Received in revised form 16 July 2023; Accepted 17 July 2023
Available online 19 July 2023

history of recurring pulmonary sarcoma, leading to the identification of the primary uterine ESS tumor and a favorable post-hysterectomy course.

2. Case presentation

A 43-year-old female patient presented to the thoracic surgery department with a pulmonary opacity that had been observed during a periodic medical examination. Computed tomography (CT) revealed a tumor in the right lower lobe of the lung (Fig. 1), and a malignant tumor was diagnosed after a CT-guided biopsy. Subsequently, the tumor was diagnosed as an unclassifiable small round cell sarcoma after partial resection.

Metachronous recurrences were found in the bilateral lungs 2 years later, and partial pulmonary resection was repeated. Ten years after the initial surgery, simultaneous bilateral lung recurrences were observed again, leading to the third round of partial pulmonary resections.

Although histology showed spindle-to-round cell sarcoma, suggesting several differential diagnoses including *BCOR-CCNB3* and synovial sarcomas, immunohistochemistry supported neither (Fig. 2A-E). Subsequently, fluorescence *in situ* hybridization for detecting *YWHAE* gene rearrangement was performed, and split signals were observed (Fig. 2F).

In this case, the patient was referred to our department because of the possibility of metastasis since *YWHAE* gene-abnormal sarcoma in adult females is extremely rare outside of gynecological organs. Additionally, uterine fibroids were detected since the lung lesions first appeared. As for the uterine fibroids, after the first pelvic MRI, the patient underwent outpatient follow-up every six months to confirm the lack of any symptoms due to the fibroids including abnormal bleeding, and that there was no sign of malignancy or tumor enlargement on ultrasound examinations. However, at this time, a polypoid mass was found in the uterus on preoperative MRI, showing an intermediate signal mass on a T2-weighted image with diffusion restriction (Fig. 3). Histopathological examination, the excision of a polypoid tumor protruding from the cervical os, and endometrial biopsy revealed findings similar to those of the lung tumor compatible with a high-grade sarcomatoid malignancy (Fig. 4A-F).

Subsequently, therapeutic total abdominal hysterectomy, bilateral salpingo-oophorectomy, and omentectomy were performed. Gross uterine findings showed an endometrium-covered polypoid lesion protruding into the uterine cavity in addition to the previously detected intramuscular uterine fibroids (Fig. 4G).

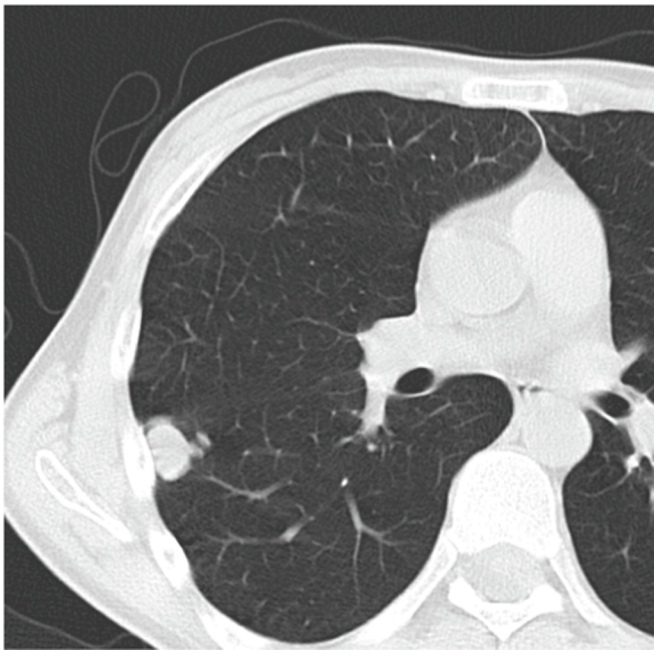

Fig. 1. Initial computed tomography finding of the lung. Computed tomography revealed a 2-cm-sized nodule in the right lower lobe of the lung.

Histological and immunohistochemical examination demonstrated spindle-to-round cell sarcoma almost identical to those of the lung tumors, while a low-grade ESS component not found in the lung lesions was focally observed (Fig. 4H). Based on similar histopathological findings between the lung and uterine lesions, the final diagnosis was HG-ESS with *YWHAE* gene alteration. However, no extrauterine lesions were observed. Therefore, to confirm the *YWHAE* fusion gene presence, we performed targeted RNA sequencing, which showed the *YWHAE-NUTM2A* fusion gene in lung and uterine lesions rather than in the fibroid (Supplemental data).

