Successful treatment of disseminated Rosai-Dorfman disease with siltuximab

Rosai-Dorfman disease (RDD) is a rare, macrophage-related disorder of unknown cause that presents as a localized or systemic disorder involving lymph nodes and other organs. RDD is often self-limiting, however, sometimes permanent or even fatal. The rarity and unpredictability of RDD renders optimal timing and modality of treatment difficult. Bone involvement is especially rare, and predicts a chronic course with decreased likelihood of spontaneous remission.[1] Aouba *et al*. found that RDD patients showing a clinical response to cladribine had normalization of interleukin-6 (IL-6) levels post-treatment from elevated levels at pre-treatment.[2] We report the successful treatment of a patient with refractory, disseminated RDD with siltuximab (Sylvant, Janssen Biotech), an IL-6 chimeric monoclonal antibody.

Our patient is a previously healthy 64-year-old man who presented with fever, cough, weight loss, and fatigue unresponsive to antibiotics. Abdominal Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) demonstrated multiple masses including a 2.8 x 2.9 cm mass in the left renal hilum, enlarged periaortic nodes, and many osseous and epidural lesions including a 1.8 x 1.6 cm epidural mass at the L1-L2 neural foramina (Figures 1 A-C). Infectious workup for viruses, tick-borne diseases, fungus, HIV, and tuberculosis were negative. Serologic testing for autoimmune disease was also unrevealing. Biopsy of four abnormal lymph nodes revealed marked expansion of sinuses by atypical histiocytes containing frequent intracytoplasmic viable lymphocytes, neutrophils, and plasma cells, a phenomenon known as emperipolesis (Figures 2 A-C). These histiocytes were positive for S100 and CD68 but negative for CD1a by immunohistochemistry. A small proportion of cells stained positive for IgG4 and serum IgG4 level was elevated, but the IgG4/IgG ratio was less than 40%, which was not consistent with IgG4 related lymphadenopathy. The overall findings supported a diagnosis of Rosai-Dorfman disease.

After six cycles of intravenous vinblastine 3 mg/m^2 and oral prednisone, he had not achieved remission. He was then started on siltuximab intravenously 11 mg/kg every 21 days and prednisone 40mg daily. He had prompt resolution of nearly all of his symptoms the day following his first treatment. After one cycle, he achieved complete metabolic response (Figure 3). After eight cycles, which constituted treatment every 21 days for six months, a trial of a four-month interval between treatments resulted in a partial relapse with return of fever, fatigue, and anemia. Treatment interval of three months was resumed and remission was again achieved. Abdominal CT after 18 months revealed complete resolution of left renal pelvis mass and periaortic lymphadenopathy (Figure 1D).

