Clinicopathological analysis of neuroendocrine carcinoma discovered incidentally in hemorrhoids: A case report and literature review

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Abstract. The present study describes the clinical, histopathological and immunohistochemical features of a case of neuroendocrine carcinoma (NEC) incidentally discovered in hemorrhoidal tissue of a 46-year-old female patient, and also reviewes the relevant literature. The patient was admitted because a colonoscopy revealed hemorrhoids, accompanied by diarrhea. Following surgical resection, pathological examination revealed that the majority of the specimen was hemorrhoidal tissue, with intravascular tumor thrombus and a focus of poorly differentiated NEC (maximum diameter of ~0.5 cm) in the mucosa and submucosa of a single tissue. Furthermore, immunohistochemical results showed a 95% Ki-67 proliferation index and positivity for pan-cytokeratin, chromogranin A and synaptophysin. However, special stains such as Alcian blue and periodic acid-Schiff were negative. Subsequently, the patient received chemotherapy. The 6-month postoperative follow-up computed tomography revealed suspicious metastatic lesions in the perirectal fat space. Subsequent pathological examination of percutaneous needle biopsy specimens confirmed metastatic poorly differentiated NEC. Following confirmation of the diagnosis, the patient underwent radical resection for anal canal carcinoma. The patient reported multiple metastases and signs of systemic failure at 23 months of follow-up. Based on this case and limited literature reports, poorly differentiated NEC of the anal canal incidentally detected in hemorrhoidal tissue-particularly those accompanied by intravascular tumor thrombus and a high Ki-67 index-may indicate high aggressiveness. Long-term and close postoperative monitoring is recommended. Owing to the rarity of such cases, their universal invasive characteristics and the optimal treatment regimen still require validation with more clinical data. The findings of this study can provide a reference for clinical diagnosis and management.

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Introduction

Originating from neuroendocrine cells, neuroendocrine neoplasms (NENs) are a heterogeneous group of tumors that occur in multiple organs throughout the body; the gastrointestinal tract is one of the most common primary sites (1). According to the 2019 World Health Organization (WHO) classification criteria, NENs are classified as either well-differentiated neuroendocrine tumors (NET, G1-G3) or poorly differentiated neuroendocrine carcinomas (NEC, large cell NEC and small cell NEC). The latter is characterized by a higher proliferative activity, significant invasiveness and poor prognosis (2). Anal canal NEC is extremely rare, accounting for <1% of anal canal malignant tumors (3,4). However, the incidental detection of poorly differentiated anal canal NEC in hemorrhoidal tissues is even more rarely reported. Hemorrhoids are the most common benign anorectal condition (5). Surgery primarily helps in symptom relief and hemorrhoids are typically confirmed by postoperative pathological examination. However, hemorrhoidal tissue may harbor malignant lesions, such as squamous cell carcinoma, adenocarcinoma, malignant melanoma and NEC (6). Patients' prognosis may suffer if a missed diagnosis is made. Microscopically, tumor cells of poorly differentiated NEC exhibit poor differentiation, manifesting as either small-cell NEC or high-grade large-cell NEC (3,6,7). Immunohistochemistry plays a crucial role in the diagnosis and differential diagnosis of poorly differentiated NECs. In such cases, the Ki-67 proliferation index is >20%, while markers such as cytokeratin (CK) are positive, and neuroendocrine tumor markers such as chromogranin (Cg)A, synaptophysin (Syn) and CD56 are primarily positive (3,7). Poorly differentiated NEC is primarily treated with surgery and chemotherapy; however, immunotherapy may be beneficial in treating this tumor (8,9). The present study reported

a case of poorly differentiated NEC, incidentally discovered in hemorrhoid tissue. The report described its clinicopathological features, immunohistochemical phenotype, treatment and prognosis in detail. The relevant diagnostic and treatment strategies combined were also analyzed with a literature review, aiming to improve the vigilance of clinicians and pathologists regarding NEC.

Case report

Case presentation. A 46-year-old female was admitted to The First People's Hospital of Xiaoshan District (Hangzhou, China) in October 2022, with the complaint of hemorrhoids and acute diarrhea for 9 days. At 9 days before admission, the patient was diagnosed with hemorrhoids by a colonoscopy at another hospital and did not receive any special treatment. Simultaneously, the patient developed diarrhea, characterized by watery stools 1-2 times daily, without any fever, abdominal pain, nausea, vomiting or mucopurulent bloody stools. Weight loss was insignificant and the patient reported no previous history of tumors, surgery or any family history of malignant tumors.

Physical examination. Vital signs were stable, and cardiopulmonary auscultation was normal. The abdomen was soft, without any tenderness or rebound tenderness. The liver and spleen were not palpable. Digital rectal examination revealed soft prolapsed hemorrhoids, without any induration or mass. No enlarged bilateral inguinal lymph nodes were palpable.

Laboratory examination. The patient's laboratory examination provided the following values: Serum carcinoembryonic antigen (CEA) was 1.04 μg/l (normal range: 0.00-5.00 μg/l), carbohydrate antigen 19-9 (CA199) was 13.31 KU/l (normal range: <37.00 KU/l) and alpha-fetoprotein was 2.00 μg/l (normal range: <10.00 μg/l); The hemoglobin content was 123 g/l (normal range: 115-150 g/l), while the white blood cell count was 4.48 10^9/l (normal range: 3.50-9.50 10^9/l). The patient's fecal occult blood test (immunological method) was weakly positive.

Colonoscopy findings and surgery. Protruded external hemorrhoids (red and bulging with a maximum diameter of 1.0 cm) were observed along with prolapsed internal hemorrhoids (with a maximum diameter of 1.0 cm. The anal canal showed local) redness and vesicle formation (Fig. 1A and B). No ulcers, polyps or masses were discovered in the colorectal mucosa. The clinical diagnosis was mixed hemorrhoids. Under general anesthesia, the patient underwent hemorrhoidectomy, anal canal plasty and hemorrhoidal sclerotherapy. The hemorrhoidal tissue was completely resected and no abnormal mass was discovered.

