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(CASE REPORT)

Diagnosis of Neuroendocrine Tumor of the Pancreas by External Ultrasound-Fine Needle Aspiration Cytology Sampling: Case Report and a Brief Review of the Literature

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Abstract

Pancreatic neuroendocrine tumors (PanNETs) are uncommon pancreatic neoplasms that develop from islet cells. The existing method of preoperative tissue diagnosis and grading is ultrasound-guided fine-needle aspiration of the mass. We present a case of a 42-year-old female who presented with a six-month history of nonspecific epigastric pain and unintentional weight loss. Imaging showed a small pancreatic mass with increased vascularity in the pancreatic tail. Chromogranin A serum levels were elevated.

The diagnostic material was not collected according to the standard Endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) procedure, but rather via the less common external (abdominal, percutaneous) ultrasound-guided fine-needle aspiration (US-FNA) with rapid onsite evaluation (ROSE). It was well-differentiated, Grade 1 PanNET, and, with immunohistochemistry (IHC), positive for Synaptophysin and Chromogranin A, with low Ki-67 (2%). Laparoscopic distal pancreatectomy, splenectomy, and R0 resection were performed. At 3-year follow-up, she was recurrence-free. The case has shown that external US-FNA has high diagnostic accuracy, especially in facilities with limited EUS expertise, or when the lesion can be approached percutaneously, which has proved useful for good preoperative grading even in small tumors and for leading to definitive curative surgery.

Keywords: Pancreatic neuroendocrine tumors; Endoscopic ultrasound-guided fine-needle aspiration; External (abdominal, percutaneous) ultrasound fine needle aspiration; Rapid on-site evaluation; Cytology; Grading

1. Introduction

PanNETs are tumors that arise from the islet cells of the pancreas and constitute approximately 1–2 % of pancreatic neoplasms [1] Their clinical presentation varies, as some are asymptomatic while others, known as functional tumors, present with a wider range of symptoms. The majority of PanNETs are nonfunctional and present with symptoms attributable to mass effect, such as abdominal pain or unintentional weight loss. [2] The case discussed in this paper involves a nonfunctional PanNET that initially presented with persistent stomach pain and early satiety. The treatment planning required a definite diagnosis and correct grading.

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Although imaging techniques such as Computed Tomography (CT) can suggest a diagnosis, EUS-FNA is currently the recommended procedure for obtaining cellular tissue with high accuracy. [3] However, in certain circumstances when endoscopic ultrasound (EUS) expertise is unavailable, external (abdominal, percutaneous) ultrasound-guided FNA (US-FNA) can yield sufficient material, especially when lesions are easily accessible. This method enables cytomorphological analysis and requires ancillary studies, such as immunohistochemistry (IHC), which can evaluate tumor growth and grading using the Ki-67 index and validate neuroendocrine characteristics, such as synaptophysin and chromogranin A positivity. [3]

2. Case presentation

2.1. Clinical presentation

A 42-year-old female reported to her local primary care physician with a 6-month history of epigastric pain and early satiety. She considered these symptoms were related to stress and dietary indiscretion and tried antacids with no symptomatic relief. She had been experiencing on and off for 2 months continuous postprandial nausea with nonspecific upper abdominal complaints. She had no flushing, diarrhea, palpitations, or hypoglycemic symptoms. Her symptoms worsened for some time when she presented to the hospital with more prolonged and disabling epigastric pain.

She had inadvertently lost some weight (unquantifiable, but her clothes hung more loosely over three months), and she had initially been pleased; however, she became concerned when this was associated with epigastric pain and reduced appetite. The patient had no history of jaundice, dark urine, pale stool, or noticeable itch. She denied any alcohol abuse or smoking. Her primary care physician ordered initial laboratory tests, and abdominal imaging revealed a pancreatic mass, prompting referral to gastroenterology for further evaluation.

2.2. History and physical examination

Past medical history was significant only for hypothyroidism, well managed with levothyroxine. There was a strong family history with a paternal aunt presenting with pancreatic adenocarcinoma at 68 years. There was no history of pancreatitis, diabetes, or other GI diseases. Physical examination revealed a well-appearing female in no acute distress, with vital signs within normal limits. Abdominal examination showed mild epigastric tenderness and no guarding, rebound, or palpable mass. The liver edge was impalpable, and no splenomegaly or ascites was noted. No peripheral lymphadenopathy was detected. The remainder of the physical examination was unremarkable.