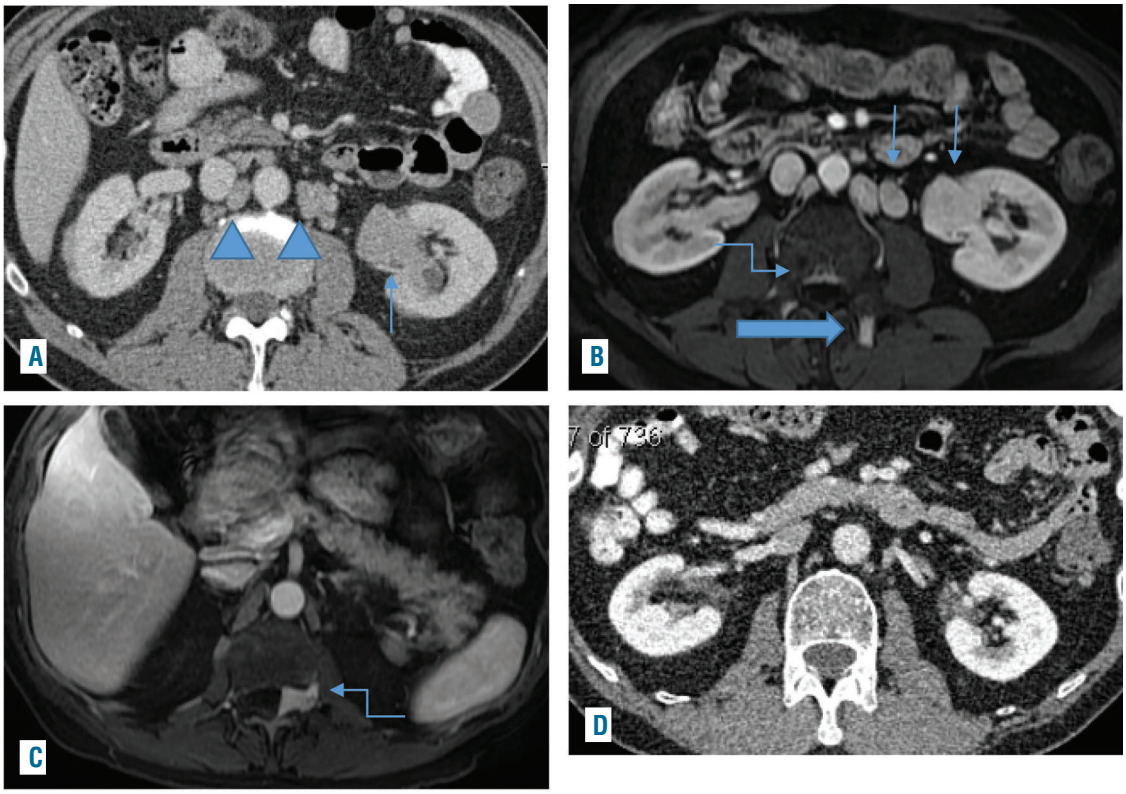

Figure 1. Imaging findings before and after treatment. A. Axial image of contrast enhanced CT at the level of right renal vein reveals enlarged periaortic nodes (arrowheads) and soft tissue in left renal pelvis (thin arrow). B. Axial image of contrast enhanced MR at the level right renal vein reveals enlarged periaortic nodes and soft tissue in left renal pelvis (thin arrow). Osseous (thick arrow) and epidural lesions (zigzag arrow) are also noted. C. Axial contrast enhanced MR image at the level of L1-L2 level reveals enhancing mass extending into left neural foramen at that level with mass effect on spinal cord (zigzag arrow). Many other osseous lesions were noted on MR spine (not shown) D. Axial image of contrast enhanced CT at the level of right renal vein reveals resolved periaortic lymphadenopathy and soft tissue in left renal pelvis dated 2 years after anti-IL-6 therapy.

