

An unusual mullerian carcinoma with myoepithelial differentiation (adenoid cystic carcinoma-like) of the ovary: case report

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Background: Adenoid cystic carcinoma (ACC) of the ovary is an extremely rare malignancy referred to eight cases in the literature. Here we report a new case of adenoid cystic carcinoma tumor of the ovary (Mullerian carcinoma with myoepithelial differentiation, adenoid cystic carcinoma-like). **Case:** The patient is 54-years old female with stage IIIC ovarian cancer treated with cytoreductive surgery and platinum-based adjuvant chemotherapy. During the subsequent follow-up period, the patient was diagnosed with a recurrence of the ACC of the ovary in the pelvis. She was treated with second-line palliative chemotherapy, including Carboplatin and Caelyx, a total of six cycles. The patient is alive 44 months since diagnosis. The prognosticators of survival are based on the previous 8 cases. The disease stage is the most crucial prognosticator for survival; other relevant factors to a worse outcome in ACC of the ovary are advanced age, residual tumor after initial surgery, and suboptimal cytoreduction. **Conclusion:** The best treatment currently is unknown; however, optimal cytoreduction surgery and platinum-based chemotherapy appear to be effective for the ACC of the ovary. Despite this tumor's intrusive nature, the prognosis can be improved if diagnosed early and treated.

Keywords

Carcinoma; Adenoid cystic; Ovarian neoplasms; Treatment; Prognosis

1. Introduction

Adenoid cystic carcinoma (ACC) typically arises in salivary glands and accounts for 10–15% of all salivary gland tumors with a peak incidence between the 4th–6th decades with a female preponderance [1]. They are slow-growing lesions with a propensity for local destruction, perineural invasion, multiple local recurrences, regional lymph node, distant metastasis, in keeping with an aggressive tumor. The occurrence of ACC in other organs is uncommon but has been reported in the female genital tract, specifically the uterine cervix and Bartholin's gland. ACC of the cervix accounts for less than 1% of cervical carcinomas and usually occurs in post-

menopausal women with frequent local recurrences and an aggressive disease course [2–4].

We report an unusual case of aggressive Mullerian carcinoma with myoepithelial differentiation (adenoid cystic carcinoma-like) of the ovary treated with cytoreductive surgery and platinum-based adjuvant chemotherapy. During the subsequent follow-up period, the patient was diagnosed with breast cancer, as well as recurrent ovarian carcinoma. This case report presents the pathological characteristics and the diagnostic and treatment challenges associated with this unusual case.

2. Case report

2.1 Clinical data and follow-up

A 54-year-old nulligravida female was admitted to the outpatient department due to abdominal discomfort, which she stated as having been present for a year. The initial CT and MRI of the abdomen and pelvis demonstrated bilateral heterogeneously enhancing solid ovarian masses, an ovoid retro-uterine mass, no retroperitoneal lymphadenopathy, and sigmoid colonic wall thickening (Fig. 1A–D). The CA-125 was elevated at 150 IU (standard <35 IU). The patient underwent a total abdominal hysterectomy, bilateral salpingo-oophorectomy, bilateral ureterolysis, sigmoid colon resection with side-to-side anastomosis, omentectomy, and bladder peritonectomy with optimal tumor debulking was performed. Intraoperatively, subcentimeter tumor deposits were noted in the pelvis and pouch of Douglas, no upper abdominal carcinomatosis or enlarged retroperitoneal lymph nodes were noted.

According to the International Federation of Gynecology and Obstetrics criteria (FIGO), the patient had stage IIIC ovarian cancer. After primary surgery, she received adjuvant chemotherapy with two Carboplatin/Taxol cycles

