



# Malignant gastrointestinal neuroectodermal tumor, presenting as a second malignancy after gastric adenocarcinoma: a case report and literature review

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**Abstract:** Malignant gastrointestinal neuroectodermal tumor (GNET), is a rare soft tissue sarcoma. Here we report a case of GNET arising in the intestine of a 33-year-old female, who had been treated for gastric adenocarcinoma with surgery and chemotherapy at the age of 19, in 2001. Since then, she underwent follow-up care annually and kept disease free. Nevertheless, in 2015 she presented with vomiting and was found to have a mass in the small intestine. Surgical excision was performed. Histologically, the tumor was characterized by polygonal cells with clear or eosinophilic cytoplasm, and variably scattered osteoclast-like multinucleated giant cells. Immunohistochemically, the tumor cells showed diffuse and strong expression for S100, but AE1/AE3 cytokeratin, HMB-45 and Melan-A were negative. Genetically, *EWSR1* gene rearrangement was detected by fluorescence in situ hybridization (FISH). All these alterations were different from primary gastric adenocarcinoma. Moreover, the tumor gave metastases to ileal mesentery and lung in 1 and 4 years later, respectively. In summary, this is the first report of primary intestinal GNET with multiple metastases in a young woman who had a known history of chemotherapy for gastric adenocarcinoma. In consistence with previous literature, which reported a secondary GNET following chemotherapy for hepatoblastoma, we speculate that the chemotherapy might trigger the rearrangement of *EWSR1* and then promote the tumorigenesis of GNET.

**Keywords:** Gastrointestinal neuroectodermal tumor (GNET); gastric neoplasms; secondary primary

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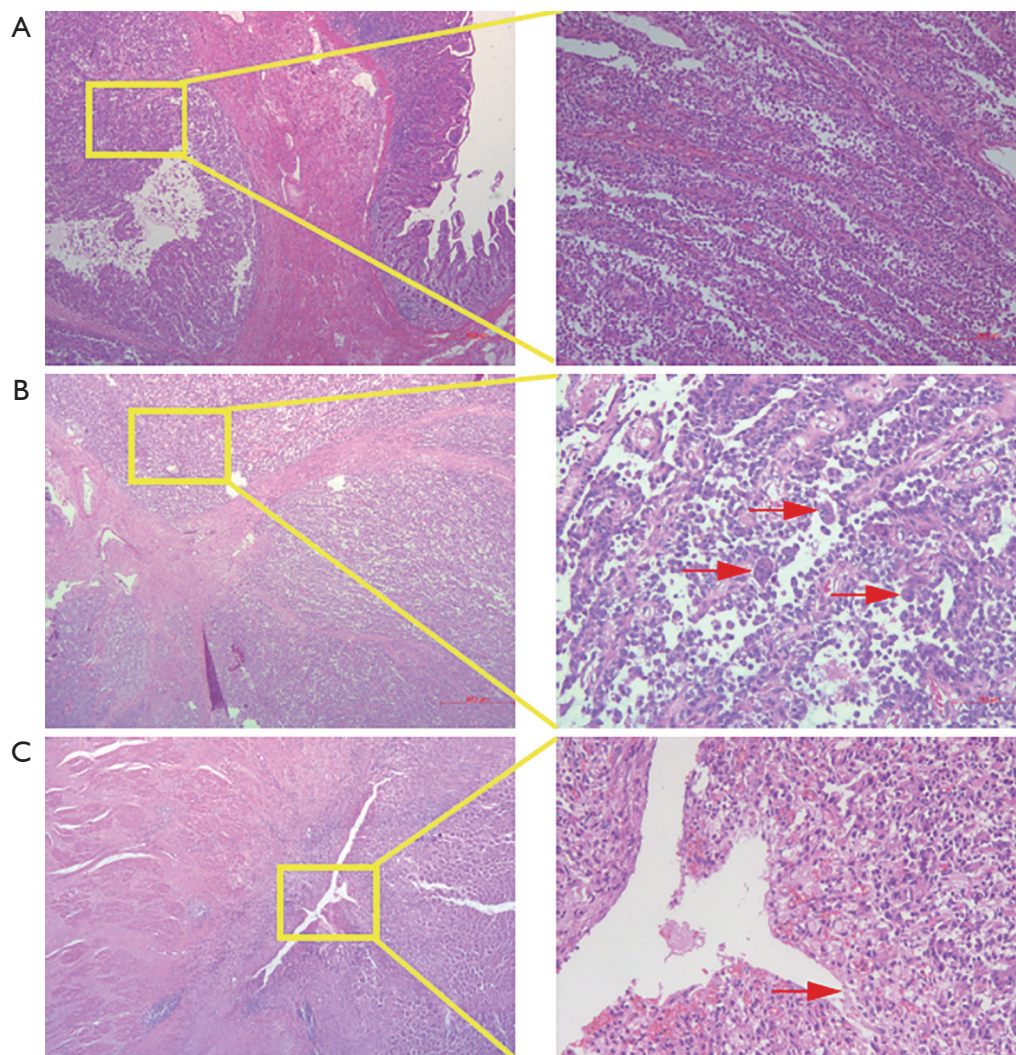
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## Background

