

Exaggerated placental site in a cesarean scar: Misdiagnosed as gestational trophoblastic neoplasia: A case report

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Abstract. The present study reports a rare case of an exaggerated placental site (EPS) in a caesarean scar that was misdiagnosed as gestational trophoblastic neoplasia (GTN) by imaging, resulting in unnecessary surgical treatment. A 38-year-old woman underwent hysteroscopic resection of a cesarean scar pregnancy (CSP). The patient's serum β -human chorionic gonadotropin (β -hCG) level was elevated (76,196 mIU/ml) at the 24-day postoperative follow-up visit. On postoperative day 51, the patient experienced vaginal bleeding for three days and β -hCG levels were 2,799 mIU/ml. Ultrasonography and MRI revealed a heterogeneous mass and hypervascularity. The patient was diagnosed with a GTN in a cesarean scar and treated with methotrexate (MTX). β -hCG levels decreased after 3 MTX doses, but the mass did not change in size and was still hypervascular on imaging. Total hysterectomy was performed due to the serious side effects of chemotherapy and the lack of desire to preserve fertility. The histological findings supported the diagnosis of an EPS reaction. The present case is unique because of the rare intrauterine mass and possibility of retained trophoblastic changes causing EPS. EPS differs from GTN both clinically and pathologically and should be considered a possible diagnosis in any woman who has irregular bleeding following CSP resection.

Introduction

Gestational trophoblastic disease (GTD) covers a spectrum of disorders, which includes hydatidiform molar pregnancies, and neoplastic and neoplastic tumor-like lesions arising from trophoblasts (1). Gestational trophoblastic neoplasia (GTN) includes invasive moles, choriocarcinoma, placental site trophoblastic tumor (PSTT) and epithelioid placental site nodules (ETTs) (1). Exaggerated placental sites (EPSs) are rare neoplastic tumor-like trophoblastic lesions that occur in ~1.6% of terminations of pregnancy, as well as following normal pregnancy, ectopic pregnancy or molar pregnancy (2). Despite being associated with uterine bleeding and massive hemorrhage (2), EPS is generally described as an exaggerated physiological process that differs from GTN in that it involves villi and shows no confluent growth or mitosis (1). However, the clinical manifestations are similar, and it is, at times, difficult to distinguish EPS from GTN, particularly PSTT and choriocarcinoma. The importance of identifying EPS lies in the fact that GTN warrants surgical intervention and/or chemotherapy. Although a differential diagnosis algorithm between EPS and GTN for histological and immunohistochemical workup has been established (3), it remains ambiguous for certain cases due to the subjectivity of the assessment, and a definite diagnostic criterion has not been officially reported by the World Health Organization (1).

Cesarean scar pregnancy (CSP), occurring in 1.5% of women with previous cesarean scars, has shown an increasing prevalence in recent years (4). CSP refers to an early pregnancy in which a CSP is implanted on a prior cesarean scar defect, in which trophoblasts pathologically invade the myometrium (5). EPSs or GTNs secondary to cesarean scar are rare; however, both have been rarely reported (2,6). The current study presents a case of EPS occurring in a cesarean scar in a patient who underwent hysteroscopic resection and was misdiagnosed with GTN by postoperative imaging, including magnetic resonance imaging (MRI) and ultrasound, because of a heterogeneous mass and hypervascularity.

Case report

A 38-year-old G2P4 Cantonese woman was referred to Jinan University First Affiliated Hospital, Guangzhou, Guangdong,

