

Case Report

Pazopanib-Induced Cutaneous Leukocytoclastic Vasculitis: An Exclusion Diagnosis of a Multidisciplinary Approach

Diogo Alpuim Costa^a Susana Baptista de Almeida^b
Pedro Coelho Barata^c António Quintela^a Pedro Cabral^d Ana Afonso^e
João Maia Silva^f

^aHaematology and Oncology Department, Instituto CUF de Oncologia (I.C.O.), Lisbon, Portugal; ^bOncology Department, Hospital Prof. Doutor Fernando Fonseca, Lisbon, Portugal; ^cExperimental Therapeutics Fellow, Cleveland Clinic, Cleveland, OH, USA; ^dRadiology Department, Instituto CUF de Oncologia (I.C.O.), Lisbon, Portugal; ^ePathology Department, Instituto CUF de Oncologia (I.C.O.), Lisbon, Portugal; ^fDermatology Department, Instituto CUF de Oncologia (I.C.O.), Lisbon, Portugal

Keywords

Renal cell carcinoma · Leukocytoclastic vasculitis · Pazopanib

Abstract

In phase II/III trials, cutaneous side effects of pazopanib were reported in less than 20% of patients, with only 1–3% being grade 3/4. We present a case of a 66-year-old man with a previous history of left nephrectomy for a stage II clear cell renal carcinoma. Approximately 18 months later, recurrent disease in the lungs, mediastinum, and left psoas and bulky abdominal/pelvic nodal metastasis were documented. He was initially treated with pazopanib 800 mg q.d. and 1 week after starting this therapy, the patient presented with palpable purpura on his ankles. These lesions regressed within 2 weeks off pazopanib, but had recurred 4 weeks after he resumed medication at 400 mg q.d. Biopsy of the lesions revealed leukocytoclastic vasculitis. Despite tumour response to therapy, pazopanib was discontinued with total

resolution of this skin toxicity within 2 weeks of his cutaneous toxicity. To the best of our knowledge, we report a rare yet significant cutaneous adverse reaction to pazopanib.

© 2017 The Author(s)
Published by S. Karger AG, Basel

Introduction

Several tyrosine kinase inhibitors (TKIs) of vascular endothelial growth factor receptors (VEGFRs) have been established in the treatment of metastatic renal cell carcinoma (mRCC) [1]. Pazopanib hydrochloride (VOTRIENT; Novartis Europharm) is an oral, multitargeted anti-VEGFR-1, -2, and -3, platelet-derived growth factor receptor α and β , and stem cell factor receptor (c-KIT) [2]. Pazopanib is approved for the treatment of mRCC in the first-line setting following the results of two randomised phase III trials demonstrating superiority to placebo and proved to be noninferior to sunitinib with a more favorable safety profile and improved patient-reported quality of life domains [3, 4]. In these studies, cutaneous side effects of pazopanib were reported in less than 15–20% of patients. These side effects are usually mild with only 1–3% of grade 3 or 4 toxicities reported [2, 5]. The pathophysiology of skin changes is largely unknown and all cutaneous manifestations cannot be attributed to the same mechanism [6, 7]. Vasculitis, as a consequence of pazopanib treatment, has been rarely reported [8, 9]. Cutaneous leukocytoclastic vasculitis (CLCV) may be idiopathic or secondary to another disease, such as malignancy (including mRCC) or an adverse drug reaction (ADR) to a drug [6]. To our knowledge, this is the first report of this cutaneous ADR to pazopanib and, therefore, oncology providers should be aware of this clinical association.

Case Presentation

A 66-year-old Caucasian man, ex-smoker (1 pack per day), underwent a left nephrectomy for a stage II (T2N0M0), clear cell, Fuhrman grade 2/4 RCC in June 2015. His past medical history included hypertension, dyslipidaemia, obstructive sleep apnoea and benign prostatic hypertrophy, for which he is chronically medicated with irbesartan/hydrochlorothiazide, pitavastatin, and *Serenoa repens* (permixon). Family history was significant for gastric cancer in his father at 63 years of age.

