

Clinical Communications

Multicentric Castleman disease revealing complete signal transducer and activator of transcription 1 deficiency treated by JAK1/2 inhibition

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Clinical Implications

- Patients presenting with early-onset human herpesvirus 8—negative multicentric Castleman disease should be screened for primary immunodeficiency. Complete signal transducer and activator of transcription 1 deficiency should be considered as a possible etiology of hemophagocytic lymphohistiocytosis. JAK1/2 inhibitors could be useful in treating immune dysregulation in signal transducer and activator of transcription 1 deficiency.

Castleman disease (CD) is a rare and poorly understood nonmalignant lymphoproliferation of unclear pathogenesis. First described in 1954, CD has two main clinical presentations: a localized or unicentric CD (UCD) and a multifocal or multicentric CD (MCD), which is frequently associated with systemic inflammation through the secretion of IL-6. The UCD phenotype is the most commonly reported in children and has the most favorable outcome.¹ The diagnosis of CD remains histopathologic with two defined pathologic types: (1) the hyaline vascular type, which is characterized by abnormal germinal centers, penetrating hyalinized vessels, and abnormal follicular dendritic cells; and (2) the plasma cell variant, in which normal or enlarged germinal centers are associated with interfollicular plasma cell infiltration. Interestingly, CD is also classified according to the presence or not of human herpesvirus 8 (HHV8), because this association is established in HIV-infected adults. Multicentric CD has rarely been described as associated with primary immunodeficiency. We report a 6-month-old girl presenting with a complete signal transducer and activator of transcription 1 (STAT1) deficiency revealed by MCD. The JAK1/2 inhibitor ruxolitinib allowed complete remission of the MCD.

Born from nonconsanguineous parents, the patient had no relevant medical history except for horseshoe kidney diagnosed before birth. At 5 months, she developed an extensive facial rash, first diagnosed as atopic dermatitis, which showed a poor response to topical steroids. At age 6 months, she was hospitalized for fever, irritability, worsening of the rash, and tongue dyskinesia. Cerebrospinal fluid analysis, brain magnetic resonance imaging, and electroencephalography were normal. Pulmonary X-ray demonstrated bilateral hilar lymphadenopathy

compatible with an infectious process. An extensive infectious workup was performed and evidenced a positive influenzae B polymerase chain reaction in the nasal secretion. She recovered with symptomatic treatment and was discharged from the hospital. At age 10 months, she was again hospitalized for prolonged fever associated with increased rash and a lymphoproliferative syndrome consisting of polyadenopathy and hepatosplenomegaly. She met criteria for hemophagocytic lymphohistiocytosis (HLH)² with (1) prolonged fever greater than 38.5°C, (2) hepatosplenomegaly, (3) anemia and thrombocytopenia (Table 1), (4) hypertriglyceridemia (5.21 mmol/L) and hypofibrinogenemia (0.61 g/L), (5) hyperferritinemia (54,765 ng/mL), and (6) increased HLA-DR/CD8⁺ T cells (39%). Other remarkable biologic features were lymphocytosis (up to $18 \times 10^9/L$) with normal T-, B- and natural killer-cell proportions, eosinophilia (up to $5.7 \times 10^9/L$), and cholestatic hepatitis. Naive T-cell proportion was within normal range with a slight increase in immunoglobulin level (Table 1). Extensive viral, bacterial, mycobacterial, and fungal workup was negative. A positron emission tomography scan revealed a hypermetabolic tumoral syndrome composed of cervical, hilar, axillar, inguinal, and mesenteric adenopathy with hepatomegaly and splenomegaly (see Figure E1, A in this article's Online Repository at www.jaci-inpractice.org). Pleural effusion and ascites were also noted. Skin biopsy found a nonspecific focal vacuolar dermatitis, with lymphohistiocytic superficial and profound perivascular infiltrate. Immunohistochemical study for Langerhans histiocytosis was negative in both skin and bone marrow biopsy. The latter also excluded malign hematologic disease and did not show signs of hemophagocytosis.

A lymph node biopsy performed on axillar lymphadenopathy found no sign of histiocytosis, but a loss of normal lymph node architecture was noted with diffuse and hypertrophic vascular frame and concentric hyalinosis with no plasma cells leading to the diagnosis of MCD (Figure E1, B). Immunohistochemical staining for HHV8 was negative. Because the patient presented with HLH, we investigated primary familial lymphohistiocytosis by functional testings, which showed normal perforin expression and natural killer cell degranulation (data not shown). Given the unusual early-onset presentation, we performed genetic testing using a local whole-genome sequencing program.

