

Clinical Communications

Rituximab-induced Henoch-Schonlein purpura in a patient with mantle cell lymphoma

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Clinical Implications

- Henoch-Schonlein purpura vasculitis can occur secondary to rituximab infusion in patients with mantle cell lymphoma. Further studies are needed to determine factors for Henoch-Schonlein purpura development in patients treated with rituximab.

TO THE EDITOR:

Rituximab is a chimeric mouse/human mAb against CD20 antigen, a glycosylated transmembrane phosphoprotein expressed on the surface of B cells. This medication has been used to treat many diseases such as B-cell non-Hodgkin lymphoma, cryoglobulinemia, and collagen vascular disease. Various side effects including headache, fever, dyspnea, and hypotension have been reported. There are a few publications regarding rituximab-induced vasculitis. However, to our knowledge, there have been no reports of Henoch-Schonlein purpura (HSP) development secondary to rituximab infusion.¹⁻³ Therefore, we report the clinical presentation and laboratory studies of a rituximab-induced HSP in a patient with mantle cell lymphoma.

A 59-year-old male with a recent diagnosis of mantle cell lymphoma presented with fever of 39.1°C 10 days after receiving the first course of chemotherapy with rituximab and bendamustine. Empirical antibiotic treatment for sepsis with intravenous (IV) vancomycin and cefepime was given. He continued having a fever up to 39.4°C. Four days after the administration of antibiotics, he was afebrile and was discharged home without antibiotics. Infectious disease workup including Histoplasma antigen, Aspergillus galactomannan antigen, Blastomyces antibody, Ehrlichia PCR, and bacterial/fungal/mycobacterium culture of the venous blood was negative. Computed tomographic scans of the chest, abdomen, and pelvis were done, with no clear source of fever. After 2 days, he presented to the emergency department with multiple non-blanching, purpuric macules coalescing into plaques on the forearms, lower legs, lower back, and buttocks. He also developed proteinuria, hematuria, and an increase in serum creatinine level from a baseline of 1.0 mg/dL to 2.05 mg/dL within a day consistent with acute kidney injury (AKI). High-dose prednisone 80 mg daily was given with resolution of the rash and AKI in 2 weeks. Because of a concern of small-vessel vasculitis, a renal biopsy was done (see this article's [Online Repository](http://www.jaci-inpractice.org) at www.jaci-inpractice.org). Right renal core biopsy indicated IgA nephropathy (Figure 1). Skin biopsy from a purpuric patch on the left forearm demonstrated perivascular and interstitial mixed inflammatory cell infiltration, including lymphocytes, histiocytes, eosinophils, and neutrophils, which was consistent with leukocytoclastic vasculitis. Other laboratory evaluations were unremarkable with

negative antinuclear antibody, antineutrophil cytoplasmic antibodies, hepatitis C virus antibody, and cryoglobulin. Levels of C3 (100 mg/dL) and C4 (18.8 mg/dL) were normal. Anti-streptolysin O titer (235 IU/mL) was within normal limits. Bacterial culture of the venous blood was negative.

Two weeks later, he received the second cycle of rituximab. He developed flushing, lightheadedness from orthostatic hypotension, cramping pain of his lower legs, and rigors with fever up to 38.5°C during the rituximab infusion. Dexamethasone 4 mg IV, hydrocortisone 100 mg IV, diphenhydramine 50 mg IV, meperidine 25 mg IV, 8 mg oral ranitidine, 650 mg oral acetaminophen, and a bolus of normal saline were administered with resolution of symptoms. Three hours after the rituximab infusion, he developed a diffuse nonblanchable purpuric rash with tenderness on the legs and arms, which progressed to the back and chest (Figure 2). He was also found to have decreased urine output and developed AKI with elevated creatinine to 2.65 mg/dL. Prednisone 80 mg was given daily. Four days later AKI resolved with improvement of the rash. He was discharged home with tapering oral prednisone. Laboratory evaluations showed normal tryptase level (6.4 ng/mL), normal troponin I (<0.03 ng/mL), and negative multiplex PCR for respiratory pathogens and bacterial blood culture.

We have described this rare case of a patient with mantle cell lymphoma who developed leukocytoclastic vasculitis with skin rash and IgA nephropathy after receiving rituximab infusion. According to the clinical presentation and laboratory investigation, this clinical presentation fits with a rituximab-induced HSP, which is a small-vessel leukocytoclastic vasculitis mediated by IgA immune complex deposition with clinical manifestations such as palpable purpura and renal abnormalities.⁴ Renal involvement in HSP usually occurs early in the disease and ranges from mild hematuria or proteinuria to end-stage renal disease. In addition, an association between adult HSP and malignancy has been reported. Most patients presented with HSP before a malignancy diagnosis.⁵ It was initially planned for the patient to have rituximab administered for 6 cycles, 28 days each. However, he developed HSP 2 weeks after the first infusion and within hours after the second infusion with rituximab. Because of the development of HSP, his chemotherapy protocol was changed. Rituximab was discontinued and systemic steroids were given for both episodes with symptomatic improvement.

