

# Pazopanib monotherapy in a patient with a malignant granular cell tumor originating from the right orbit: A case report

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**Abstract.** Granular cell tumors are uncommon, usually benign tumors of Schwann cell origin. The malignant variant is extremely rare, representing <2% of all granular cell tumors. Therefore, standard systemic chemotherapy for this disease does not exist. The present study reports the case of a 40-year-old female with a malignant granular cell tumor that originally arose in the right orbit and subsequently relapsed. The patient was started on pazopanib monotherapy following treatment with two investigational drugs, a smoothened inhibitor and then a phosphatidylinositol 3-kinase inhibitor, as part of a clinical trial. Although additional radiotherapy for local control was necessary, the lung metastases remained stable during the pazopanib monotherapy, which lasted for 7 months, following which a clinically stable disease state was determined. This case suggests that pazopanib can be a treatment option for the stabilization of disease progression in metastatic malignant granular cell tumor.

## Introduction

Granular cell tumors (GCTs) are rare tumors that can occur at various sites in the body, with the most common locations being the skin and subcutaneous tissues (1). GCTs are believed to be Schwann cell derivatives (1) and are listed under the neural tumors in the 2006 World Health Organization (WHO) classification of tumors (2). The majority of GCTs are benign, and malignant cases are scarce, representing <2% of all GCTs (2,3). The new WHO classification of tumors of the soft tissue and bone incorporates peripheral nerve sheath tumors, including GCTs, into a category with soft-tissue tumors (4).

For patients with unresectable malignant GCTs, the current clinical opinion is to treat the condition in line with the sarcoma-based protocol (5). However, there is little evidence for the use of systemic therapy for this rare malignancy, with only a few published case studies (6-8).

The present study reports a case of metastatic malignant GCT treated with pazopanib monotherapy.

## Case report

In 2011, a 40-year-old female was referred to Nagoya University Hospital (Nagoya, Japan) for treatment of a malignant GCT that originally arose in the right orbit and subsequently relapsed. The primary tumor was initially resected surgically when the patient was aged 38 years, followed by two other resections for local recurrence after a year. The pathological findings of the last resected tumor met five of the six criteria (spindling, vesicular nuclei with large nucleoli, increased mitotic activity, a high nuclear to cytoplasmic ratio and pleomorphism, but no necrosis) proposed by Fanburg-Smith *et al* (3) to define histological malignancy (Fig. 1). No other chemotherapy or radiotherapy was administered. At the time of presentation to Nagoya University Hospital, the patient exhibited a locally recurrent tumor in the right orbit, and multiple metastases in the pulmonary and cervical lymph nodes. The patient initially received radiotherapy (50 Gy/25 fractions) to the local lesion for pain control, followed by treatment with a smoothened inhibitor and then a phosphatidylinositol 3-kinase inhibitor in the setting of a clinical trial. The primary and metastatic lesions remained stable for 9 months during treatment with the latter agent. When tumor regrowth was diagnosed, pazopanib monotherapy was commenced at a standard oral dose of 800 mg daily, 2 weeks after completing treatment with the last investigational drug. At 2 months after the initiation of pazopanib treatment, computed tomography scans of the chest showed that a number of the pulmonary metastases had partially shrunk (Fig. 2). The major adverse events included grade 2 fatigue and grade 2 hypertension. The hypertension was well controlled using 5 mg amlodipine

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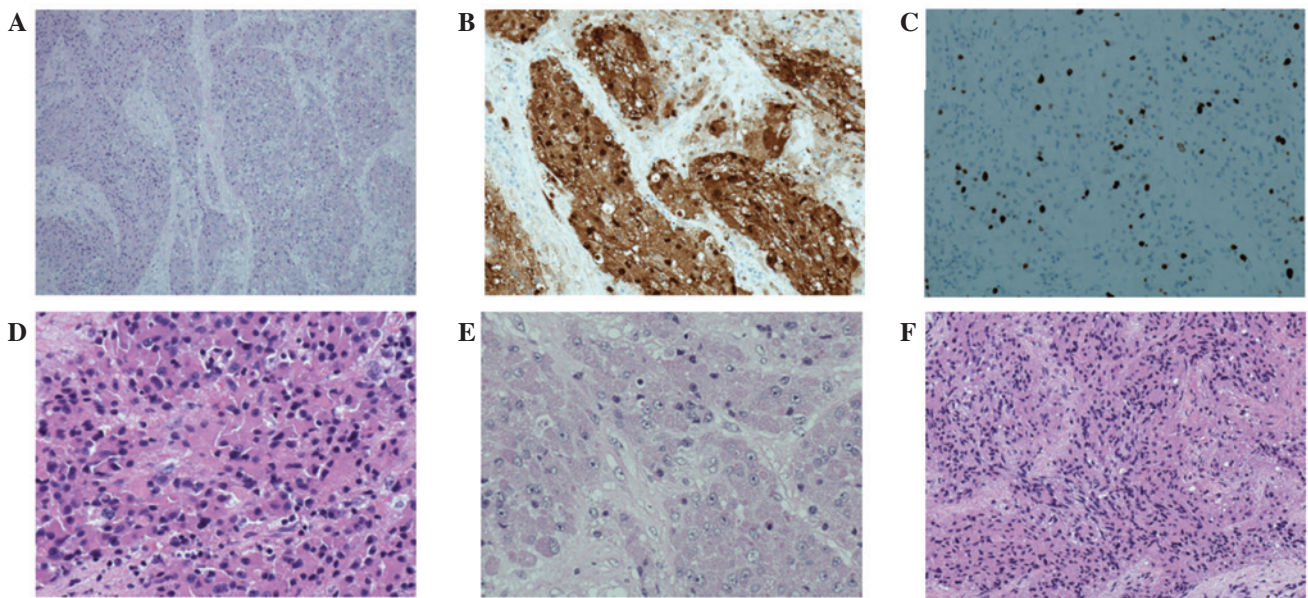


