Effective Treatment of Pleural Epitheloid Hemangio-endothelioma with Pazopanib: A Case Report

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Abstract. *A patient with a pleural epitheloid hemangio-endothelioma (EHE) who failed to respond to six cycles of initial chemotherapy with iphosphamide and epirubicine was treated with pazopanib in second-line. A significant subjective and objective metabolic response on ^{18}F-fluoro-deoxyglucose positron-emission tomography-computed tomography was noted. Based on this observation, the role of vasculoendothelial growth factor receptor inhibitors such as pazopanib (or other tyrosine kinase inhibitors), in the treatment of pleural EHE should be established through prospective collaborative studies as upfront medication and in combination with chemotherapy.*

Epitheloid hemangio-endothelioma (EHE) is a rare vascular tumor of borderline to low-grade malignancy occurring predominantly in the liver, lung, pleura and other organs such as soft tissue or bone (1). The prognosis is very unpredictable, with life expectancy ranging from 1 to 15 years (2). Cytotoxic chemotherapy is relatively ineffective leading at most to stable disease, clinical improvement in some patients and is often associated with major toxicity. Immunohistochemical techniques demonstrated the presence of vasculoendothelial markers (3). Several case reports and phase II studies have explored the activity of inhibitors of angiogenesis including monoclonal antibodies and anti-vasculoendothelial growth factor receptor (VEGFR) tyrosine kinases in EHE in first-, second- and further-line treatment. However, only one case with the pleura as major initial tumor was reported, a case in which a combined bevacizumab-paclitaxel treatment was not effective (4, 5).

Pazopanib is a second-generation tyrosine kinase inhibitor with high selective activity against VEGFR, platelet-derived growth factor (PDGFR) and mast/stem cell growth factor receptor (c-KIT) that has demonstrated significant clinical benefit in a variety of malignancies, especially as a first-line treatment in metastatic renal clear cell cancer and in second-line treatment in soft tissue sarcoma (STS) (6, 7). We herein report, to our knowledge for the first time, a patient with a pleural EHE who failed first-line standard chemotherapy but showed a remarkable, albeit relatively short-lasting objective and subjective response to second-line pazopanib monotherapy.

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Case Report

A 39-year-old male patient was referred from the Pulmonology Department of another Hospital for treatment of inoperable pleural EHE in the right hemi thorax. This patient underwent a partial amputation and conservative plastic surgical interventions of the left foot because of osteomyelitis in his childhood. He was treated for hypertension with 400 mg acebutolol, 20 mg enalapril and 1.25 mg indapamide per day. He was a non-smoker but indicated a brief episode of possible exposure to asbestos during his childhood. The patient reported right shoulder pain of 2 years' duration. Standard chest radiography and computerized tomography (CT) of the thorax demonstrated disseminated thickening of the right pleura with a small pleural effusion. On 7/05/2014, limited thoracotomy with multiple biopsies was performed to rule-out mesothelioma. Histopathology demonstrated the presence of EHE with a solid growth pattern (Figure 1). No bronchoscopy was performed at initial presentation. In order to relieve pain in the right chest wall and shoulder a symptomatic treatment with analgesics and anti-inflammatory medication (1,000 mg paracetamol and 75 mg diclofenac) was prescribed. The patient was referred to our Hospital for systemic treatment. Between 3/07/14 until 20/10/14 (last administration), six cycles of iphosphamide (2,000 mg total dose per day intravenously for 5 days) and epirubicine (150 mg total dose intravenously on day 1 of each cycle) with standard supportive medication consisting of intravenous 4 mg

ondansetron, 40 mg methylprednisolone, 50 mg methylene blue and 2000 mg mesna each day were completed with an interval of three weeks. ^{18}F-Fluoro-deoxyglucose positron-emission tomography (FDG-PET)/CT acquired before and after this treatment showed stable disease (SD) (Figure 2A and B), while no decrease in pain occurred (intake of analgesic medication remained identical). A second-line treatment with pazopanib, at 2×400 mg per day was started from 18/12/14. Immediately (at the first toxicity checkup visit 14 days after the start of the new medication), the patient reported less pain in the right chest wall/shoulder and reduction and ultimately ending of pain/anti-inflammatory medication was achieved.