Malignant gastrointestinal neuroectodermal tumor (GNET), previously known as clear cell sarcoma-like tumor of the gastrointestinal tract (CCSLT-GT), is a rare mesenchymal tumor mainly occurring in gastrointestinal tract (1). In 1985, a tumor in jejunum characterized as “malignant neuroendocrine tumor with osteoclast-like giant cell” was firstly reported (2). Then in 2003, six cases of clear cell sarcomas in gastrointestinal tract were collected and its common features of pathological entity were concluded (3). Microscopically, it is characterized by epithelioid cells with clear or eosinophilic cytoplasm that

grow in nest and presence of osteoclast-like giant cells. Immunohistochemically, it usually shows diffuse and strong reactivity for S100 and is negative for cytokeratin, HMB-45, A103. Recently, the translocation of *EWSR1* has been documented, and identification of this genetic derangement is useful for diagnosis. Biologically, GNET is extremely malignant and prone to local recurrence and metastasis (4). Nevertheless, its etiology is still not clear. Here we described a case of a 30-year-old woman, who received chemotherapy for gastric adenocarcinoma and subsequently developed a new neoplasm of GNET in the small bowel wall.



**Figure 1** HE staining showed the morphology of GNET. (A) GNET located under the ileum mucosa, arranging in pseudopapillary pattern (left 40 $\times$ ; right 200 $\times$ ); (B) osteoclast-like multinucleated giant cells (red arrow) were seen in GNET (left 40 $\times$ ; right 200 $\times$ ); (C) the gastric tumor was poorly differentiated adenocarcinoma (left 40 $\times$ ; right 200 $\times$ ) with ring-like cells (red arrow). HE, hematoxylin and eosin; GNET, gastrointestinal neuroectodermal tumor.

