

Successful pazopanib treatment of undifferentiated pleomorphic sarcoma with coamplification of *PDGFRA*, *VEGFR2* and *KIT*: A case report

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Received February 6, 2024; Accepted June 3, 2024

DOI: 10.3892/mco.2024.2767

Abstract. Undifferentiated pleomorphic sarcoma (UPS) is a high-grade, aggressive soft tissue sarcoma (STS) with a poor prognosis, and no definitive or effective treatment is currently available for it. Pazopanib, an orally available multiple tyrosine kinase inhibitor, has been approved for the treatment of advanced STS. The present study documents the case of a 51-year-old man with advanced UPS with coamplification of platelet-derived growth factor receptor A (*PDGFRA*), vascular endothelial growth factor receptor 2 (*VEGFR2*) and stem cell factor receptor (*KIT*) genes. The patient exhibited a marked and sustained response to pazopanib. The patient presented with a retroperitoneal tumour with pancreatic head lymph node metastasis, and bone metastases in the second/fifth thoracic vertebrae and left femur. Based on the histological analysis of the retroperitoneal tumour and femoral mass, the patient was diagnosed with UPS. Palliative radiation therapy was administered to the left femur and second/fifth thoracic vertebrae to prevent fractures. After radiation therapy, the patient achieved a partial response after eight courses of

doxorubicin. A comprehensive genomic profiling analysis (FoundationOne[®] CDx) revealed coamplification of *PDGFRA*, *VEGFR2* and *KIT* genes. Hence, pazopanib was initiated as a second-line treatment. Notably, the retroperitoneal tumour shrank, and no new lesions developed for 3 years after the initiation of pazopanib treatment. This response suggests that the coamplification of *PDGFRA*, *VEGFR2* and *KIT* may predict favourable outcomes in response to pazopanib.

Introduction

Soft tissue sarcomas (STSs) are rare malignant tumours, which account for approximately 1% of adult cancers and include more than 50 histologic subtypes (1,2). Although several treatments are available, the prognosis of metastatic STSs is poor, with a median overall survival (OS) of 12 months (3). Undifferentiated pleomorphic sarcoma (UPS) is characterized by no identifiable line of differentiation and multiple cellular patternless forms. The prognosis of patients with UPS with recurrence and metastasis is poor (4,5).

Pazopanib is an oral tyrosine kinase inhibitor (TKI) with activity against vascular endothelial growth factor receptor 1 (VEGFR1), VEGFR2, VEGFR3, platelet-derived growth factor receptor A (PDGFRA), PDGFRB, and stem cell factor receptor (KIT). Pazopanib has been approved for the treatment of advanced STSs (6). The phase III PALETTE trial included patients with non-adipocytic STSs and progressive disease after standard chemotherapy. Pazopanib improved progression-free survival (PFS) by 3 months than placebo in this trial. However, OS did not improve (2). The genetic features of patients with STSs who responded to pazopanib are unclear. Herein, we report the case of a patient with advanced UPS characterized by coamplification of *PDGFRA*, *VEGFR2*, and *KIT* genes who experienced a lasting and complete response to pazopanib.

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Abbreviations: ALK, anaplastic lymphoma kinase; CR, complete response; CT, computed tomography; EGFR, epidermal growth factor receptor; MRI, magnetic resonance imaging; OS, overall survival; PFS, progression-free survival; PR, partial response; RTK, receptor tyrosine kinase; SD, stable disease; STS, soft tissue sarcoma; TKI, tyrosine kinase inhibitor; UPS, undifferentiated pleomorphic sarcoma

Key words: STS, UPS, *PDGFRA*, *VEGFR2* amplification, pazopanib, 4q12 amplification

Case report

A 51-year-old man presented with abdominal pain and was admitted to Mitsui Memorial Hospital (Tokyo, Japan) in