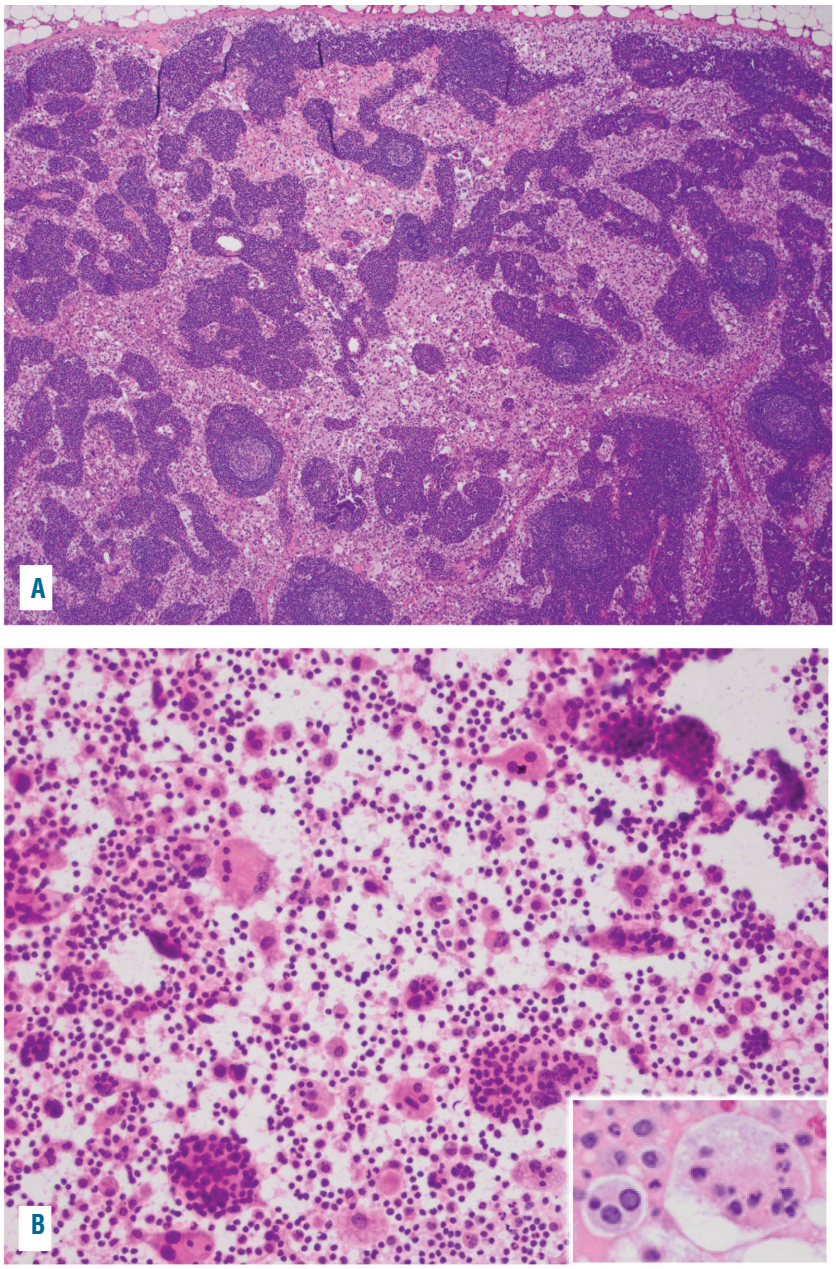

Figure 2. Pathology of lymph nodes. A. A. Lymph node with markedly expanded sinuses. (Hematoxylin-eosin, original magnification x 40). B. The touch imprint shows frequent histiocytes with emperipolesis (inset), a phenomenon of histiocytes in the expanded sinuses contain viable lymphocytes, plasma cells and neutrophils. (Hematoxylin-eosin, touch imprint).

At present, 42 months since starting siltuximab, he continues to be in remission on a quarterly treatment schedule without any adverse effects.

RDD or sinus histiocytosis with massive lymphadenopathy (SHML), is a rare histiocytic disorder with painless, impressive cervical lymphadenopathy first described by Drs. Rosai and Dorfman in 1969. Bones may also be involved, as in this patient. The pathogenesis of RDD is unknown. Infectious causes, such as HHV-6 and EBV have been questioned, as some patients have had positive serology and *in situ* DNA hybridization, in respective order.[3,4] However, no evidence of active infection has been documented. IgG4-related diseases have been considered an etiology when IgG4$^+$ plasma cells were described in RDD lesions along with elevated serum IgG4 levels, but these have not been consistent.[5] Mutations in MAPK/ERK pathway have been documented in 33% of RDD patients in a retrospective study, and interestingly, the mutational profile was correlated with the location of disease -head and neck-, but not with clinical outcomes.[6]

The diagnosis of RDD is heavily reliant on histology and immunohistochemistry. Emperipolesis with nondestructive phagocytosis of intact lymphocytes, plasma cells, and neutrophils is a classical finding in involved lymph nodes.[7] Immunohistochemical stains of the histiocytes are positive for S100, CD68, and CD163, but negative for CD1a. The differential diagnosis includes Langerhan's cell histiocytosis, which is positive for CD1a and often has BRAF V600E mutations, and Erdheim-Chester Disease, which also frequently has BRAF V600E mutation but does not stain positive for S100.