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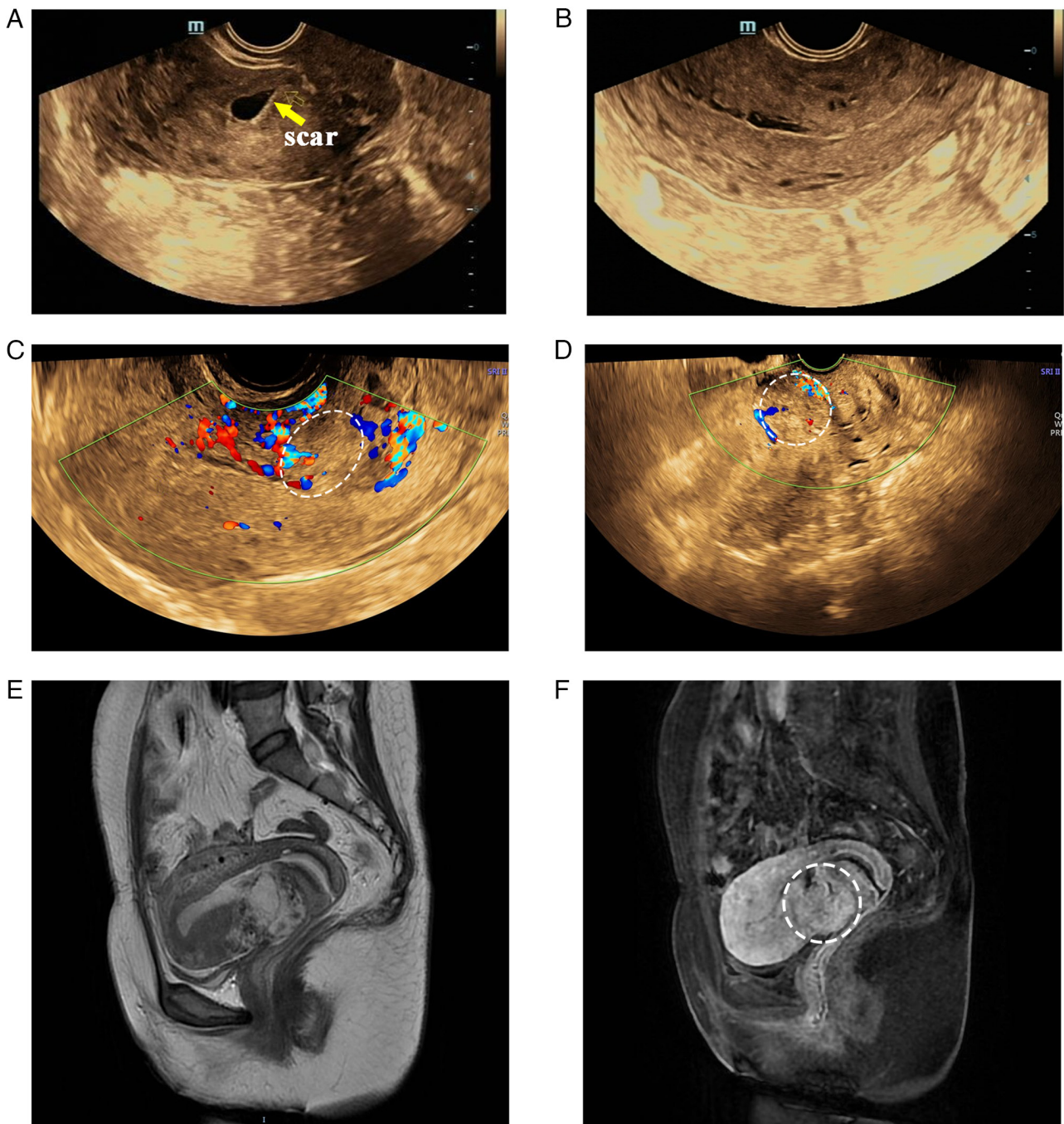


Figure 1. Imaging results. Ultrasonographic exam showing (A) a cesarean scar (yellow arrow) before the operation; (B) a widened uterine cavity in the lower segment at 24 days postoperatively; (C) a heterogeneous mass (dashed circle) and hypervascularity at 51 days postoperatively; (D) a shrunk lesion with reduced blood flow after three methotrexate treatments; (E) T1-weighted and (F) T2-weighted pelvic MRI confirming that the mass was 4.0x4.4x4.0 cm (white arrow) at 51 days postoperatively. MRI, magnetic resonance imaging.

China, because of suspected GTD in October 2022. Review of the patient's obstetric history revealed 1 prior miscarriage and 2 uncomplicated cesarean deliveries in 2012 and 2017. The patient had no remarkable past medical history, no additional past surgical history and no family history of malignancy.

