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CASE REPORT

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Recurrent secondary hyperparathyroidism due to a gradually increasing intrathyroidal parathyroid adenoma in a fifth parathyroid gland of a patient undergoing long-term haemodialysis: Road to evil

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Abstract

Background An intrathyroidal parathyroid adenoma (IPA) is a very rare cause of recurrent hyperparathyroidism after parathyroidectomy in patients undergoing long-term haemodialysis. An IPA is often difficult to localize preoperatively, making diagnosis and treatment challenging. We herein report a rare case of recurrent hyperparathyroidism due to a gradually increasing IPA in a fifth parathyroid gland.

Case presentation A 24-year-old Chinese woman had end-stage renal disease secondary to chronic glomerulonephritis and started regular haemodialysis in March 2007. She was diagnosed with renal hyperparathyroidism as indicated by elevated parathyroid hormone and calcium levels in 2011. One year later, the parathyroidectomy with right forearm autotransplantation was performed in January 2012. Pathology revealed parathyroid nodular hyperplasia in four of the nodules. Twelve years after surgery, the nodule in the right thyroid was detected by multiple imaging modalities. In addition to the recurrence of renal hyperparathyroidism, the nodule gradually increased in size. Total right thyroid lobectomy was performed, and the patient was diagnosed with an IPA. At the 3-month follow-up examination, she had no signs of recurrence despite regular haemodialysis, and her PTH and serum calcium levels were stable.

Conclusions This is a rare case of recurrent hyperparathyroidism due to a gradually increasing fifth parathyroid gland in a patient who underwent long-term haemodialysis after parathyroidectomy. We suggest vigilant postoperative monitoring for prompt and early identification of culprit parathyroid lesions, even if the four parathyroid glands have been dissected.

Keywords Recurrent hyperparathyroidism, Intrathyroidal parathyroid adenoma, Haemodialysis

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Background

In nearly all patients with end-stage renal disease (ESRD) undergoing dialysis, renal hyperparathyroidism is the result of a combination of hyperphosphatemia, hypocalcaemia, and vitamin D deficiency [1]. Approximately 15% of patients must undergo parathyroidectomy after 10 years of ongoing dialysis therapy, especially when parathyroid hormone (PTH) levels exceed 800 pg/mL for more than 6 months, exhaustive medical interventions (i.e., calcimimetics and vitamin D analogues) are proven ineffective, and parathyroid nodular hyperplasia is confirmed via imaging [2–4]. Approximately 2.0-22.3% of patients experience persistent or recurrent disease after total parathyroidectomy [5, 6]. Persistent or recurrent hyperparathyroidism is the manifestation of an ectopic gland, supernumerary glands, parathyroid carcinoma, or overgrowth of a remnant or parathyroid autograft [7–11]. Preoperative diagnostic imaging studies are necessary for localizing as many parathyroid glands as possible. Small ectopic remnant parathyroid glands may be present but are often unable to be identified before preoperative imaging or surgery [12]. ESRD may persistently stimulate remnant parathyroid tissue, thus causing the tissue to increase in size and inducing the recurrence of hyperparathyroidism [1, 10, 13]. Herein, we report a rare case of recurrent hyperparathyroidism after parathyroidectomy due to an intrathyroidal parathyroid adenoma (IPA) in a patient who underwent long-term haemodialysis.

