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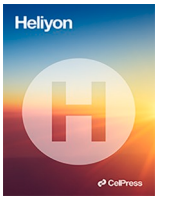

Case report

Efficacy of surufatinib in the treatment of advanced parathyroid carcinoma: A case report

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ABSTRACT

Parathyroid cancer is an extremely rare form of neuroendocrine malignancy. Apart from surgery, the effectiveness of chemotherapy and radiotherapy is limited, and the efficacy of targeted drugs remains unclear. In this study, we demonstrate the therapeutic effectiveness and adverse reaction of the targeted drug surufatinib in treating a case of parathyroid cancer, and concurrently review the recent advancements in the treatment of parathyroid cancer. The patient, a 55-year-old male, underwent his first surgery for a "right cervical mass" in May 2011. Postoperative pathology indicated an atypical adenoma of the parathyroid gland. In August 2016, the patient underwent a second surgery for recurrence of the right cervical tumor, with a pathological diagnosis of parathyroid cancer based on clinical history. In November 2017, the patient underwent a third surgery for recurrence of the right cervical tumor. In December 2017, the patient underwent adjuvant external radiation therapy. In August 2022, the patient developed spinal and lung metastases and underwent spinal surgery. Subsequently, the patient received three rounds of chemotherapy on October 5, 2022, October 28, 2022, and November 18, 2022, but the tumor showed slight enlargement. In January 2023, the patient began treatment with surufatinib. After two cycles of treatment, the tumor showed regression. Given the scarcity of systemic treatment options for parathyroid cancer, the targeted drug surufatinib may offer a promising potential treatment option.

1. Introduction

Parathyroid carcinoma is an extremely rare type of neuroendocrine malignant tumor. It was first reported in 1909 [1]. Most parathyroid cancers are functional, producing high levels of parathyroid hormone, resulting in hypercalcemia. They are a rare cause of primary hyperparathyroidism, accounting for approximately 1 % of cases [2]. Non-functional parathyroid cancer, lacking endocrine function and producing no parathyroid hormone, is notably rare, making up approximately 10 % of all parathyroid cancers [3]. According to a recent study based on the database of the National Cancer Institute in the United States, the incidence rate of parathyroid carcinoma is estimated to be 3.6 cases per 10 million people. In recent years, the overall incidence rate of parathyroid cancer has steadily increased [4].

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Diagnosing parathyroid carcinoma can be challenging due to the difficulty in differentiating it from atypical parathyroid adenoma based on pathological findings. Unfortunately, many patients are diagnosed with parathyroid carcinoma only after experiencing a recurrence following initial surgery [5]. Surgery is currently the only potential cure for parathyroid cancer [6], but the risk of post-operative recurrence and metastasis remains high.

Owing to the infrequency of parathyroid cancer cases and the scarcity of large-scale clinical studies, a unified consensus on systemic treatment has not been reached. Here, we present a highly unusual case of non-functional parathyroid cancer. This patient has undergone numerous surgeries and recurrences, and has undergone both radiotherapy and chemotherapy, with limited efficacy. Ultimately, we administered surufatinib, a novel oral tyrosine kinase inhibitor, achieving unexpected and positive outcomes. We share this case to inspire meaningful insights into the treatment of parathyroid cancer in challenging circumstances. This is the first documented case internationally that demonstrates the effectiveness of surufatinib in the treatment of parathyroid carcinoma.