Treatment is reserved for symptomatic disease or critical organ involvement. Reports on the clinical course of

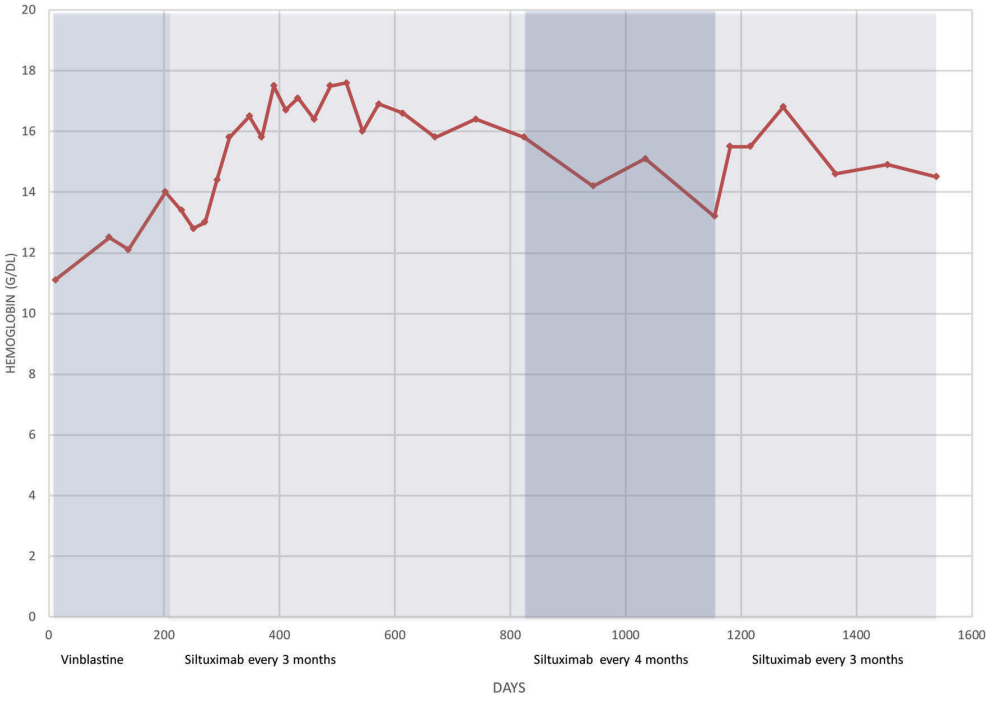

Figure 3. Blood counts during treatment with siltuximab. Note the initial rise in hemoglobin (Hbg) with treatment and fall when intervals increased to 4 months with return on resumption of treatment every 3 months.

RDD are variable with some series reporting that the majority of patients had spontaneous, complete resolution while others, indicating up to 70%, will have permanent disease.[8,9] Symptomatic, localized disease can be managed with complete surgical resection or radiation, while a watch-and-wait strategy is used for asymptomatic disease.[1,10,11] Extensive and systemic disease, as in this case, have been managed with a variety of largely ineffective therapies including steroids, rituximab, and cytotoxic chemotherapy with vinca alkaloids, anthracyclines, alkylating agents and antimetabolites.[2,5,9,12,13] Details of these are limited to small studies and case reports, and nothing has been shown to be of consistent long-term benefit. Most recently, a case of RDD with activating *KRAS* mutation was treated with targeted therapy of cobimetinib, but again with limited follow up of a radiographic response after two months.[14]

Bone involvement, as seen in our case, is rare and a predictor for a chronic disease that likely requires some modality of treatment.[1] Mosheimer *et al.* reviewed 108 RDD patients with bone involvement, 69 of whom received treatment. Most (53 out of 69, 76.8%) had undergone surgical resection, and either total or partial remission was achieved in 54 (78.3%). Other interventions include glucocorticoid therapy (29%) and chemotherapy (11.6%) including vinblastine, 6-mercaptopurine, vincristine, cladribine, clofarabine, chlorambucil, and etoposide.

A report by Aouba *et al.* described treatment of RDD with the purine analog, cladribine.[2] Notable in this report was the normalization of TNF-α and IL-6 levels post-treatment from elevated values at pre-treatment that correlated with clinical response. Our initial hypothesis for this study was that cytokine dysregulation in RDD offers novel therapeutic targets and that siltuximab would fill this role.