Pathological and histopathological examination. The lesion, measuring 2.5 cm, exhibited a grayish-red red soft cut surface without any hard nodules palpable, and was fixed in 3.7% neutral formaldehyde for 24 h at room temperature.

The entire HE staining procedure was performed at room temperature (25˚C). Sections were dewaxed in two consecutive jars of pure xylene for 10 min each, followed by hydration in serial graded ethanol solutions (absolute ethanol; 95, 85 and 75% ethanol) with 3 min of immersion per concentration. After hydration, sections were stained with hematoxylin at room temperature for 8 min, rapidly differentiated in 1% hydrochloric acid ethanol for 3 sec, rinsed under running water, blued in dilute ammonia water for 30 sec, washed, and counterstained with eosin for 1 min. Post-counterstaining, sections underwent serial dehydration from 75% ethanol to absolute ethanol for 2 min at each grade, cleared in two jars of xylene for 5 min each, and finally mounted with neutral gum at room temperature. Slides were air-dried before microscopic examination. As indicated in Fig. 2A-D, histological analysis of the lesion with light microscopic examination revealed hemorrhoidal tissue with submucosal vascular dilatation, congestion and a small amount of chronic inflammatory cell infiltration. One portion of the hemorrhoidal tissue's mucosa and submucosa exhibited a solid sheet-like tumor focus with unclear boundary (maximum diameter of ~0.5 cm and infiltration depth of ~0.2 cm). Under high magnification, tumor cells were medium-sized, round or oval, with hyperchromatic nuclei, a high nuclear-cytoplasmic ratio and clear nucleoli in some cells. Although there was no tumor necrosis, intravascular tumor thrombus, nuclear deviation and occasional mitotic figures were observed.

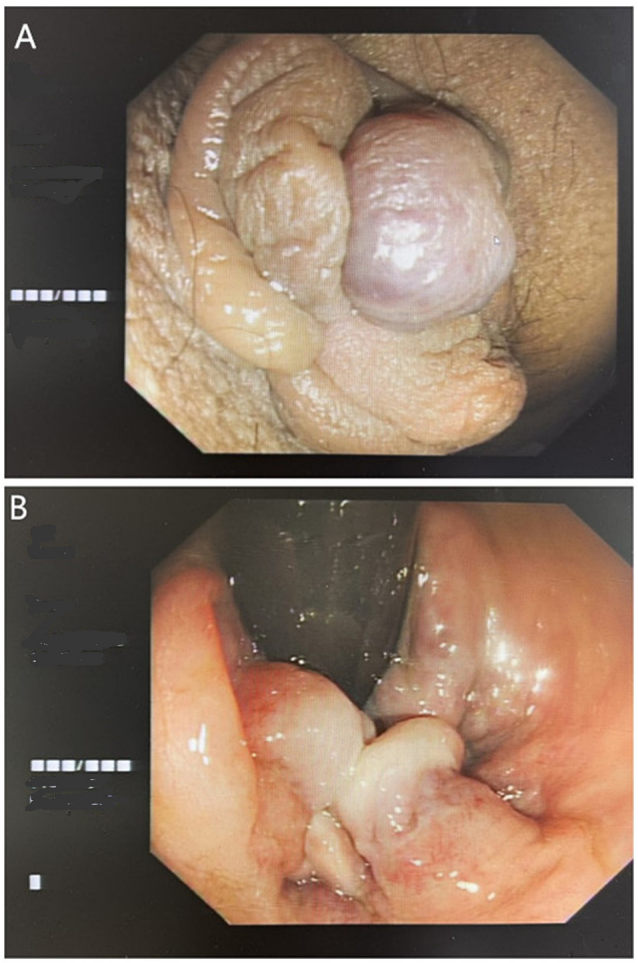

Figure 1. Colonoscopy images. (A) External hemorrhoids; (B) internal hemorrhoids.