Case presentation

A 24-year-old Chinese woman had end-stage renal disease secondary to chronic glomerulonephritis and started regular haemodialysis in March 2007. She was diagnosed with renal hyperparathyroidism due to elevated parathyroid hormone and calcium levels in 2011. Cervical computed tomography (CT) revealed four nodules consistent with orthophoric parathyroid glands (Fig. 1). Ultrasonography also revealed four hyperplastic parathyroid nodules posterior to the thyroid and a small nodule (distinct, hypoechoic, and round, approximately 4 mm) in the right thyroid parenchyma (Fig. 1). Parathyroidectomy with right forearm autotransplantation was performed in January 2012. The final pathology report revealed four hyperplastic parathyroid nodules (Fig. 1). On the first postoperative day, PHT was 134 pg/mL (normally 15–65), serum calcium was 1.92 mmol/L (normally 2.11–2.52), and serum phosphate was 1.32 mmol/L (normally 0.85–1.51). Her recovery was unremarkable, and regular haemodialysis was performed at a local hospital. In 2021, nine years after parathyroidectomy, her PTH and serum calcium levels were increased. Neck ultrasonography revealed well-circumscribed heterogeneous nodular lesions in the right thyroid gland measuring 1.6 × 1.5 cm and no nodules posterior to the thyroid (Fig. 2). Calcimimetics, vitamin D analogues and lanthanum carbonate were recommended, but the treatment was ineffective after 3 years. In April 2024, she was referred to our institution due to itch for 3 months. The patient showed no signs of hoarseness, dysphonia or dysphagia. Her past medical history included surgery for prolactinoma. There was no relevant family medical history. Her laboratory tests revealed normal levels of thyroid hormones, calcitonin and carcinoembryonic antigen. Her serum calcium was 2.62 mmol/L, PHT was 1740 g/mL, serum alkaline phosphatase was 258 U/L (normally 35–100), and serum phosphate was 1.71 mmol/L. Ultrasonography

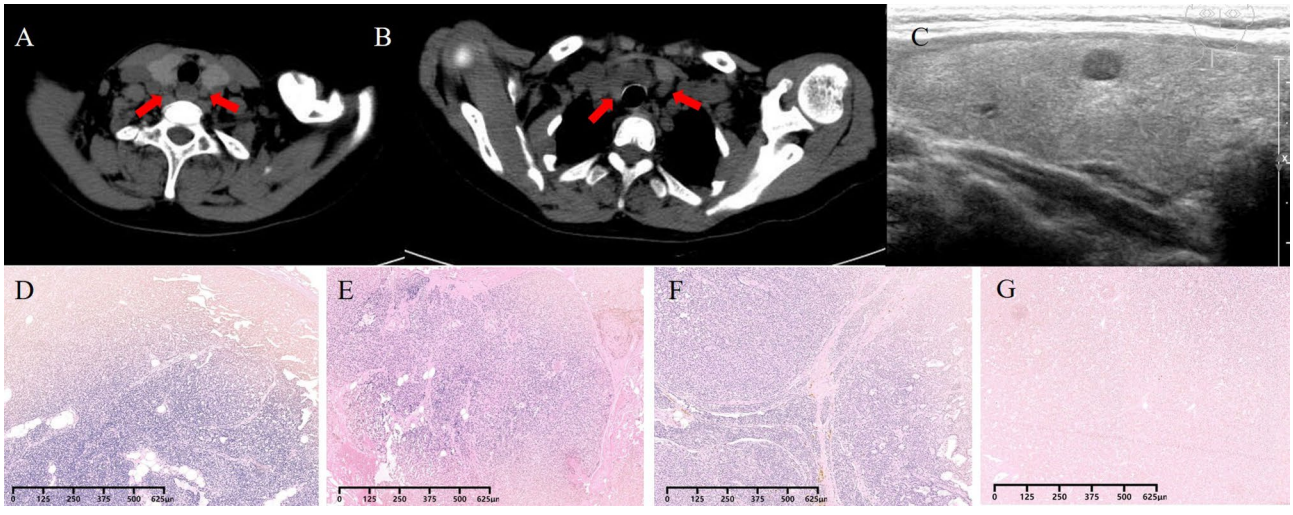

Fig. 1 Axial CT scan (**A-B**) revealing four nodules (arrows) located posterior and inferior to the thyroid gland. Ultrasonography (**C**) revealing a small nodule located in the right lobe of the thyroid gland. Histopathology (haematoxylin-eosin (HE) staining, magnification ×40; **D**, left superior parathyroid nodule; **E**, right superior parathyroid nodule; **F**, left inferior parathyroid nodule; **G**, right inferior parathyroid nodule) showing nodular hyperplasia composed mainly of chief cells