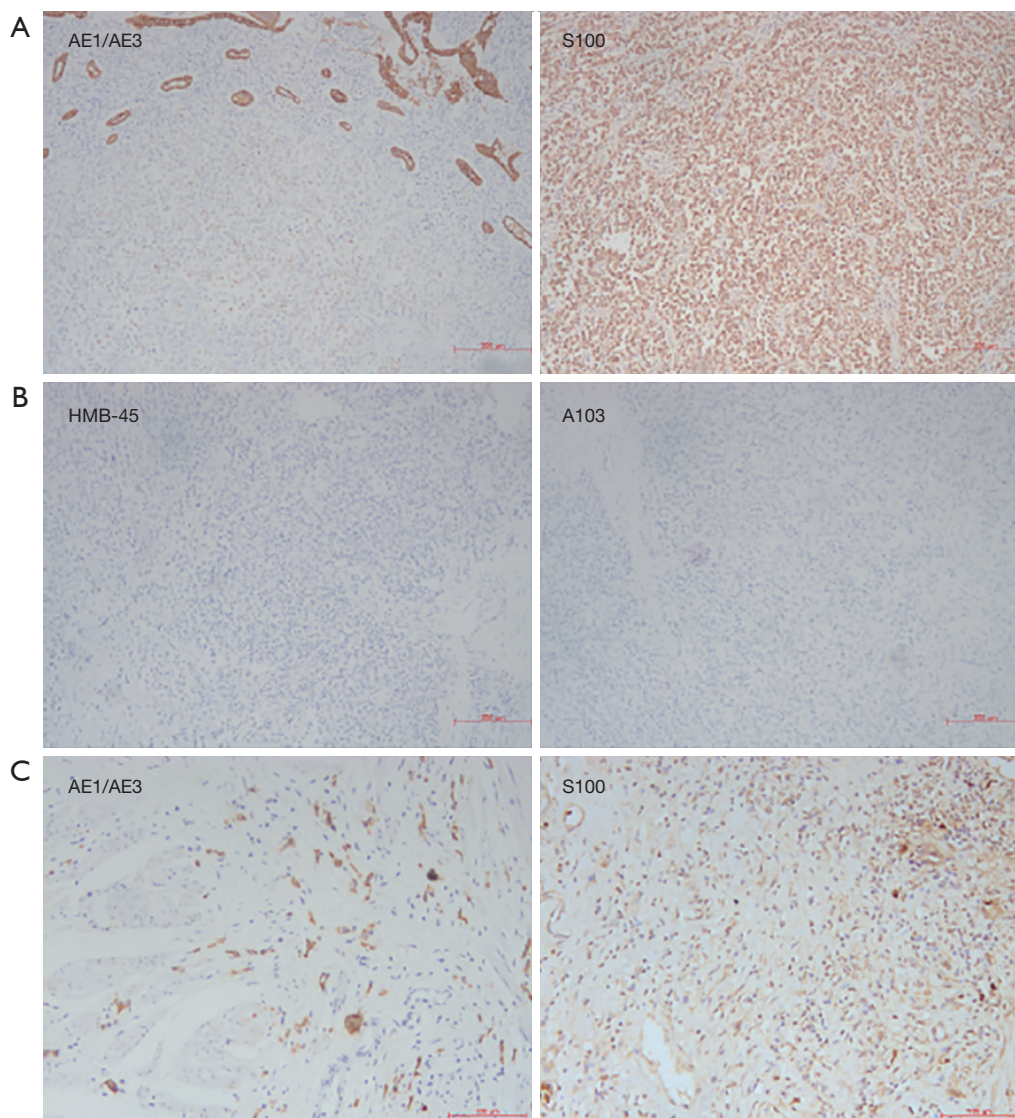
### Case presentation

In 2004, a 19-year-old woman was diagnosed as poorly differentiated adenocarcinoma of the stomach. The carcinoma invaded into the main muscular layer and spread to four lymph nodes, which was classified as stage IIB. Then a total gastrectomy and five cycles of EOF (oxaliplatin + epirubicin + calcium folinate + 5-FU) chemotherapy was conducted. There was no recurrence or metastasis in patient follow-up until 2015 when she presented symptoms of abdominal distension and vomiting. Computer tomography

(CT) scan of abdomen and pelvis showed an obstruction in the small intestine. Emergent exploratory surgery revealed a mass located in the middle of intussusception of the ileum, and an excision of the ileum mass was performed. It was thought to be a metastasis of previous gastric adenocarcinoma clinically.

Macroscopically, resected ileum showed a 3 $\times$ 2.7 $\times$ 2 cm<sup>3</sup> mass. The cutting surface was grey-white. Microscopic findings revealed that the tumor was located under the ileum mucosa, arranged in a solid and pseudopapillary pattern (Figure 1A). Characteristically, the cells were polygonal in