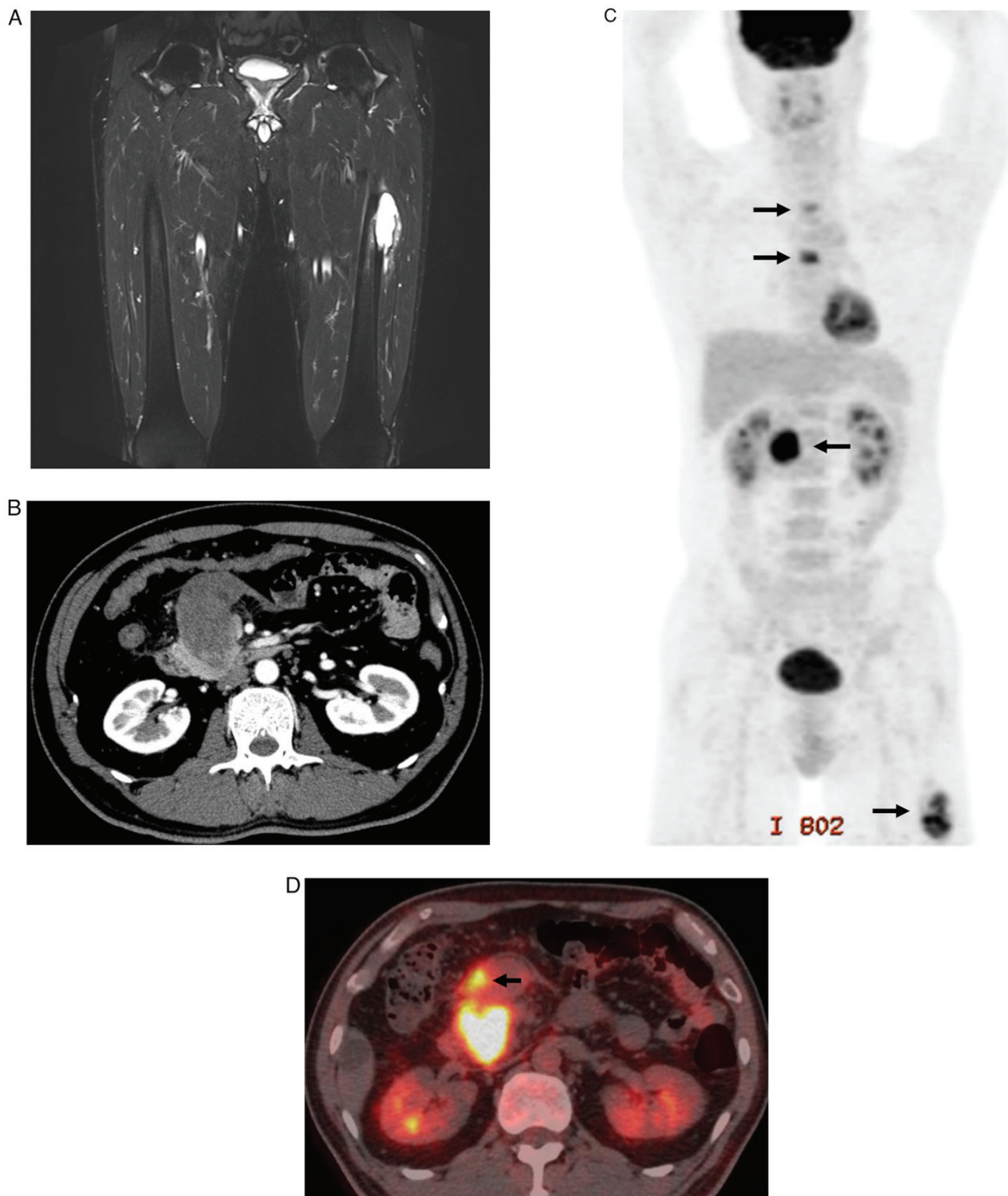


Figure 1. (A) Magnetic resonance imaging (T2-STIR) of the lower legs before treatment. (B) Computed tomography before treatment. (C) Coronal section and (D) axial section of positron emission tomography-computed tomography at the hospital visit. Black arrowheads indicate hypermetabolism.

March 2019, 10 months before visiting our hospital, Osaka International Cancer Institute (Osaka, Japan). Computed tomography (CT) revealed an unexplained intra-abdominal haemorrhage close to the pancreatic head. Pain and haemorrhage spontaneously improved with rest. One month before admission, the patient experienced swelling and pain in the left thigh. Magnetic resonance imaging (MRI) revealed a 6.5-cm femoral bone tumour in the left thigh with haemorrhage and

cortex osteolysis (Fig. 1A). Furthermore, 3 weeks before visiting our hospital, the abdominal pain reoccurred. CT revealed a retroperitoneal tumour with bleeding located in the groove adjacent to the pancreatic head (Fig. 1B). Hypermetabolism in the retroperitoneal tumour was detected using positron emission tomography-CT (PET/CT) at the time of the hospital visit. In addition, pancreatic head lymph nodes, second/fifth thoracic vertebrae, and left femoral bone tumours

Table I. Genomic findings.