Because of the deterioration of her general condition, the patient was started on methylprednisone 2 mg/kg per day and dramatically and rapidly improved. Treatment was completed with rituximab (four doses of 375 mg/m²) and rapamycin (trough level of 7–10 ng/mL). After an initial response, the patient relapsed as prednisone was tapered down to 1 mg/kg per day. Meanwhile, we obtained results from the genetics investigation, which showed a homozygous deletion of *STAT1* (chr2:190987042_191003806del encompassing exons 6–13). This deletion resulted from a maternal unidisomy of chromosome 2 (confirmed by a comparative genomic hybridization array). Complete STAT1 deficiency was confirmed by western blot, which showed absent protein expression, and flow cytometry, which showed absent IFN- γ -induced STAT1 phosphorylation (Figure 1).

TABLE I. Hematologic and immunologic features

Biological parameter	Patient	Normal values
Blood count, g/L		
Total white blood cells	22.6	6-17
Polynuclear neutrophils	5.8	1.5-5.5
Lymphocytes	10.1	3-10.1
Monocytes	2.1	0-0.9
Eosinophils	4.6	0-0.4
Hemoglobin	84	105-135
Reticulocytes	1.7	18-158
Platelets	14	140-440
Lymphocyte count		
Total count, μ L	10,100	3800-8400
CD3+ count, μ L	6161	2128-5822
CD3+CD4+, μ L	2323	1482-4160
CD45RA+/CD4+ (%)	87	86-97
CD45RA+CD31+/CD4+ (%)	53	53-82
Foxp3+CD25+CD127low/CD4+ (%)	3.6	3.1-10
CD3+CD8+, μ L	2828	434-1769
CCR7+CD45RA+/CD8+ (%)	58	52-73
CCR7+CD45RA-/CD8+ (%)	6	3-15
CCR7-CD45RA-/CD8+ (%)	23	11-20
CCR7-CD45RA+/CD8+ (%)	12	16-28
TCR $\gamma\delta$ /CD3+ (%)	25	3-10
CD19+, μ L	1616	614-2016
CD27/CD19+ (%)	17	3-15
CD3-CD56+CD16+, μ L	939	139-848
HLADR/CD3+ (%)	39	2-8
HLADR/CD4+ (%)	2	
HLADR/CD8+ (%)	39	
IgG, g/L	8.77	1.10-7.00
IgA, g/L	0.57	0.08-0.30
IgM, g/L	0.71	0.20-0.90
Anti-diphtheria IgG, UI/mL	0.01	>0.1
Anti-tetanus IgG, UI/mL	0.03	>0.1

From a therapeutic standpoint, we decided to introduce treatment with ruxolitinib (5 mg three times a day) for the following reasons. First, the drug has been proven to treat HLH efficiently in mouse models and several case reports.³ Second, JAK1 and 2 are part of the IL-6 signaling pathway, which is targeted by immunotherapies recognized as the standard of care for MCD. We also maximized the patient's anti-infectious therapy by adding cotrimoxazole prophylaxis and subcutaneous immunoglobulin replacement. Strikingly, introduction of ruxolitinib allowed complete withdrawal of steroids without relapse of HLH feature or cutaneous vasculitis. This treatment was maintained until the patient underwent allogeneic hematopoietic stem cell transplantation.

Complete STAT1 deficiency results in a broad infectious phenotype with susceptibility to intramacrophagic bacteria (mainly mycobacteria) and viruses, principally owing to impairment of IFN- γ -mediated and IFN- α /beta-mediated immunity, respectively.⁴ Viral infections can sometimes trigger HLH-like hyperinflammation in this context.⁵ Although the patient in this report presented with

asymptomatic influenza B infection at an early age, we did not find an infectious trigger to the MCD. We hypothesize that the phenotype of this patient could be explained by hyperactivation of the STAT3 pathway as compensation for STAT1 deficiency through type I and II interferon signaling.⁶ Indeed, type I and type II interferons can induce the recruitment and phosphorylation of both STAT1 and STAT3 through JAK1/2 kinases with opposing effects.⁷ Whereas STAT1 activates several proapoptotic and antiproliferative genes, STAT3 promotes proliferation by inducing antiapoptotic genes and oncogenes. STAT3 is constitutively activated in HHV8-driven MCD, promoting both angiogenesis and cellular transformation.⁸ Furthermore, enhanced STAT3 signaling could account for this patient's eosinophilia, because it has been associated with the pathogenesis of the lymphocytic variant of the hypereosinophilic syndrome.⁹ Although we did not observe an obvious biologic imbalance of STAT3 signaling by flow cytometry in the patient's monocytes after stimulation with IL-6 and IL-10 (data not shown), a deeper assessment of the STAT3 signaling pathway in the STAT1-deficient context is required to confirm our hypothesis.

