Leukocytoclastic vasculitis with late-onset Henoch-Schönlein purpura after trifluridine/tipiracil treatment

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Abstract

Trifluridine/tipiracil has been approved for the treatment of refractory metastatic colorectal cancer. Adverse effects of this drug combination include leukopenia, neutropenia, fatigue, diarrhea, and vomiting. We present a case of trifluridine/tipiracil-induced leukocytoclastic vasculitis (LCV) with late-onset Henoch-Schönlein purpura (HSP) in a 42-year-old man with metastatic appendiceal cancer. The patient's biopsy-proven LCV developed one month after he began trifluridine/tipiracil treatment and resolved after discontinuation of the drug. He presented to the emergency department two months after the appearance of his LCV with shortness of breath, elevated blood pressure, elevated creatinine, hematuria, and proteinuria. A kidney biopsy was performed and the presence of IgA deposits and cellular crescents indicated rapidly progressive glomerulonephritis secondary to Henoch-Schönlein purpura (HSP). Neither LCV nor HSP have been reported as adverse effects of trifluridine/tipiracil treatment. Malignancy as a cause of our patient's HSP is another possibility. The delay between our patient's skin findings and acute renal failure indicates that suspected HSP should be monitored by urinalysis for a period of time owing to the risk of life-threatening renal disease.

Keywords: drug reaction, leukocytoclastic vasculitis, Henoch-Schönlein purpura, trifluridine, tipiracil, appendiceal cancer

Introduction

Trifluridine/tipiracil (Lonsurf, Taiho Oncology, Inc., Japan) was approved by the Japanese Ministry of Health, Labour, and Welfare in 2014; US Food and Drug Administration in 2015; and the UK National Institute for Health and Care Excellence in 2016 for the treatment of metastatic colorectal cancer in patients previously treated with chemotherapeutic agents such as 5-fluorouracil (5-FU), oxaliplatin, irinotecan, anti-vascular endothelial growth factor (VEGF) therapy, and epidermal growth factor receptor (EGFR) inhibitors. Trifluridine is a nucleoside analog, which is incorporated into replicating DNA in cancer cells, inhibiting cellular proliferation [1]. Tipiracil increases the amount of trifluridine by inhibiting thymidine phosphorylase, the enzyme responsible for trifluridine metabolism [1]. Adverse effects of trifluridine/tipiracil therapy include neutropenia, leukopenia, anemia, thrombocytopenia, fatigue, diarrhea, and vomiting [1]. We describe a case of leukocytoclastic vasculitis (LCV) with late-onset Henoch-Schönlein purpura (HSP) in a patient with metastatic appendiceal cancer undergoing treatment with trifluridine/tipiracil.

Case Synopsis

The patient is a 42-year-old man with metastatic appendiceal cancer diagnosed in 2008. Prior treatments included a combination of folinic acid, 5-FU, and oxaliplatin (FOLFOX), and radiation therapy in 2008; a combination of folinic acid, 5-FU, irinotecan (FOLFIRI), bevacizumab, mitomycin, and capecitabine in 2011; and FOLFOX and bevacizumab in 2015. Restaging in January 2016 showed stable disease. The patient remained in remission off therapy until progression of disease was seen on

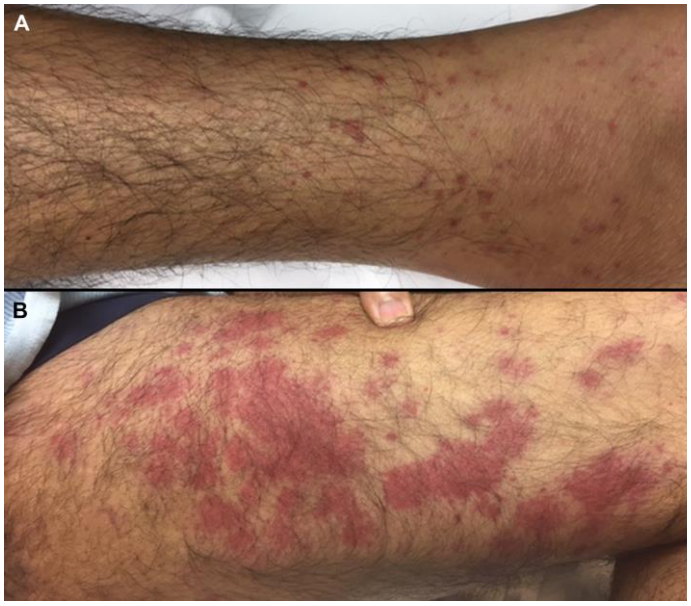

Figure 1. ***A)*** *Leukocytoclastic vasculitis. Erythematous palpable non-blanching petechiae present on the bilateral distal legs, and* ***B)*** *coalescing purpura on the bilateral inner thighs.*

imaging in June 2016. He was started on oral trifluridine/tipiracil in July 2016 and had a normal WBC count.