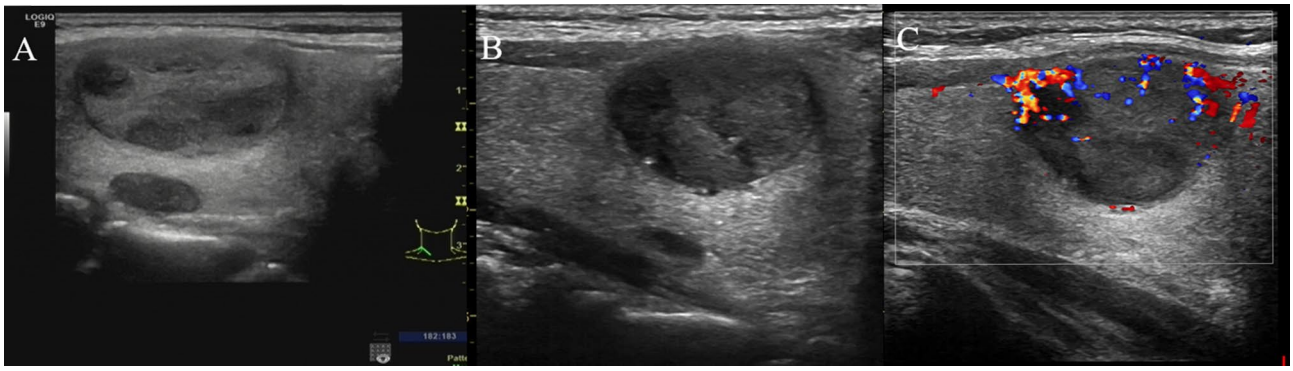

Fig. 2 Ultrasonogram (**A**) showing the growth of the mass with a well-marginated heterogeneous echoic region in the right thyroid in November 2021. Ultrasonography showing a mixed echoic mass (**B**) in the right thyroid in April 2024. Colour Doppler ultrasonography (**C**) showing markedly increased vascularity in the right thyroid mass

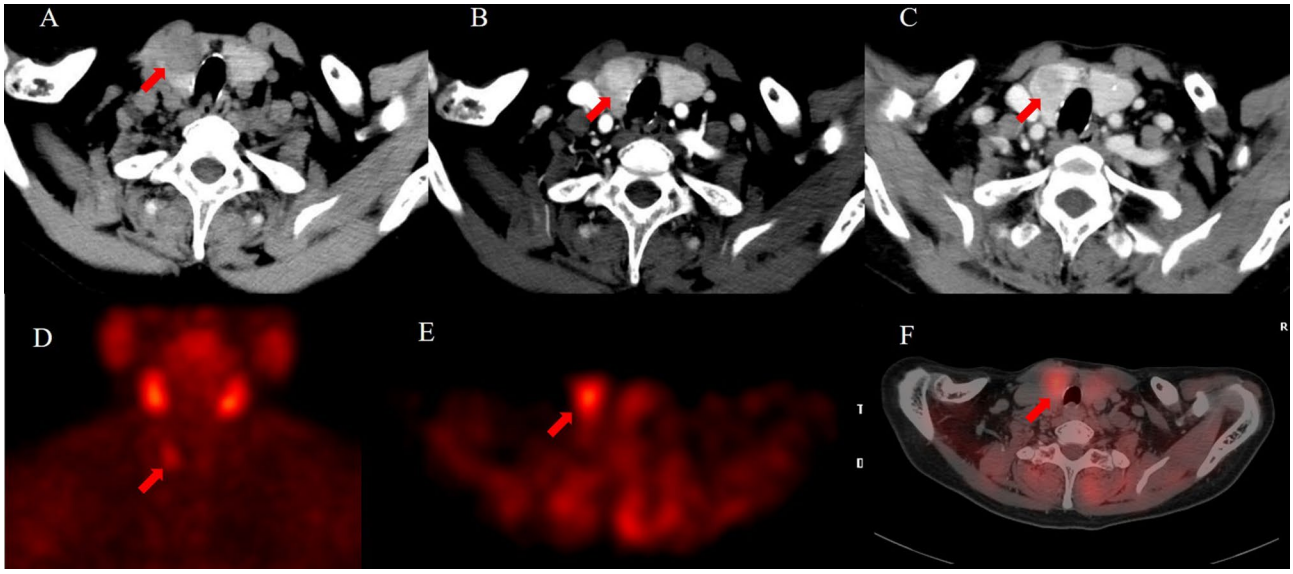

Fig. 3 Axial CT images (**A**, pre-contrast; **B**, arterial phase; **C**, venous phase) revealing a moderately enhanced low-density mass (red arrows) in the right thyroid. 99mTc-MIBI SPECT/CT images (**D**, maximum intensity projection; **E**, axial SPECT; **F**, axial SPECT/CT fusion) showing focal tracer accumulation in a mass (red arrows) located in the right thyroid

