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Prolonged Remission Achieved in a Relapsing Idiopathic Multicentric Castleman Disease Patient with a Novel, Targeted Treatment Approach

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Abstract

Idiopathic multicentric Castleman disease (iMCD) is a polyclonal lymphoproliferative disorder involving cytokine-induced multiple organ dysfunction. Unlike Human Herpesvirus-8 (HHV-8)-associated MCD, which is caused by HHV-8, the etiology of iMCD is unknown. While excessive IL-6 drives systemic symptoms and pathogenesis in some iMCD patients and IL-6 inhibition with siltuximab is approved for treating iMCD, approximately one-half of patients do not improve with IL-6 inhibition. The pathological cell types, dysregulated signaling pathways, and cytokine cascade in these anti-IL-6 refractory cases are unknown. As such, mechanistic approaches for treating anti-IL-6 refractory patients are much needed, particularly given that second line, off-label treatment options comprise corticosteroids, rituximab and cytotoxic chemotherapy, which have varying efficacies and significant toxicities.

We report successful treatment with a novel, targeted regimen for a 25-year-old male with relapsing iMCD. The patient presented with generalized lymphadenopathy, right upper quadrant abdominal pain, diffuse eruption of cherry hemangiomas, thrombocytopenia, anasarca, fever, reticulin myelofibrosis, renal dysfunction, and organomegaly (TAFRO Syndrome). A lymph node biopsy revealed atrophic germinal centers, expanded mantle zones with 'onion-skin' appearance, vascular proliferation, interfollicular plasmacytosis, and paracortical hyperplasia. Combination chemotherapy with velcade-dexamethasone-thalidomide-adriamycin-cyclophosphamide-etoposide-rituximab (VDT-ACE-R) induced 15 month and 16 month remissions, but all attempted maintenance therapies (corticosteroids, rituximab, siltuximab, and velcade-dexamethasone-thalidomide (VDT)) failed to prevent relapse, and the patient experienced five disease flares requiring more than seven months of hospitalizations and intensive care in the first 3.5 years after diagnosis.

Following the fifth disease flare, clinical data were reviewed and flow cytometry, proteomics, and immunohistochemistry studies were performed to identify a novel and rational treatment option. Retrospective analyses of thirteen serum inflammatory markers revealed that two markers rose before the onset of symptoms and tracked with disease activity. Serum soluble IL-2 receptor (sIL-2R), a marker of T cell activation, rose above the upper limits of normal 20 weeks before onset of the flare and peaked at 10-fold above the upper limits of normal during flare. Vascular endothelial growth factor (VEGF), an angiogenic factor, levels approached the upper limits of normal eight weeks before flare and peaked at three-fold above the upper limits of normal during flare. Flow cytometry confirmed the presence of increased activated $CD38^{+}CD8^{+}$ T cells during disease flare, compared to healthy controls. Quantification of 315 serum analytes revealed that VEGF was the most up-regulated cytokine between flare and remission. Striking VEGF-related clinical features observed during disease flares, such as eruptive cherry hemangiomatosis, capillary leak syndrome, and hypervascularized lymph nodes, further supported an important role of VEGF in pathogenesis. Considering targetable, central signaling pathways involved in T cell activation, lymphoproliferation, and VEGF expression, we hypothesized that increased PI3K/Akt/mTOR signaling could be involved in pathogenesis. Immunostaining for phosphorylated ribosomal protein S6 (pS6), a read-out for mTOR activity, was performed on the patient's lymph node, which revealed intense staining compared to control tissues. Therefore, we initiated treatment with the mTOR inhibitor, sirolimus, along with once monthly low dose IVIg, to replete treatment-induced low immunoglobulin levels.

As of August 2017, this patient has been in a complete remission for 43 months, five times longer than the patient's previous average remission duration, with pre-disease quality of life, no clinical symptoms, and no significant complications of therapy. VEGF, sIL2R, and 11 other inflammatory marker levels remain within normal limits. Previously observed T cell activation markers are absent on flow cytometry.

The results of this study suggest that sirolimus is an effective maintenance treatment for this patient and that it should be further investigated as a potential treatment for similar relapsing iMCD patients.

Disclosures

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