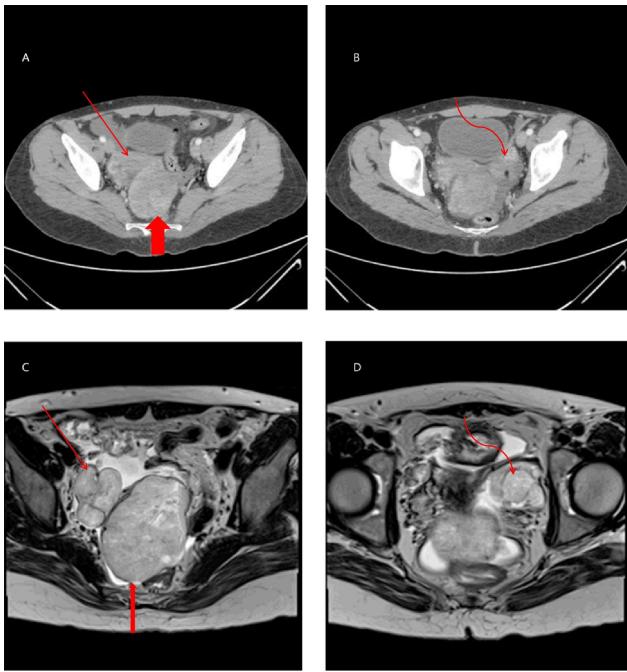


Fig. 1. CT (A,B) and MRI (C,D) of the pelvis. The bilateral ovarian and retro uterine masses demonstrate heterogeneous intermediate T2 signal, patchy diffusion restriction, as well as avid heterogeneous enhancement without internal fat or hemorrhage (C and D; AX T2). (A) Thin arrow: Right ovarian mass. Thick arrow: Retrouterine mass. (B) Curvy arrow: Left ovarian mass. (C) Thin arrow: Right ovarian mass. Thick arrow: Retrouterine mass. (D) Curvy arrow: Left ovarian mass.

and was changed to single-agent Carboplatin chemotherapy due to moderate to severe peripheral neuropathy. One year later, she was diagnosed with IC right breast invasive lobular carcinoma. She underwent wire-guided right lumpectomy and sentinel lymph node biopsy followed by adjuvant anti-estrogen therapy. Two months following breast surgery (20 months from initial diagnosis of ACC of the ovary), on routine CT of the abdomen and pelvis, recurrence of ACC of the ovary was found: pathologically enlarged inter-aortocaval node (3.2×1.7 cm), adenopathy along the left paracolic gutter (1.7×0.8 cm); nodal conglomeration/tumor deposit along the left pelvic sidewall (1.5×1.0 cm), and within the right hemipelvis (3.7×3.7 cm). CT head, chest, and bone densitometry revealed no evidence of metastatic disease. She was treated with second-line combination chemotherapy with Carboplatin and Caelyx. She completed 2 cycles, but due to hypersensitivity to Caelyx, it was switched to single-agent carboplatin, and she completed a total of six cycles. Six weeks post-chemotherapy, a follow-up CT scan of the abdomen and pelvis reported a complete recurrence resolution. One year after completion of recurrence treatment, routine CT of abdomen and pelvis (36 months from initial diagnosis) demonstrated interval enlargement of the inter-aortocaval node, which had regressed entirely after second-line chemotherapy, as well as the previously described bilateral pelvic sidewall lesions. These lesions were

not typical for high-grade serous ovarian carcinoma (HG-SOC) or low-grade serous ovarian carcinoma (LGSOC) but aggressive none less and maybe indicated unusual Mullerian origin malignancy.

There is no routine surveillance CT protocol for ovarian cancer at our institute. In this case, CT scan was done in six weeks and one year after completing the second-line chemotherapy. The patient was offered to consider third-line chemotherapy or observation as she was asymptomatic; however, the patient declined treatment for the time being. The patient is alive with a slow progression of the disease (44 months since diagnosis).