2.3. Laboratory and imaging findings

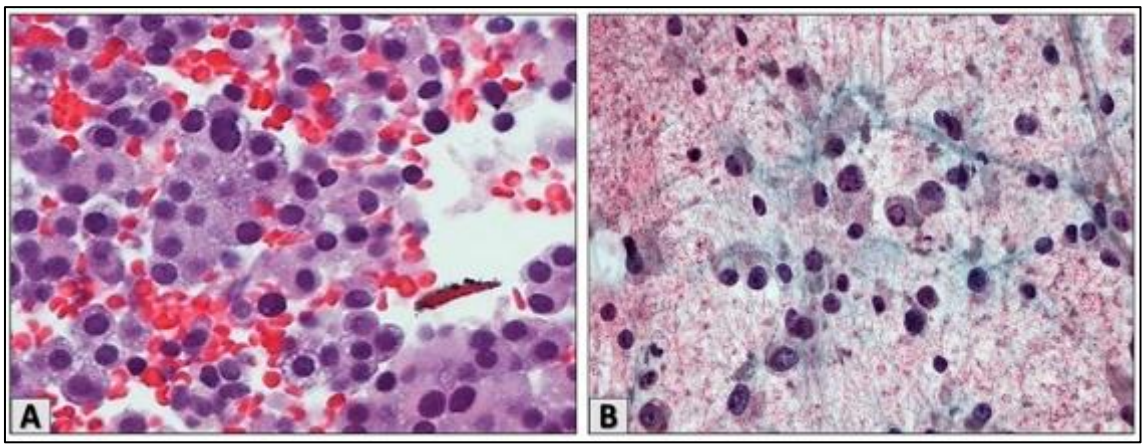
Initial labs, including complete blood count, comprehensive metabolic panel, and liver function tests, were entirely unremarkable. Serial serum chromogranin A levels were obtained, with a value of 425 ng/mL. The fasting glucose was 92 mg/dl, and the hemoglobin A1c was 5.4%. Pancreatic polypeptide, gastrin, insulin, and vasoactive intestinal peptide levels were normal, suggesting a non-secreting tumor. Abdominal CT revealed a complex, vascular-rich 1.4 mass with mixed solid and cystic components, along with distal acoustic enhancement in the pancreatic tail. Pancreatic ductal dilation, vascular invasion, or distant metastasis were absent. There was no evidence of local invasion, and the lesion was well-demarcated. Differential diagnoses were pancreatic neuroendocrine tumor, solid pseudopapillary neoplasm, acinar cell carcinoma, metastasis, and atypical shape of ductal adenocarcinoma.

2.4. Multidisciplinary Discussion and Diagnostic Approach

The case was reviewed at the multidisciplinary pancreatic tumor board. Imaging features suggestive of pancreatic neuroendocrine tumor were discussed, considering the elevated chromogranin A; however, the differential was broad, given a mixed solid-cystic appearance. The cytopathology group explained their diagnostic approach, which includes immediate onsite assessment to assess adequacy, direct smears and liquid-based cytology preparations, a cell block preparation for morphologic and architectural studies, and immunohistochemistry. The possibility of molecular studies was considered if necessary. In the absence of EUS expertise and given that the lesion was easily accessible, the team agreed that US-FNA was sufficient to confirm an accurate diagnosis before undergoing any surgery.

US-FNA was performed, and a cytopathologist reviewed the adequacy of the cytology sampling. Several rounds of sampling were performed to maximize sample collection. The sample contained sufficient cellular material for both cytomorphologic evaluation and ancillary studies. The cytology aspirates from the pancreatic mass showed high cellularity with a hemorrhagic background, but no necrosis or mucin. The smears were cellular and composed of dyscohesive cells and a relatively large number of isolated cells, many of which were in loose aggregates, while a few

exhibited a pseudo-rosette arrangement. The cells were medium-sized to small, monotonous, and round to oval. Cytologically, the tumor cells had moderate, finely granular, eosinophilic cytoplasm, and many appeared plasmacytoid, with an eccentrically placed nucleolus. The nuclei were round to oval with smooth nuclear outlines, a finely coarse chromatin pattern, and no nucleoli or mitotic figures. (**Figure 1**)



