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Refractory idiopathic multicentric Castleman disease responsive to sirolimus therapy

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A 20-year-old Turkish male presented with fatigue, abdominal pain, weight loss, and night sweats. Physical examination revealed hepatosplenomegaly and axillary lymphadenopathy; vital signs were normal. Hepatosplenomegaly, multiple nodular involvements in the lung parenchyma, hilar lymphadenopathy, and axillary lymphadenopathy were present on imaging. The mediastinal lymph node was described as having plasmacytic histomorphological features compatible with Castleman disease (CD) if other entities were excluded.

CD, or angiofollicular hyperplasia or giant lymph node hyperplasia, is a rare non-neoplastic lymphoproliferative disorder with variable clinicopathologic subtypes, heterogeneous outcomes, and poorly understood epidemiology (1). It was first described by Castleman et al. in 1954 in a group of patients with localized lymph node hyperplasia. CD patients demonstrate a spectrum of histomorphological features ranging from hyaline vascular to plasmacytic, with “mixed” cases in between (1,2). CD is first divided into unicentric Castleman disease (UCD) and multicentric Castleman disease (MCD) based on the number of regions of enlarged lymph nodes (1–3). UCD presents as a solitary (unifocal) lymph node, often in the mediastinum. Most patients are asymptomatic, but some can occasionally develop systemic symptoms, such as fever, night sweats, fatigue, and weight loss, as well as other clinical and laboratory abnormalities, including splenomegaly, anemia, and hypergammaglobulinemia (1–4). Regardless of symptomatology, surgical excision is nearly always curative (4,5). MCD presents with generalized lymphadenopathy and systemic symptoms that can resemble a malignant lymphoma, acute infection, or severe

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autoimmune disease. MCD is further subcategorized by etiology into human herpes virus-8 (HHV-8)-associated MCD (HHV8-MCD), polyneuropathy, organomegaly, endocrinopathy, monoclonal plasma cell disorder, and skin changes (POEMS)-associated MCD (POEMS-MCD), and idiopathic MCD (iMCD), which refers to patients with neither HHV-8 infection nor POEMS syndrome (1,3,4). iMCD patients typically either have the thrombocytopenia, anasarca, fever, myelofibrosis, renal dysfunction, and organomegaly (iMCD-TAFRO) subtype or thrombocytosis and hypergammaglobulinemia with a less severe clinical course (iMCD-not otherwise specified, iMCD-NOS). Diagnosis of CD requires histopathological and immunohistochemistry evaluations of a lymph node biopsy, radiological imaging, and clinical and laboratory evaluations (8,9). The etiology of CD remains unknown, except for HHV8-MCD.

Our case had constitutional symptoms, generalized lymphadenopathy, and hepatosplenomegaly (Figure 1). Abnormal laboratory tests included hemoglobin (7.7 g/dL), total protein (11.4g/dL), albumin (1.8g/dL), and erythrocyte sedimentation rate (ESR) (91mm/h). The platelet count was 377 $\times 10^3$/uL. Human immunodeficiency virus and HHV-8 serologies were nonreactive. The results of protein electrophoresis demonstrated polyclonal hypergammaglobulinemia (gammaglobulin 57.3%). Based on these results and the lack of TAFRO criteria, iMCD-NOS was diagnosed.

The most commonly described clinical findings in MCD include fever, night sweats, malaise, generalized lymphadenopathy, splenomegaly, and edema (6). Laboratory findings include elevated inflammatory markers, such as C-reactive protein and ESR, hypergammaglobulinemia, elevated creatinine, hypoalbuminemia, anemia, and thrombocytopenia or thrombocytosis. This inflammatory syndrome, or ‘cytokine storm,’ is considered a consequence of elevated cytokines, such as interleukin-6 (IL-6), IL-2, and vascular endothelial growth factor (VEGF) (4). The prognosis in case of iMCD is poor; 35% of patients die within 5 years of diagnosis, and 60% die within 10 years (1,3,7).