Gene	Alteration
ATM	S2283
DNMT3A	R882H
TP53	R267P
CDKN2A/B	Loss
KIT	Amplification
PDGFRA	Amplification
VEGFR2	Amplification
NRAS	Amplification
CDK6	Amplification

Gene alterations were detected with the FoundationOne® CDx, a next-generation sequencing test. Microsatellite status: MS-Stable. Tumour Mutation Burden: 5 Muts/Mb.

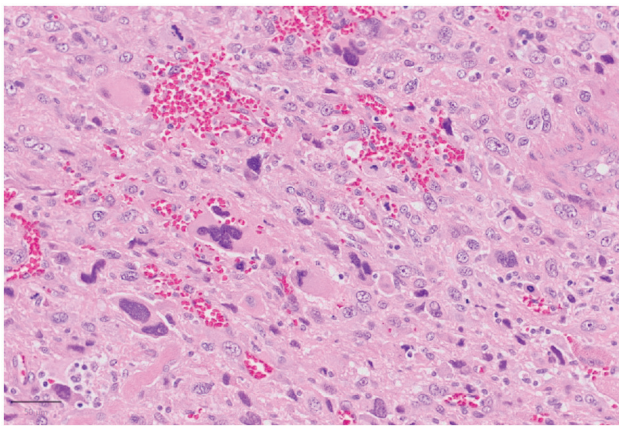


Figure 2. Haematoxylin and eosin staining of tissue sections revealed severe pleomorphism. Scale bar, 50 μ m.

were detected (Fig. 1C and D). Blood test did not show any abnormal condition, such as elevated inflammatory response, tumour marker changes, or anaemia. Histological analysis of retroperitoneal and left thigh tumour biopsies revealed pleomorphic cell proliferation in a haphazard arrangement (Fig. 2). The tumour cells were focally positive for α SMA and CK AE1/AE3 and negative for desmin, h-caldesmon, S-100, SOX10, and MDM2. Based on the morphology, immune profile, and clinical presentation, the patient was diagnosed with UPS arising from the retroperitoneum with bone and lymph node metastases.

To prevent pathological fractures due to bone metastases, the patient was treated with denosumab and radiation therapy (35 Gy in 5 fractions) of the left femur and second/fifth thoracic vertebrae. The patient was then treated with 75 mg/m² doxorubicin administered on day 1 of a 21-day cycle for 8 cycles. Due to fatigue, nausea, and vomiting, the dose was reduced to 80% and then to 60%. After chemotherapy, the retroperitoneal primary lesion and bone metastases shrank and no new lesions emerged, suggesting tumour partial response (PR) (Fig. 3A). To determine the second-line chemotherapy after doxorubicin reached the upper limit,