1A: High power view showing markedly cellular smear composed of dyscohesive cells and a relatively large number of isolated monotonous cells, many of which were in loose aggregates, while a few exhibited a pseudo-rosette arrangement (H&E stain X40); **1B:** High power view showing medium-sized to small, monotonous, and round to oval cells. The tumor cells have moderate, finely granular, eosinophilic cytoplasm, and many appear plasmacytoid due to an eccentrically placed nucleus (H&E stain X40)

Figure 1 Cytomorphologic features of well-differentiated grade 1 Pancreatic Neuroendocrine Tumor (External Ultrasound-Fine Needle Aspiration, US-FNA)

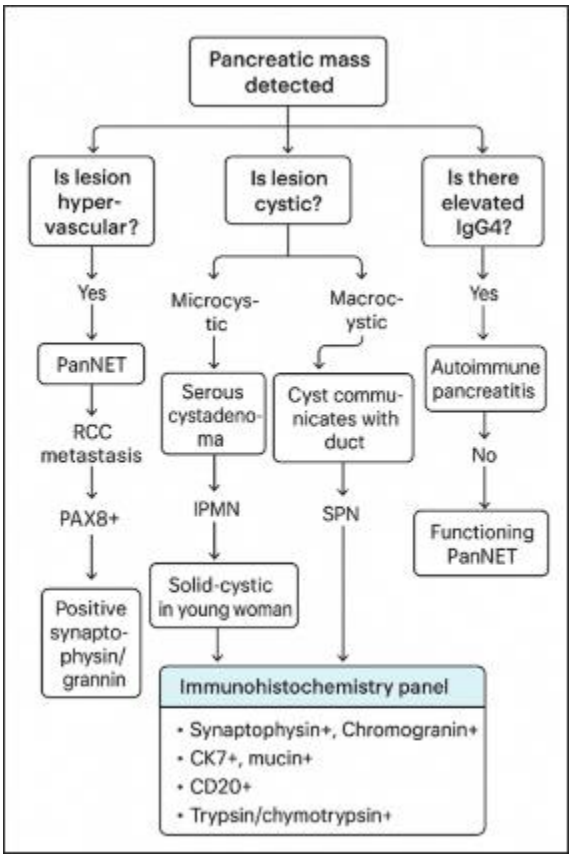
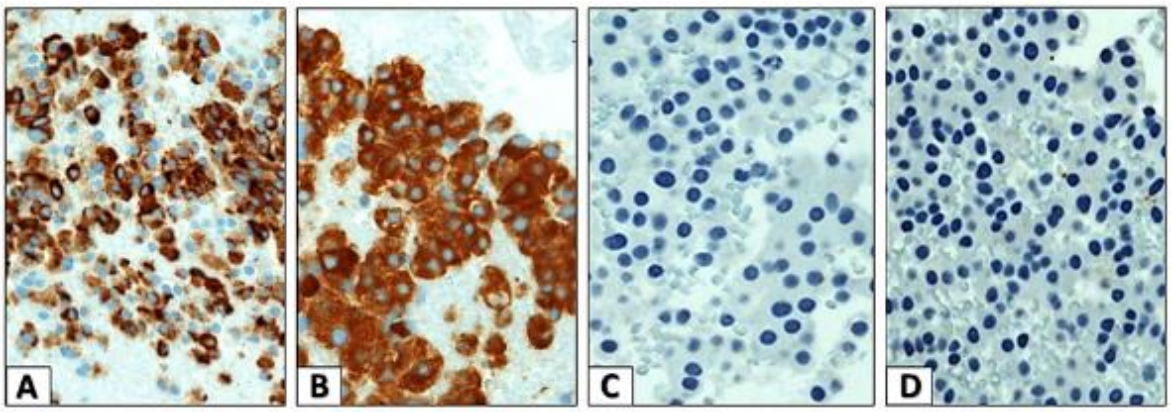


Figure 2 Flowchart for differential diagnosis of a pancreatic mass with characteristic features, compiled from various studies. [2] [4] [5] [6] [7] [8] [9] [10]

Differential diagnosis included: pancreatic adenocarcinoma (hypovascular, ductal obstruction, mucin-producing carcinoma), solid pseudopapillary neoplasm (young females, mixed solid cystic, β-catenin nuclear stain), serous cystadenoma (microcystic, benign, central scar), mucinous cystic neoplasm (body–tail lesions in women, ovarian-type stroma), autoimmune pancreatitis (IgG4 elevation, corticosteroid response), metastasis to pancreas (known primary tumor elsewhere such as renal cell carcinoma), acinar cell carcinoma (exocrine differentiation, trypsin+/chymotrypsin+), and pancreatic lymphoma (characteristic lymphoid population). [2] [4] [5] [6] [7] [8] [9] [10]. **Figure 2** Details a flowchart for the differential diagnosis of a pancreatic mass with characteristic features compiled from various studies.