Approximately 18 months after his renal surgery, the patient was admitted with progressive shortness of breath and fatigue for about 1 week. On general physical examination, he had an Eastern Cooperative Oncology Group performance status score of 1; his clinical evaluation was essentially normal, with the exception of inaudible breath sounds in the lower 2/3 of the left lung; no jaundice, rash, purpuric spots, or lymphadenopathy was noted. The laboratory findings are presented in Table 1 and were significant for anaemia grade 1 (CTCAE v4.03) and elevated LDH. The transthoracic echocardiography documented an extensive left pleural effusion, conditioning the remaining imaging evaluation: electrocardiogram with low-voltage waveforms; chest CT presenting large left pleural effusion, several pleural nodules measuring more than 5 cm, associated left lower lobe atelectasis, and a secondary nodule in the apical segment of the right lower lobe; abdominal CT showing an ex-

pansive heterogeneous mass adjacent and infiltrating the left psoas, measuring 6 × 3 cm, and bulky retroperitoneal para-aortic adenopathies, larger than 3 cm in diameter (Fig. 1). Video-assisted thoracic surgery allowed pleural drainage of 3,000 mL of serohaematic fluid and pulmonary decortication with significant clinical improvement and confirmed the histological confirmation of the metastatic clear cell RCC.

Given the evidence of multi-organ recurrent disease, symptomatology, and his intermediate risk (IMDC risk score) [10], the patient was initially treated with pazopanib 800 mg q.d. After having completed 1 week on treatment, he developed palpable purpura lesions on his ankles, grade 3 (CTCAE v4.03) (Fig. 2). There was no haematological or biochemical abnormality and urinalysis was normal (Table 1). Concomitant new medication was ruled out as a possible cause of vasculitis. The patient held pazopanib with significant improvement of his skin changes therapy and reintroduced 2 weeks after at 400 mg q.d. Approximately 4 weeks later, he again developed recurrent skin lesions with the same severity. At this time, a dermatologist examined the patient and a skin biopsy was performed, which set the diagnosis of CLCV (Fig. 2). Autoantibodies were negative and rheumatoid factor and C3/C4 levels were within normal limits (Table 1). Viral serological testing was negative. Doppler ultrasound arterial/venous mapping of the lower limbs showed moderate bilateral tibioperoneal obliteration disease. The pazopanib treatment was discontinued and he had complete resolution of the skin lesions within 2 weeks.

Considering the absence of disease progression, the clinical improvement, and laboratorial response (LDH normalisation) to pazopanib (despite the short-term treatment), the option was to switch to sunitinib 50 mg q.d. on a 4-week on/2-week off schedule. Approximately 3 weeks later, he presented again with the same palpable purpura grade 3 on his ankles. Sunitinib was discontinued and he started on prednisone 30 mg q.d. with rapid resolution of the vasculitic skin lesions. The present case was discussed with the Dermatology team and although it was felt that his skin toxicity was likely anti-VEGF related rather than pazopanib related, the decision was to resume sunitinib at a lower dose of 37.5 mg q.d. on a 4-week on/2-week off schedule and to taper down prednisone to 5 mg q.d. The patient stayed at the lower dose of sunitinib and corticotherapy for 6 more months, without any skin toxicity or any other significant adverse events. Unfortunately, his restaging scans at 6 months revealed progressive disease and sunitinib was discontinued (Fig. 3). The patient is currently on nivolumab 3 mg/kg q2w and expected for the first assessment scans at 12 weeks.

Discussion

CLCV, cutaneous small-vessel vasculitis, hypersensitivity vasculitis or angitis, are all used interchangeably for a type of skin-predominant vasculitis, which most commonly presents with palpable purpura or nonspecific lesions on the lower extremities. Histologically, CLCV is characterised by leukocytoclasia, which refers to a vascular damage caused by nuclear debris from infiltrating neutrophils (Fig. 2) [6].

A clinically useful classification scheme for CLCV could be based on aetiology, differentiating between primary (idiopathic) and secondary disease. Approximately 50% of cases are idiopathic, while infection (15–20%), inflammatory diseases (15–20%), drugs (10–15%),

and malignancy (<5%) are the predominant secondary causes of CLCV. This disease is presumed to be associated with an aberrant hypersensitivity reaction to an exogenous antigen such as a drug, an infectious agent, or an endogenous antigen, such as vasculitis associated with neoplasms, connective tissue diseases, retroperitoneal fibrosis, ulcerative colitis, or congenital/acquired deficiencies of complement system [6].