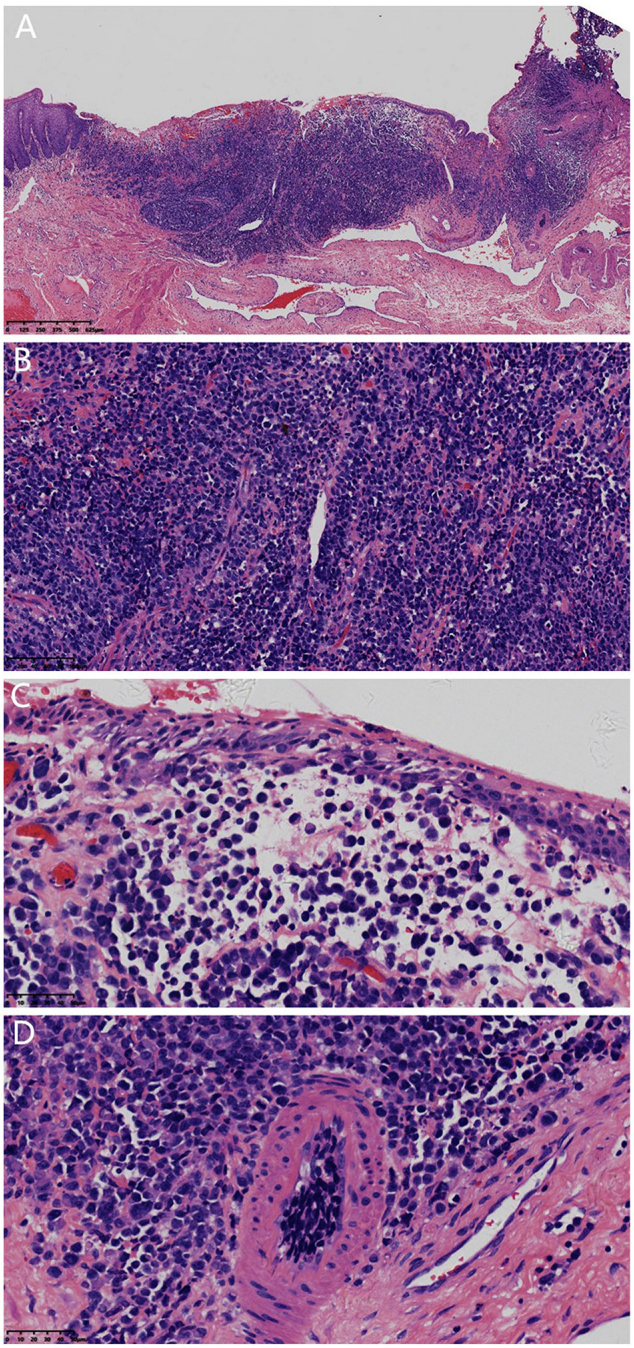

Figure 2. Histological analysis staining of tumor tissue (H&E staining). (A) The tumor infiltrated the submucosa in solid sheets, adjacent to hemorrhoidal tissue (magnification, x32; scale bar, 625 μm); (B) medium-sized, round or oval tumor cells with hyperchromatic nuclei (magnification, x200; scale bar, 100 μm); (C) local nuclear deviation was observed; (D) vascular tumor thrombus was noticed with a tumor cell crush artifact (magnification, x400; scale bar, 50 μm).

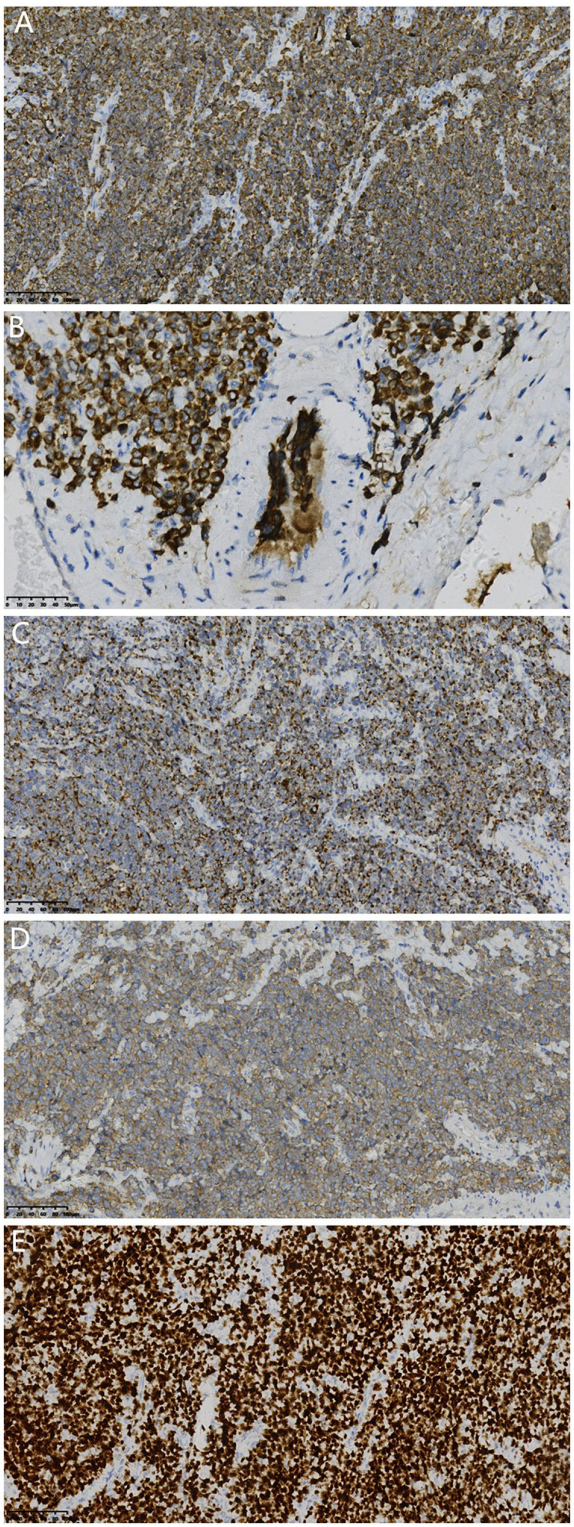

Figure 3. Immunohistochemical results. (A) CKpan positive expression was observed in the tumor cells (magnification, x200; scale bar, 100 μm); (B) CKpan positive intravascular tumor cells (magnification, x400; scale bar, 50 μm); (C) chromogranin A positive cells; (D) synaptophysin positive cells; and (E) Ki-67 proliferation index of 95% (magnification, x200; scale bar, 100 μm).

All immunohistochemical markers had negative and positive controls. Ki-67 detection was performed using the 'hot spot counting method' in strict accordance with clinical pathological testing standards: A total of three high-power fields with the most active tumor cell proliferation were selected, 500 tumor cells were counted in each field and the proportion of positive cells was calculated. In this case, a total of 1,500 tumor cells were identified in 3 fields and 75 of them were Ki-67 negative, with a proliferation index of 95%. During the detection process, positive controls (small cell lung cancer tissue with known high proliferative activity) and negative controls (normal colorectal mucosal tissue) were set simultaneously (tissues were obtained from Fuzhou Maixin Biotechnology Development Co., Ltd.). The staining