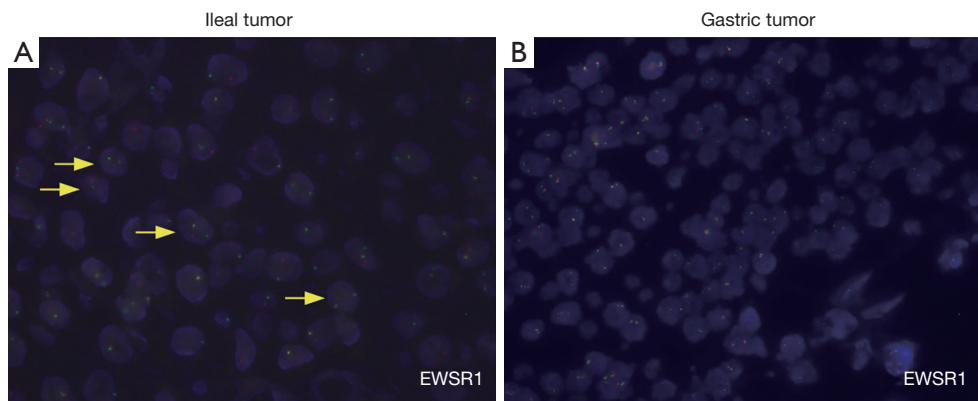




**Figure 2** Immunohistochemistry staining of GNET and gastric tumor. (A) The GNET cells were strongly and diffusely positive for S100 staining, but poorly scattered positive for AE1/AE3 (100 $\times$ ); (B) the GNET cells were negative for A103 and HMB-45 (100 $\times$ ); (C) gastric tumor cells were positive for AE1/AE3, but negative for S100 staining (200 $\times$ ). GNET, gastrointestinal neuroectodermal tumor.

shape, contained clear to eosinophilic cytoplasm and oval nuclei with a single small nucleolus. Scattered osteoclast-like multinucleated giant cells were also identified (*Figure 1B*). Mitotic Figures were found in some fields, but necrosis and ulcer were not extensive. To carefully exclude that the neoplasm was not a metastatic lesion of gastric tumor, we reviewed the slides of the past gastric tumor. The histological and immunohistological findings were quite different. Gastric tumor cells were poorly cohesive with

occasional signet-ring cells (*Figure 1C*), and the cells were positive for AE1/AE3 cytokeratin, confirming its epithelial origin. The GNET cells were strongly and diffusely positive for S100 staining, but were negative for AE1/AE3 cytokeratin, A103 and HMB-45 (*Figure 2*). Thus, we considered ileum lesion was a second new neoplasm of different origin in digestive tract compared with previous gastric tumor. To further confirm the results, we conducted fluorescence in situ hybridization (FISH) analysis for



**Figure 3** FISH analysis for *EWSR1*. (A) Rearrangement of *EWSR1* in ileum tumor is 50% (1,000×) (yellow arrows indicate split green and red signals, consistent with gene rearrangements); (B) while in gastric tumor rearrangement of *EWSR1* was not detected (1,000×). FISH, fluorescence in situ hybridization.

*EWSR1* rearrangement. Fifty percent of the cells showed a split signal of *EWSR1* in ileum tumor (Figure 3A), while in stomach tumor rearrangement of *EWSR1* was not detected (Figure 3B).

One month after surgical resection, the patient received chemotherapy. During the clinical follow-up, the patient kept disease free for 14 months. However, she presented a mesentery mass of small intestine in September 2016. Then she received a surgical removal of the mesentery mass. It turned out to be GNET metastasis through pathological examination (Figure 4A). After she recovered from surgery, unfortunately, she was found to have mesenteric and lung lesions by the CT scan in January 2018. By conducting percutaneous lung biopsy under the CT, the lesion was confirmed to be a GNET metastasis (Figure 4B). The patient was then switched to take sunitinib and still alive till January 2019.