In October, two days after receiving his fourth cycle of trifluridine/tipiracil therapy, the patient presented with multiple palpable, non-blanching petechiae on his feet and distal legs bilaterally, a few petechiae on the right forearm, and erythematous, coalescing purpura present on the inner thighs bilaterally (**Figure 1**). He had two days of right knee swelling. There had been no dosage change of trifluridine/tipiracil and he tolerated the medication well previously. No new medications had been added after he started trifluridine/tipiracil therapy and he had no evidence of infection. At the time, he was taking heparin PF, loperamide-simethicone, metoprolol tartrate, ondansetron, prochlorperazine, and tramadol in addition to trifluridine/tipiracil. He denied a history of hepatitis B or C infection, abdominal pain, or hematuria. His complete blood count in the clinic included a WBC count of 6,500/µL, platelet count of 326,000/µL, hemoglobin of 10.2 g/dL, and hematocrit of 30.9%. A punch biopsy of the left medial thigh showed superficial perivascular inflammation with neutrophils and focal vascular damage consistent with LCV (**Figure 2**). Because the patient's urinalysis was negative for blood and protein, a direct immunofluorescence (DIF) test of the patient's skin biopsy wasn't performed.

The patient's rash resolved completely within three weeks of discontinuing trifluridine/tipiracil. Two weeks later, he presented to the emergency department with worsening hypertension, dark urine, and shortness of breath. Labs were notable for: WBC 12,800/µL, blood urea nitrogen level 23 mg/dL, creatinine level 3.16 mg/dL (baseline 1.2 mg/dL), urinalysis with >100 RBCs per high power field, and 15 grams of proteinuria. The patient subsequently underwent a renal biopsy which revealed a highly active rapidly progressive glomerulonephritis with 80% cellular crescents (**Figure 3**). Immunofluorescence staining was strongly positive for IgA and C_3. Kappa and lambda staining was equal, which argued against underlying monoclonal gammopathy. The differential diagnosis included HSP, IgA dominant lupus nephritis, or staphylococcal infection associated glomerulonephritis. Given the history of LCV, lack of other criteria for lupus nephritis, and negative cultures at admission, HSP was thought to be the likely diagnosis. The patient was started on rituximab and corticosteroids with improvement of his serum creatinine from 4.4 to 2.2 mg/dL and marked reduction in his proteinuria. However, the patient developed recurrent acute kidney injury in the setting of pneumonia and

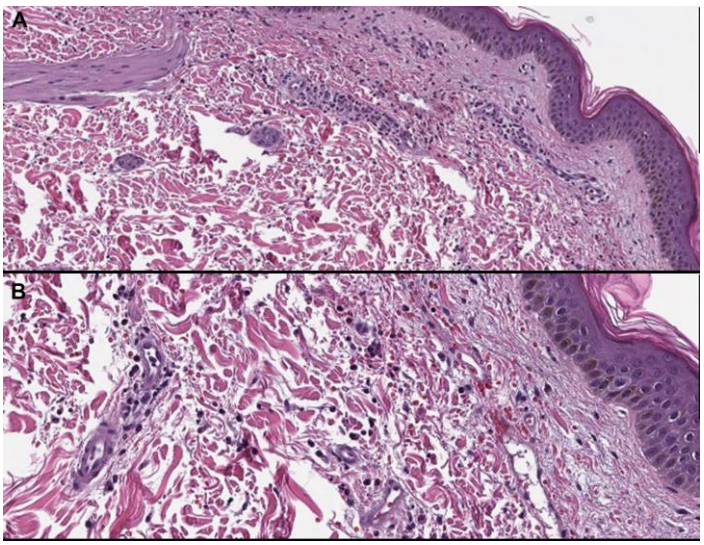

Figure 2. *Leukocytoclastic vasculitis. Superficial perivascular inflammation with neutrophilic infiltration and fibrinoid necrosis of vessel walls. H&E,* ***A)*** *5×;* ***B)****10×.*