2. Case presentation

The patient is a 55-year-old male who complained of a right neck mass for 5 years. He experiences no other discomforts, such as fever, pain or diarrhea. He has never undergone any treatment. His family history is free of cancer or genetic diseases. Preoperative PTH and blood calcium levels were normal. Physical examination revealed a right neck mass measuring approximately 10cm in diameter, which was non-tender. The following is a summary of key events and findings from the patient's medical history (Table 1): Preoperative ultrasound showed a solid, hypoechoic mass measuring 11.4 * 7 * 3 cm in the right neck, suggestive of a neuroendocrine tumor. Contrast-enhanced CT imaging confirmed the size of the right neck mass at 13*6*3.8 cm. In May 2011, the patient underwent the initial surgery, which completely removed the entire tumor. The pathological report is atypical parathyroid adenoma with an intact capsule (Fig. 1A) , not parathyroid cancer, as no evidence of malignancy has been found (Fig. 1B). Immunohistochemical staining indicated positive expression of Ki-67 (>30 %), CK (pan), CgA and Syn, whereas TTF-1 and calcitonin (CT) were negative. In August 2016, the patient was admitted to the hospital for the "recurrent mass in the right neck for 8 months without other symptoms" and underwent a second surgery to completely remove the recurrent mass and adjacent lymph nodes. The pathological results revealed metastatic tumors in the lymph nodes, indicating that they originated from parathyroid cancer (3 cm in diameter). Immunohistochemical staining indicated positive Ki-67 (about 5 %), CK, CGA, SYN and CD56, while TTF-1 and S-100 were negative. In November 2017, the patient was admitted to the hospital for the "right neck mass without other symptoms for 1 month" and underwent a right cervical lymph node dissection. Postoperative pathology confirmed the presence of metastatic low-differentiated neuroendocrine cancer originating from parathyroid glands. The largest tumor measured 3.8 cm in diameter. Immunohistochemical staining indicated positive Ki-67 (about 35 %), CK (pan), CgA, Syn and CK18, while CK19 was negative. In December 2017, the patient underwent adjuvant neck radiotherapy with a total dose of 60 Gy. In August 2022, the patient was admitted to the hospital due to chronic lower back pain and recent numbness in both lower limbs. Imaging studies revealed the following:1. Chest CT Imaging (Fig. 2A and D): Multiple solid nodules were observed in both lungs and ribs, suggesting a primary consideration for metastatic lesions. These findings indicated the likely spread of the cancer to the lungs. 2. Thoracic Spine MRI: Abnormal signal intensity and the formation of a soft tissue mass were detected around the T7 vertebral body. Degenerative changes were observed in the corresponding spinal cord.

Based on the patient's medical history and the imaging findings, a metastatic tumor was suspected. To alleviate the pain and

Table 1
Key events in the patient's medical history.

Time	Chief complain	Examination	Treatment	Pathology
2011.05	Right neck mass for 5 years	US and CT: a right neck mass	First surgery to remove the entire neck mass	Atypical parathyroid adenoma with an intact capsule
2016.08	Recurrent right neck mass for 8 months	US: a right neck mass	Second surgery to remove the recurrent neck mass	Parathyroid cancer with lymph node metastasis
2017.11	Recurrent right neck mass for 1 months	US and CT: a right neck mass	Third surgery to resect right neck lymph node	Metastatic poorly differentiated neuroendocrine carcinoma originating from the parathyroid
2017.12	One month after lymphadenectomy in the right neck		Radiation therapy with a total dose of 60 Gy	
2022.08	Chronic lower back pain and numbness in both lower limbs	CT: Multiple metastatic lesions in both lungs. MRI：For mation of a soft tissue mass around the T7.	Remove the spinal tumor and replace the affected vertebral body with an artificial one	Metastasis from a neuroendocrine tumor originating from parathyroid cancer
2022.09–2022.12	One month after the surgery for spinal metastases	After three cycles of Chemotherapy, lung CT was performed: comparison with the previous CT showed a slight increase in the size of certain lung metastases.	Three cycles of chemotherapy using the EC regimen (Etoposide and Carboplatin)	
2023.01	One month after three cycles of chemotherapy	After two cycles of surufatinib, lung CT was performed: Comparison with the previous CT showed a slight reduction in the size of certain lung metastases.	Treatment with surufatinib	