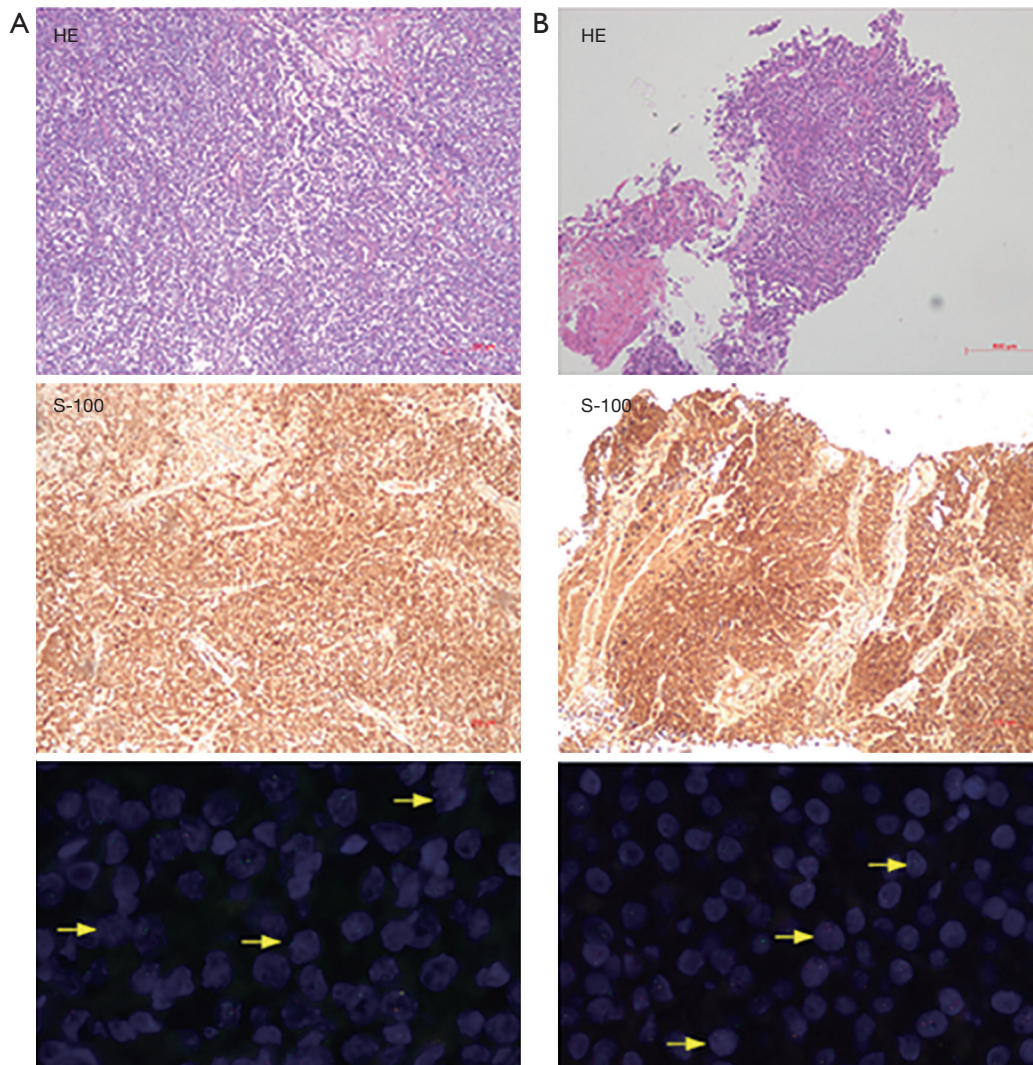
## Discussion

Malignant GNET is a rare malignant neoplasm arising in the intestinal tract, stomach, or colon, and occurs predominantly in young adults. Patients usually develop anemia and abdominal pain (5,6). CT scan of the abdomen and pelvis helps to detect lesion. GNET is usually associated with high rate of local recurrence, metastasis and its average survival time is 18.5 months (1,3). Until now, the etiology of the neoplasm is still unclear and its tumorigenesis is obscure at the initial stages of development.

We reviewed published case reports of GNET, most of which have no history of previous malignancy of any different kind (Table 1). Only two of them were present as a second primary GNET after previously known malignancy. Both patients had been treated with surgery plus low-dose radiotherapy or surgery plus chemotherapy for the previously neoplasm (7-9). One of these patients was diagnosed as hepatoblastoma at age of 13, then he was treated with surgery and followed by six cycles of PLADO regimen chemotherapy (cisplatin and doxorubicin), who eventually developed GNET 20 years later (7). The same as above, our patient was diagnosed as poorly differentiated adenocarcinoma of stomach 14 years ago, and then received total gastrectomy and five cycles of EOF chemotherapy (oxaliplatin 150 mg 1d + epirubicin 60 mg day 1 + calcium folinate 0.1 g days 1-5 + 5-FU 0.5 g days 1-5). We realized that these two patients underwent similar chemotherapy agents when they were young and developed the same disease eventually, which suggested that chemotherapy might play a role in the tumorigenesis of GNET.