During the disease course, serum levels of lactate dehydrogenase (LDH), neuron-specific enolase, cancer antigen 125, cancer antigen 19–9, and carcinoembryonic antigen were within normal range. Patients with high-grade ESS are often recommended to receive adjuvant chemotherapy because of their aggressive clinical course and high risk of recurrence. However, the efficacy of systemic chemotherapy for these patients has not been established. After explaining to the patient that there were no metastases other than the resected lung lesions, complete surgery was performed, and owing to the complications associated with chemotherapy, the patient ultimately chose not to receive additional treatment.

Subsequently, the patient underwent outpatient follow-up every month for the first year after surgery, CT scans every 3 months, and PET-CT after 6 months; in the second year, outpatient follow-up was planned for every 2 months, with other imaging studies at intervals. Continued follow-up was planned for this patient for up to 10 years. After 18 months had passed since the patient's surgery, she had experienced an uneventful course without signs of recurrence.

3. Discussion

HG-ESS diagnosis is sometimes difficult, and the recent recognition of diverse genotypes suggests that some tumors classified as undifferentiated uterine sarcomas are misdiagnosed HG-ESS (Cotzia et al., 2019). *BCOR* immunohistochemistry is a useful marker to distinguish LG-ESS from HG-ESS, while molecular studies confirm HG-ESS diagnosis (Alkanat et al., 2022). However, *BCOR*-associated genes are unclear; this is particularly true regarding the presence of fusion genes, which we examined here.

In this case, after four recurrences of lung lesions, a specimen from a uterine lesion that had been considered a fibroma resulted in an HG-ESS diagnosis. Although HG-ESS reportedly has a poor prognosis, the patient had no further disease deterioration after repeated resections of the lung lesions for >10 years. The patient underwent outpatient consultations and MRI examinations at the gynecology department; however, no obvious malignant findings were observed during the disease course. However, identifying the peculiar gene fusion of the lung tumor enabled HG-ESS diagnosis, which involved the macroscopically benign polyp; therefore, if the patient had initially undergone a detailed gene screening, several lung surgeries could have been prevented.

Notably, no clinical or cytological evidence of malignancy was produced from MRI or blood tests during the patient's 10-year clinical course, making diagnosis more difficult.

Immunophenotyping is a method for diagnosing HG-ESS if a gene screening is too challenging. The absence of CD10, ER, and PR expression and the strong and diffuse presence of cyclin D1 staining are characteristic of the round cell component of *YWHAE-NUTM2* HG-ESS, while variable cyclin D1 staining and positive CD10, ER, and PR staining are considered low-grade components.

Regarding preoperative diagnosis, ESS is reportedly difficult to differentiate from myoma based on imaging findings (Yamaguchi et al., 2016). One study suggests that positron emission tomography-CT with a

