Systemic vasculitis associated with vemurafenib treatment

Case report and literature review

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Abstract

Rationale: Vemurafenib, an inhibitor of mutated B-rapidly accelerated fibrosarcoma, is frequently used in the treatment of melanoma and Erdheim–Chester disease (ECD) patients. Inflammatory adverse effects have been increasingly reported after vemurafenib treatment.

Patient concerns and diagnosis: We report 6 cases of vemurafenib-associated vasculitis, of whom a personal case of a 75-year-old man with history of ECD who developed purpura and rapidly progressive pauci-immune glomerulonephritis during treatment with vemurafenib.

Intervention: In the 5 others cases from the literature, all patients presented skin vasculitis, and with joint involvement in 60% of them. Vemurafenib treatment was stopped (n=3), continued at reduced doses (n=1), or continued at the same dose (n=2).

Outcomes: Three patients (50%) received corticosteroids combined with cyclophosphamide (n=1), and all achieved remission of vasculitis. One patient experienced vasculitis relapse after vemurafenib therapy was restarted.

Lessons: Systemic vasculitis is a rare vemurafenib-associated adverse event that may be life-threatening.

Keywords: case report, histiocytosis, immunotherapy, melanoma, vasculitis, vemurafenib

1. Introduction

Vemurafenib (PLX4032) is an inhibitor of mutated B-rapidly accelerated fibrosarcoma (BRAF), especially BRAF\textsuperscript{V600E}.\textsuperscript{1} Metastatic melanoma patients treated with vemurafenib showed a response rate of 48% and improved survival.\textsuperscript{1,2} Erdheim–Chester disease (ECD) is a rare non-Langerhans cell histiocytosis where BRAF\textsuperscript{V600E} mutation is frequently found.\textsuperscript{1,3} ECD patients with BRAF\textsuperscript{V600E} presented good response when treated with vemurafenib.\textsuperscript{5,6}

Serious adverse effects (SAEs) were reported in 8% of patients treated with vemurafenib for metastatic melanoma.\textsuperscript{2} SAEs were also reported in 94% of ECD or Langerhans cell histiocytosis patients treated with vemurafenib.\textsuperscript{6} Main side effects included skin (rash, squamous cell carcinoma, hyperkeratosis, alopecia) and gut involvement (nausea, diarrhea), cytopenia, and arthralgia.\textsuperscript{2} More recently, inflammatory adverse effects like panangiitis have been reported.\textsuperscript{7} Very few cases of vemurafenib-associated vasculitis have been reported.\textsuperscript{8–10} Vasculitis may be life-threatening depending on which organ is involved.

Herein, we report a patient with ECD with vemurafenib-associated severe systemic vasculitis. We reviewed the literature and analyzed 5 additional cases of vemurafenib-associated vasculitis.

2. Methods

The patient reported was followed in Internal Medicine and Clinical Immunology Department at Pitie-Salpetriere University Hospital, Paris, France. Demographic, medical history, laboratory, imaging, histology, treatment, and follow-up data were extracted from medical records. Patient gave his informed consent.

2.1. Literature review

MEDLINE (National Library of Medicine, Bethesda, MD) search was performed until April 2016 using [vemurafenib] or [BRAF inhibitor] and [vasculitis]. Five cases were identified and analyzed.
2.2. Patient