IHC studies were performed on cytology aspirate slides, and results showed strong positivity of the tumor cells for Synaptophysin and Chromogranin A, and negative reactions for lipase and trypsin. The Ki-67 proliferation index was 2%. All other differential diagnoses were excluded using IHC markers, with negative tumor cell reactions for β-Catenin, Bcl-10, CDX2, and TTF-1. (**Figure 3**)



1A: Tumor cells positive for Chromogranin; **1B:** Tumor cells positive for Synaptophysin; **1C**: Tumor cells negative for Lipase; **1D**: Tumor cells negative for Trypsin

Figure 3 Immunohistochemistry studies on cytology slides from well-differentiated grade 1 Pancreatic Neuroendocrine Tumor

Considering the cytomorphologic features and IHC, the final diagnosis of the tumor was a well-differentiated grade 1 PanNET.

2.5. Management

After cytologic diagnosis of a well-differentiated PanNET (Grade 1, Ki-67 <3%), the tumor board discussion centered around surgical vs. conservative management. After a detailed explanation of both approaches, the patient chose the surgical approach. Laparoscopic distal pancreatectomy with splenectomy was performed. No peritoneal or hepatic metastases were found on intraoperative examination. The lesion of the pancreatic tail was well circumscribed and did not invade the surrounding structures. Negative surgical margins were confirmed by frozen section.

Gross pathology's findings revealed a 1.5 cm well-circumscribed, tan-yellow tumor with focal cystic degeneration. Microscopic examination revealed a well-differentiated PanNET (WHO Grade 1) with an organoid pattern; bland cytological features, and minimal mitotic activity (<2 mitotic activity/10 HPFs). The Ki-67 proliferation index was 2%, which correlated with the cytology diagnosis. None of the eleven dissected regional lymph nodes had metastatic involvement. Surgical margins were negative.

2.6. Outcome and follow-up

The postoperative course was uncomplicated. The patient was experiencing usual, mild postoperative pain, which was relieved by oral analgesic regimens, and she was discharged on the fifth postoperative day. At 4 months after her surgery, she had returned to normal activity with the disappearance of symptoms. No recurrence was found on follow-up, enhanced CT at 6 months. Serum chromogranin A was within the normal range. Because of the complete resection for a Grade 1 neuroendocrine tumor with negative margins and nodes, surveillance was recommended with annual cross-sectional imaging and chromogranin A for 5 years. The patient was in good condition with no recurrence or metastasis at a 3-year follow-up.

3. Discussion

3.1. Background (History, epidemiology, and WHO classification)

The history of PanNETs dates back to 1869, when Paul Langerhans described the pancreatic islet cells that give rise to these tumors. The nomenclature and more precise classification of PanNETs were established in the 20th century, following the discovery of a few functional tumors, including insulinoma (1924) and gastrinoma (1955). [11] Even though 1-2% of pancreatic tumors are PanNETs, the epidemiological pattern indicates increasing reported cases, most probably due to better imaging technology such as EUS-FNA sampling. Although there are a few cases related to hereditary disorders like MEN1, hereditary disorders are not the case in most instances. [1]

The differentiation and grading of PanNETs are based on the 2017 World Health Organization (WHO) classification, which clearly defined these tumors. [5] Well-differentiated and graded G1, G2, or G3 (by the number of mitoses and Ki-67 proliferation index [G1 2%, G2 3-20%, G3 >20%) and neuroendocrine carcinoma, which are highly aggressive in nature. [12]