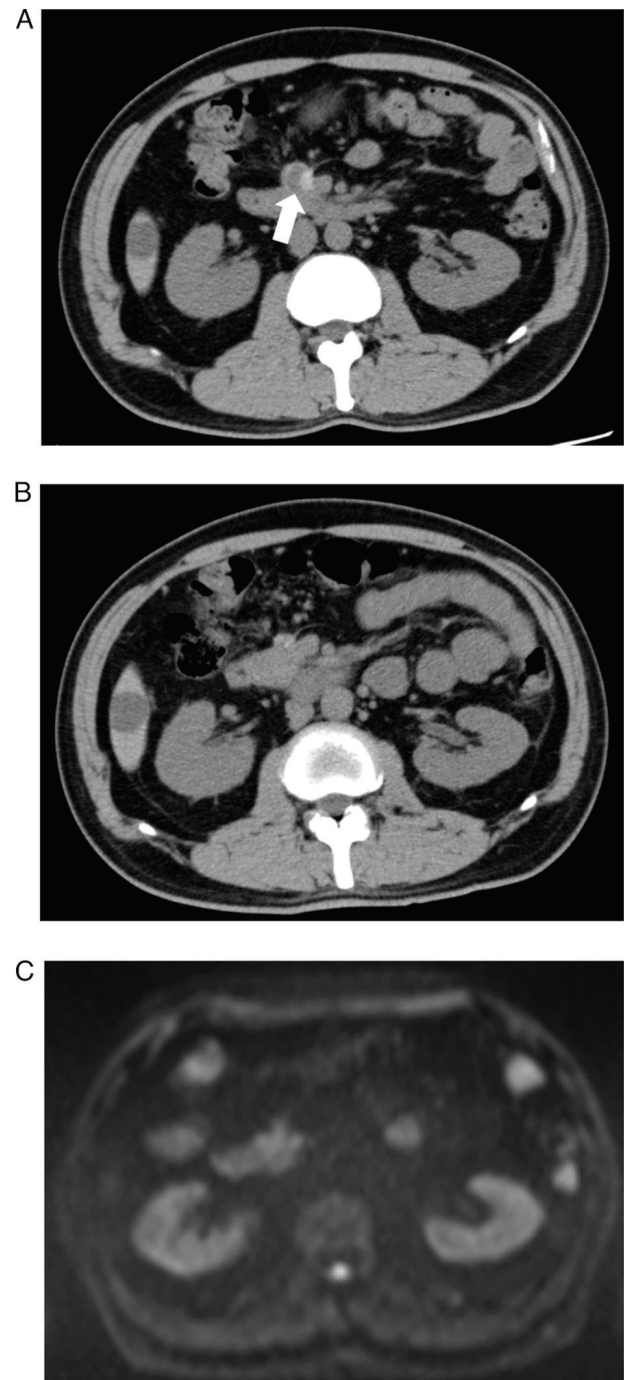


Figure 3. (A) Computed tomography after 8 cycles of doxorubicin. (B) Computed tomography 3 years after starting pazopanib. The white arrow-head indicates the retroperitoneal primary tumour. (C) Magnetic resonance imaging (diffusion-weighted imaging) after 3 years of pazopanib initiation.

a comprehensive genomic profiling test (FoundationOne® CDx, Foundation Medicine, Inc., Cambridge, MA, USA) was performed when the patient was receiving doxorubicin. FoundationOne CDx gene profiling can comprehensively identify 324 gene mutations using a next-generation sequencer and evaluate biomarkers, such as microsatellite status and tumour mutation burden (detailed information available at <https://www.foundationmedicine.com/genomic-testing/foundation-one-cdx>). Coamplification of the *PDGFRA*, *VEGFR2*, and *KIT* genes was detected (Table I). Pazopanib treatment

was recommended by the expert, which is an inhibitor of receptor tyrosine kinases (RTKs), based on *VEGFR2* amplification. Additionally, because pazopanib had inhibitory effects on *VEGFR2*, *PDGFRA* and *KIT*, it could be suitable. Therefore, 600 mg/day pazopanib was administered as second-line chemotherapy. However, the dose was reduced to 400 mg/day because of severe fatigue and diarrhoea. Surprisingly, the retroperitoneal primary tumour shrank more, and no new lesions developed for 3 years after the start of pazopanib treatment, indicating complete response (CR) (Fig. 3B and C). We performed follow-up imaging of the entire body by MRI and CT instead of PET-CT and did not observe any recurrence or metastasis after CR. Although grade 1 hypothyroidism and grade 2 hypertension were observed during 400 mg/day pazopanib treatment, no serious adverse events such as grade 3 or higher cytopenia occurred. Spontaneous pneumothorax is an evident and complicated side effect of pazopanib, and its occurrence is associated with lung metastasis (7,8). However, in this case, no lung metastasis or spontaneous pneumothorax was observed. Denosumab was discontinued within 3 years of treatment initiation.

Discussion

Matching treatment strategies with tumour biology is a central principle of precision medicine, and the ectopic activation of RTKs is a universal theme in oncogenesis. Oncogenic fusions involving RTKs such as anaplastic lymphoma kinase (*ALK*) and proto-oncogene 1 (*ROS1*), and small deletions in epidermal growth factor receptor (*EGFR*) predict patient response to target-matched TKIs, especially in the context of non-small-cell lung cancer (9,10). Amplification of wild-type RTK genes, such as human epidermal growth factor receptor 2 (*HER2*), in breast and gastric cancers drives oncogenesis, and RTKs are therapeutic targets (11,12). Thus, the coamplification of *PDGFRA*, *VEGFR2*, and *KIT*, which is related to chromosome 4q12 amplification, may be an oncogenic driver and therapeutic target (13). Phase II trial of axitinib, a TKI of PDGFRs, *VEGFR2*, and *KIT*, included patients with recurrent adenoid cystic carcinoma. The longest responder (nearly four times longer than the median PFS for the study cohort) in this trial was a patient with amplified *PDGFRA*, *VEGFR2*, and *KIT* (14). We detected the coamplification of *PDGFRA*, *VEGFR2*, and *KIT* in UPS. Therefore, we treated the patient with pazopanib with second-line therapy. Interestingly, CR was achieved and maintained for 3 years with pazopanib. To the best of our knowledge, this is the first report to demonstrate that pazopanib was effective against STS with coamplified *PDGFRA*, *VEGFR2*, and *KIT*.