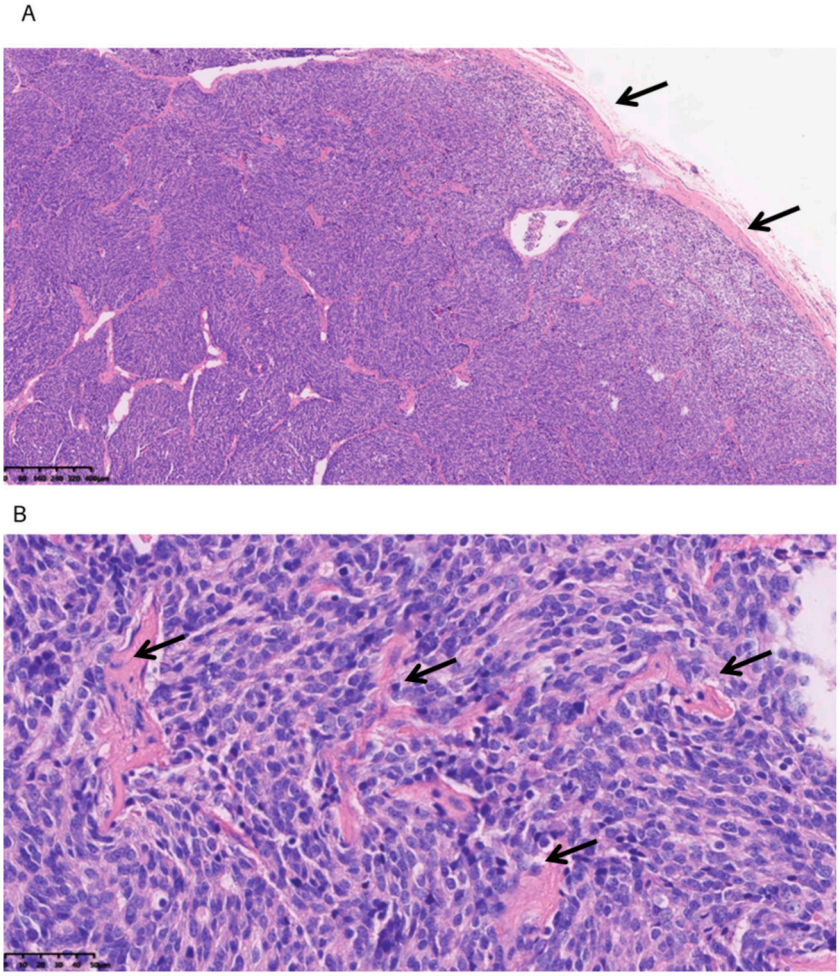

Fig. 1. Parathyroid carcinoma: histological features (hematoxylin-eosin staining). A: The tumor capsule is clear and intact (arrows). Original magnification × 100. B: The tumor shows prominent fibrous bands (arrows). The neoplastic chief cells of the parathyroid glands were arranged in nests and active proliferation. The cytoplasm is transparent, the nucleus is enlarged, and nuclear division can be seen. original magnification × 400.

numbness caused by spinal cord compression, a surgical procedure was performed to remove the spinal tumor and replace the affected vertebral body with an artificial one. Postoperative pathology examination confirmed the metastasis from a neuroendocrine tumor to the T7 vertebral body, indicating a metastatic spread originating from parathyroid cancer (Fig. 3). The immunohistochemical staining results showed positive findings for Ki-67 (10 %), CK (pan) (nuclear dot-like), CgA, Syn, P53 (sporadic), RB1, PTH, and CD56. However, TTF-1 and CK19 staining were negative.

Following the surgery, the patient underwent chemotherapy using the EC regimen (Etoposide 160mg on days 1–3 + Carboplatin 350mg on day 1, every three weeks) from October to December 2022. After completing three cycles of the chemotherapy protocol, a lung CT scan was performed to assess the treatment response. A comparison with the previous CT scan conducted in April 2022 showed a slight increase in the size of certain lung metastases (Fig. 2B). Additionally, changes in the morphology and density of the 11th rib, along with surrounding soft tissue density, indicated the presence of metastatic lesions (Fig. 2E). The treatment response was evaluated as stable disease (SD) with suboptimal effect, leading to the decision to discontinue chemotherapy (Fig. 2).

In December 2022, the patient underwent NGS (Next-Generation Sequencing) genetic testing at our hospital's key pancreatic disease laboratory to explore potential treatment options. DNA sequencing was conducted on paraffin-embedded tissues using the pan-cancer 520 gene detection kit. The results of the genetic testing were as follows: 1. Somatic variants: Four variants were identified, but none of them demonstrated clear or potential clinical significance. Additionally, no mutations were detected in commonly targeted drug-related genes such as ALK, BRAF, BRCA1, BRCA2, CSF-1R, CSF-3R, FGFR-1, FGFR-2, FGFR-3, FGFR-4, EGFR, ERBB2, KIT, MET, NRAS, NTRK1, NTRK2, NTRK3, PDGFRA, RET, KRAS, ROS1, VEGFA or VEGFB. Four variants with unclear clinical significance were detected, namely CTNNB1, FLT3, KMT2D, and PTPRD. 2. Tumor Mutational Burden (TMB): The TMB was determined to be 2.99. Based on the genetic testing results, no suitable targeted agents were identified, and there was no evidence supporting the use of immunotherapy as a treatment option.