2.2 Pathologic findings

Examination of the specimen demonstrated bilateral solid, lobulated ovarian masses with a smooth surface, 8.3 cm (right) and 4.5 cm (left), multiple tumor nodules involving the right posterior uterine serosa (6 cm), pelvic wall (4.5 cm), bladder peritoneum (4.5 cm), posterior cul de sac (3.8 cm), sigmoid colon (multiple nodules up to 3 cm), and omentum (10 nodules up to 3.5 cm in size). The cut surface of the tumor was solid, pale tan with a small hemorrhagic area without cystic spaces or necrosis. Histology showed tubules, microcystic reticulated pattern, and cribriform nests with variable sized spaces lined by cells with mild to moderately enlarged hyperchromatic nuclei. Some spaces contained eosinophilic to mucoid secretions. The stroma was predominantly myxoid (Fig. 2). There were approximately 7 mitotic figures/10 hpf. There was no associated surface epithelial or sarcomatous component. This case highlights the distinct histologic features from classic ovarian tumors. The histomorphology, reminiscent of adenoid cystic like carcinoma of salivary gland tumor, raised a wide differential diagnosis which was excluded by appropriate immunohistochemical workup: (a) Metastasis from a primary salivary gland/head and neck tumor and gastrointestinal malignancy (*PAX8* and *CK7* positive, *CDX2* and *CK20* Negative), (b) High grade serous ovarian carcinoma (wild type expression with *p53*), (c) endometrioid ovarian carcinoma (*WT-1* positive, *ER*, *PR* negative), (d) mucinous ovarian carcinoma (*CDX2* and *CK20* negative), (e) sex cord-stromal tumor (*Inhibin A* and *FOXL2* negative), (f) germ cell tumor (alpha-fetoprotein, *OCT-3/4*, *CK5/6*, *p40* negative), (g) neuroendocrine tumor (*Synaptophysin* and *chromogranin* negative), and (h) mesonephric like carcinoma of the ovary (*ER*, *PR*, *CD10*, *calretinin*, *GATA-3*, and *TTF-1*). Variable positivity for desmin, *S-100*, and smooth muscle actin confirmed myoepithelial differentiation. Based on these morphologic and immunohistochemical features, as well as expert opinion, the case was given a diagnosis of Mullerian carcinoma with myoepithelial differentiation, adenoid cystic like. MMR protein expression was intact. It was negative for *BRCA 1* and *2* mutations, and the Illumina RNA fusion panel by next-generation sequencing failed to detect any diagnostic or actionable translocation, including *MYB* or *MYBL1* fusion seen in the salivary gland adenoid cystic carcinoma and *EWSR1* fusion seen in soft tissue myoepithelial tumor [2, 3].

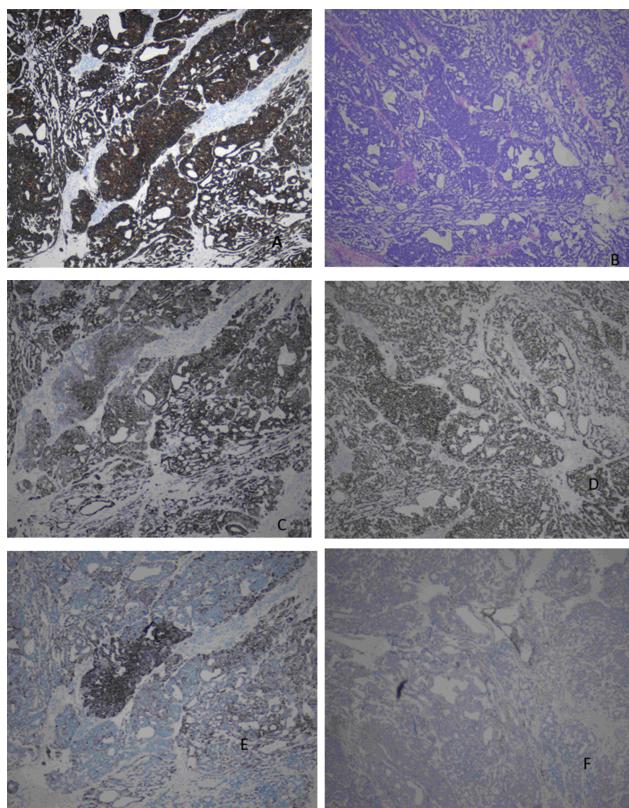


Fig. 2. Representative photomicrograph shows predominantly cribiform architecture with some areas. (B) showing microcystic reticulated appearance with prominent myxoid stroma. Nuclei show moderate nuclear pleomorphism with slightly prominent nucleoli. Neoplastic cells are positive for CD56 (A), WT-1 (C), CK-7 (D), Desmin (E), and PAX-8 (F).