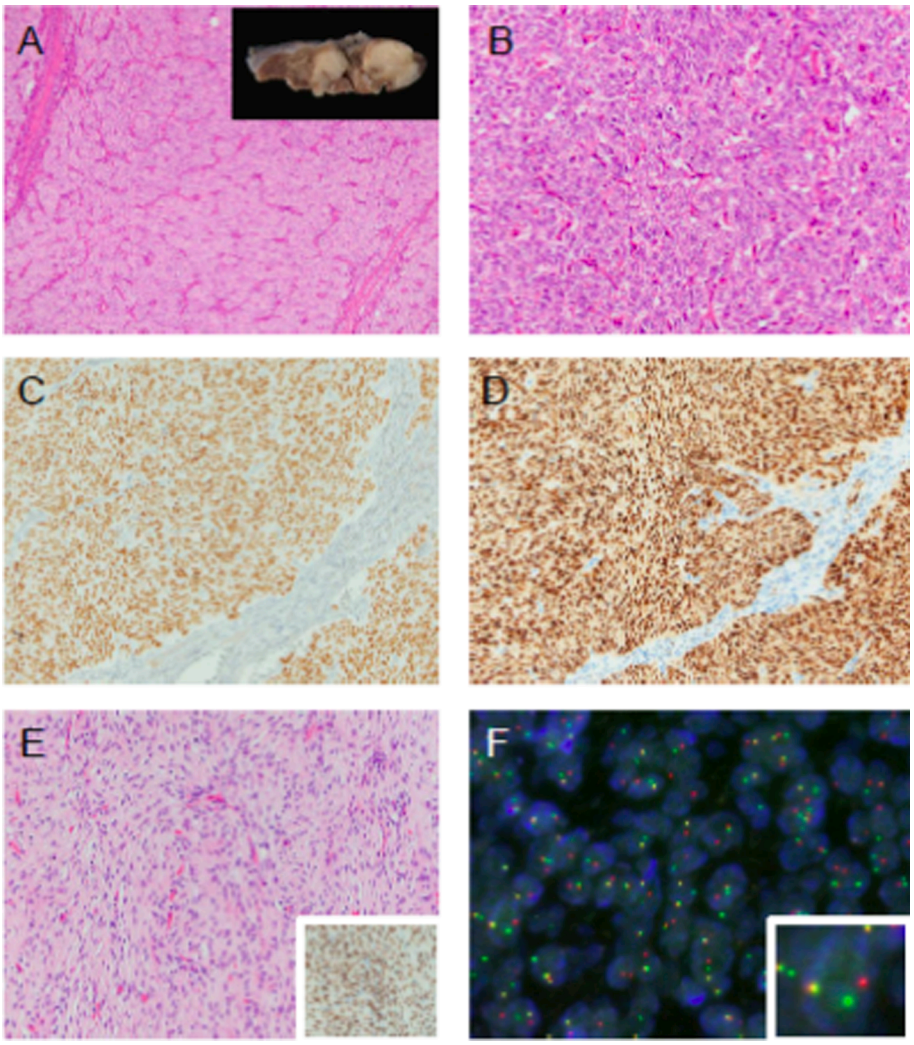

Fig. 2. Pathological findings of lung tumor. A-D: The lung tumor recurred repeatedly over 10 years with five lesions, of which four exhibited almost identical histological features. A: The tumor comprises spindle-to-round-shaped tumor cells that densely proliferate. B: Under high magnification, delicate blood vessels with slit-like lumina are observed throughout the tumor. The histological features suggest synovial or *BCOR-CCNB3* sarcoma as differential diagnoses. C, D: Immunohistochemical staining shows that the tumor cells are positive for *BCOR* and cyclin D1 while negative for CCNB3, SSX (C-term), SS18-SSX, SATB2, CD10, ER, PR, and NUT (C: *BCOR*, D: cyclin D1). This result excludes synovial and *BCOR-CCNB3* sarcomas as potential diagnoses. E: One of the recurrent lesions 10 years later shows slightly different histological features comprising spindle-shaped cells that primarily proliferate. Immunohistochemical staining reveals this tumor to be positive for ER and PR but negative for CD10 (inset, ER). F: Fluorescence *in situ* hybridization for *YWHAE* rearrangement shows split signals (inset, high magnification of split signal). Therefore, the diagnosis is *YWHAE*-rearranged sarcoma. ER: estrogen receptor; PR: progesterone receptor.

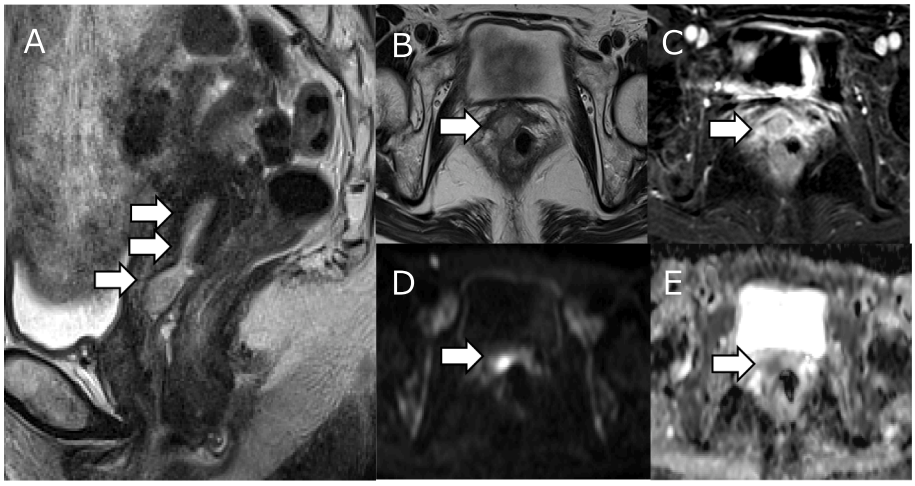

Fig. 3. Magnetic resonance imaging of the polypoid mass. A: sagittal and B: axial T2-weighted image showing an intermediate signal polypoid mass protruding from the anterior wall of the uterus to the vagina. C: Contrast-enhanced axial fat-saturated T1-weighted image shows the mass with moderate enhancement. D: Diffusion-weighted image (b = 800) and E: Apparent diffusion coefficient map shows diffusion restriction of the mass.