FDG-PET/CT performed after 3 and 6 months of pazopanib treatment showed a dramatic metabolic response, while the CT image remained stable (Figure 2C; only the image at 6 months is shown). A repeated biopsy of the pleura performed after 8 months of treatment at another localization, compared with the initial biopsy, showed vital cancer cells in approximately 5% of the biopsy and hyaline fibrosis in the remainder. After 6 months of treatment, the administration of pazopanib had to be stopped for 2 weeks because of digestive toxicity (abdominal cramps, bloating and anorexia, with significant weight loss). Treatment was then resumed at 400 mg per day for 7 days and in the absence of toxicity, continued with 2×400 mg afterwards. Immediately after stopping pazopanib, the aforementioned side-effects gradually disappeared but the patient again reported more pain in the right thoracic wall and shoulder and the analgesic and anti-inflammatory drugs had to be increased compared with the period before discontinuation. This situation was completely reversed within 2 weeks when pazopanib was again increased to 2×400 mg per day. Finally, the patient complained of more pain in the right shoulder and increased use of more analgesics upon withdrawal of the drug, again due to digestive toxicity. Unfortunately a few weeks later, he was admitted to the hospital with high fever and frank right-sided pneumonia was diagnosed. At this time, an occlusion of the right stem bronchus with macroscopic tumor was found at bronchoscopy and biopsy showed infiltration with EHE cells, compatible with the initial biopsy. A checkup with CT scan also showed massive progressive disease in the left lung and bone. A third-line treatment with trabectidin was initiated without success. The patient finally died in respiratory failure.

Discussion

STS and EHE are rare, heterogeneous tumors from mesenchymal/connective tissue origin with vasculo-angiogenic properties. These tumors can originate from any organ and can vary from an indolent metastatic tumor to an aggressive rapidly-growing disease. Systemic chemotherapy of these locally advanced and metastatic tumor types is generally associated with disappointing results, with 5-year survival rates in the range of 30% (2). The sometimes low malignant potential and low cellular proliferative rate of this type of tumor may account for this.

The anti-angiogenic drug pazopanib has been licensed as second-line treatment in STS and hints of anti-tumoral activity have been noted using this drug in first-, second- or further-line treatment (4). We herein report the effect of pazopanib on the pleural variant of EHE. In our patient, an almost immediate analgesic effect was observed. Serial FDG-PET/CT scans demonstrated a significant metabolic response in lung and pleural lesions, with only minimal changes in lesion size on CT imaging. The regression of metabolic activity occurring under treatment with pazopanib has to be considered as a true antitumor effect because it is very unlike that the lesions were induced by *e.g.* limited thoracotomy and regressed spontaneously. Firstly, this patient underwent a limited thoracotomy for multiple biopsies without pleurodesis, approximately two months before the initiation of chemotherapy. It has been shown that pleural PET positivity induced by pleurodesis may persist for 3 to 6 months post-pleurodesis (8). Because no pleurodesis was performed in our patient, the possibility of spontaneous regression of FDG-PET-positive lesions in the pleura following the potential inflammatory action of pleural talcage is ruled out. Secondly, the metabolic and clinical subjective response observed in our patient was in strict correlation with the initiation, withdrawal and restart of pazopanib therapy. The impact on lesion size (CT), however, was much less pronounced compared to the decrease in metabolic activity on FDG-PET. It has been suggested that PET rather than CT be used to assess response with cytostatic drugs such as angiogenesis inhibitors (9, 10). In the present patient, the CT response was classified as SD and was clearly inferior compared to the clinical and PET response.