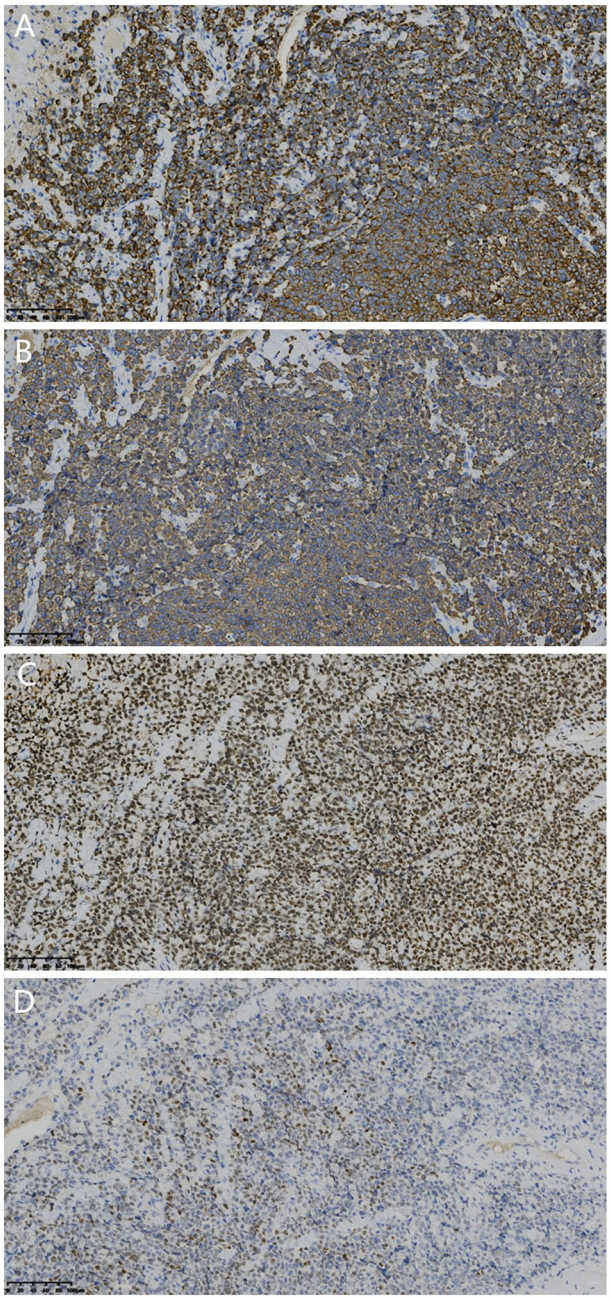

Figure 4. Immunohistochemical results: (A) CK7 positive expression was observed in the tumor cells; (B) CK20 positive intravascular tumor cells; (C) SMARCB1 (IN-1) positive cells; and (D) caudal type homeobox 2 focal positive cells (magnification, x200; scale bar, 100 μm). CK, cytokeratin.

results of the control tissues were consistent with expectations, excluding technical errors such as antibody inactivation and staining operations. A total of two senior pathologists independently conducted counting and result determination with high consistency, effectively avoiding result deviations caused by differences in observers' subjective judgments.

For the EnVision two-step immunohistochemical method, paraffin tissue sections were baked at 60˚C, dewaxed in xylene and rehydrated with gradient ethanol at room temperature (25˚C), followed by heat-induced antigen retrieval at 98˚C using citrate buffer. After cooling to room temperature and rinsing with Tris-Buffered Saline (TBS), 3% hydrogen peroxide was added to block endogenous peroxidase at room temperature for 10 min. Next, the slides were washed with TBS and incubated with diluted primary antibody at room temperature for 1 h or at 4˚C overnight in a humid box. After repeated rinses in TBS, the sections were incubated with HRP-labeled EnVision polymer secondary antibody at room temperature for 20-30 min, washed thoroughly with TBS again, stained with freshly prepared DAB working solution under real-time microscopic monitoring to adjust staining depth, washed with tap water and counterstained with hematoxylin. Sections were differentiated in hydrochloric acid alcohol, blued with running water, dehydrated by ethanol, cleared with xylene and sealed with neutral gum for microscopic observation. The following antibodies were used: CKpan (dilution, 1:100; cat. no. 21061509), CK7 (dilution, 1:100; cat. no. 21050820), CK20 (dilution, 1:100; cat. no. 20083095), CgA (working fluid; cat. no. 20012003), Syn (working fluid; cat. no. 20082029), SMARCB1 (IN-1) (working fluid; cat. no. 20122832), CD56 (dilution, 1:100; cat. no. 21082702), caudal type homeobox 2 (CDX-2) (dilution, 1:100; cat. no. 2010150631c5), CD99 (working fluid; cat. no. 20022018), human melanoma black 45 (HMB45) (working fluid; cat. no. 1912040098e), S-100 (dilution, 1:100; cat. no. 2012240585C8), Melan-A (working fluid; cat. no. 19122684), leukocyte common antigen (LCA) (working fluid; cat. no. 201140037a), CD31 (dilution, 1:100; cat. no. 20073115), D2-40 (working fluid; cat. no. 2109010567d), p40 (working fluid; cat. no. 21060811), p63 (dilution, 1:200; cat. no. 21063006), p53 (dilution, 1:100; cat. no. 20082125), CD117 (working fluid; cat. no. 1910300632e), and Ki-67 (dilution, 1:100; cat. no. 20112609) (purchased from Beijing Zhongshan Jinqiao Biotechnology Co., Ltd. and Fuzhou Maixin Biotechnology Development Co., Ltd.). The immunohistochemical results (Figs. 3A-E and 4A-D) showed positivity for CKpan, CK7, CK20, CgA, Syn and IN-1, as well as focal positivity for CDX-2. Although the CD99, CD56, HMB45, S-100, Melan-A, LCA, p40, p63, p53 and CD117 expressions were negative, the Ki-67 proliferation index was 95%.

Sections were subjected to combined Alcian blue (AB) and periodic acid-Schiff (PAS) staining at 25˚C. Paraffin sections were dewaxed and hydrated to distilled water, stained with Alcian blue solution for 30 min and rinsed with distilled water. Subsequently, sections were oxidized in 0.5% periodic acid for 10 min, washed and incubated with Schiff reagent in the dark for 15 min. After sufficient running water washing for 5 min, hematoxylin was used for brief nuclear counterstaining, followed by differentiation, bluing, graded ethanol dehydration, xylene clearing and neutral gum mounting for microscopic observation. Acidic mucins were stained blue-green by AB, while neutral mucins and glycogen showed magenta staining by PAS. AB and PAS stains showed negative results.

The pathological diagnosis was as follows: i) Poorly differentiated NEC of the anal canal with a maximum diameter of 0.5 cm. Although all surgical margins were negative, it had infiltrated the submucosa (0.2 cm), accompanied by intravascular tumor thrombus. ii) Mixed hemorrhoids.