3. Discussion

This case highlights the distinct histologic features from classic epithelial ovarian cancers. The histomorphology, reminiscent of adenoid cystic like carcinoma of salivary gland tumor, raised a wide differential diagnosis which included surface epithelial tumors with a variant morphologic pattern, mesonephric like carcinoma, sex cord-stromal tumor, germ cell tumor, adenoid cystic like carcinoma, and neuroendocrine tumor. Metastasis from a primary salivary gland/head and neck tumor and gastrointestinal malignancy was also considered but thought to be less likely given the targeted panel confirmed Mullerian lineage (*PAX8* positive). A broad immunohistochemistry panel excluded: High grade serous ovarian carcinoma (wild type expression with *p53*), endometrioid carcinoma (*WT-1* positive, ER, PR negative), mucinous ovarian carcinoma, metastasis from colon carcinoma (*CDX2* and *CK20* negative), sex cord-stromal tumor (*Inhibin A* and *FOXL2* negative), germ cell tumor (*alpha-fetoprotein*, *OCT-3/4*, *CK5/6*, *p40* negative), and neuroendocrine tumor (*Synaptophysin* and *chromogranin* negative). These histological features can be seen in recently described mesonephric-like carcinoma of the ovary. However, our case was negative for ER, PR, *CD10*, calretinin, *GATA-3* and *TTF-1*; hence there is no objective immunophenotypic

support for mesonephric-like carcinoma of the ovary. Variable positivity for desmin, S-100, and smooth muscle actin confirmed myoepithelial differentiation, which also argues against mesonephric-like carcinoma. Based on these morphologic and immunohistochemical features, as well as expert opinion, the case was given a diagnosis of Mullerian carcinoma with myoepithelial differentiation, adenoid cystic like.

Ovarian ACC is a rare tumor with approximately eight cases reported in the literature (Table 1). Eichhorn and Scully first reported this entity in 1995 and described six cases with a mean age at presentation of 67 years (range 60–78 years), average tumor size of 9.4 cm (range 2–18 cm), and stages IA-IIIC [4]. Fezco *et al.* [5] and Zamecnik *et al.* [6] reported two cases in 45- and 23-year-old females with stage 1A lesions, 9.5 and 6 cm, respectively. Of all these eight cases, three demonstrated primary ovarian ACC-like morphology, and five cases were comprised of two distinct components, surface epithelial and ACC-like, in a variable proportion. The surface epithelial part was either adjacent to or interspersed with the ACC-like component. In two cases, the predominant surface epithelial component consisted of invasive low-grade serous carcinoma (75%), in two cases, endometrioid carcinoma (5 and 25% respectively), and one case of mixed clear cell/endometrioid carcinoma (75%). The FIGO grade of associated endometrioid carcinoma in these cases was not described. Histologically, the ACC-like pattern comprised tubules, nests, and sheets of small, uniform cells surrounding multiple round lumens, and cysts containing mucoid, hyaline material, or hyaline stromal cylinders between rows and nests of epithelial cells. In these three-case series and case reports, the IHC staining was limited and was performed on 4 cases. Neoplastic cells were positive for pan cytokeratins AE1/AE3, CAM 5.2. In two of four cases, the tumor cells were focally positive for S-100 and muscle-specific actin. Electron microscopic examination was performed in the only case and showed rare, scattered-dense cells located around the periphery of the nests. These cells had convoluted nuclei and cytoplasm and contained poorly preserved microfilamentous structures and dense peripheral bodies. These findings were thought to be suggestive of myoepithelial differentiation. Eichhorn and Scully [4] noted that all but one of the tumors had an associated surface epithelial component that was adjacent to or intermingled with the adenoid cystic component, suggesting that adenoid cystic like carcinoma of the ovary has an atypical growth pattern in surface epithelial tumors.

Furthermore, the coexistence of such associations may suggest a common cellular origin. Our case did not have an associated surface epithelial component, and all the cells were diffusely positive for *PAX8*, in keeping with Mullerian lineage. ACC of the cervix and vulva occurs in pure form or as carcinoma with mixed differentiation. In some case reports and series, ACC of the cervix has been shown to occur simultaneously with squamous cell carcinoma (SCC) and the

Table 1. Published cases of adenoid cystic carcinomas of the ovary [4–6].