According to international treatment guidelines, first-line therapy is IL-6 inhibition, but siltuximab and tocilizumab were not available due to social security reimbursement problems. Rituximab, cyclophosphamide, vincristine, and prednisolone (R-CVP) was initiated. Six cycles were given, and his condition improved, including complete regression of the hepatosplenomegaly, axillary lymphadenopathy, and pulmonary changes. However, after six months, symptoms recurred along with high levels of IL-6 in the blood, and tocilizumab and cyclosporine A were started. Symptoms regressed initially but recurred twenty-two months later. Bortezomib was started as the third-line treatment, but severe peripheral neuropathy developed immediately. Next, lenalidomide was started as the fourth-line treatment (5,10). After five cycles, progression occurred. Sirolimus treatment was started as the fifth-line therapy with a rapid and excellent response (Figure 2).

IL-6 inhibitors (siltuximab, tocilizumab) are the first-line treatment for iMCD; however, there is no established treatment for cases that are resistant to IL-6 inhibitors (5). IL-6 monoclonal antibodies (tocilizumab and siltuximab) are particularly useful in the alleviation of systemic manifestations and organ dysfunction (11). In fact, the development of siltuximab, an IL-6 neutralizing monoclonal antibody (mAb), and tocilizumab, a humanized

mAb that binds to the IL-6 receptor, has changed the treatment paradigm for iMCD (12). In a randomized, double-blind, placebo-controlled phase 2 trial, approximately one-third of patients treated with siltuximab were found to have a durable complete or partial response, whereas no patients treated with placebo responded (5). Similarly, in a nonrandomized prospective study of tocilizumab in iMCD, approximately half of the patients had a significant reduction in their lymphadenopathy and improvement in their iMCD symptoms (13). Based on these results, siltuximab was approved for the treatment of iMCD in the United States, Canada, and Europe, and tocilizumab was approved for the treatment of iMCD in Japan. The response duration to tocilizumab in our case was about twelve months. However, rituximab with or without combination cytotoxic chemotherapy and corticosteroids are the most commonly used choices in cases in which IL-6 inhibitors could not be reached due to financial problems. Other reported treatments include lenalidomide, bortezomib, cyclosporine A, sirolimus, thalidomide, baricitinib, intravenous immunoglobulins, plasmapheresis, radiotherapy, and autologous hematopoietic stem cell transplantation (3,14). While IL-6 blockade represented a significant breakthrough in iMCD treatment, a substantial portion of patients with iMCD remains refractory to therapy with siltuximab or tocilizumab or unable to access them. This suggests that additional pathways may underlie iMCD pathogenesis and be important targets for iMCD therapies. Determination of these additional pathways, however, is limited by an absence of cell lines, animal models, or large data sets of IL-6 blockade refractory iMCD.

We used tocilizumab and cyclosporine A, bortezomib, and lenalidomide, but disease recurred or could not be continually given due to toxicity. As fifth-line treatment, we used sirolimus.

Although sirolimus, a mammalian target of rapamycin (mTOR) inhibitor, has been suggested to be effective in a small number of iMCD patients who have been reported to receive it, the long-term safety and efficacy of sirolimus on individuals with IL-6 inhibitor-resistant iMCD has not been evaluated. Our case was resistant to the IL-6 receptor inhibitor tocilizumab, immunomodulator lenalidomide, and NFKB blocker bortezomib but had a dramatic response to sirolimus therapy.