Postsurgical management. The presence of intravascular tumor thrombus and high Ki-67 index suggested an aggressive disease with high metastatic potential. At the same

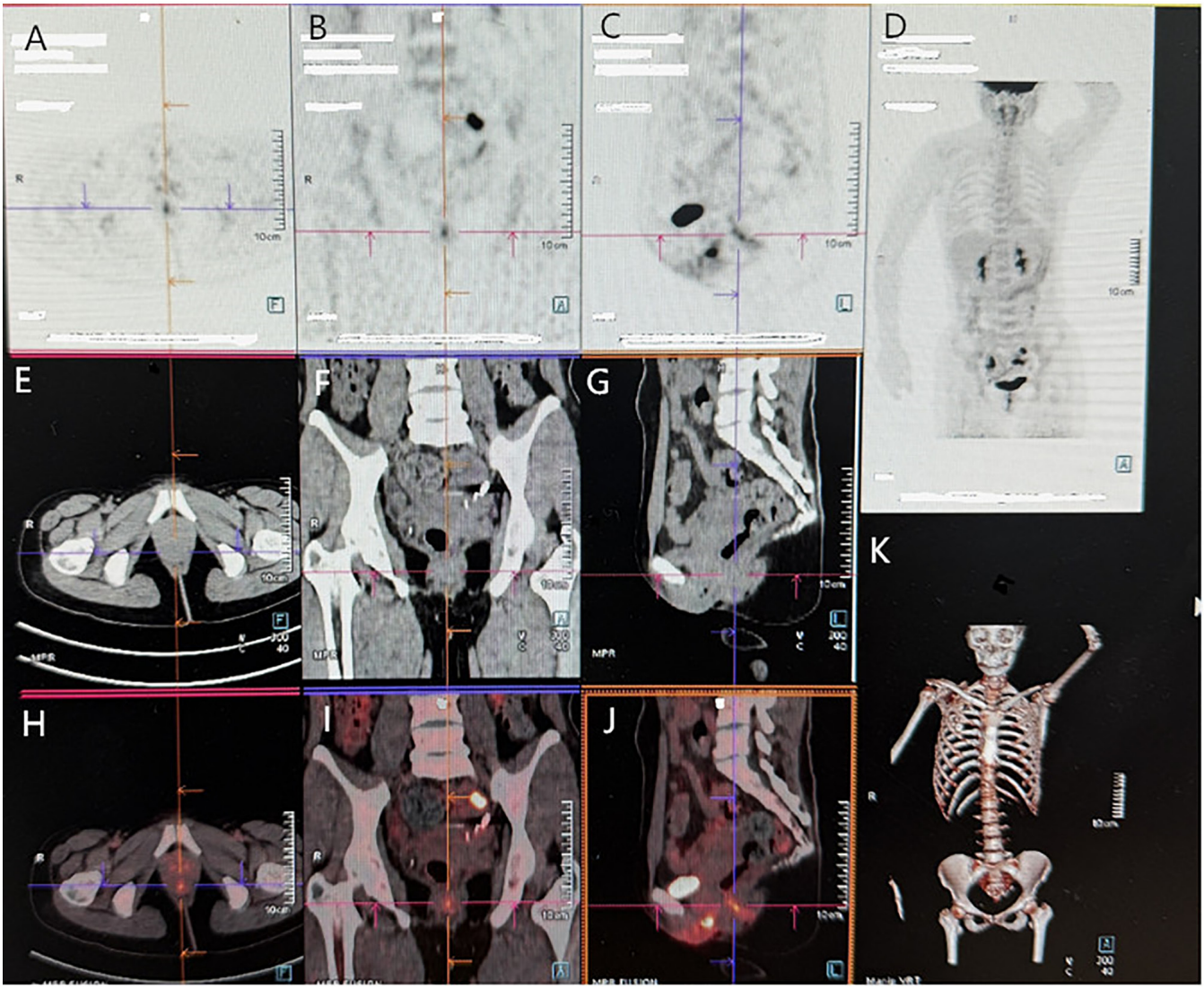

Figure 5. Positron emission tomography-CT examination did not find any residual tumor in the anal canal and para-rectum, lymph node enlargement or metastasis. (A) Transverse PET: No large abnormal concentrations in the pelvis. (B) Coronal PET: A single hypermetabolic black spot in the middle and lower pelvic cavity. (C) Sagittal PET: Well-defined, hyperdense foci in the pelvic cavity anterior to the sacrum. (D) Whole body reconstruction PET panorama: No abnormal concentration in the head, neck, chest and bones, and a small number of hypermetabolic spots in the pelvis. (E) Transverse CT: Pelvic bone integrity without destruction, pelvic soft tissue space was clear, and small nodular soft tissue shadow was seen in the corresponding area of metabolism. (F) Coronal CT: Lumbosacral and pelvic bone intact, small soft tissue nodules in the middle of the pelvis matched with PET hypermetabolism location. (G) Sagittal CT: The bladder, rectum and sacrococcygeal layers could be distinguished, and the soft tissue thickening nodules between the bladder and rectum were corresponding to the PET abnormal lesions. (H) Transverse fusion map: Bright red hypermetabolic hot spots without bone accumulation in the pelvic soft tissue. (I) Coronal fusion map: Localized orange-red hypermetabolic nodules were seen in the pelvic cavity, and there was no hot spot of bone metastasis in the lumbosacral pelvis. (J) Sagittal fusion map: A large red hypermetabolic area was seen in the pelvic soft tissue, which could distinguish the lesion from the bladder, intestine and sacrum. (K) No lesions were found in the whole body skeleton 3D reconstructed skeleton.

time, the maximum diameter of the tumor was 0.5 cm, the surgical margin was clean, and positron emission tomography (PET)-computed tomography (CT) examination (Fig. 5A-K) did not find any residual tumor in the anal canal and para-rectum, lymph node enlargement or metastasis. As radical surgery would have been associated with a large range of damage and poor postoperative quality of life, systemic therapy was prioritized to address the risk of distant spread. At the same time, active follow-up was carried out and radical surgery was performed if local recurrence was found. The patient received 4 cycles of EP regimen chemotherapy: Etoposide (d1-3, 30 mg/day) + cisplatin (d1-3, 100 mg/day) every 3 weeks. During chemotherapy, the patient had obvious bone marrow suppression and gastrointestinal adverse reactions. At 6 months after the initial surgery, pelvic enhanced CT (Fig. 6) indicated metastatic lesions in the perirectal fat space, and subsequent needle biopsy pathological diagnosis confirmed poorly differentiated NEC (examinations were performed at the Department of Pathology, the First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China; data not shown/based on pathology reports); thus, radical resection of anal canal carcinoma was performed. Postoperative pathological examination showed no tumor in the anal canal and rectum, metastatic poorly differentiated NEC in the perirectal adipose tissue, no lymph node metastasis (0/13) and negative surgical margins (examinations were