The patient first visited Jinan University First Affiliated Hospital in August 2022, presenting with vaginal spotting and abdominal discomfort after amenorrhea for 37 days. Laboratory tests revealed elevated serum β -human chorionic gonadotropin (β -hCG) levels (22,200 mIU/ml) (normal, 217-71,380 mIU/ml) (UniCel DXI 800; Beckman Coulter, Inc.).

Ultrasound examination revealed a gestational sac located at the anterior part of the uterine isthmus within the previous hysterotomy site, which was diagnosed as CSP (Fig. 1A). The next day, a hysteroscopic resection was performed and the postoperative course was uncomplicated, with a decreased β -hCG level (17,965 mIU/ml) on the second postoperative day. At the 24-day postoperative follow-up visit, the patient's physical examination revealed no abnormalities except for elevated β -hCG levels (76,196 mIU/ml). During transvaginal ultrasonography (TVUS) examination, the uterine cavity in the lower segment was widened by 6 mm compared to normal

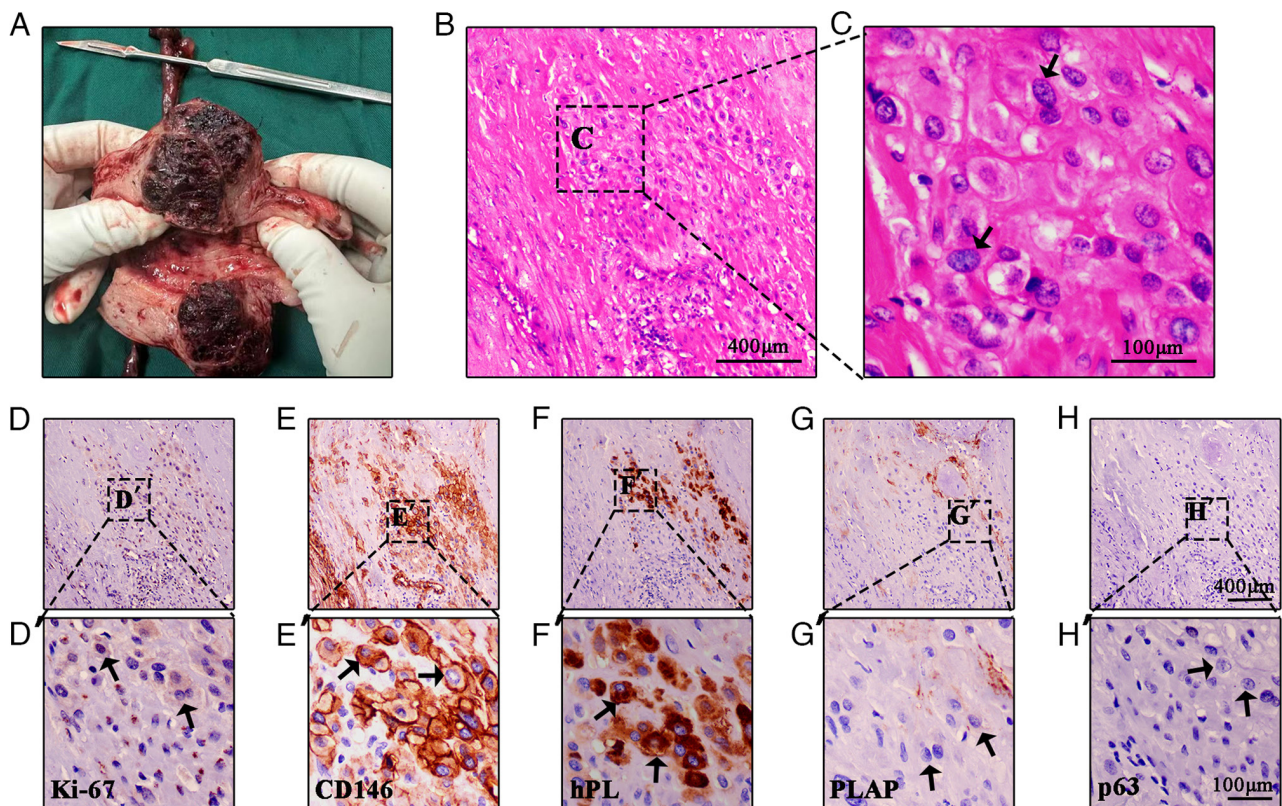


Figure 2. Macroscopic and microscopic findings. (A) Gross appearance of hysterectomy specimen. (B and C) H&E staining [scale bars, (B) 400 μ m and (C) 100 μ m]. Arrowheads indicate implantation site intermediate trophoblast cells. Immunohistochemical staining showed (D) weak positive of Ki-67 (5%), (E) strong staining of CD146 (100%), (F) strong staining of hPL (45%), (G) negative staining of PLAP and (H) negative staining of p63 in intermediate trophoblasts. Inserts: Higher magnification of the dashed boxed areas. Arrowheads indicate implantation site intermediate trophoblast cells (scale bars, 400 μ m in D-H and 100 μ m in D'-H'). H&E, hematoxylin and eosin; hPL, human placental lactogen; PLAP, placental alkaline phosphatase.

uterine cavity, No mass was detected in the wall of the uterus (Fig. 1B). The patient was encouraged to maintain close follow-up.

At 51 days postoperatively, the patient experienced vaginal bleeding for three days and was readmitted. β -hCG levels were 2,799 mIU/ml. TVUS showed a hypoechogenic tumor-like area, 5.8x2.7 cm in size, with unclear borders within the myometrium of the lower uterine segment, at the site of the previous cesarean section (Fig. 1C). The color Doppler image revealed an abundant blood flow signal (Fig. 1D). T1 and T2-weighted magnetic resonance imaging (MRI) (Discovery MR750 3.0T; GE Healthcare) further confirmed a heterogeneous mass in the