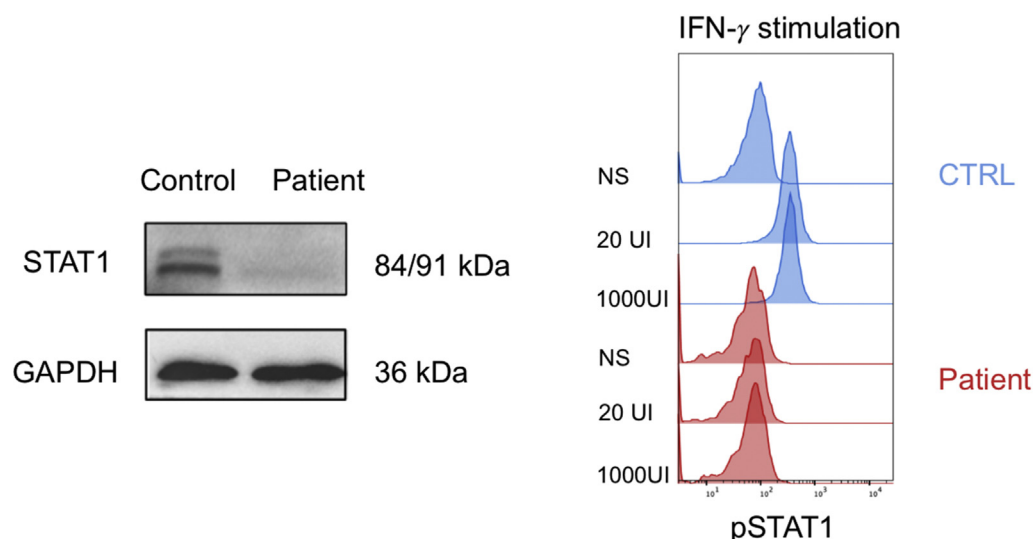


FIGURE 1. Signal transducer and activator of transcription 1 (STAT1) expression by (A) western blot on peripheral blood mononuclear cells and (B) STAT1 staining on CD14 monocytes after IFN-gamma stimulation. *CTRL*, control; *GAPDH*, glyceraldehyde 3-phosphate dehydrogenase.

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This report was carried out in accordance with the recommendations of the CHU Sainte-Justine Institutional Review Board with written informed consent obtained from the parents' patient in accordance with the Declaration of Helsinki.

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Conflicts of interest: The authors declare that they have no relevant conflicts of interest.

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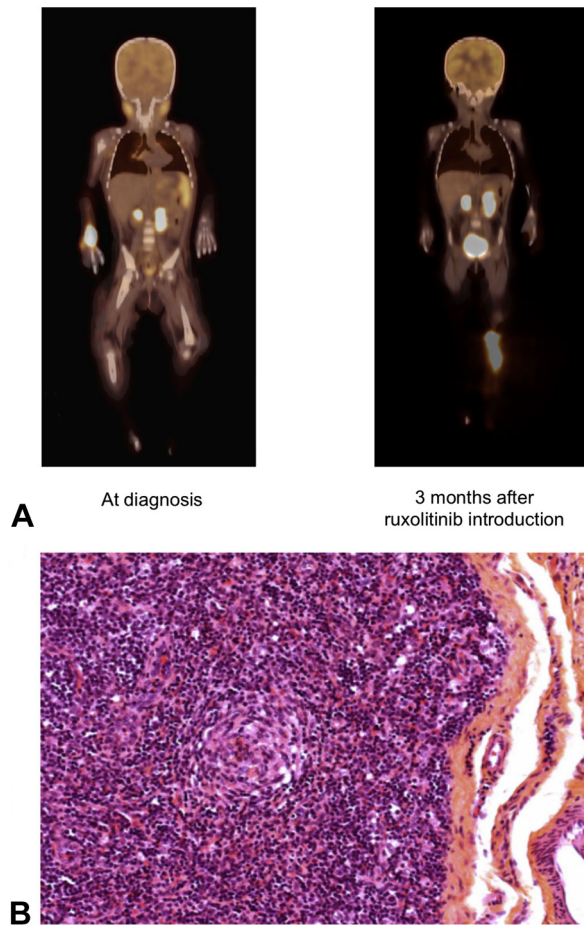


FIGURE E1. (A) Positron emission tomography scan showing hypermetabolic lymphoproliferation affecting peripheral and mediastinal lymph nodes as well as the spleen (left panel) and its complete remission 3 months after the introduction of ruxolitinib (right panel). (B) Lymph node showing classic features of Castleman disease, with fibrosed hyaline concentric nodule associated with a hypertrophic arteriole (hematoxylin-eosin stain, $\times 200$).