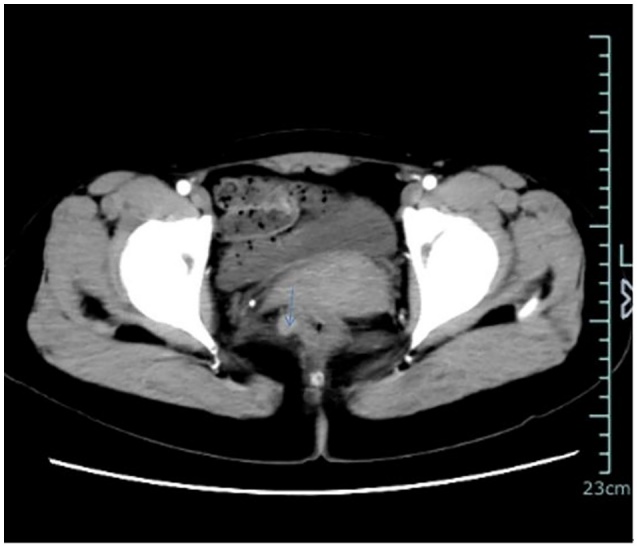

Figure 6. At 6 months after the initial surgery, pelvic enhanced CT indicated metastatic lesions in the perirectal fat space (arrow).

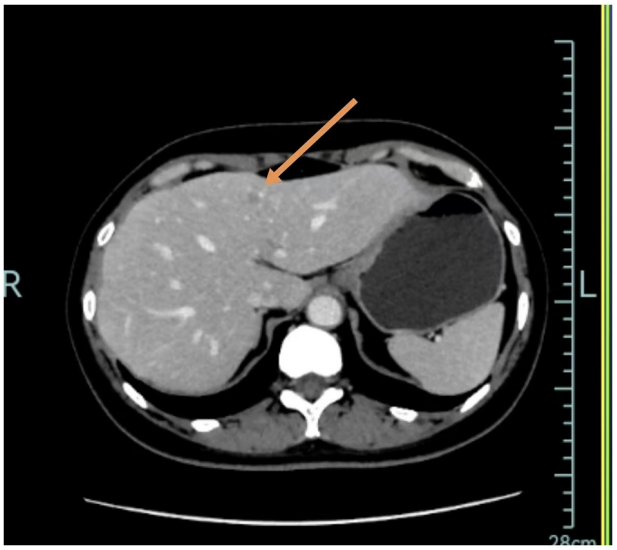

Figure 7. CT indicating that hepatic metastasis occurred 21 months after the initial surgery (arrow).

performed at the Department of Pathology, the First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China; (data not shown/based on pathology reports).

The multidisciplinary team (MDT) recommended subsequent chemotherapy combined with radiotherapy (10). However, due to concerns regarding the severe adverse reactions of previous chemotherapy and uncertainty about efficacy, the patient explicitly refused this treatment regimen; meanwhile, the patient also refused radiotherapy and only received nutritional support therapy. Clinical recommendation is to perform molecular testing, including programmed death-ligand 1 (PD-L1) expression detection, microsatellite instability (MSI) status assessment and tumor mutational burden (TMB) measurement (10). However, the patient lacks recognition and confidence in immunotherapy and molecular targeted therapy administered after disease recurrence. In addition, the high cost of the above tests resulted in delayed testing. Postoperative follow-up evaluations were conducted every 3 months, including abdominal and pelvic magnetic resonance imaging (MRI), chest CT and serum tumor marker detection, revealing nothing notable. Hepatic metastasis occurred 21 months (Fig. 7) after the initial surgery, and the disease rapidly progressed to multiple systemic metastases accompanied by systemic failure 23 months after the surgery. The patient ultimately chose to abandon all anti-tumor treatments and was lost to follow-up.

Discussion

Incidentally detected NEC in hemorrhoidal tissue is a special type of 'occult primary lesion' and has the following unique clinical characteristics: i) Low incidence: Only few cases have been reported worldwide (Table I) (3,6,7). The present case is the fourth detailed report of incidentally discovered poorly differentiated anal canal NEC in hemorrhoidal tissue; ii) atypical symptoms: Patients usually seek medical attention due to typical hemorrhoid symptoms, such as hematochezia, and anal protrusion, since tumor-related symptoms (such as abdominal pain, weight loss) are not apparent; iii) high potential risk of invasion: Three previously reported cases had already developed distant metastases (including hepatic, pulmonary or multiple systemic metastases) at the time of diagnosis. In the present case, the primary lesion's maximum diameter was only 0.5 cm, yet intravascular tumor thrombus was identified, and local metastasis occurred 6 months post-operatively. This observation aligns with the previous research that poorly differentiated NEC may be associated with early vascular invasion and metastasis (11,12). This indicates that such small-sized poorly differentiated NEC may exhibit a high invasive potential. However, its universal invasive characteristics cannot be fully established due to the paucity of such cases.