Figure 1. Pathological features of the tumor that (A) consisted of cells with abundant eosinophilic granular cytoplasm [hematoxylin and eosin (H&E) staining; magnification, x200] and (B) stained positive for S-100 (magnification, x200). (C) The MIB1-index was 9.7% (magnification, x200) and the tumor exhibited (D) a high nuclear to cytoplasmic ratio (H&E; magnification, x400), (E) vesicular nuclei with large nucleoli (H&E; magnification, x400) and (F) spindle cells (H&E; magnification, x200).

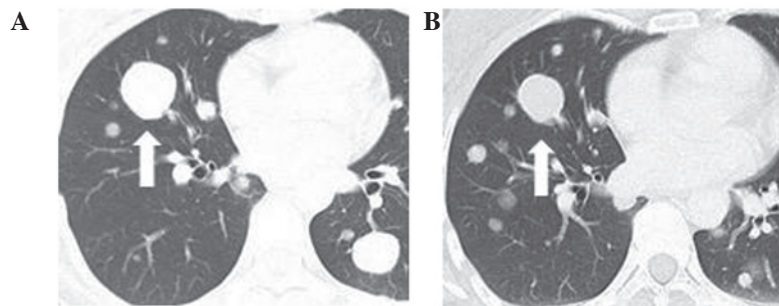


Figure 2. Chest computed tomography scans (A) prior to pazopanib treatment and (B) 2 months after pazopanib treatment began, showing shrinkage of a few of the pulmonary metastases (arrow).

tablets, once a day. Although additional radiotherapy to the local recurrent tumor (34 Gy/17 fractions) and cervical lymph nodes (40 Gy/20 fractions) was considered necessary, the lung metastases remained stable during the pazopanib monotherapy for 7 months, suggesting that pazopanib was effective at least in terms of stabilizing disease progression. Pazopanib therapy was discontinued after 7 months due to fatigue. Next-generation sequencing using the Foundation Medicine T5a platform (Foundation Medicine, Inc., Cambridge, MA, USA) implemented in the clinical trial by Novartis revealed that the tumor from the last surgical resection exhibited a somatic mutation in the additional sex comb-like 1 (*ASXL1*) gene (1174C>T; Q592\*) (9).

This study was approved by the institutional review board of Nagoya University Hospital, and consent was obtained from the patient.

## Discussion

Malignant GCTs are rare tumors. The criteria proposed by Fanburg-Smith *et al* (3) for diagnosing malignant GCTs is

well-known. However, the diagnosis between a benign tumor and a malignant tumor without metastases is difficult. Also, in the present case, the primary tumor behaved in a benign fashion and acquired aggressiveness whenever it locally recurred. Following the last resection of the local recurrence, it metastasized within a short span of only 6 months. For malignant GCT, the only standardized therapy is a local wide excision, and the role of chemotherapy and radiotherapy remains indefinite. To the best of our knowledge, there has been only one reported case of a good response of a malignant GCT to chemotherapy (6). Malignant GCT is believed to be an aggressive chemorefractory disease. Recently, Conley *et al* (7) reported a case of metastatic malignant GCT in which pazopanib monotherapy achieved a response; this was similar to the experience recorded for pazopanib monotherapy in the present study. Pazopanib is an oral, small-molecule inhibitor of vascular endothelial growth factor receptor-1, -2 and -3, platelet-derived growth factor receptor- $\alpha$  and - $\beta$ , and c-kit, which has shown single-agent activity in patients with advanced soft-tissue sarcomas (10,11). Pazopanib therapy was used in the present study as the phase

III study of pazopanib in advanced soft-tissue sarcoma included one patient with a malignant GCT who experienced stable disease and tumor shrinkage (8,11). To this date, three patients with malignant GCT who achieved clinical benefits with pazopanib monotherapy, including the present case, have been recorded. This is a noteworthy finding for the treatment of this rare tumor.

The present patient had been enrolled in investigational drugs studies and had undergone next-generation sequencing. The tumor exhibited a somatic mutation in the *ASXL1* gene (1174C>T; Q592\*). The *ASXL1* gene is one of the human homologues of the *Drosophila Asx* gene, which is located at human chromosome 20q11.21. ASXL1 protein is involved in transcriptional activation and repression in a context-dependent manner (9). The initial study on human *ASXL1* mutation was performed in 2009, in patients with myeloid malignancies (12). Now, gene amplification and truncation mutations of *ASXL1* are known to exist in various types of cancer (9). Although *ASXL* is worthy of note as a new target of cancer therapy, it is necessary to clarify the clinical significance of *ASXL* gene alternation. This is the first report to discover the presence of the *ASXL1* mutation in a patient with a malignant GCT.

In conclusion, the results of the present study together with two previous cases suggest that pazopanib may be a safe, effective and reasonable treatment option for GCT. This finding should be investigated and validated, preferably by clinical trials or given the rarity of this disease, by other case studies.

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