It is not clear from the literature which patients with STS benefit the most from treatment with pazopanib. In a sub-analysis of two studies [European Organization for Research and Treatment of Cancer clinical trials 62043 and 62072 (PALETTE)], it was shown that patients who presented with good performance score, low/intermediate grade of the primary STS and a normal hemoglobin at baseline were long-term survivors (11). All these elements were present in the described case.

No routine predictive biomarkers for response and long-term survival in the plasma or in tumor tissue are available at this moment for STS. It was, however, demonstrated that VEGF and VEGFR are overexpressed in EHE and solitary fibrous tumor/hemangiopericytoma resistant to classical chemotherapy (12). Therefore, it may be useful to study the markers of dysfunctional angiogenesis before embarking on chemotherapy or tyrosine kinase inhibitor therapy for STS.

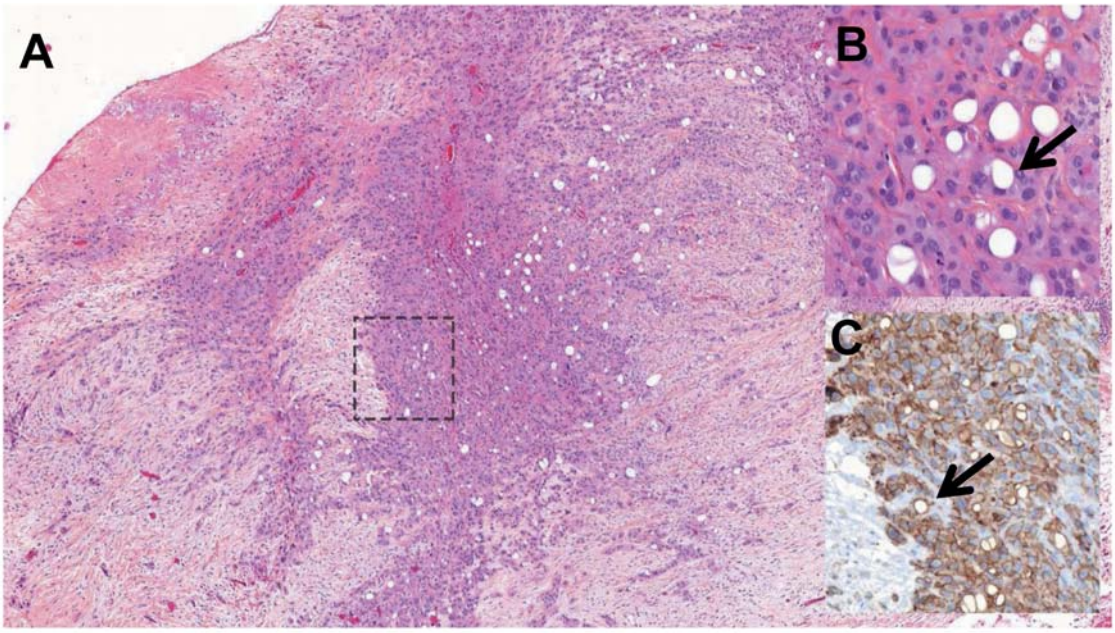

Figure 1. *Hematoxylin-eosin-saffron staining (magnification ×5) of pleura showing vital epitheloid hemangio-epithelioma cells with solid growth pattern (A). In the inset (B; ×20), the characteristic cytoplasmic vacuolization, well-defined limited atypical cells and myxohyaline stroma can be observed (arrow). Immunohistochemistry inset (C) shows strong membranous staining that also highlights the cytoplasmic vacuoles (arrow), confirming the endothelial origin of the neoplastic cells.*