3.2. Pathogenesis, pathophysiology

PanNETs derive from pancreatic islet pluripotent cells and develop neoplasias associated with alterations in chromatin remodeling, cell-cycle regulators, or mTOR signaling. The majority of well-differentiated PanNETs harbor mutations in MEN1, DAXX, or ATRX, leading to defective chromatin regulation and telomere homeostasis alterations, frequently involving the alternative lengthening of telomeres (ALT) mechanism. [13] [14] Defects in MEN1 result in the loss of Menin. This tumor suppressor protein functions in transcription and DNA repair, thereby promoting the proliferation of neuroendocrine cells. [13] DAXX/ATRX mutations are linked to disruption of histone H3.3 deposition, leading to genomic instability, explaining the low proliferative but persistent course of low-grade PanNETs. [14] Some tumors also show activation of the PI3K/AKT/mTOR pathway, which promotes enhanced cellular proliferation and survival. [15]

The pathogenesis of Grade 1 PanNETs mirrors their well-differentiated neuroendocrine nature, as evidenced by a low proliferative fraction (Ki-67 <3%) and the retention of neurogranules, with preserved expression of markers such as chromogranin A and synaptophysin. Their indolent course is based on their lack of local invasiveness, low proliferation index, and slow metabolic turnover; an explanation for the absence of hormonal symptoms in nonfunctional forms , such as in this case. [5] These tumors are hypervascular on arterial-phase imaging, given their extensive capillary network, and this is consistent with observed upregulation in angiogenic signaling from molecular studies. [16] Although typically indolent in growth pattern, their metastatic potential remains relatively well preserved, correlating with larger tumor size and higher histologic grade, representing the biological diversity within PanNET tumorigenesis.

3.3. Comparative analysis of our case with the existing literature

With the advent of FNA cytology, the preoperative diagnosis of PanNETs has changed, as it is now possible to grade tumors using the Ki-67 proliferation index accurately. [17] [18] EUS-FNA is now considered the gold standard for obtaining tissue due to its ability to visualize small, deep-seated lesions and its high diagnostic accuracy. However, in our case, in the absence of EUS expertise and given the mass's easy accessibility, the tumor board team agreed that US-FNA is sufficient to confirm an accurate diagnosis before undergoing any surgery. This was proved in our case, and the patient received the accurate diagnosis and grading essential before surgery.

Research studies comparing percutaneous US-FNA and EUS-FNA for solid pancreatic masses have demonstrated that both are safe and effective. [19] [20] Although earlier studies reported percutaneous US-FNA is equally diagnostic, especially when the lesion is in the body and tail EUS-FNA is now recognized as the favored and recommended procedure. [19] [20] [21] **Table 1** summarizes the comparison between EUS-FNA, and US-FNA in diagnosis of pancreatic tumors.

Table 1 Comparison between EUS-FNA, and US-FNA in diagnosis of pancreatic tumors*

Feature	EUS-FNA (Endoscopic, internal)	US-FNA (External/percutaneous, abdominal)
Approach	Needle introduced through GI tract under endoscopic ultrasound visualization	Needle inserted through abdominal skin under external ultrasound guidance
Access to lesion	Excellent for deep, small lesions & central pancreas	Best for superficial or peripherally-located lesions close to abdominal wall

Suitability for small lesions	Highly suitable, high resolution close-range imaging	Limited, small deep lesions may not be visualized or reachable
Location advantage	Superior for tumors in pancreatic head, uncinate process, or deep body	More suitable for tumors in tail or body near skin surface
Visualization quality	Very high, probe positioned immediately adjacent to the pancreas	Can be limited by bowel gas, obesity, depth of pancreas
Diagnostic yield for PanNET	Higher yield, better cellularity for small NETs	Lower yield for small, deep lesions.
Complication risk	Low; common: mild pancreatitis or post-procedure discomfort	Low; common: bleeding, hematoma, rare infection
Sedation	Typically requires conscious sedation or anesthesia	Usually done with local anesthesia only
Operator skill requirement	Requires specialized endoscopic expertise	Widely available; less specialized
Patient experience	Internal procedure; no skin puncture	Quick, superficial skin puncture
Availability	Limited to centers with advanced endoscopy	Broadly available in most hospitals
Cost	Higher	Lower

*Compiled from references [2] [3] [17] [21] [22] [23]