Platinum drugs were conventional chemotherapy drugs for many different solid tumors, including gastric cancer (10). While doxorubicin was a routine chemotherapy drug in breast cancer, which was rarely administered in gastric cancer in recent years. Actually, combined chemotherapy with platinum and epirubicin was a routine treatment strategy in gastric cancer in early years (11,12). Interestingly, the risk of gastric adenocarcinoma increased after chemotherapy of diffuse large B cell lymphoma (13,14), and yet secondary malignant tumors after gastric





**Figure 4** Metastatic lesion in ileal mesentery and lung. HE, specific S100 staining and *EWSR1* gene rearrangement identified metastatic lesion in (A) ileal mesentery (the topside 100 $\times$ ; the middle 100 $\times$ ; the bottom 1,000 $\times$ ), and (B) the right lung (the topside 40 $\times$ ; the middle 100 $\times$ ; the bottom 1,000 $\times$ ). Yellow arrows indicate split green and red signals, consistent with gene rearrangements. HE, hematoxylin and eosin.

adenocarcinoma chemotherapy were rarely reported. Moreover, there were rare reports showing that platinum-based drugs and doxorubicin, alone or combination, would induce a new neoplasm.

Generally, advanced poorly differentiated gastric adenocarcinoma progresses quickly, and five-years overall survival rate is 31%. However, the patient in our case has lived a long life after gastric surgery and chemotherapy. We hypothesized that there might be some unknown germline

mutation which played an important role in the natural history of gastric carcinoma in this case, and eventually contributed to the small bowel lesion. Furthermore, germline mutation and prolonged survival made the carcinogenicity of chemotherapy more obvious. Thus, more work should be done to demonstrate if the combination of platinum-based drugs and doxorubicin could contribute to increased possibility of *EWSR1* rearrangement, which might cause the onset of GNET.

**Table 1** Review of reported GNET cases

No.	Reference	Age (year)/sex	Size (cm)	Location	Molecular confirmation	History of tumor/treatment	Recurrent or metastasis/outcome
1	Seung Hwan Song, <i>et al.</i>	23/M	NA	Esophageal	No	No	Rec after 2 years/NA
2	Gülçin Yegen, <i>et al.</i>	25/F	3.2	Ileum	No	No	Liver Mets at diagnosis/NA
3	Celia Green, <i>et al.</i>	33/M	3.0	Ileum	Yes	No	Liver Mets after 1 month/ DOD 10 months
4	Surbhi Kansal, <i>et al.</i>	55/F	4.5	Jejunum	No	No	NA
5	Keduovinuo K. Keditsu, <i>et al.</i>	37/F	NA	Ileum	Yes	No	Liver Mets at diagnosis/NA
6	Mohammed J. Alyousef, <i>et al.</i>	18/M	11	Jejunum	Yes	No	Rec after 36 months/ DOD 1 year
7	Vivek Subbiah, <i>et al.</i>	27/F	NA	Small bowel	Yes	No	Liver and lymph node Mets at diagnosis/NA
8	Thibault Kervarrec, <i>et al.</i>	41/F	7	Small bowel	No	No	Liver met at diagnosis/NA
9	Gokce Askan, <i>et al.</i>	28/M	4.2	Small bowel	Yes	No	Liver and lymph node Mets at diagnosis/NA
10	Takashi Kato, <i>et al.</i>	47/F	NA	Small bowel	Yes	No	NA
11	Kota Washimij, <i>et al.</i>	32/F	6.5	Transverse colon	Yes	No	Rec and liver Met 38 months later/NA
12	A. Gahanbani Ardakani, <i>et al.</i>	22/M	7	Ascending colon	Yes	No	NA
13	Jie Kong, <i>et al.</i>	17/M	6	Gastric antrum	Yes	No	NA
14	Khin Thway, <i>et al.</i>	33/M	3	Small bowel	Yes	Hepatoblastoma/ chemotherapy	Lymph node Mets at diagnosis/DOD 7 months
15	Joanna C. Yang, <i>et al.</i>	15/M	NA	Distal ileum	NA	Neuroblastoma/ radiotherapy	Liver Met at diagnosis/NA
16	Nicolaus Friedrichs, <i>et al.</i>	41/M	8.7	Jejunum	Yes	No	NA
17	Przemyslaw Wolak, <i>et al.</i>	12/M	4	Small intestine	No	No	NA

GNET, gastrointestinal neuroectodermal tumor; NA, not available; rec, recurrence; DOD, die of this disease; met, metastasis.

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## Footnote

**Conflicts of Interest:** The authors have no conflicts of interest to declare.

**Ethical Statement:** The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Written informed

consent was obtained from the patient for publication of this Case report and any accompanying images.

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