On January 1, 2023, following the recommendations outlined in the Chinese Society of Clinical Oncology (CSCO) Neuroendocrine

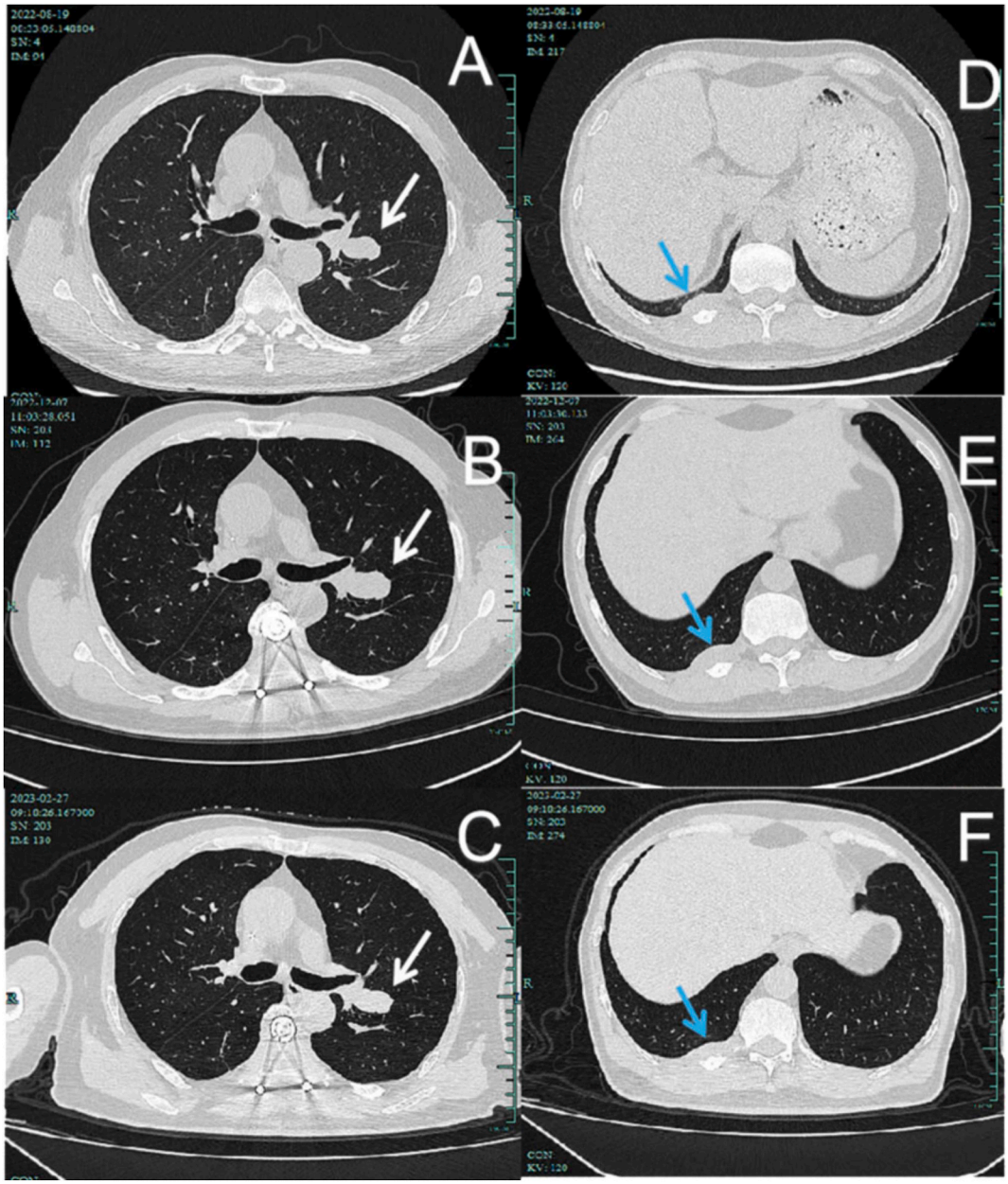

Fig. 2. Pulmonary metastasis originating from parathyroid carcinoma. A: In August 2022, lung metastases occurred. B: After three cycles of chemotherapy in December 2022, the volume of lung metastases slightly increased. C: After two courses of Surufatinib treatment in March 2022, lung metastases slightly regressed. D: In August 2022, a rib metastases was found. E: After three cycles of chemotherapy in December 2022, the volume of rib metastases slightly increased. F: After two courses of Surufatinib treatment in March 2022, the rib metastases slightly regressed.