cut-off standardized uptake value max of 7.5 and serum LDH levels are useful in differentiating uterine fibroids from sarcomas (Kusunoki et al., 2017). However, data on ESS are limited, and preoperative imaging diagnosis is difficult. In our case, uterine fibroids were observed on initial pneumonectomy without malignant findings, suggesting that early diagnosis would have been difficult. The removed uterus was

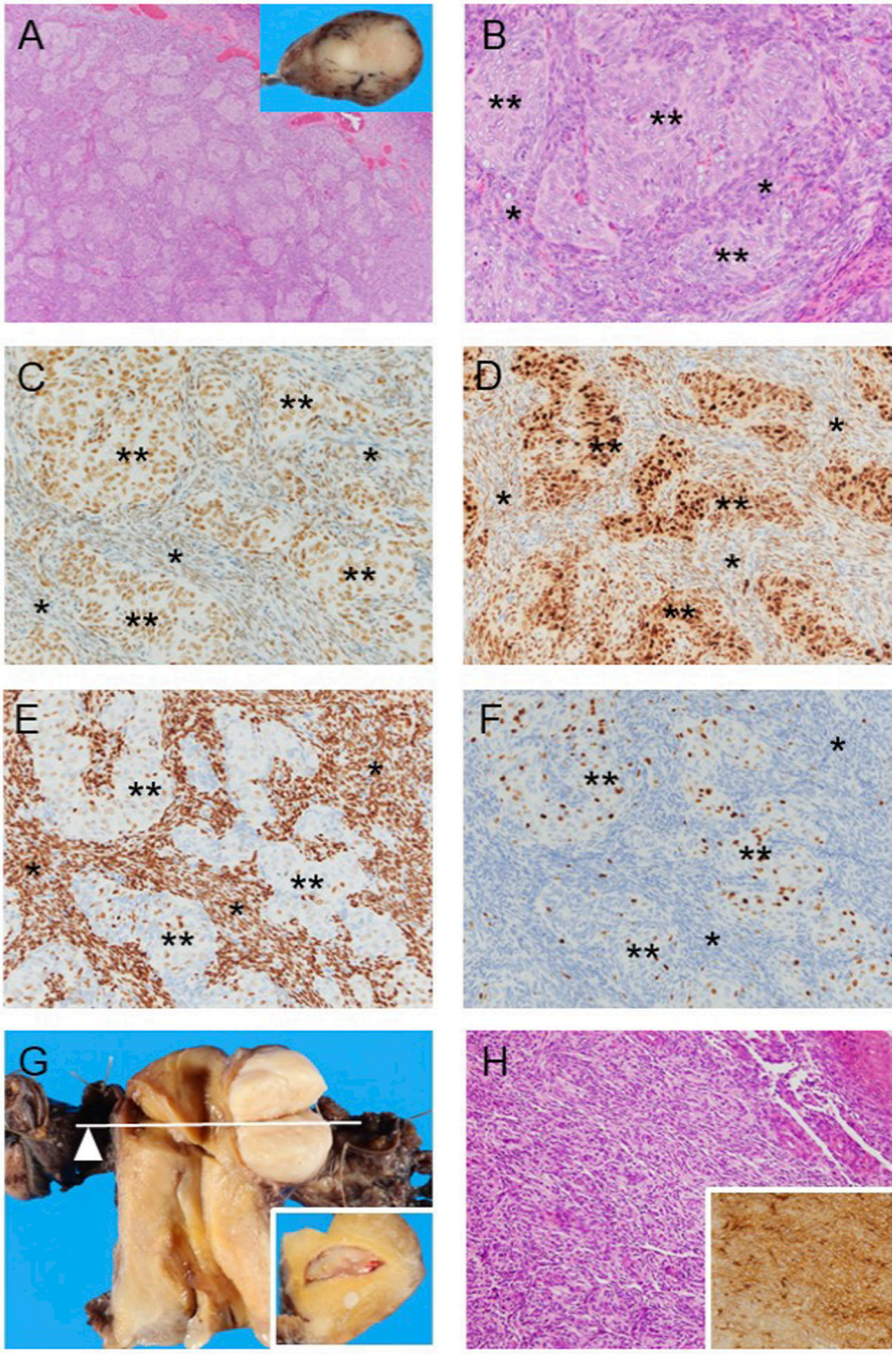

Fig. 4. Pathological findings of uterine polypoid tumor. A, B: The polypoid mass resected from the uterus shows a biphasic histological pattern and comprises an epithelioid component with round cells and a spindle cell component (A inset, gross finding of the polypoid lesion; B ** epithelioid component; * spindle cell component). C, D: The immunohistochemistry results are similar to those of the lung tumors. The epithelioid and spindle cell components are positive for *BCOR* and cyclin D1 but negative for CD10. ER and PR shows strong positivity in the spindle cell component, and Ki-67 positive cells are mainly observed in the epithelioid component (C: *BCOR*, D: cyclin D1, E: ER, F: Ki-67, ** epithelioid component; * spindle cell component). Based on these results, it is speculated that most of the metastatic lung tumors (Fig. 2 A-D) are metastases from the epithelioid component, whereas one metastatic lesion (Fig. 2 E) was from the spindle cell component. G: Macroscopic findings of the hysterectomy and bilateral salpingo-oophorectomy specimen. In addition to the intramuscular fibroid previously identified, a polypoid tumor protruding into the uterine cavity is observed (arrowhead, cut line of the inset figure; inset, polypoid tumor protruding into the uterine cavity). H: In the hysterectomy specimen, besides the residual tumor displaying a biphasic pattern (A-F), a low-grade endometrial stromal sarcoma immunohistochemically positive for CD10 is also observed (inset, CD10). This component is not observed in lung metastatic lesions.

obfuscated by multiple fibromas, complicating the diagnosis.

ESS may be intermingled with the diagnosis of uterine fibroids in our daily practice. However, in this case, it was preceded by a pulmonary sarcoma lesion of unknown primary cause. Therefore, we considered that the possibility of ESS should be investigated during examination of the primary lesion.

The recent rapid development and widespread use of genetic diagnostic techniques have led to the publication of many reports of molecular characteristics, which are essential for personalized chemotherapeutic protocol selection, particularly for HG-ESS. Although data on the treatment of these tumors are limited, one case series reported that HG-ESS tumors with the *YWHAE* rearrangement have substantial responsiveness to cytotoxic chemotherapeutic therapy (Hemming et al., 2017). New treatment prospects have also been reported based on these