Pathological diagnosis is the core: Since the primary NEC focus in hemorrhoidal tissue is small and concealed, it can be easily overlooked by routine gross examination. Hence, precise pathological sampling (multi-section, multi-block sampling) and immunohistochemical detection are crucial for its detection. According to WHO criteria (2), the diagnosis of poorly differentiated NEC requires the following: i) Morphological features comprising poorly differentiated, small to large-sized cells with a high nuclear-cytoplasmic ratio and active mitoses; ii) immunohistochemically, the tumor cells are positive for neuroendocrine markers such as CgA, Syn, insulinoma-associated protein 1 and CD56; and iii) the Ki-67 proliferation index should be >20% (95% in the present case, consistent with a high invasiveness). Being a classic neuroendocrine marker, CD56 exhibits a high positive expression rate but low specificity. However, in the present case, CgA and Syn were positive but CD56 was negative, which is rare in poorly differentiated NEC, thereby suggesting heterogeneity in the expression of markers in this tumor. It is imperative to avoid a missed diagnosis due to the negative expression of any single marker in pathological diagnosis. In NEC, the Ki-67 proliferation index is usually >50% (10,11). The 95% index in this case is a key pathological finding, reflecting the overall high proliferative characteristics of the tumor. The result of

Table I. Clinical and pathological characteristics of NEC in hemorrhoid tissues.

First author(s), year	Age, years/sex	Clinical manifestations/size, cm	Pathological characteristics	Immunohistochemistry	Treatment	Prognosis/outcome	(Refs.)
Khan, 2017	60/M	Hematochezia and anal pain/2.0	High-grade large cell NEC	CK(+), CgA(+), Syn(+), Ki-67 90%	CT	Clinical symptoms relieved, liver lesions shrank (during follow-up, long-term prognosis not mentioned)	(3)
Navale, 2021	70/M	Hemorrhoid-related symptoms/NM	Poorly differentiated NEC	Not mentioned	CT	Liver and lung metastases, lost to follow-up	(6)
Allmark, 2021	66/F	External hemorrhoids and constipation/3.0	High-grade small cell NEC with liver, lymph node and bone metastases	CKpan(+), CD56(+), Syn(+), CgA(-), Ki-67 >20%	HE + CT + RT	Died 4 months after diagnosis	(7)
Present study	46/F	Hemorrhoids discovered by colonoscopy and diarrhea/0.5	Poorly differentiated NEC	CKpan(+), CK7(+), CK20(+), CgA(+), Syn(+), Ki-67 95%, CD56(-)	HE + CT + RACCR	6 months after chemotherapy, perirectal metastasis was discovered. 23 months after radical resection of anal canal cancer: Systemic metastasis and failure.	-

NEC, neuroendocrine carcinoma; CT, chemotherapy; HE, hemorrhoidectomy; RACCR, radical anal canal cancer resection; RT, radiotherapy; F, female; M, male; CK cytokeratin; CgA, chromogranin A; Syn, synaptophysin.

Table II. Differential diagnosis of neuroendocrine neoplasms.

Differential points	NET, G1-G3	Poorly differentiated NEC
Morphological features	Arranged in nests, trabeculae or glandular tubes; uniform cell morphology, delicate chromatin; no obvious nuclear-cytoplasmic ratio abnormality.	Arranged in solid sheets; tumor cells are round/oval with hyperchromatic nuclei, extremely high nuclear-cytoplasmic ratio, no glandular structure, and intravascular tumor thrombus is easily observed.
Mitotic count	G1: <2/10 HPF; G2: 2-20/10 HPF; G3: >20/10 HPF.	Mitotic figures are easily seen; no clear grading threshold, and the overall proliferative activity is significantly increased.
Ki-67 proliferation index	G1: <3%; G2: 3-20%; G3: mostly 20-50%.	Usually >50%, reflecting extremely high proliferative characteristics.
Treatment strategy	Surgical resection is the main treatment; adjuvant chemotherapy can be used for G3 NET, and its sensitivity to chemotherapy is lower than that of NEC.	Chemotherapy (EP regimen is the first-line recommendation) is the main treatment; radical surgery requires an expanded resection range.
Prognosis	Favorable prognosis for G1-G2 NETs; the 5-year survival rate of G3 NETs is ~30-50%.	The 5-year survival rate is <10%; the disease progresses rapidly, and multiple systemic metastases and exhaustion are prone to occur.

NEC, neuroendocrine carcinoma; NET, neuroendocrine tumor; HPF, high-power field; EP, etoposide + cisplatin.

this case further supports the aggressive biological behavior of this type of tumor and has important clinical reference value.

Differential diagnosis from other diseases: i) Squamous cell carcinoma: In the present case, negative expressions of p40 and p63 in tumor cells ruled out squamous cell carcinoma; ii) adenocarcinoma: Negative AB and PAS stains, as well as absence of mucus secretion, excluded adenocarcinoma; iii) melanoma: Negative expression of HMB45, S-100 and Melan-A eliminated melanoma; iv) Table II shows the key points in the differentiation of rectal/anal well-differentiated NET from poorly-differentiated NEC; and v) lymphoma: Negative LCA expression excluded lymphoma.

Currently, there is no standard treatment regimen for poorly differentiated NEC incidentally discovered in hemorrhoidal tissue. Individualized treatment plans should be formulated based on the tumor stage and the patient's physical condition. Combined with the treatment process of this case and guideline recommendations (10), the analysis indicated the following:

i) Surgical treatment: After resection of the primary lesion (hemorrhoidectomy), if metastasis or high-risk factors (such as vascular invasion, high Ki-67 index) are identified, further radical surgery (i.e., radical resection of anal canal carcinoma) is required to achieve R0 resection. In this case, the high-risk factor of intravascular tumor thrombus and 95% Ki-67 index were detected after the initial surgery, and local metastasis occurred after chemotherapy, which met the surgical indications in the European Neuroendocrine Tumor Society (ENETS) guidelines (10). Therefore, radical resection of anal canal carcinoma was performed. Postoperative pathology confirmed negative surgical margins, achieving the goal of local control. Consistent with the ENETS guideline (4B grade) that 'R0 resection is preferred for localized resectable NEC', this surgical decision is evidence-based.