Severe post-rituximab infusion reactions have been described, including Stevens-Johnson syndrome, serum sickness, and a few reports of vasculitis.^{1,3,6} However, none of them has reported rituximab-induced HSP. Kim et al³ reported a cutaneous vasculitis occurring a day after rituximab administration in a 38-year-old man who received rituximab for rheumatoid arthritis.³ Kandula and Kouides² described a case in a 67-year-old woman with follicular non-Hodgkin lymphoma. She developed generalized hemorrhagic vesicles and bullae on the arms, legs, and trunk after receiving the third dose of a 4-week course of rituximab. Skin biopsy from both reports demonstrated typical features of leukocytoclastic vasculitis.

Pathogenesis of vasculitis in patients treated with rituximab is not well understood. This could be due to rituximab antigen-antibody complex and cytokine release syndrome (CRS).⁷ CRS

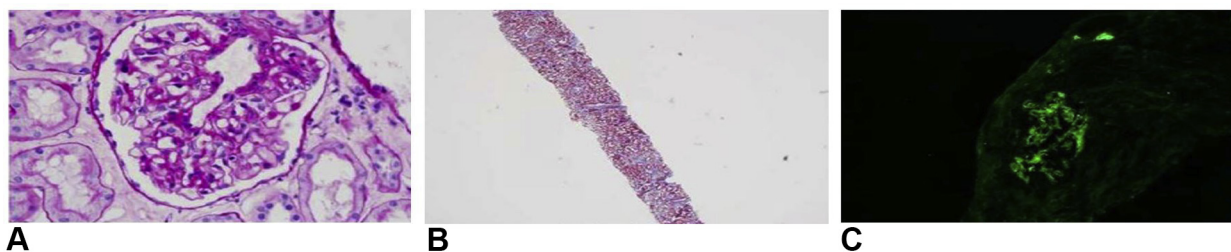


FIGURE 1. Core renal biopsy with H&E stain demonstrated (A) unremarkable glomeruli without mesangial hypercellularity and (B) no significant interstitial fibrosis, tubular atrophy, or inflammation of the cortical tubulointerstitial tissue. (C) Direct immunofluorescence microscopy with positive staining of arterioles with IgA. *H&E*, Hematoxylin and eosin.



FIGURE 2. Diffuse nonblanchable palpable purpuric rash with tenderness on legs after second rituximab infusion.

has been characterized by increased serum levels of proinflammatory cytokines, such as TNF- α , IFN- γ , IL-6, and IL-10. The onset of CRS could range from minutes to 2 weeks after the administration of medication. Clinically, CRS ranges from nonspecific to severe life-threatening symptoms such as fever, headache, nausea, vomiting, rash, myalgia, rigor, dyspnea, and hypotension.⁸ It is not entirely clear regarding the mechanism of rituximab-induced HSP. In general, severe reactions to mAbs are more likely to happen in patients with high circulating tumor cells. We speculate that this patient developed mixed reactions including immune complex-mediated CRS and infusion-related reactions.⁷ Rituximab infusion in a patient with mantle cell lymphoma might lead to high levels of immune complexes between rituximab and components of B cells and/or anti-rituximab antibody, which could result in HSP vasculitis.

Conversely, it is interesting that rituximab has also been used for the treatment of chronic steroid-dependent HSP and adult-onset HSP.^{9,10} Over time, decreased circulating IgA levels, impairment of B-cell function including the role of the B cell as an antigen-presenting cell, and T-cell stimulation are proposed mechanisms.^{9,10}

Similar to the approach in an oncologic patient who recently received chemotherapy treatment, tumor lysis syndrome (TLS) and infection should be considered. Although TLS can mimic CRS, this patient had no hyperuricemia, hyperkalemia, hyperphosphatemia, or hypocalcemia. Therefore, TLS was ruled out. CRS often responds well to treatment with antihistamines, corticosteroids, and discontinuation of the culprit medication. Nevertheless, it is difficult to distinguish sepsis from CRS. Thus, in our case, empiric antibiotics were given, but after an infectious disease evaluation was negative, antibiotics were discontinued.

In summary, HSP vasculitis can occur secondary to rituximab infusion in patients with mantle cell lymphoma. Nonetheless, other factors especially TLS and infection should also be considered. Further study is needed to determine the pathophysiology and risk factors for HSP development in patients treated with rituximab.

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ONLINE REPOSITORY**KIDNEY BIOPSY STAINING METHOD**

Frozen sections of tissue submitted for immunofluorescence microscopy were stained with hematoxylin and eosin and evaluated by light microscopy. Seven glomeruli were present for evaluation, 0 globally sclerotic. Direct immunofluorescence microscopy was performed on frozen sections, with appropriate controls, stained with fluoresceinated antisera to IgG, IgA, IgM, C1q, C3, albumin, fibrin, and kappa and

lambda light chains to evaluate for immune-mediated kidney disease. On a scale of 0 to 3+, the glomeruli showed predominantly mesangial staining for IgG (0-1+), IgA (3+), IgM (2+), C3 (3+), C1q (1+), kappa (1+), and lambda (3+). There was positive staining of arterioles with C3 and tubular casts with IgA. Tubular casts and protein resorption droplets stained positive for kappa and lambda of equal intensity. The remaining stains were negative. Section quality was satisfactory, and positive and negative controls stained appropriately.