previous cesarean scar, ~4.0x4.4x4.0 cm in size, surrounded by an enlarged and thickened vascular shadow (Fig. 1E and F). Based on these findings, a gestational trophoblastic tumor was suspected. Finally, a diagnosis of GTN (stage I, low risk) was made. The patient then received adjuvant single-agent chemotherapy with methotrexate (MTX, 20 mg/d) for 5 days (3 cycles). The serum β -hCG level decreased sharply to 8.5 mIU/ml 60 days after MTX treatment, and TVUS examination revealed that there was no change in the size of the hypoechogenic area. The patient requested hysterectomy due to the serious side effects of chemotherapy and no desire to preserve her fertility, and she ultimately underwent total laparoscopic hysterectomy and bilateral salpingectomy 76 days after MTX treatment. Intraoperative exploration revealed that the uterus

was enlarged and distorted, and there was a purple bulge in the anterior and inferior segments of the uterus. The dissected whole uterus including the lesion is presented in Fig. 2A. A 5x4x3 cm mass was observed in the lower uterine segment near the endocervix, which appeared to infiltrate almost the full thickness of the myometrium on both the anterior and posterior walls with a thin rim of intact myometrium. The mass appeared tough in texture with hemorrhage and necrosis indicated by a dark red color (Fig. 2A). The tissues were fixed in 10% (v/v) neutral buffered formalin for 24 h at room temperature, dehydrated in ethanol, cleared in xylene and embedded in wax, sectioned and stained with hematoxylin and eosin (H&E) at room temperature for 10 min. Serial sections (5 μ m) were also prepared for immunohistochemistry staining. The histopathological examination and immunohistochemistry staining was performed as previously described (5). However, histopathological examination revealed a few intact hydropic chorionic villi and intermediate trophoblast cell aggregation in the superficial myometrium (Fig. 2B and C). Intermediate trophoblasts had large eosinophilic cytoplasm and hyperchromatic nuclei of variable shapes and sizes, and were surrounded by calcification areas and a hyaline matrix with low Ki-67 (1:2,000 dilution; cat. no. 27309-1-AP; Proteintech Group, Inc.). Intermediate trophoblast cells were diffusely positive for CD146 [ready-to-use; cat. no. GT234602; GeneTech (Shanghai) Co., Ltd.] and human placental lactogen [hPL; ready-to-use, cat. no. GT220502; GeneTech (Shanghai) Co.,