Siltuximab is an anti-IL-6 chimeric monoclonal antibody that reduces inflammation and acute phase reactants with antiangiogenic effects. Its current approved use is for the treatment of HIV and HHV-8 negative multicentric castleman disease (MCD).[15] Its mechanism of action is through binding and inhibition of IL-6, a proinflammatory cytokine involved in stimulating the production of acute phase reactant proteins, neutrophils, and the development of B-cells. Additionally, it plays a role in the differentiation, survival, and angiogenesis of malignant cells. When used in MCD, siltuximab has a limited side effect profile including upper respiratory infection and skin rash.

We present a case of refractory, disseminated RDD that achieved a complete remission with siltuximab indicating a major role for IL-6 in this disease. The treatment schedule of quarterly infusion appears to have long term benefit with minimal adverse effects. The limitation of this case is the lack of measurement of IL-6. However, the clinical response suggests cytokine dysregulation as part of the pathophysiology and should be answered in future studies. Based on the excellent response in this case, larger clinical trials with siltuximab should be considered.

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References

1. Mosheimer BA, Oppl B, Zandieh S, et al. Bone involvement in Rosai-Dorfman disease (RDD): a case report and systematic literature review. Curr Rheumatol Rep. 2017;19(5):29.
2. Aouba A, Terrier B, Vasiliu V, et al. Dramatic clinical efficacy of cladribine in Rosai-Dorfman disease and evolution of the cytokine profile: towards a new therapeutic approach. Haematologica. 2006;91(12 Suppl):ECR52.
3. Ortonne N, Fillet AM, Kosuge H, et al. Cutaneous Destombes-Rosai-Dorfman disease: absence of detection of HHV-6 and HHV-8 in skin. J Cutan Pathol. 2002;29(2):113-118.
4. Tsang WY, Yip TT, Chan JK. The Rosai-Dorfman disease histiocytes are not infected by Epstein-Barr virus. Histopathology. 1994;25(1):88-90.
5. Liu P, Wang P, Du J, Zhang J. Successful treatment of refractory cutaneous Rosai-Dorfman disease with vincristine. J Dermatol. 2015;42(1):97-98.
6. Garces S, Medeiros LJ, Patel KP, et al. Mutually exclusive recurrent KRAS and MAP2K1 mutations in Rosai-Dorfman disease. Mod Pathol. 2017;30(10):1367-1377.
7. Gaitonde S. Multifocal, extranodal sinus histiocytosis with massive lymphadenopathy: an overview. Arch Pathol Lab Med. 2007;131(7):1117-1121.
8. Foucar E, Rosai J, Dorfman R. Sinus histiocytosis with massive lymphadenopathy (Rosai-Dorfman disease): review of the entity. Semin Diagn Pathol. 1990;7(1):19-73.
9. Pulsoni A, Anghel G, Falcucci P, et al. Treatment of sinus histiocytosis with massive lymphadenopathy (Rosai-Dorfman disease): report of a case and literature review. Am J Hematol. 2002;69(1):67-71.
10. Paryani NN, Daugherty LC, O'Connor MI, Jiang L. Extranodal rosai-dorfman disease of the bone treated with surgery and radiotherapy. Rare Tumors. 2014;6(4):5531.
11. Saboo SS, Jagannathan JP, Krajewski KM, et al. Symptomatic extranodal Rosai-Dorfman disease treated with steroids, radiation, and surgery. J Clin Oncol. 2011;29(31):e772-775.
12. Nasseri E, Belisle A, Funaro D. Rosai-Dorfman disease treated with methotrexate and low-dose prednisone: case report and review of the literature. J Cutan Med Surg. 2012;16(4):281-285.
13. Goyal G. 3573 Clinical features and treatment approaches in patients with Rosai-Dorfman disease: the Mayo Clinic experience. Blood. 2017;130(Suppl 1):3573.
14. Jacobsen E, Shanmugam V, Jagannathan J. Rosai-Dorfman disease with activating KRAS mutation - response to cobimetinib. N Engl J Med. 2017;377(24):2398-2399.
15. van Rhee F, Wong RS, Munshi N, et al. Siltuximab for multicentric Castleman's disease: a randomised, double-blind, placebo-controlled trial. Lancet Oncol. 2014;15(9):966-974.