| Case No | Age (yr) | Tumor size (cm) | Ovarian lesion (unilateral/bilateral) | Surgery | Other organs involved | Stage | Associated histologic pattern | Adjuvant (chemotherapy) | treatment | Overall survival |
|------------|----------|-----------------|---------------------------------------|---|-----------------------------------|-------|---|--|-----------|-------------------|
| 1 [4] | 65 | 9 | bilateral | Partial BSO | omentum, peritoneum bladder | IIIC | none | unknown | | unknown |
| 2 [4] | 71 | 18 | unilateral-left | TAH, BSO, omentectomy, peritoneal biopsies | none | IA | invasive low-grade serous carcinoma in SBT (75%) | Chlorambucil, number of courses is unknown | | 3 years 1 month |
| 3 [4] | 60 | 2 | unilateral-right | TAH, BSO, omentectomy, peritoneal biopsies | left fallopian tube | IIIC | Endometrioid carcinoma <5%, sarcomatoid in recurrence | 12 cycles cisplatin, cyclophosphamide, and doxorubicin | | 10 years 3 months |
| 4 [4] | 68 | 12.5 | unilateral-left | TAH, BSO, omentectomy, PBs | omentum, peritoneum | IIIC | mixed clear cell/endometrioid (75%) | 6 cycles cisplatin and cyclophosphamide | | 1 year 1 month |
| 5 [4] | 78 | | unilateral ovarian mass | TAH, BSO, LND | metastasis to femoral lymph nodes | IIIC | endometrioid carcinoma | unknown | | 11 years |
| 6 [4] | 61 | 5.5/5.2 | bilateral | TAH, BSO, omentectomy, cholecystectomy, PBs | omentum, peritoneum | IIIC | invasive low-grade Serous carcinoma | yes | | 2 years 3 months |
| 7 [5] | 45 | 9.5 | unilateral-left | LSO | none | IA | none | no | | >7 years |
| 8 [6] | 23 | 6 | unilateral-left | LSO | none | IA | none | no | | >11 months |
| 9 our case | 54 | 8.3/4.5 | bilateral | TAH, BSO, bowel resection, omentectomy, PBs | omentum, peritoneum | IIIC | none | 2 cycles carboplatin/Taxol cycles, and 4 cycles carboplatin. | | >3 years alive |

Abbreviations: TAH, total abdominal hysterectomy; LND, lymph node dissection; BSO, bilateral salpingo-oophorectomy; LSO, left salpingo-oophorectomy; PBs, peritoneal biopsies.

integration of high-risk HPV DNA in both ACC and SCC components, suggesting a role HPV in the development of ACC [7]. Furthermore, cervical ACC with mixed differentiation was associated with high-risk HPV compared to pure ACC of cervix and vulva, representing a distinct entity [8]. Similar results were reported in a recent study of 15 cases of SCC with mixed ACC, using IHC and molecular studies [9]. These data suggest that in cervical mixed SCC/ACC are related to high risk-HPV and most likely represent the morphological mimics of salivary ACCs rather than a collision tumor. Besides, these lesions did not express myoepithelial phenotype or the MYB-NFIB gene translocation. Cytogenetic and molecular studies of breast and head and neck ACC have reported a reciprocal translocation between the terminal part of the long arm of chromosome 6 in *MYB* and the short arm of chromosome 9, within nuclear factor I/B (NFIB), resulting in a novel oncogenic fusion protein *MYB-NFIB* [2, 5]. A subset of pure vulva (Bartholin's gland) ACC is reported to harbor *MYB-NFIB* fusion transcripts suggesting a different entity than mixed HPV positive carcinoma of the cervix [6, 8]. In our case, the Illumina RNA fusion panel by next-generation sequencing failed to detect any *MYB-NFIB* and any other translocations or actionable mutations.

The data is limited in ovarian ACC. There are only three cases of pure ACC like carcinoma of the ovary, including our case. It may be quite possible that our case may also represent one of the five histologic types of ovarian carcinoma, probably low-grade serous carcinoma or endometrioid carcinoma with mimics of salivary ACC and aberrant immunophenotype, or it could represent a pure form of ACC.

ACC of the salivary glands is generally a locally aggressive tumor with a high propensity for local recurrence and distant metastasis [10]. Management of salivary adenoid cystic adenocarcinoma depends on the stage of the disease. Patients with an early stage I/II with resectable tumor undergo surgical treatment, while patients with an advanced stage III/IV will undergo radiotherapy or chemoradiotherapy as an initial treatment. Postoperative radiotherapy is used in patients with high-risk factors as an adjuvant treatment. As the disease is rare, there is no enough evidence on the efficacy of chemotherapy in patients with an advanced stage of the disease [11].