Tumor Diagnosis and Treatment Guidelines (2022 edition), the patient started treatment with surufatinib, a novel oral tyrosine kinase inhibitor and targeting neuroendocrine tumors. The prescribed dose was 250 mg to be taken once daily for four consecutive weeks, constituting one treatment cycle. After completing two treatment cycles, a lung CT scan was performed to assess the treatment response on February 27, 2023. Compared to the CT scan taken two months earlier, the lung metastatic lesions showed a slight reduction in size (Figrue 2C). Additionally, the metastatic lesion in the right 11th rib exhibited slight regression compared to the previous scan (Fig. 2F). The treatment response was evaluated as a reduction in size with stable disease (SD), indicating an effective response. However, due to impaired renal function (severe proteinuria), the patient temporarily interrupted the use of surufatinib and is currently undergoing treatment to restore kidney function.

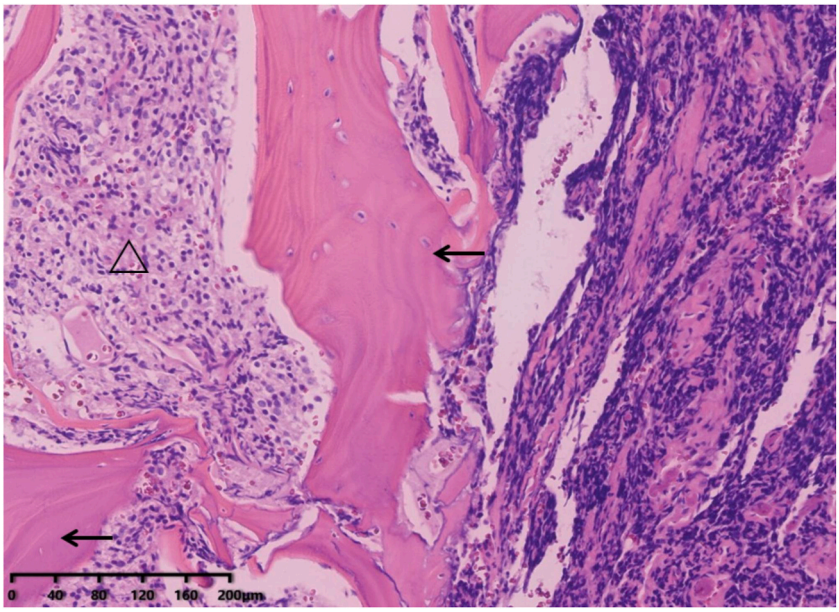

Fig. 3. Bone metastases originating from parathyroid carcinoma: histological features (hematoxylin-eosin staining). Bone (arrows) destruction, Partial cytoplasm of tumor cells (Triangel) is transparent, part of the cytoplasm is eosinophilic, and the nuclear atypia can be seen. original magnification × 200.

3. Discussion

The majority of parathyroid cancer cases present as hyperparathyroidism, typically resulting in severe complications including severe hypercalcemia, osteoporosis, fractures and the formation of urinary tract stones. However, this patient has an extremely rare form of non-functional parathyroid cancer, hence no severe complications; the only clinical manifestation is a neck lump. Prognosis for non-functional parathyroid cancer is often worse than that of functional parathyroid cancer [7–9].