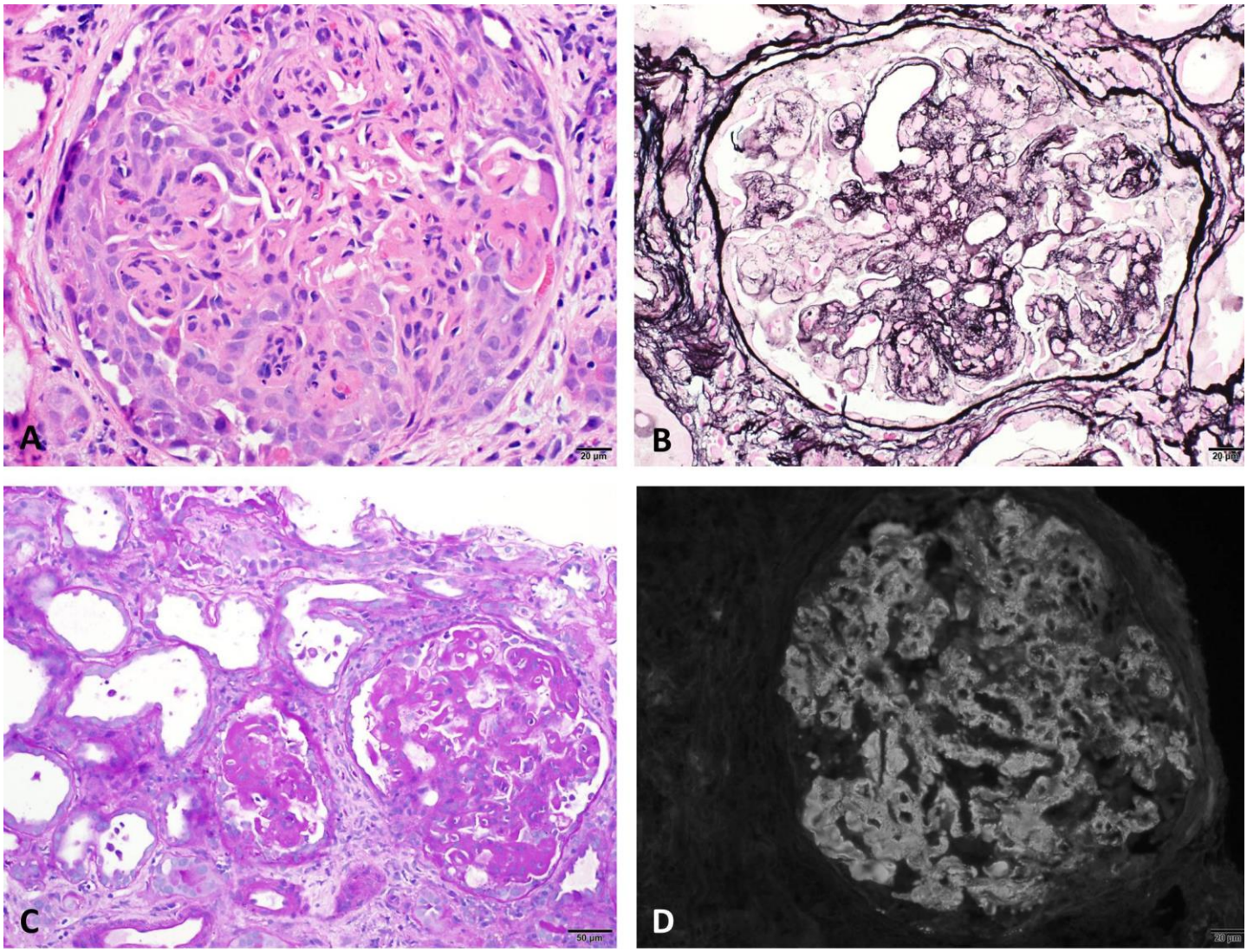

Figure 3. ***A)*** *Glomerulus with endocapillary proliferation and cellular crescent; H&E, scale bar equals 20µm.* ***B****) Glomerulus with segmental basement membrane destruction; Jones silver), scale bar equals 20µm.* ***C)*** *Glomerulus with global mesangial matrix expansion, and ectatic proximal tubules with flattened epithelial cells and loss of brush borders, PAS, scale bar equals 50µm.* ***D)*** *Mesangial and segmental capillary granular IgA immunofluorescence, scale bar equals 50µm.*

subsequently developed end stage renal disease. He expired 5 months after his initial presentation.

Case Discussion

Chemotherapeutic agents such as capecitabine and oxaliplatin have been reported to cause LCV. Improvement was seen with cessation of the responsible drug and systemic corticosteroid treatment [2, 3]. Similarly, our patient's LCV improved with discontinuation of trifluridine/ tipiracil. To see if our patient's LCV had IgA deposits, we performed a retrospective DIF study on unstained paraffin-embedded tissue slides of his prior skin biopsy, and was found to be negative. Although diagnostic utility of the use of DIF on paraffin-embedded kidney biopsies has been shown in the literature [4], there is limited data regarding the use of this technique on skin biopsies. Thus, the possibility of drug-induced HSP cannot be ruled out. Reports of drug-induced HSP include a patient with *S. aureus* sepsis treated with vancomycin and a patient with Crohn disease treated with adalimumab who developed HSP without and with renal involvement, respectively; the HSP in both of these patients resolved with discontinuation of their respective treatments [5, 6]. A review of 250 adult patients with HSP found an average time of two

months between the appearance of systemic symptoms and eventual renal involvement, which is similar to our patient's time course [7]. Additionally, 11% of the study patients progressed to end-stage renal failure [7]. Although it is possible that our patient's HSP was an adverse effect of his trifluridine/tipiracil treatment, it could also have been caused by his underlying malignancy. One review reported 31 cases of patients with malignancy-induced HSP, with a single case related to a small bowel malignancy [8]. These patients had a mean age of 60 years, were mostly male (94%), and were likely to have solid tumors, the most common of which were lung (8 cases) and prostate (5 cases) [8].

Conclusion

It is important for physicians to be aware of the risk of the development of LCV in patients taking trifluridine/tipiracil. DIF studies are recommended when LCV is suspected [9]. Although no overt recommendations regarding adult patients believed to have HSP and serial urinalyses exist in the literature, it is recommended that children with findings suggestive of HSP receive a urinalysis each week during active disease and once a month for three months after the disease has resolved [10]. Adult patients with suspected HSP should likely be monitored by urinalysis for a period of time owing to the risk of life-threatening renal disease which can appear months after initial skin findings.

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