Similarly, ACC of the Bartholin gland and cervix are also locally aggressive with a poor prognosis. Mixed carcinoma of the cervix with SCC/ACC-like histology did poorly compared to SCC histology alone [12, 13]. A high risk of recurrence and mortality in cervical ACC was associated with large tumor size, deep stromal invasion, and lymphovascular invasion. The outcome in advanced disease (stage III and IV) had been reported to be invariably poor. Among the eight ovarian ACC cases reported in the literature, those with a localized tumor (FIGO stage I) had an excellent overall survival. Cases with poor overall survival were FIGO stage III with spread to peritoneum and omentum. Besides, most ovarian ACC had an associated second malignant surface epithelial

component (endometrioid, or invasive low-grade serous carcinoma). Given the paucity of literature, it is challenging to assess the ACC-like component's additional impact on overall survival. However, it appears that stage at presentation rather than histotype is predictive of overall prognosis. Spiro and Huvos [14] did not consider the histological features of salivary gland ACC as significant predictors of clinical behavior. However, clinical factors such as stage, tumor size, and lymph node involvement were more predictive of distant metastasis and ultimate prognosis.

Traditionally, epithelial ovarian cancers (EOCs) patients are being treated with primary surgery followed by adjuvant systemic treatment and, in some cases, neoadjuvant chemotherapy followed by surgery. ACC like carcinoma of the ovary is extremely rare, and there are no guidelines for treatment. It is very likely that these rarer subtypes of EOC are distinct entities and may not respond as well to standard treatment approaches and warrant further investigation for novel therapies. ACC of the cervix and vulva are rare neoplasms, and limited data shows that ACC of the cervix is treated as squamous cell carcinoma of the cervix. Standard treatment is surgery if the tumor is resectable, and radiotherapy usually is used as adjuvant treatment for high-risk features (positive margins). Radiotherapy is also used to treat local recurrence as these tumors tend to recur locally and develop metastatic diseases over time. Chemotherapy is also used in recurrence or metastatic disease; however, no significant effects were noticed [13, 15]. ACC of the vulva are also treated as squamous cell carcinoma of the vulva; however, ACC of the vulva more frequently has positive margins after surgery, and wider excisions of margins are needed. Radiotherapy is used in an adjuvant setting. In the case of local recurrence of the disease or regional metastatic disease, radiotherapy has been used. Chemotherapy for ACC of the vulva is palliative [16, 17]. In our case, the patient presented with stage IIIC disease, and in the absence of clinical guidelines and rarity of ACC of the ovary, the patient was treated similarly to high-grade serous carcinoma with an expectation of a good prognosis. Approximately 20 months after the initial diagnosis, our patient had a recurrence of the disease in the pelvic and para-aortic lymph nodes, which recurred again after responding to second-line systemic chemotherapy.

4. Conclusions

In summary, ACC of the ovary is an extremely rare tumor characterized by advanced stage at presentation, frequent local recurrences, and poor prognosis. Based on limited studies of cervical and Bartholin gland ACC, optimal treatment is cytoreduction surgery and radiotherapy. The majority of the data exists for salivary gland ACC, and treatment is cytoreduction surgery and radiotherapy. In our case, adenoid cystic carcinoma of the ovary was treated with debulking surgery and platinum-based chemotherapy. However, the patient had a recurrence of the disease 20 months after the initial diagnosis and again was treated with platinum-based

chemotherapy. She had complete radiological regression of the disease. As it can be seen, in this case, adenoid cystic carcinoma of the ovary was treated with debulking surgery and platinum-based chemotherapy, which appears to be effective. If the disease continues to progress after the third line of treatment, it will decrease the patient's overall five-year survival rate. Apart from chemotherapy, radiation therapy could be performed as part of subsequent treatment. Despite the unclear but aggressive nature of this tumor, the prognosis can be improved if the clinician can be made aware of the diagnosis and be more vigilant in follow-up, using imaging early when suspicion exists. Overall five-year survival varies with FIGO stage, recurrence time, and treatment options.

Author contributions

AA and RajC conceived of the presented idea. AA focused on the clinical part. RicC performed the pathology part. JG performed the imaging part and provided pictures with the description. CHL reviewed pathology slides and described them. AA encouraged MK to investigate literature on adenoid cystic carcinomas and supervised the findings of this work. RC was responsible for editing the manuscript. All authors discussed the results and contributed to the final manuscript.

Ethics approval and consent to participate

The patient has consented to the submission of the case report for submission to the journal.

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Conflict of interest

The authors declare no conflict of interest.

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