

## Rituximab Treatment in a Child with Rosai-Dorfman Disease and Systemic Lupus Erythematosus

To the Editor:

Rosai-Dorfman disease (RDD) is a rare disorder in childhood. The association of RDD and systemic lupus erythematosus (SLE) is very rare, with only 2 previously reported cases, and neither of these in a child<sup>1,2</sup>. We describe a child who presented with histopathology-confirmed RDD, and developed SLE 3 years later.

A 7-year-old boy of Canadian First Nations background presented at age 4 years to the pediatric hematology/oncology clinic with a 3-month history of asymptomatic, bilateral massive lymphadenopathy involving the cervical, supraclavicular, mediastinal, hilar, and axillary lymph nodes. He has a healthy fraternal twin, and there is no family history of connective tissue diseases. The lymphadenopathy failed to respond to a course of antibiotics. Laboratory tests showed mild microcytic hypochromic anemia with lymphopenia [white blood cells (WBC)  $6.29 \times 10^9/l$ , hemoglobin 103 g/l, mean corpuscular volume 74.3 fl, mean corpuscular hemoglobin 23.5 pg/cell, platelets  $262 \times 10^9/l$ , lymphocytes  $0.63 \times 10^9/l$ , absolute neutrophil count  $4.98 \times 10^9/l$ ] and high erythrocyte sedimentation rate, 63 mm/h. Serial chest radiographs showed persistent nonprogressive large bilateral mediastinal, hilar, right infrahilar, and paratracheal lymphadenopathy (Figure 1). Computed tomography scan showed adenopathy, airway nar-



Figure 1. Chest radiograph shows large mediastinal and hilar lymphadenopathy.



Figure 2. Chest computed tomography scan shows a narrowed superior vena cava, displaced by the large adenopathy.

rowing, and atelectasis as well as superior vena cava displacement (Figure 2). These lymph nodes were gallium avid. Investigations for infectious causes including tuberculosis, toxoplasmosis, mycoplasma, Epstein-Barr virus, cytomegalovirus, human immunodeficiency virus, and hepatitis viruses were negative. Lymph node specimens for bacterial, viral, and fungal cultures were negative. Immune investigation confirmed lymphopenia with reversed CD4/CD8 ratio. Flow cytometry for double-negative T cells was negative for autoimmune lymphoproliferative syndrome. Immunoglobulin G was 21.9 g/l (normal 5.04–14.65), immunoglobulin A 1.87 g/l (0.27–1.95), and immunoglobulin M 1.85 g/l (0.31–2.08). The patient developed protective antibodies against tetanus and diphtheria, and lymphocyte stimulation test was normal. A biopsy of the largest cervical lymph node showed sinus histiocytosis with lymphohagocytosis (emperipolesis). Immunohistochemical staining for S100 protein was positive in lesional histiocytes and diagnostic of RDD (Figures 3 and 4).

Initially, the patient was followed without specific treatment, and 4 months later he presented with progressive cough and orthopnea. A radiograph showed progression of the mediastinal and perihilar lymphadenopathy.

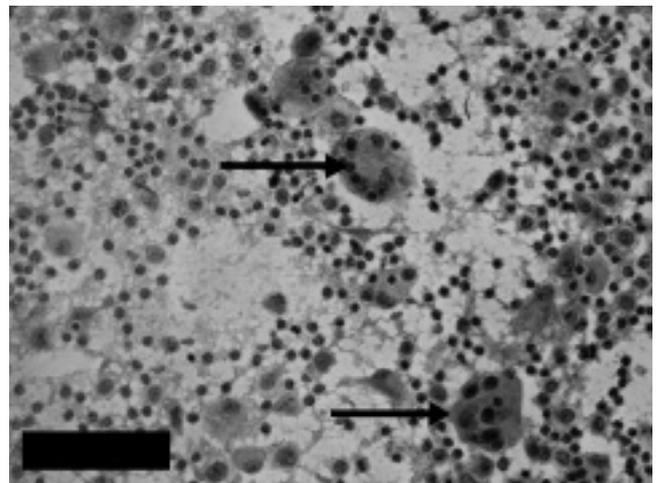


Figure 3. Lymph node biopsy sample (original magnification x400). There are numerous macrophages with abundant cytoplasm in a background of mixed infiltrates. The majority of these macrophages include numerous intracytoplasmic lymphocytes (arrows). This is called emperipolesis and is characteristic of Rosai-Dorfman disease.