Pathological diagnosis of parathyroid carcinoma is exceedingly challenging. Preoperative fine needle aspiration cytology and intraoperative rapid frozen section pathology have been found to be unreliable [10,11]. Pathologically, it is extremely difficult to differentiate parathyroid carcinoma from atypical parathyroid adenomas (APA), with certain features such as active mitosis, cellular atypia, and fibrotic bands being overlapping [12]. In fact, approximately 50 % of parathyroid cancers are initially misdiagnosed as parathyroid adenomas [5]. The reliable criteria for diagnosing parathyroid cancer are limited to the presence of tumor invasion of the capsule, along with evidence of invasive growth and distant metastasis. However, many cases of parathyroid cancer may not exhibit typical pathological features, but rather exhibit characteristics that overlap with APA, such as cellular dysplasia (Fig. 1B). As seen in this case, they may be easily misdiagnosed as APA in the early stages, and it is not until the disease shows signs of recurrence or metastasis that pathologists realize they are actually parathyroid cancer. Immunohistochemistry can be helpful in distinguishing APA from parathyroid carcinoma. When the KI-67 proliferation index is greater than 5 %, parathyroid carcinoma should be strongly suspected [13]. However, in this specific case, although the KI-67 index was greater than 30 % during the initial surgery, the intact capsule without signs of invasion led to the pathological diagnosis of atypical parathyroid adenoma. Subsequent immunohistochemical analysis following three recurrence surgeries revealed that while there were variations in KI-67 levels, they consistently exceeded 5 % (Table 2) . These variations in the KI-67 levels may be attributed to tumor heterogeneity. Additionally, despite multiple relapses, no changes in the differentiation level of tumor cells were observed in this case.

Surgical intervention is the primary and only treatment method that has the potential to achieve a cure for parathyroid cancer [6,8,14]. Complete removal of the tumor along with excision of adjacent tissues to achieve negative margins is crucial [15]. In cases where there is suspicion of the parathyroid tumor involving the thyroid gland, removal of the ipsilateral thyroid lobe is recommended. Maintaining the integrity of the tumor capsule during surgery is essential to prevent potential dissemination of the tumor [7]. The recurrence rate of parathyroid cancer is relatively high, typically occurring around 3 years on average after initial treatment, with a recurrence rate of up to 50 %. However, due to the slow progression of parathyroid cancer, there is generally a good long-term survival rate. The 5-year and 10-year survival rates range from 77 % to 100 % and 49 %–91 % respectively [16]. In the specific case being discussed, despite enduring multiple recurrences and undergoing several surgeries, the patient has achieved an impressive 12-year survival rate and remarkable resilience since their initial surgery.

Apart from surgery, there is a lack of effective systemic treatment for parathyroid cancer, and there is no unified consensus. Traditional systemic treatment methods, such as radiotherapy and chemotherapy, have very poor therapeutic effects [7,17]. The same scenario is also applicable to this case. In recent years, there have been sporadic reports indicating that certain targeted drugs have demonstrated promising efficacy in treating parathyroid cancer [18]. However, there is still a lack of large-scale clinical studies to

Table 2
Immunohistochemical indicators detected during previous surgeries.

Surgery	Ki-67	Syn	CgA	CK (pan)	TTF1	CD56	CK	CD56	S-100	CK18	CK19	RB1	P53	PTH	Calcitonin
The initial surgery	30 %	pos	pos	pos	neg	/	/	/	/	/	/	/	/	/	neg
The second surgery	5 %	pos	pos	/	neg	/	pos	pos	neg	/	/	/	/	/	/
The thrid surgery	35 %	pos	pos	pos	/	/	/	/	/	pos	neg	/	/	/	/
The fourth surgery	10 %	pos	pos	pos	neg	pos	/	/	/	/	neg	pos	pos	pos	/

confirm these findings. Therefore, in the current context, it is a reasonable choice to tailor personalized systemic treatment plans for each case of parathyroid cancer.

In a study, whole genome and RNA sequencing were conducted on patients with advanced parathyroid carcinoma to identify potential targeted drugs. In two cases, genomic and transcriptomic profiling identified targets for experimental treatments: one case, characterized by a high tumor mutation burden and single base substitution features associated with APOBEC (apolipoprotein B messenger ribonuclease, catalyzing peptide-like activities), was treated with pembrolizumab; the other case showed overexpression of FGFR1 (fibroblast growth factor receptor 1) and Ret (Ret proto-oncogene), and was treated with lenvatinib. Both treatments resulted in favorable biochemical responses and extended disease stabilization [19]. Mutations in the PI3K/AKT/mTOR pathway also have been found in certain cases of parathyroid cancer, suggesting the potential effectiveness of mTOR inhibitors [20–24]. A study reported that the combination of everolimus and vendetanib in the treatment of advanced parathyroid cancer achieved disease control and positive treatment response [25]. In addition, several studies have shown that the off-label use of antiangiogenic agents and tyrosine kinase inhibitors (TKIs) in the treatment of parathyroid cancer has also yielded positive therapeutic responses and disease control [25–28]. In the specific case mentioned, next-generation sequencing (NGS) gene testing was conducted, but no clinically significant gene target mutations were detected, and no suitable targeted drugs were identified. Immunotherapy is also not suitable for this patient, as his TMB is only 2.99, significantly below the threshold of 10.