We report a 75-year-old man with a 7-year history of ECD admitted in our department. He had a past medical history with arterial hypertension, type 2 diabetes, ST-elevation myocardial infarction (STEMI) without chronic heart failure, and nonalcoholic steatohepatitis. ECD was diagnosed in 2009 on a biopsy sample of perirenal fibrosis, showing foamy CD68+ CD1a− histiocytes. Immunohistochemistry analysis detected the presence of BRAFV600E mutation. Thoracoabdominal computed tomography (CT) scan showed a right pleural effusion, mesenteric panniculitis, right upper femoral metaphysis osteosclerosis, and perirenal fibrosis with hairy kidney sign. Brain magnetic resonance imaging (MRI) showed a left retro-orbital mass. Pegylated interferon α (PEG-IFN) treatment was started in October 2009. Because of disease progression, PEG-IFN was stopped in September 2010 and a recombinant human interleukin-1 (IL)-1 receptor antagonist treatment was initiated. This treatment permitted disease control, but was stopped in September 2013 because of skin adverse effects. Our patient was treated with infliximab from September 2013 to January 2014. This treatment was stopped due to disease progression. A targeted therapy with BRAFV600E inhibitor (vemurafenib) was initiated in January 2014 at 480 mg/d. In September 2014, the dose was reduced to 240 mg/d because of cholestasis. In February 2015, the treatment dose was resumed to 480 mg. This treatment permitted disease control. In February 2016, our patient was admitted to our department for annual disease re-evaluation. Clinical evaluation showed leg edema, infiltrated purpura on the legs, and bilateral lung crackles. Biological explorations found acute kidney injury with serum creatinine level of 225 μmol/l and C-reactive protein (CRP) was elevated at 16 mg/l. Kidney ultrasound showed no renal dilatation. Urine sediment analysis showed microscopic hematuria (47.10⁴ red blood cells/ml). Urine biological explorations found a glomerular proteinuria, with urine protein-to-creatinine ratio of 0.25 g/mmol and albumin-to-creatinine ratio of 0.2 g/mmol. Immune explorations found no complement consumption, no antineutrophil cytoplasmic antibody (ANCA), no cryoglobulins and rheumatoid factor, and no anti-glomerular basement membrane antibody (anti-GBM). Antinuclear antibodies (ANAs) were positive at a 1:320 dilution, with no anti-DNA (ELISA) and no anti-extractable nuclear antigen (ENA). Kidney function worsened in few days to a serum creatinine level of 410 μmol/l. Kidney biopsy reveals extracapillary crescent (Trichrome stain; original magnification: ×400). Kidney ultrasound showed no renal dilatation. Kidney biopsy sample analysis showed pauci-immune glomerulonephritis (ie, no immunoglobulin, no C1q deposit, no light chains deposit, and some C3 deposits). Thoracoabdominal CT scan and brain MRI showed microscopic hematuria (47.10⁴ red blood cells/ml). Urine biological explorations found a glomerular proteinuria, with urine protein-to-creatinine ratio of 0.25 g/mmol and albumin-to-creatinine ratio of 0.2 g/mmol. Immune explorations found no complement consumption, no antineutrophil cytoplasmic antibody (ANCA), no cryoglobulins and rheumatoid factor, and no anti-glomerular basement membrane antibody (anti-GBM). Antinuclear antibodies (ANAs) were positive at a 1:320 dilution, with no anti-DNA (ELISA) and no anti-extractable nuclear antigen (ENA). Kidney function worsened in few days to a serum creatinine level of 410 μmol/l. Kidney biopsy sample analysis showed 13 glomeruli with normal permeability (Fig. 1). One glomerulus presented a crescent, compatible with extracapillary proliferative glomerulonephritis. Immunofluorescent analysis showed pauci-immune glomerulonephritis (ie, no immunoglobulin, no C1q deposit, no light chains deposit, and some C3 deposits). Thoracoabdominal CT scan and brain MRI findings showed no signs of ECD evolution. We retained the diagnosis of vemurafenib-associated vasculitis with skin and kidney involvement. Vemurafenib was stopped. Our patient was treated with high-dose glucocorticosteroids (methylprednisolone pulse of 1 g/d during 3 days) and cyclophosphamide (0.5 g/m²), monthly during 2 months. Glucocorticosteroids were pursued with prednisone orally at 1 mg/kg/d. The outcome was favorable with quick renal function improvement (Fig. 1).

2.3. Literature review

To our knowledge, there are only 5 additional reported cases of vemurafenib-associated vasculitis (Table 1). Apart from our patient, all 5 other patients received vemurafenib as treatment for metastatic melanoma. Median age was 47 (29.8; 58.5) years and sex ratio was 1. Vasculitis appeared 15.5 (9.5; 232.8) days after treatment initiation. Three patients (60%) described arthralgia associated with skin vasculitis. All patients presented biological inflammatory syndrome with elevated CRP. Elevated ANA titers were detected in 3 cases. Vasculitis was biopsy-proven in every case. Vemurafenib treatment was stopped in 3 cases, continued with reduced doses in 1 case, and continued at the same dose in 2 cases (Table 2). Three patients (60%) received steroids as vasculitis treatment. In 1 case, vasculitis relapsed after vemurafenib therapy was restarted. No progressive neoplasm was reported after vasculitis treatment.

3. Discussion

Since BRAF inhibitors have entered the field of neoplasm therapy, inflammatory adverse effects have been increasingly reported.[8–11] These adverse effects were mainly skin reactions like panniculitis. Skin vasculitis has already been described in 5 patients treated with vemurafenib.[8–11] Severe systemic vasculitis, including rapidly progressive kidney glomerulonephritis, has never been described to our knowledge.

Other vasculitis-reported cases involved mainly skin and joints. In these cases, vasculitis appeared early after vemurafenib treatment initiation, within the first month. In 1 case, vasculitis appeared 11 weeks after treatment initiation.[10] In our case, serum creatinine level began to increase 20 months after vemurafenib treatment initiation. A delay of more than 1 year...
It explains why incidence of some neoplasms, like BRAF, but unexpectedly enhance signaling in cells with wild-type signal-regulated kinase (ERK) signaling in cells with mutant clear. It has been shown that RAF inhibitors inhibit extracellular superior to the risk of kidney failure.

For our patient, vemurafenib might induce kidney failure and require extrarenal replacement case, vemurafenib has been stopped because kidney vasculitis. In our metastatic melanoma, vemurafenib could be continued or restarted after vasculitis management. This is very important for neoplasm control and patient survival. However, restarting vemurafenib treatment may induce vasculitis relapse. In conclusion, inflammatory disorders associated with BRAF inhibitors are increasingly reported. Vasculitis is a rare vemurafenib-induced adverse event that may be life-threatening. Kidney involvement might lead to kidney failure. Continuing or restarting vemurafenib therapy may induce vasculitis relapse.

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