and contrast-enhanced CT revealed heterogeneous enhancement of a mass in the right thyroid. 99mTc-sestamibi single-photon emission computed tomography/CT (99mTc-MIBI SPECT/CT) revealed that the right nodule in the right thyroid had persistent uptake (Fig. 3). No other evidence of focal accumulation or nodules was found in the neck or mediastinum. This result was consistent with the presence of a parathyroid adenoma in the right thyroid. Neck exploration was performed in April 2024, at which time no extracapsular parathyroid nodule was identified. Total right thyroid lobectomy was performed as a result of findings on multiple preoperative imaging scans. Pathological examination confirmed IPA because the mass located in the thyroid was surrounded by thyroid tissue (Fig. 4). The mass was composed of chief cells without evidence of malignancy. Laboratory tests on the first postoperative day revealed a PTH concentration of 319 pg/mL and a serum calcium concentration of 2.03 mmol/L, and the patient reported gradual alleviation of the itching. The patient recovered well and was discharged on the 4th postoperative day. During 3 months of follow-up, her PTH and calcium levels fluctuated between 237 and 318 pg/mL and between 2.00 and 2.23 mmol/L, respectively, despite undergoing haemodialysis regularly (Table 1). Clinical Research Ethics Committee of the First Affiliated Hospital, Zhejiang University School of Medicine approved this study (IIT-20240732 A).

Discussion and conclusions

IPA is an uncommon cause of renal hyperparathyroidism recurrence after parathyroidectomy in patients undergoing long-term haemodialysis. The patient in our study had four orthophoric nodular hyperplastic parathyroid