It's worth noting that surufatinib has been recommended as a treatment option for unresectable neuroendocrine tumors in the 2022 edition of the Chinese Society of Clinical Oncology (CSCO) guidelines. Given the lack of better alternatives, we speculate that surufatinib might offer some therapeutic benefit in parathyroid cancer, after securing the patient's informed consent, we administered surufatinib to the patient. After two treatment cycles, a CT scan of the lungs surprisingly revealed a significant regression of lung metastases, indicating a positive treatment response evaluated as a reduction in stable disease (SD). Surufatinib is an oral angio-immuno kinase inhibitor that selectively targets VEGFR, FGFR1 and CSF-1R. However, genetic testing on this patient revealed no mutations in VEGF, FGFR1 and CSF-1R. Surufatinib, nevertheless, demonstrated exciting therapeutic efficacy. This is indeed an intriguing development. Surufatinib appears to exert its inhibitory effect on parathyroid cancer via molecular pathways that are not yet fully understood. This finding also serves as a reminder that beyond the well-known disease gene targets, there may be additional valuable targets yet to be identified. It warrants further investigation.

After two courses of 8-week of Surufatinib, the patient developed severe proteinuria. As the patient had no prior kidney disease, it was concluded that the proteinuria was caused by Surufatinib. Proteinuria is a common adverse reaction of Surufatinib, typically appearing after 4 weeks of use. Consequently, we suspended the use of Surufatinib and will resume it once the renal function has recovered.

Drawing upon the aforementioned research reports, including this case, targeted drugs have demonstrated promising prospects in treating parathyroid cancer, yet these are merely isolated reports. Additionally, different studies have identified varying targets through genetic testing, leading to the selection of distinct targeted or immunotherapy drugs. This underscores the considerable individual variation within parathyroid cancer, necessitating tailored systemic treatments for each case.

4. Conclusion

Owing to the rarity of parathyroid cancer, conducting large-scale clinical studies to establish standard guidelines for diagnosis and treatment proves exceedingly challenging. Consequently, offering personalized treatment to each patient, tailored to their unique circumstances, is presently the most optimal approach. Surgery offers an extremely effective treatment for early parathyroid cancer; however, it is less effective for advanced or recurrent parathyroid cancer. Chemotherapy and radiation therapy are not effective in treating parathyroid cancer. Based on the insights gained from this case and recent sporadic reports, targeted therapy may hold great promise in treating parathyroid cancer. However, personalized treatment must be provided based on genetic testing, considering the specific situation of each case. In this study, after failing to identify a suitable drug through genetic testing, we selected surufatinib for the patient on the basis of empirical treatment, unexpectedly achieving favorable results—this appears to be the first case worldwide of using surufatinib for parathyroid cancer. This indicates, firstly, that surufatinib is effective against parathyroid cancer, making it a favorable treatment option; Secondly, beyond our current understanding of genetic targets, there may be other effective genetic targets—it is possible that surufatinib acts upon these yet-unidentified targets. This warrants further exploration.

Ethics approval and consent to participate

This work has been carried out in accordance with the Declaration of Helsinki (2000) of the World Medical Associatio. This study was approved by the Ethics Committee of the First Affiliated Hospital of Zhejiang University [20230053], and all images/data are published with written informed consent from the patient.

Consent for publication

Not applicable.

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Data availability

All data included in this article are available upon request by contact with the corresponding author.

CRediT authorship contribution statement

Zhiyong Yu: Writing – original draft, Data curation, Conceptualization. **Jie Zhou:** Writing – original draft, Data curation. **Fuqiang Li:** Formal analysis, Data curation. **Xiaojun Xie:** Supervision, Data curation. **Liang Hu:** Methodology, Data curation. **Linghui Chen:** Methodology, Data curation. **Xuan Li:** Methodology, Data curation. **Qijun Zhang:** Writing – review & editing, Resources, Data curation. **Junli Wang:** Writing – review & editing, Methodology. **Yijun Wu:** Writing – review & editing, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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