Vasculitis as a consequence of pazopanib treatment has been rarely documented. Based on US Food and Drug Administration data, 12,301 patients reported to have side effects when taking this drug. Among them were 6 patients (0.05%) with vasculitis, especially female (5/6), older than 60 years (6/6), and having taken pazopanib for less than 1 month (6/6), also with medication containing calcium (1/6) and paracetamol (1/6) [8]. On the other hand, the 6,442 patients included in the European Medicines Agency data reported side effects, of which 4 patients had vasculitis (0.06%) [9]. Although these updated review analysis must be interpreted with caution given the rarity of this phenomenon, there is incomplete information about each case and none of them has yet been described in the literature. According to a PubMed and Ovid search of articles indexed to MEDLINE using the terms “Pazopanib” and “Vasculitis,” 12 articles were found, but none reported a treatment-induced vasculitis.

Several studies have found that cutaneous ADR is very common with TKIs (more than 10%). In the PharmacoVigilance Database, the most frequently reported serious cutaneous reactions were rash and hand-foot syndrome, more commonly associated with sorafenib (40%), erlotinib (25.2%), imatinib (13%), sunitinib (13%), dasatinib (3.5%), lapatinib (3.5%), and nilotinib (0.9%); no serious cutaneous ADR was reported with gefitinib or pazopanib [5]. Indeed, in the literature, there are a few cases of CLCV associated with TKIs. Six cases have been described with erlotinib, 2 cases with imatinib, sorafenib, and sunitinib, 1 secondary to gefitinib, and another one possibly related with dasatinib [5, 6].

In our case, we consider the CLCV an ADR, since all other possible causes have been excluded. Despite the fact that CLCV could be related with the chronic medication performed in the outpatient, the cause-and-effect relationship with TKIs, and mainly with pazopanib, was demonstrated. Clinical and laboratory workout revealed no association of vasculitis with an infection or an underlying chronic disease. The CLCV could be also a sign of a rare paraneoplastic syndrome associated with RCC. However, CLCV was not present at the initial diagnosis or relapse of RCC, developed while on pazopanib with tumour regression, and improved with dose reduction and drug discontinuation.

The reappearance of the skin lesions with sunitinib suggested a therapeutic class effect. The main hypothesis for the TKI-induced CLCV is the inhibition of the VEGFR pathway expressed in the cells of the immune system, including dendritic cells, T-regulatory cells, and myeloid-derived suppressor cells. At this level, the TKI molecules could enhance the anti-tumour role of these immune actors with an immunomodulatory effect [6, 11].

The management of CLCV requires treating the underlying cause, discontinuation of suspected medications, and considering topical/systemic treatment. One of the possible criticisms of our therapeutic approach may be related to the early cessation of pazopanib without considering a period of low-dose corticosteroid therapy, as was eventually done with sunitinib [6]. Another issue that might have been considered for our patient after CLCV control with corticosteroid maintenance could be related to the increased dose of sunitinib to 62.5 mg, given the induction of the CYP3A4 enzyme by prednisone, which results in a fast-

er catabolism of the TKI [6]. Unfortunately, the patient had disease progression, so it was decided to start nivolumab 3 mg/kg q2w. At this time, based on the immunosuppressive role of corticosteroids and the hypothetical interference with the immunotherapy efficacy, the duration and optimal dose of steroids is unclear. However, the recent history of CLCV and the associated risk of vasculitis with immunotherapy, including immune checkpoint inhibitors, has led us to choosing to maintain a low dose of prednisone [12–14].

Herein, we report a case of a patient with advanced RCC who developed a significant anti-VEGF-related CLCV. Interestingly, this skin toxicity was ultimately managed with dose reduction of the TKI and a low dose of steroids, allowing him to continue therapy until progressive disease. The rarity of this event leads to a lack of data regarding its management. The interdisciplinary approach is always encouraged, as it may facilitate the diagnosis and allow the initiation of the proper treatment faster. Analysis of spontaneous reports is the sole method to recognise the early signs of new drug reactions, like the one that we reported.