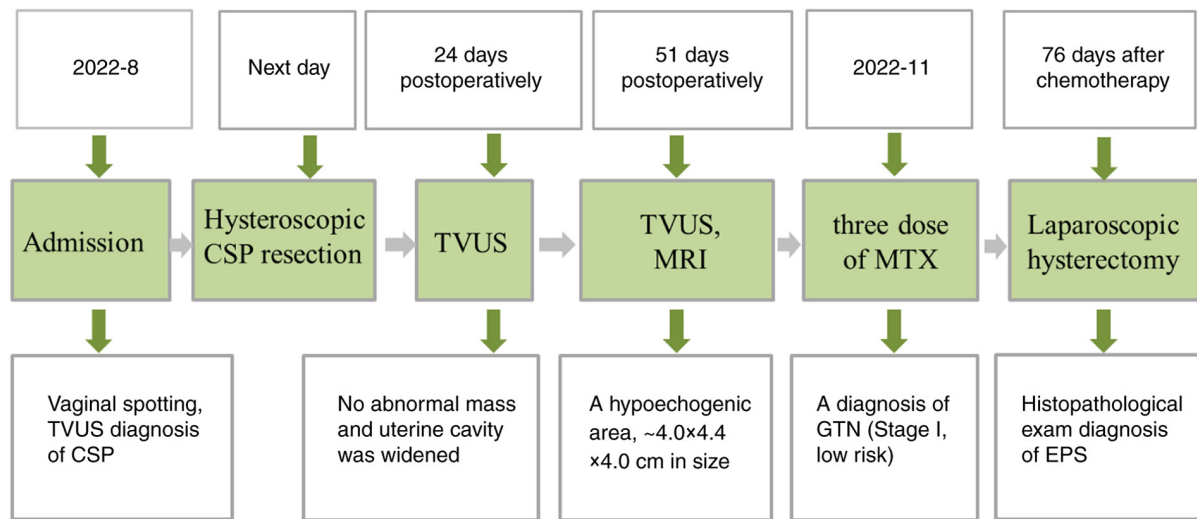


Figure 3. Timeline of events. CSP, cesarean scar pregnancy; GTN, gestational trophoblastic neoplasia; MRI, magnetic resonance imaging; TVUS, transvaginal ultrasonography.

Ltd.], but were negative for placental alkaline phosphatase (PLAP; ready-to-use; cat. no. GM719102; DaKo; Agilent Technologies, Inc.) and p63 (ready-to-use; cat. no. 790-4509; Ventana; Roche Diagnostics GmbH) (Fig. 2D-H). Based on the histological and immunohistochemical findings, the patient was diagnosed with EPS. The postoperative course was uneventful. The patient was discharged without any adjuvant treatment because she had a β -hCG level of 0.9 mIU/ml (normal, <5 mIU/ml) on postoperative day 7. There were no observable abnormalities. The β -hCG levels of the patient was checked every month and remained normal during the 12 consecutive month follow-up. The timeline of events is provided in Fig. 3.

Discussion

Although CSP is generally considered rare, its incidence has risen due to the high rate of cesarean section in recent years (5). CSP carries a risk for morbidly adherent placenta and further substantial postpartum hemorrhage, with a substantial risk of mortality and a risk of recurrence. Furthermore, the incidence of retained products of conception (RPOC), indicating the persistence of placental tissue, is greater in women with CSP than in those with intrauterine miscarriages (7). Thus, although hysteroscopic removal is used as an effective treatment, CSPs may occasionally be associated with complications due to continuous growth of the retained tissue (8). It was reported that 3.3% of GTNs are located in cesarean scars (9), with rare case reports on choriocarcinomas, PSTTs and ETs and a high rate of misdiagnosis (10). Indeed, it is crucial but challenging to make an acute diagnosis of GTN and tumor-like lesions by histology (10). For CSP choriocarcinoma, misdiagnosis can result in delayed treatment or even tumor metastasis (2). Early diagnosis and effective treatment remain key for the successful management of cesarean scar complications.