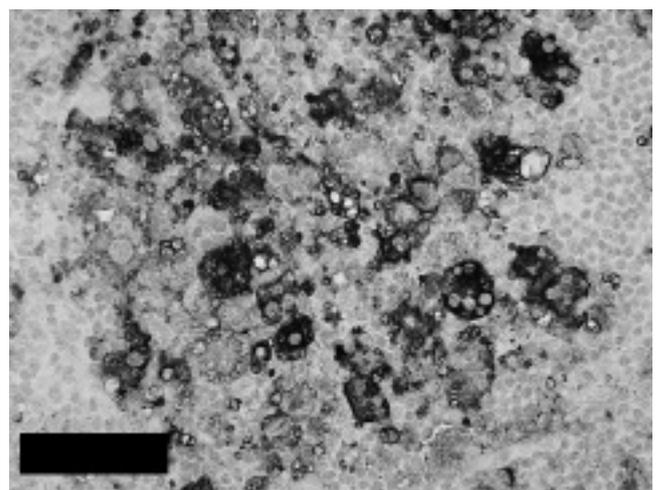


Figure 4. Lymph node biopsy stained for S100 protein: the great majority of macrophages that are expanding sinusoids show strong cytoplasmic staining for S100.

pathy. He was started on oral prednisone 40 mg/m<sup>2</sup>, with resolution of orthopnea, and a decrease in hilar and mediastinal lymphadenopathy. However, with every attempt to taper the steroid, he had worsening respiratory symptoms, and therefore he was started on 6-mercaptopurine 60 mg/m<sup>2</sup>/day and methotrexate 12 mg/m<sup>2</sup>/week orally. There was partial clinical response to this treatment, but he had persistent respiratory symptoms. A repeat lymph node and bone marrow biopsy showed findings similar to the first sample (consistent with RDD).

He presented to hospital again in July 2008 with shortness of breath and tachycardia. On examination he was found to have pulsus paradoxus and large bilateral cervical, supraclavicular, and axillary lymphadenopathy. There was no pallor, malar rash, oral ulcer, or arthritis. He had a large pericardial effusion, which required drainage due to impending tamponade. When standard pericardial fluid microscopic analysis was done, the pathologist noted the presence of LE cells. At this time, the patient had pancytopenia (WBC 2.9 x 10<sup>9</sup>/l, Hb 82 g/l, platelets 132 x 10<sup>9</sup>/l, lymphocytes 0.52 x 10<sup>9</sup>/l, ANC 1.98 x 10<sup>9</sup>/l) with positive Coombs test, strongly positive antinuclear antibody (1:1280), positive anti-double-stranded DNA antibodies, and low C3 (0.66 g/l; normal 0.77–1.43). Anti-SSA, anti-SSB, anti-SM, and anti-ribonucleoprotein were all negative. Based on these findings, a diagnosis of lupus was given. There was no evidence of renal involvement.

He was treated with prednisone 2 mg/kg/day, and he was given rituximab 500 mg/m<sup>2</sup>/dose, 2 doses 2 weeks apart. Within 7 weeks after the rituximab, he had complete remission of the massive lymphadenopathy that had been present for 3 years, and his hemoglobin and C3 had improved to 97 g/l and 0.73 g/l, respectively. WBC and platelet counts required several months to be corrected to 4.1 x 10<sup>9</sup>/l and 233 x 10<sup>9</sup>/l, respectively.

Six months after the rituximab course, he developed a flare of lupus, manifested by chest pain, recurrence of pericardial effusion, and arthritis. He was treated with pulse methylprednisone, with resolution of the SLE flare. B cells were still undetectable, so rituximab was not repeated. He is maintained on prednisone and azathioprine therapy.

A diagnosis of RDD is established on histological grounds, and malignant processes or other histiocytic proliferative processes such as Langerhans cell histiocytosis or hemophagocytic syndromes have to be excluded. Emperipolesis, which is phagocytosis of intact lymphocytes by lymphocytes, prominent plasma cells and cellular debris are characteristic histologic findings<sup>3</sup>. The atypical infiltrates in lymph nodes, including mostly diagnostic S100-positive histiocytes<sup>4</sup>, are sinusoidal with expansion of sinusoids in otherwise normal lymph nodes, retaining follicular architecture in keeping with a benign reactive condition. The histology of lymph nodes resected from our patient had the hallmarks of Rosai-Dorfman disease.

Surgery is indicated when nodal or extranodal lesions compromise vital organs. The role of additional therapies, such as chemotherapy or radiation therapy, is minimal. Responses to chemotherapy have been documented, including the combination of alkylating agents with vincristine and steroids<sup>5</sup>

and the combination of methotrexate and vinblastine<sup>4,6</sup>. Spontaneous remissions are not uncommon. However, involvement of the kidneys, lower respiratory tract, or liver was found to be a poor prognostic sign, and a patient with associated immunologic disease often fared poorly<sup>7</sup>.

The causative agent for RDD is unknown. Its diverse clinical manifestations and frequent association with subtle or severe immunologic abnormalities suggest an immune-mediated etiology or at least that immune-mediated mechanisms play a major role in the pathogenesis. RDD and SLE are a very rare association. Rituximab, an anti-CD20 monoclonal antibody, was effective and well tolerated in our case.

JUBRAN THEEB ALQANATISH, MD; KRISTIN HOUGHTON, MD, MSc, Division of Rheumatology; MASON BOND, MD, Division of Hematology and Oncology; CHRISTOF SENGGER, MD, Division of Anatomical Pathology; LORI B. TUCKER, MD, Division of Rheumatology, British Columbia's Children's Hospital, Room K4-120, 4480 Oak Street, Vancouver, British Columbia V6H 3V4. Address correspondence to Dr. Alqanatish; E-mail: jqanatish@hotmail.com

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