Statement of Ethics

The authors have no ethical conflicts to declare.

Disclosure Statement

All authors declare no support from any organisation for the submitted work, no financial relationships with any organisations that might have an interest in the submitted work in the previous 3 years, and no other relationships or activities that could appear to have influenced the submitted work.

References

- 1 Escudier B, Porta C, Schimidinger M, et al: Renal cell carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2016;27:58–68.
- 2 Pazopanib SmPC/Votrient 200 mg and 400 mg film coated tablets Summary of Product Characteristics (SPC) by Novartis Pharmaceuticals UK Ltd. The electronic Medicines Compendium (eMC). Available at: <http://www.medicines.org.uk/emc/medicine/23148/spc> (accessed May 27, 2017).
- 3 Motzer RJ, Hutson TE, Cella D, et al: Pazopanib versus sunitinib in metastatic renal-cell carcinoma. *N Engl J Med* 2013;369:722–731.
- 4 Sternberg CN, Davis ID, Mardiak J, et al: Pazopanib in locally advanced or metastatic renal cell carcinoma: results of a randomized phase III trial. *J Clin Oncol* 2010;28:1061–1068.
- 5 Faye E, Bondon-Guitton E, Olivier-Abbal P, et al: Spontaneous reporting of serious cutaneous reactions with protein kinase inhibitors. *Eur J Clin Pharmacol* 2013;69:1819–1826.
- 6 Karadimou A, Migou M, Economidi A, et al: Leukocytoclastic vasculitis after long-term treatment with sunitinib: a case report. *Case Rep Oncol* 2011;4:385–391.
- 7 Robert C, Soria JC, Spatz A, et al: Cutaneous side effects of kinase inhibitors and blocking antibodies. *Lancet Oncol* 2005;6:491–500.
- 8 Votrient and Vasculitis – from Food and Drug Administration (FDA) and social media. Available at: <https://ehealth.me/groups/votrient-and-vasculitis/votrient-andvasculitis-fda-and-social-media> (accessed May 27, 2017).

- 9 Votrient and Vasculitis – from European Medicines Agency (EMA) database of suspected adverse drug reaction reports. Available at: <https://bi.ema.europa.eu/analyticsSOAP/saw.dll?PortalPages> (accessed May 27, 2017).
- 10 Heng DY, Wanling X, Meredith MR: Prognostic factors for overall survival in patients with metastatic renal cell carcinoma treated with vascular endothelial growth factor – targeted agents: results from a large, multicenter study. *J Clin Oncol* 2009;27:5794–5799.
- 11 Karadimou A, Sereti E, Lainakis G, et al: Changes in lymphocytic populations and autoantibodies resulting from sunitinib treatment of metastatic renal cell carcinoma (mRCC). 15 ECCO-34 ESMO Multidisciplinary Congress 20–24 September 2009, Berlin. *Eur J Cancer Supplements* 2009, vol 7/2, p 435.
- 12 OPDIVO (Nivolumab) Immune-Mediated Adverse Reactions Management Guide. Approved by the U.S. Food and Drug Administration (Revised: 10/2015). Bristol-Myers Squibb.
- 13 Michot JM, Bigenwald C, Champiat S, et al: Immune-related adverse events with immune checkpoint blockade: a comprehensive review. *Eur J Cancer* 2016;54:139–148.
- 14 Zhang H, Watanabe R, Berry G, et al: Immunoinhibitory deficiency in medium and large vessel vasculitis. *Proc Natl Acad Sci USA* 2017;114: E970–E979.