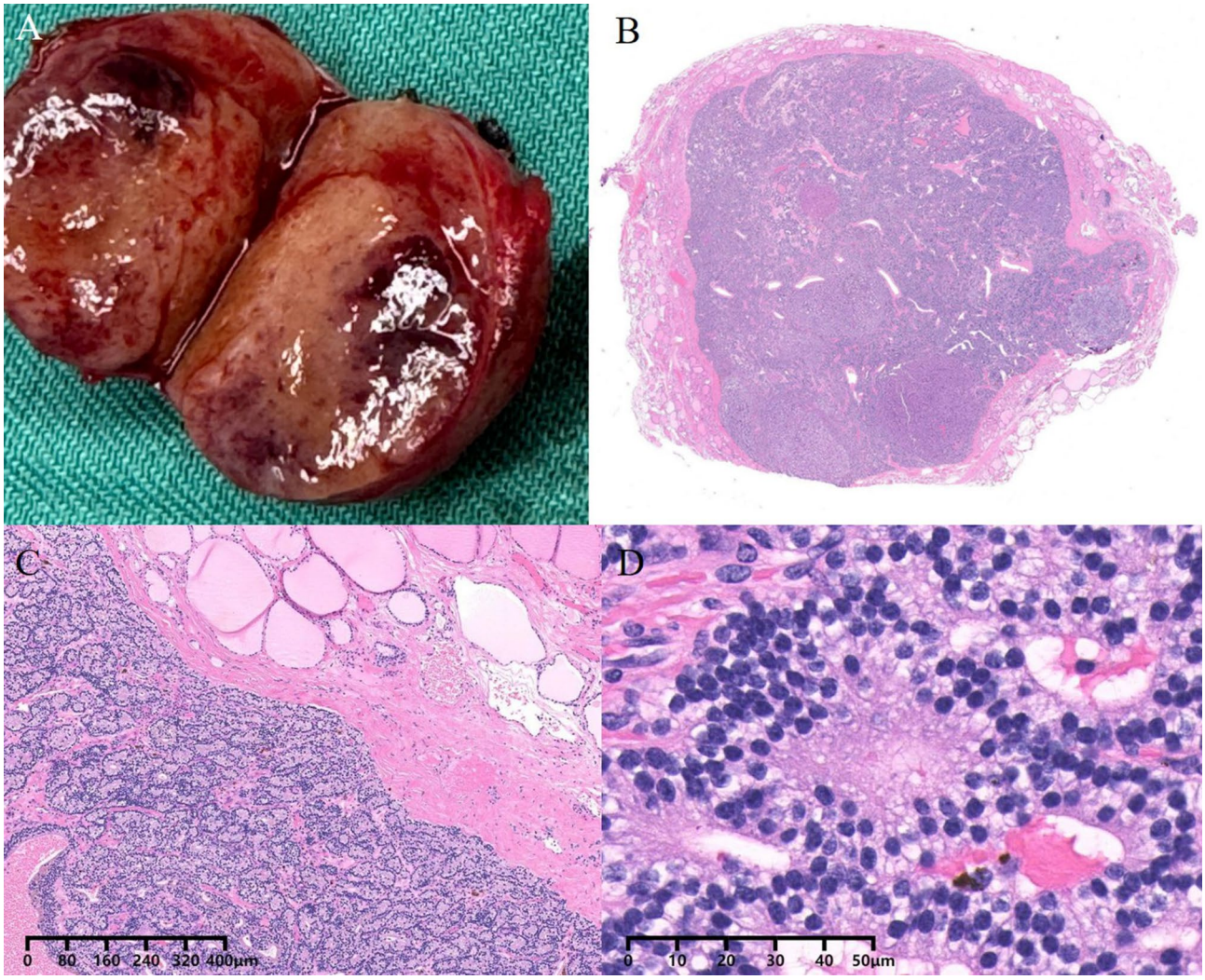

Fig. 4 Pathological specimen of gross tissue (**A**) showing that the mass was surrounded by a thyroid. Histopathology (HE; **B**, magnification ×4; **C**, magnification ×40; **D**, magnification ×400) showing that the parathyroid adenoma was composed mainly of chief cells surrounded by thyroid follicles

Table 1 Results of laboratory values during the operation and 3-month follow-up

Parameters	Reference range	Before first operation	After first day of the first operation	Before second operation	After the first day of the second operation	3-month follow-up
Date	NA	January 2012	January 2012	April 2024	April 2024	July 2024
Calcium	2.11–2.52 (mmol /L)	2.21	**1.92**	**2.62**	**2.03**	2.0-2.23
Phosphorus	0.85–1.51 (mmol/L)	**1.98**	1.32	**1.71**	**1.59**	1.45–1.50
Parathyroid hormone	12.0–65.0 (pg/mL)	**813.4**	**134**	**1740**	**319**	**337 – 318**

Bolded values are out of the reference range; NA, not available

glands and subsequently underwent parathyroidectomy. During the follow-up exam, renal hyperparathyroidism recurrence was confirmed, and the nodule in the right thyroid appeared to have gradually increased in size. Twelve years later, preoperative multimodal imaging and histopathology confirmed that the IPA was the fifth case of ectopic parathyroid adenoma diagnosed in our centre.

IPA is occasionally overlooked as the cause of surgical failure in patients with hyperparathyroidism. IPAs develop in predictable locations in less than 1%, or 11,163, of patients undergoing parathyroid surgery [14]. Another study revealed that 1.4% of patients who underwent parathyroidectomy had an IPA [15]. The incidence varies depending on the series of evaluated patients and criteria. Whether IPA originates from the superior or

inferior glands has been the subject of ongoing debates [16, 17]. However, we believe the IPA originates from the inferior glands, which is consistent with relevant literature, as the inferior parathyroid is associated with a higher rate of embryological tissue migration [14, 17]. The IPA was considered trapped within the thyroid as the lateral and medial lobes fused [18].