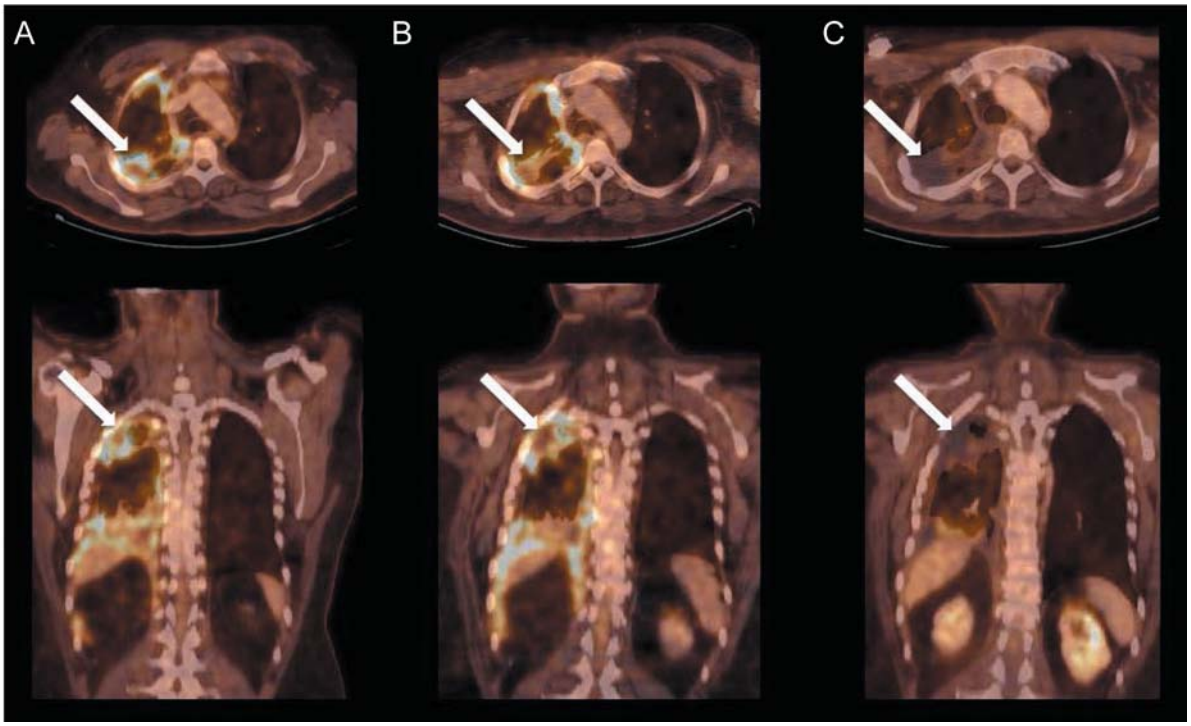

Figure 2. *Transverse and coronal ^{18}F-fluoro-deoxyglucose positron-emission tomography–computed tomographic images at baseline (A), after six cycles of chemotherapy (B) and 6 months of pazopanib treatment (C). The standard uptake value (arrows point at locations of measurements) at baseline, after six cycles of chemotherapy and 6 months of pazopanib treatment were 11.7, 12.6 and 4.6, respectively.*

Other compounds targeting the VEGF and VEGFR system have been studied in monotherapy and in combination with chemotherapy in STS but failed to show any significant activity (*e.g.* bevacizumab, thalidomide, lenalidomide and sorafenib) (4).

The toxicity produced by pazopanib administered in standard doses was initially less than grade 1. After 6 months of treatment however, the drug had to be temporarily withdrawn for 2 weeks because of grade 3 digestive symptoms with abdominal cramps, bloating, and anorexia and weight loss. A dose re-escalation to 400 mg and 800 mg per day for a limited period of time was feasible afterwards but unfortunately, pazopanib had to be stopped definitively because of progressive disease and unacceptable toxicity in this case. It is not clear if the progressive disease correlated with withdrawal of the drug. In summary, to the best of our knowledge, we herein report the first case of pleural EHE responding favorably but only temporarily to second-line pazopanib monotherapy. Future studies with VEGFR will need to determine which drug works best for the different sub-types of STS, which combination with traditional chemotherapy and other targeted therapies is most useful, and which novel molecular and imaging biomarkers are predictive for response.

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