This case demonstrated the effectiveness of external US-FNA and showed that the cytopathologist should use a multidisciplinary approach that includes Rapid Onsite Evaluation (ROSE). ROSE also played a major role in providing adequate samples for cytomorphology and ancillary diagnoses, which are among the key determinants of diagnostic success in any FNA procedure. [19] Moreover, the precise grading (Grade 1, Ki-67 2%) of the tumor, preoperatively assessed by external US-FNA cytology, was verified by final surgical pathology, demonstrating that this method can provide the essential information needed to make a definitive surgical intervention. The case confirms the still-reliable nature of external US-FNA as a safe, effective, and easily available alternative to diagnose and grade PanNETs accurately

Management guidelines from major societies, such as the European Neuroendocrine Tumor Society (ENETS) and the National Comprehensive Cancer Network (NCCN), support active surveillance (a "watch-and-wait" approach) for many PanNETs in selected patients. [24] The 2020 North American Neuroendocrine Tumor Society (NANETS) consensus endorses surveillance for asymptomatic PNETs <2 cm among low-risk patients and allows surgery in younger individuals based on tumor grade and ultimately, patient preference. [25] In our case, the patient decided to go with the surgical approach. Our practice of laparoscopic distal pancreatectomy is consistent with nuanced patient-centered considerations.

Regarding the long-term follow-up, excellent survival is associated with surgical resection of grade 1/2 PanNETs. One large meta-analysis demonstrated a significant survival advantage of surgery over nonoperative treatment, with pooled hazard ratios for mortality of approximately 0.30 in low-grade and small tumors. [26] There is a continued risk of recurrence: in pooled series, rates of recurrence following curative resection vary between 9-18%, with risk factors including lymph node metastases, tumor grade, perineural invasion, and R1 resections. In an institution series, 1-, 3-, and 5-year disease-free survival rates were 90.9%, 82.7%, and 72.5%, respectively. [27] In our patient with a node-negative, negative margin, and low Ki-67, the three-year recurrence-free and chromogranin A status were consistent with favorable prognostic features.

Finally, surveillance guidelines recommend imaging and biochemical testing every 10 years. For example, NANETS guidelines recommend imaging at 12 months postoperative and then every 12-24 months thereafter, especially for nonfunctioning tumors. [26] Our surveillance strategy is analogous and supported by the lifetime risk of recurrence despite an excellent early outcome.

4. What have we learned from this case?

This case offered several important learning points regarding the diagnosis and management of small, nonfunctional PanNET. First, it demonstrated that external US-FNA is a very safe and effective method for obtaining a definitive tissue diagnosis and accurate Ki-67 grade for PanNETs, especially when the lesion is easily accessible. This is a very important point in centers where endoscopic ultrasound expertise may be limited. Second, the case underscored the importance of the multidisciplinary tumor board in determining the diagnostic approach and the need for ROSE during FNA to obtain high-quality samples sufficient for full cytological, IHC, and molecular analysis. Finally, the strong correlation between preoperative cytological grading and postoperative surgical pathology demonstrated that a successful preoperative diagnosis is of greatest importance in choosing the treatment method, which, in this case, was curative surgical resection.

Abbreviations

Pancreatic neuroendocrine tumors (PanNETs); endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA); External (abdominal, percutaneous) ultrasound fine needle aspiration (US-FNA); Rapid onsite evaluation (ROSE); immunohistochemistry (IHC)

5. Conclusion

We present a case of a well-differentiated, Grade 1, PanNET in a 42-year-old female that was successfully diagnosed using US-FNA cytology. This case contributes to the growing understanding of PanNETs by reaffirming the diagnostic utility of external US-FNA as a safe, effective, and less invasive alternative to EUS-FNA, provided the lesion is accessible. Accurate preoperative diagnosis, including a Ki-67 proliferation index of 2% was critical for the multidisciplinary team to move to curative laparoscopic surgical resection. This report encourages clinicians to consider external US-FNA as a first-line diagnostic modality for pancreatic masses, facilitating timely and appropriate management.

Compliance with ethical standards

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Disclosure of conflict of interest

All authors make the following declarations:

- Payment/services information: All authors have declared that they received no financial support from any organization for the submitted work.
- Financial relationships: All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might be interested in the submitted work.

Statement of ethical approval

Ethical review and approval were not required for this study involving human participants. The paper has been sufficiently anonymized to maintain the patient's confidentiality.

Statement of informed consent

Consent for the publication of this case was obtained from the patient.

Data access statement

All relevant data are included in the paper.

Author contributions

All authors contributed equally to producing this manuscript.

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