Most patients have two pairs of parathyroid glands, but 5% of patient have 5 parathyroid glands, according to the literature [19]. Therefore, in patients with renal hyperparathyroidism, four parathyroid glands are identified and removed. There is still a risk of hyperparathyroidism recurrence due to the presence of additional glands. There have been some efforts to preoperatively identify pathologic IPAs. In clinical practice, imaging modalities, including ultrasonography, 99mTc-MIBI SPECT/CT and contrasted CT, have advantages and disadvantages in terms of their use for localization [20, 21]. The reported sensitivity of ultrasonography for identifying IPAs ranges from 29 to 67% [22, 23]. Although common thyroid nodules and IPAs are similar in appearance and often coexist, they must be differentiated. Owing to the absence of cystic components, IPAs are characterized by a hyperechoic line and feeding vessels [21, 24, 25]. The hyperechoic line was presumed to be characteristic of not only an IPA but also histological separation from the thyroid tissue [25]. The sensitivity and specificity of this characteristic for diagnosing IPAs are 86% and 100%, respectively [25]. According to the literature, the diagnostic criteria for IPA has high sensitivity, increasing the diagnostic accuracy of imaging from 29 to 76% [26]. In our patient, ultrasonography revealed only one nodule in the right thyroid before the first parathyroidectomy. Notably, it was also difficult to distinguish between the IPA and benign thyroid nodules on ultrasound, possibly because of the small size and shape of the nodule. Owing to the recurrence of renal hyperparathyroidism, ultrasonography revealed that the right nodule gradually increased in size and that it was accompanied by an abundant peripheral blood supply. We speculated that metabolic derangements in ESRD patients can persistently stimulate parathyroid tissue. 99mTc-MIBI SPECT/CT allows anatomic visualization that aids surgical planning. However, it is less sensitive for detecting renal hyperparathyroidism (76.2–28.6%) than for detecting primary hyperparathyroidism (88.4–44.5%) [27, 28]. Other methods, such as enhanced-contrast CT, can also be used for detecting IPAs, which can be distinguished from thyroid nodules by peak enhancement in the arterial phase and rapid washout [29]. Fine needle aspiration (FNA) of the lesion can provide information on cell type and measurement of PTH level from FNA, theoretically aiding diagnosis with reported sensitivities ranging from 82 to 94% and 100% accuracy [30, 31]. In this case, 99mTc-MIBI SPECT/CT revealed persistent uptake at the right nodule in the right thyroid, a result that is consistent with characteristic features of IPAs on enhanced CT images. A multimodal approach was used in this case. There was also no evidence of focal accumulation, and nodules were found in the neck and mediastinum. Therefore, we can conclude that the nodule on the right is an IPA.

To date, there is no standard operative strategy for IPA, as it may be difficult for surgeons to visualize the IPA during surgery unless the sheath is opened. Precise preoperative localization of the IPA is crucial for successful parathyroidectomy. If the IPA is found perioperatively, thyroid lobectomy should be considered after a comprehensive search for normal adenomas and other ectopic adenomas [14]. Variability in operative success rates is likely due to differences in factors related to the patient, surgeon, centre, and surgical technique.

In conclusion, this is a rare case of recurrent hyperparathyroidism due to a gradually increasing fifth parathyroid gland within the thyroid of a patient who underwent long-term haemodialysis after parathyroidectomy. We suggest vigilant postoperative monitoring for prompt and early identification of culprit parathyroid lesions, even if the four parathyroid glands have been dissected.

Abbreviations

IPA	Intrathyroidal parathyroid adenoma
ESRD	End-stage renal disease
PTH	Parathyroid hormone
CT	Computer tomography
^{99m}Tc-MIBI	^{99m}Tc-sestamibi
SPECT	Single-photon emission computed tomography/computed tomography. FNA: Fine needle aspiration

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12882-024-03878-3.

Supplementary Material 1

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Author contributions
JY and NHL examined and drafted the manuscript. JLW contributed to interpretation of the clinical data. XHS are corresponding author and organized the study. All authors read and approved the final manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
This study was approved by Clinical Research Ethics Committee of the First Affiliated Hospital, Zhejiang University School of Medicine (IIT-20240732 A). Clinical trial number: not applicable.

Consent for publication
Written informed consent to publish has been obtained from the patient to publish the case.

Competing interests
The authors declare no competing interests.

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