PDGFRA, *VEGFR2*, and *KIT* genes are located on chromosomal locus 4q12; hence, the concurrent amplification of these genes may be due to the overall amplification of chromosome 4q12. Coamplification of these RTKs is present in 0.86% of TCGA cases across all cancers and is more common in sarcomas and central nervous system neoplasms (13). In the Sarcoma Genome Project dataset, putative high-level amplifications of *PDGFRA*, *VEGFR2*, and *KIT* were reported in 3, 2 and 2.4%, respectively, of cancer cases (15). Although rare in absolute numbers, the coamplification frequency of these

genes is consistent with other uncommon but highly targetable oncogenic kinase alterations, such as *NTRK* (16).

Pazopanib, which is the only approved noncytotoxic STS therapy, is an orally available inhibitor of multiple RTKs, including *VEGFR1-3*, *PDGFRA/B*, *FGFR1/3/4*, and *KIT*. The antitumor activity of pazopanib is attributed to antiangiogenic effects and inhibition of pro-proliferative signals mediated by RTKs on the surface of STS cells (17-19). Several clinical trials demonstrated survival benefits of pazopanib in patients with STS. In the PALETTE trial with 246 patients, none of the patients with STS had CR, 6% (14) had PR, 67% (164) had stable disease (SD), and 23% (57) had progressive disease (PD) (2). In the placebo arm, 0% (0 of 123) of patients had CR, 0% (0) had PR, 38% (47) had SD, and 57% (70) had PD (2). In a study by the Japanese Musculoskeletal Oncology Group, none of the 125 enrolled patients achieved CR (8). Therefore, achieving CR with pazopanib is rare in patients with STS. CR can be obtained in this case; however, it was not maintained in advanced UPS as per our experience. Furthermore, no standard treatment strategy has been established for treating sarcoma. Therefore, making a decision regarding the discontinuation of pazopanib was challenging. However, because CR persisted for a long time, discontinuation of pazopanib will be an important issue for future consideration.

The challenge of establishing reliable biomarkers for responsiveness to pazopanib has been addressed by several studies. Retrospective analyses of two EORTC studies and a real-world cohort of pazopanib-treated patients revealed that specific histologic types, including synovial sarcoma and desmoplastic small round cell tumour, and clinical parameters, including good performance status, low or intermediate tumour grade, and a normal haemoglobin levels, correlated with better outcomes (20,21). Several studies also explored the importance of molecular characteristics in selecting patients who may benefit from pazopanib. Heilig *et al* (22) analysed the molecular profiles and clinical outcomes of sarcoma patients treated with pazopanib and demonstrated that *VEGFR2*-high, *NTRK3*-high, and *IGF1R*-low mRNA levels were independently associated with PFS. In patients with advanced STS who exhibited short-term high-grade PR or long-term SD, Suehara *et al* (23) demonstrated that amplified *GLI1* and elevated PDGFRB phosphorylation levels were linked to high antitumor activity of pazopanib. Using gene panel sequencing in 19 pazopanib-treated patients, Koehler *et al* (24) demonstrated that *TP53* mutations correlated with better outcomes after pazopanib therapy. The present case suggests that STSs with amplified *PDGFRA*, *VEGFR2*, and *KIT* are rare; however, patients with these features may benefit from pazopanib therapy. A limitation of this study was the absence of immunohistological analysis, including markers such as *PDGFRA*, *VEGFR2*, *KIT*, VEGF, and PDGF. Therefore, further studies are required to confirm the benefits of pazopanib in patients with coamplification of *PDGFRA*, *VEGFR2*, and *KIT*, and to establish predictive markers for pazopanib sensitivity.

Acknowledgments

Not applicable.

Funding

This research was supported by MEXT KAKENHI (grant no. JP22K09421).

Availability of data and materials

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

Authors' contributions

HM, SN, KY and ST made substantial contributions to the conception and design of the study, acquisition of data, and analysis and interpretation of data. HM and SN confirm the authenticity of all the raw data. RS, YI, HaT, MW, TW, HiT, HO, TY and SK contributed to data acquisition, conception, and reviewed and edited the manuscript. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Written informed consent was obtained from the patient to publish this case report and all accompanying images.

Competing interests

The authors declare that they have no competing interests.

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