By contrast, there is no specific treatment for EPS, although follow-up of β -hCG levels is necessary. EPS may also be present in women with CSP and there are very few reports

describing the clinical course of EPS (10,11). The pathogenesis of EPS has not been clearly determined. It has been speculated that EPS is an exuberant infiltration of the endometrium and myometrium through the implantation site intermediate trophoblasts (ISITs), mainly due to decidual deficiency. In normal pregnancy, the decidua serves to not only limit the depth of trophoblast invasion by the secretion of a range of factors, but also facilitates the differentiation of trophoblasts to noninvasive giant cells. In addition, uterine myometrial destruction in cesarean scars is an important factor in the deep invasion of ISITs (12).

Histologically, EPSs have infiltrative borders and are composed of ISITs that are arranged on cords, nests and diffusers. Although reliable quantitative histological criteria are lacking, the course of GTN may be invasive and involve metastasis. The differential diagnosis of these lesions is made using immunohistochemical staining for p63, hPL and Ki-67 in addition to histological findings (1). PSTTs are positive for hPL while having a lower serum β -hCG level, often variable mitotic activity, the absence of villi and an elevated Ki-67 index (1). In the present case, a lower percentage of positive Ki-67 staining supported a diagnosis of EPS rather than of PSTT. Furthermore, a concurrent pregnancy and no mass in the myometrium are helpful for the diagnosis of EPS. However, under rare circumstances, EPS may exhibit unusual imaging features of heterogeneous masses and can cause diagnostic confusion. In the present case, the patient presented with irregular bleeding and increased β -hCG levels, and the possibility of EPS, PSTT or choriocarcinoma was considered. Although hysteroscopic resection was used to terminate the CSP, ultrasonography and MRI showed that the mass did not change in size and was still hypervascular; this was easily mistaken for GTN in cesarean scar. The treatment option was the administration of MTX with prolonged follow-up of β -hCG levels, since chemotherapy is a standard treatment option for GTN (13).

However, with the histological findings, including the proliferation of trophoblasts in the placental site with no mitotic activity, and a low Ki-67 labeling index, the

diagnosis of EPS was suitable (3). In fact, a correct diagnosis of EPS can be made and identified by routine histological and immunohistochemical examination (1). However, EPS has not received much attention in our department. In addition, hysteroscopic resection is not needed for the management of GTN (13). Since preservation of fertility was not desired, GTN was suspected, chemotherapy had serious side effects and total hysterectomy was performed, this may have been the reason for the misdiagnosis of GTN, leading to inappropriate surgical management.

In conclusion, the current study presented a rare case of EPS in a cesarean scar that was misdiagnosed as GTN by ultrasonography and MRI, resulting in unnecessary surgical treatment. EPS differs from GTN both clinically and pathologically and should be considered a possible diagnosis in any woman who has irregular bleeding following CSP resection. The Ki67 labeling index and the ISITs (hPL and CD146) are particularly useful in the differential diagnosis of an EPS from a GTN. The present case is unique because of the rare intrauterine mass and possibility of subsequent RPOC causing trophoblastic changes. EPS is difficult to diagnose without histopathological examination of hysterectomy specimens. Awareness of EPS and recognition of various types of trophoblastic diseases in women with cesarean scars are important for preventing misdiagnosis and guiding patient management, particularly in reproductive-age women who desire further pregnancies.

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Availability of data and materials

The data generated in the present study are included in the figures and/or tables of this article

Authors' contributions

ZC recruited the patient, obtained specimens and collected the images. HS and PL conceived the study, provided financial support and wrote the manuscript. MW analyzed the data and prepared the figures. BY and PY performed the histological analyses. HS and PL confirm the authenticity of all the raw data. All of the authors have read and approved the final manuscript.

Ethics approval and consent to participate

This study was approved by the Clinical Trial Ethics Committee of the Jinan University First Affiliated Hospital (Guangzhou, China; approval no. KY-2023-143).

Patient consent for publication

Written informed consent for publication of the case report and images was obtained from the patient.

Competing interests

The authors declare that they have no competing interests.

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