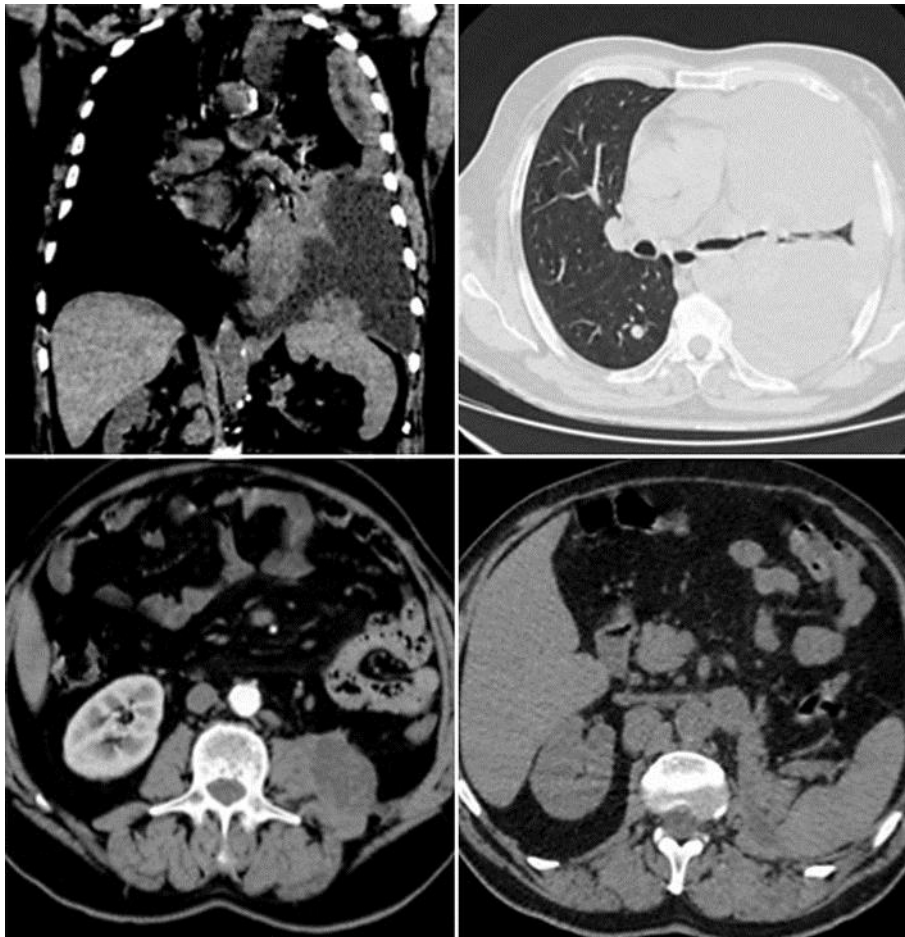


Fig. 1. Chest CT coronal view (upper left image) showing the left pleural effusion, several pleural nodules measuring more than 5 cm, and associated left lower lobe atelectasis. Chest CT axial view (upper right image) showing a secondary nodule in the apical segment of the right lower lobe. Abdominal CT axial views showing an expansive heterogeneous mass adjacent and infiltrating the left psoas, measuring 6 × 3 cm (lower left image) and bulky retroperitoneal para-aortic adenopathies, larger than 3 cm in diameter (lower right image).

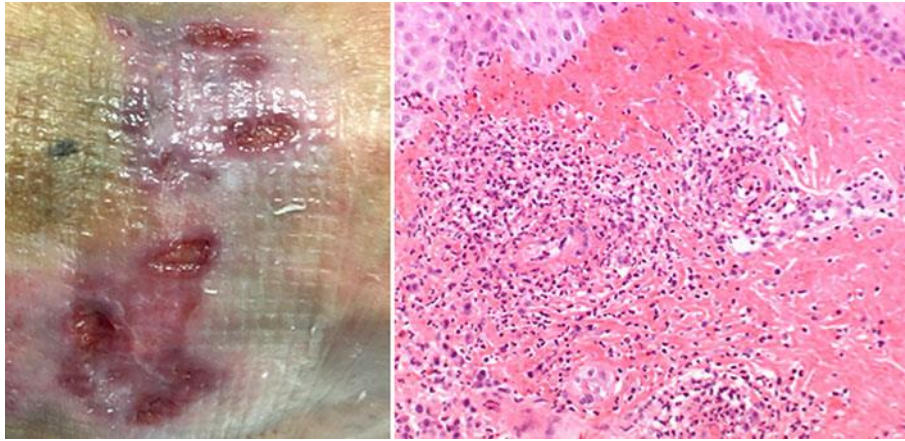


Fig. 2. Scattered purpuric plaques on the left ankle surrounded by cicatrization areas, reflecting a few weeks of evolution (left image). Histological examination revealed superficial capillaries with necrotic vessel walls infiltrated with polymorphonuclear leukocytes (right image, HE staining, magnification $\times 400$).