targets. First, a common feature of HG-ESSs is the strong expression of cyclin D1, which activates CDK4 kinase, promoting cells to pass through the G1/S checkpoint. Therefore, all available evidence suggests that targeting the Wnt pathway and downstream effectors—particularly CDK4 kinase— may benefit patients with HG-ESS or LG-ESS. For this case, we were considering Adriamycin for postoperative chemotherapy, and if that does not work or if the patient relapses, there is possible that hormone therapy or other off-label use like CDK4/6 inhibitors as a clinical trial could be an option. Another study reported that Ki-67 index staining may be a useful prognostic marker for ESS (Meng et al., 2022). However, cases of ESS, and particularly HG-ESS, remain rare. HG-ESS may coexist with uterine fibroids, as in this case, making differential diagnosis difficult. This case is a reminder of the importance of accurately diagnosing ESS; asymptomatic

uterine fibroids may not be treated with therapeutic intervention or prompt regular check-ups. Therefore, additional case series are needed to improve the differential diagnosis, identify poor prognostic factors, and determine evidence for effective treatment.

CRediT authorship contribution statement

Yuko Takahashi: Conceptualization, Data curation, Writing – original draft, Writing – review & editing. **Yoshinao Kikuchi:** Conceptualization, Data curation, Writing – original draft, Writing – review & editing. **Junji Mukaiyama:** Data curation, Writing – review & editing. **Shiori Watabe:** Data curation, Writing – review & editing. **Toshihiro Haga:** Data curation, Writing – review & editing. **Yuko Miyagawa:** Data curation, Writing – review & editing. **Asako Yamamoto:** Data curation, Writing – original draft, Writing – review & editing. **Yoshikane Yamauchi:** Conceptualization, Data curation, Writing – original draft, Writing – review & editing. **Haruko Hiraike:** Writing – review & editing. **Kenbun Sone:** Writing – review & editing, Supervision. **Yuko Sasajima:** Data curation, Writing – review & editing, Supervision. **Akihiko Yoshida:** Writing – review & editing, Supervision. **Kazunori Nagasaka:** Conceptualization, Data curation, Writing – original draft, Writing – review & editing, Supervision.

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.

Acknowledgments

All authors contributed to the article and approved the submitted version of the manuscript. The study was approved by the ethics committee of the medical faculty at Teikyo University Hospital.

***Informed** consent*

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

Funding

This work was supported by a Grant-in-Aid for Scientific Research C (grant no. 19K09834 to K.N.) from the Ministry of Education, Science, and Culture, Japan.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.gore.2023.101248.

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