ii) Chemotherapy: Poorly differentiated NEC is sensitive to platinum-based regimens combined with etoposide (especially when the Ki-67 proliferation index >55%), and the EP regimen (etoposide + cisplatin) is the first-line standard regimen for young patients with intact renal function and a good performance status. EC (etoposide + carboplatin) is preferred for elderly patients with impaired renal function, combined with underlying chronic diseases and poor tolerance. For relapsed disease treated with second-line therapy, the two platinum agents exhibit no cross-resistance; carboplatin may be substituted following disease progression on first-line cisplatin, and cisplatin may likewise replace carboplatin after progression on first-line carboplatin (10,13,14). The patient (46 years old and in good condition) received four cycles of EP (etoposide + cisplatin) regimen chemotherapy. Although significant myelosuppression and gastrointestinal adverse reactions occurred, it created conditions for subsequent surgery, which is consistent with the principles recommended by the guidelines. However, the ENETS guideline explicitly points out that 'carboplatin is better tolerated than cisplatin and can replace cisplatin to reduce adverse reactions'. In the present case, the choice of cisplatin may have exacerbated treatment-related toxicity, which is an important reason for the patient's subsequent refusal of further treatment. Alternative options supported by the guideline should include carboplatin + etoposide as the initial adjuvant chemotherapy regimen to improve tolerance. In addition, for the second postoperative period, the guideline recommends 'fluoropyrimidine + irinotecan (FOLFIRI)' as the preferred second-line regimen for platinum-resistant NEC, which has a different toxicity profile from platinum-based drugs and may be a viable option for patients who cannot tolerate cisplatin. Unfortunately, this alternative low-toxicity regimen was not fully communicated to the patient in this case.

iii) Potential value and controversies of chemoradiotherapy: According to the ENETS guidelines (10), the benefit of chemoradiotherapy for localized rectal NEC remains unclear and lacks high-level evidence support (2bB grade). MDT discussion of this case recommended chemotherapy combined with radiotherapy, mainly based on the patient's high-risk factors such as intravascular tumor thrombus and high Ki-67 index. Theoretically, concurrent chemoradiotherapy can reduce the local recurrence rate. However, the following factors were considered: i) The patient had severe adverse reactions to previous chemotherapy and subjectively refused further chemotherapy; ii) This rare disease lacks large-sample data on the benefits of chemoradiotherapy, and the existing evidence is insufficient to confirm its efficacy; iii) Radiotherapy may increase the risk of perianal tissue damage and affect the quality of life. Therefore, this regimen was not adopted in the end. Objective analysis of the pros and cons of alternative options was as follows: The guideline mentions that 'radiotherapy is often used for anal NEC, mainly for younger patients and higher-stage diseases' and 'chemoradiotherapy may bring long-term local control for anorectal NEC'. For this case with high local recurrence risk (perirectal fat metastasis), concurrent chemoradiotherapy may have further reduced local recurrence risk, but its effect on distant metastasis control is still uncertain. In clinical practice, the trade-off between efficacy and toxicity should be fully communicated to patients and the decision should be made based on individual willingness and physical status rather than simply abandoning the option due to previous adverse reactions.

iv) Potential of immunotherapy: Studies have shown that patients with gastrointestinal neuroendocrine tumors positive for PD-L1 expression may benefit from anti-PD-L1 immunotherapy, especially high-grade neuroendocrine tumors (8,9). PD-L1 detection was not performed in this case, which is a limitation in treatment decision-making. In addition, the ENETS guideline recommends early molecular detection (including MSI, TMB and BRAF V600E) for NEC. For patients who refuse chemotherapy, if MSI/high TMB or BRAF V600E mutation is detected, immunotherapy (such as pembrolizumab) or targeted therapy (such as encorafenib + cetuximab) can be considered as alternative options. The lack of molecular detection in this case deprived the patient of potential low-toxicity treatment opportunities, which is a key deficiency in the treatment process.

Due to the high risk of recurrence and metastasis of this type of tumor, with reference to the NEN diagnosis and treatment guidelines (10,15), it is recommended to conduct reexaminations every 3 months in the first 2 years after surgery (including abdominal-pelvic MRI, chest CT and CEA/CA199 detection), and every 6 months from the 3rd to 5th year. Whole-body PET-CT may be performed once a year, but the radiation risk needs to be weighed. This monitoring protocol is based on small-sample evidence and should be adjusted according to the patient's individual condition.

In the literature, 3 cases of poorly differentiated NEC detected in hemorrhoidal tissue were reported, all of which had distant metastases at the time of diagnosis. Among them, 2 cases had no long-term follow-up after chemotherapy and 1 case died 4 months after diagnosis (3,6,7). Although the patient of the present study was diagnosed early and received timely chemotherapy and subsequent radical surgery, extraintestinal metastases occurred as early as 6 months after the initial surgery and multiple systemic metastases developed within <2 years after surgery. This clinical course suggests that the tumor may have strong invasive potential. However, it should be clearly stated that this conclusion is based on a limited number of cases, and its general applicability still needs to be verified by more clinical data.

In conclusion, poorly differentiated anal canal NEC is a rare but highly invasive disease. An early diagnosis relies on meticulous pathological and immunohistochemical assessments. Following a definitive diagnosis, a comprehensive treatment approach-including chemotherapy, radical surgery and close follow-up-should be implemented. This case suggests that poorly differentiated NEC can metastasize early, even if the primary lesion is small, which reminds clinicians and pathologists to be vigilant against this entity to reduce the incidence of missed diagnoses and misdiagnoses. Nevertheless, due to the limitations of a single case and the scarcity of relevant evidence, the conclusions drawn in this study should be interpreted with caution. The optimal treatment regimen and long-term prognosis of this disease still need to be verified by a comprehensive analysis of additional clinical cases.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

BH and HL were responsible for the conceptual framework design and initial manuscript drafting of this case report. JS and HZ participated in the conceptual design, methodological design, data collation, formal analysis and implementation of the study. BH was responsible for project management, result validation, initial manuscript writing, and manuscript revision and review. BH checked and confirmed the authenticity, accuracy and integrity of all raw clinical data of this study and is responsible for the validity of the original data. All authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate

The human-related data collection of this case report was reviewed and approved by the Ethics Committee of Xiaoshan District First People's Hospital (Hangzhou, China; approval no. 2025-22). All procedures complied with local regulatory provisions and institutional review requirements.

Patient consent for publication

The patient provided written informed consent for the publication of clinical information and images.

Competing interests

The authors declare that they have no competing interests.

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