Fig. 3. Chest CT coronal view (left image) showing size reduction of the pleural nodules and only slight residual left pleural effusion remaining in the costophrenic angle. Abdominal CT axial view (right image) clearly showing the infiltrative retracting tumour lesion adjacent to the left psoas and invading the descending colon. It is also depicted enlargement of the bulky retroperitoneal para-aortic adenopathies.

Table 1. Laboratory examinations

| | Value | Normal range |
|--|----------|--------------|
| Haemoglobin, g/dL | 10.3 | 13.0–17.0 |
| Erythrocytes, $\times 10^{12}$ cells/L | 3.5 | 4.5–5.5 |
| Haematocrit, % | 32.5 | 40.0–50.0 |
| Mean corpuscular volume, fL | 91.8 | 80.0–97.0 |
| Mean cellular haemoglobin, pg | 29.1 | 27.0–32.0 |
| Leukocyte count, $\times 10^9$ cells/L | 10.2 | 4.0–10.0 |
| Neutrophil count, $\times 10^9$ cells/L | 7.6 | 40.0–80.0 |
| Lymphocyte count, $\times 10^9$ cells/L | 1.3 | 20.0–40.0 |
| Platelet count, $\times 10^9$ cells/L | 352 | 150–400 |
| Prothrombin time, s | 12.8 | 10.3–12.8 |
| Activated partial thromboplastin, s | 27.7 | 23.0–31.9 |
| Erythrocyte sedimentation rate, mm/h | 36.0 | <13 |
| C-reactive protein, mg/dL | 14.5 | <1.0 |
| Glucose, mg/dL | 90.0 | 70–110 |
| Urea, mg/dL | 29.0 | <50 |
| Creatinine, mg/dL | 1.1 | 0.7–1.3 |
| Albumin, g/L | 3 | 3.4–5.0 |
| Total protein, g/L | 8.3 | 5.7–8.2 |
| Total bilirubin, mg/dL | 0.3 | 0.30–1.2 |
| Direct bilirubin, mg/dL | 0.1 | <0.30 |
| γ -GT, U/L | 72 | <73 |
| Alkaline phosphatase, U/L | 73 | 45–129 |
| Alanine aminotransferase, IU/L | 35 | 10–49 |
| Aspartate aminotransferase, IU/L | 25 | <34 |
| Uric acid, mg/dL | 6.4 | 3.7–9.2 |
| Lactate dehydrogenase, mg/dL | 473 | 120–246 |
| Creatine phosphokinase, mg/dL | 73 | 32–294 |
| Sodium, mmol/L | 143.0 | 132.0–146.0 |
| Potassium, mmol/L | 3.5 | 3.5–5.5 |
| Chloride, mmol/L | 100 | 99.0–109.0 |
| Calcium, mg/dL | 8.4 | 4.6–5.3 |
| Phosphorus, mg/dL | 3.1 | 2.4–5.1 |
| Urinalysis | | |
| Protein | Negative | |
| Haemoglobin | Negative | |
| Blood cells | Negative | |
| Antinuclear antibodies (ANA) | Negative | |
| Anti-dsDNA | Negative | |
| Antimitochondrial antibodies (AMA) | Negative | |
| Anti-smooth muscle cell antibodies (ASMA) | Negative | |
| Perinuclear antineutrophil cytoplasmic antibodies (p-ANCA) | Negative | |
| Cytoplasmic antineutrophil cytoplasmic antibodies (c-ANCA) | Negative | |
| C3, mg/dL | 145.60 | 90–180 |
| C4, mg/dL | 39.6 | 10–40 |
| Rheumatoid factor, IU/mL | 8.4 | <14 |