In 2019, Fajgenbaum et al. identified the mTOR pathway as a pharmacologically targetable pathway within IL-6 blockade–refractory iMCD. mTOR is an atypical serine/threonine protein kinase that is part of the phosphoinositide 3-kinase–related (PI3K-related) family (15). Based on these findings, as well as the limited remaining therapeutic options for IL-6 blockade–refractory patients, Fajgenbaum et al. treated these patients with sirolimus. Sirolimus is a known antiproliferative and immunosuppressive drug that directly inhibits mTOR. It is generally well tolerated and is used in several conditions including after kidney transplantation, lymphangioleiomyomatosis, and autoimmune lymphoproliferative syndrome. Sirolimus treatment normalized VEGF-A levels and decreased circulating activated CD8+T cells in all three patients. Moreover, the patients tolerated the sirolimus without significant side effects, have experienced symptomatic benefits, and have been in remission for 64, 17, and 17 months, as of the time of publication (11,15). These findings serve as an excellent starting point for future trials that will investigate both the efficacy and safety of sirolimus in the treatment of IL-6 blockade–refractory iMCD

patients. Nevertheless, several questions remain. First, while Fajgenbaum et al. convincingly demonstrated the role of mTOR signaling in IL-6 blockade–refractory iMCD, the etiologic trigger of iMCD and whether mTOR is associated with this trigger remains unknown. Second, it is not evident whether the authors' findings will be generalizable across a larger cohort of IL-6 blockade–refractory iMCD patients. This is of particular concern since iMCD-TAFRO has been shown to have different proteomic profiles from other patients with iMCD (3,16). Third, multiple pharmacologic agents target the mTOR pathway, and it remains to be determined whether sirolimus is the optimal choice. Finally, many cytokines are expressed in locally restricted sites, limiting the capacity of serum proteomics to detect their role in disease pathogenesis, even when their impact is systemic (3,15,16).

Since this initial publication, further work has been done to characterize mTOR activation across iMCD patients, identify potential mechanisms leading to increased mTOR activation, and uncover further pathways, but few additional sirolimus-treated patients have been reported (11,12,15). There are currently two clinical trials open of sirolimus in anti-IL-6 refractory patients and an international Castleman disease registry (www.CDCN.org/ACCELERATE) that patients can enroll in directly that should help to continue to improve understanding and treatment of CD (12).

At the last follow-up (3/22), we observed this patient to be in complete remission while undergoing sirolimus treatment for 32 months (Figure 3).

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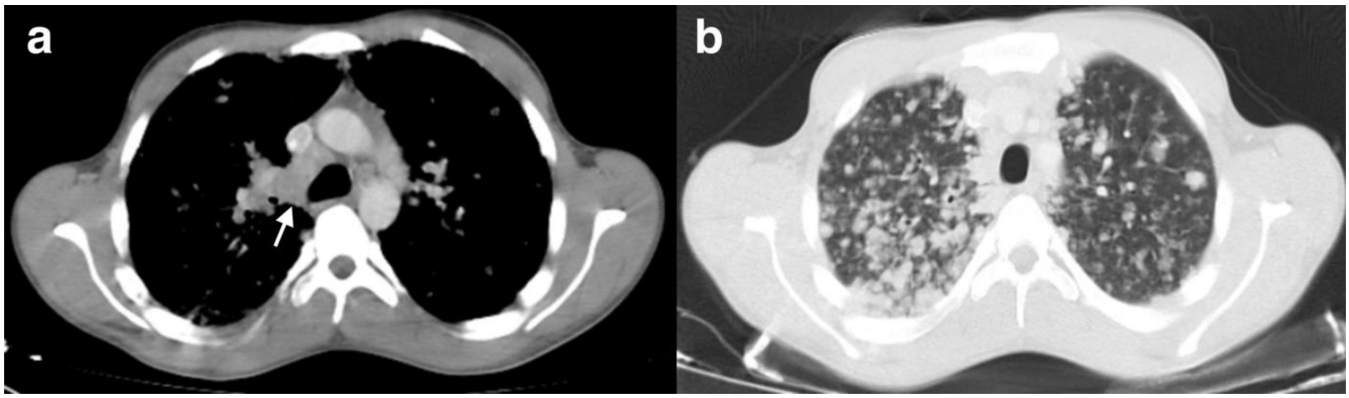

Figure 1:
Multiple conglomerated hilar lymphadenopathies (arrow in a) and diffuse nodular involvement in the lung parenchyma (b)

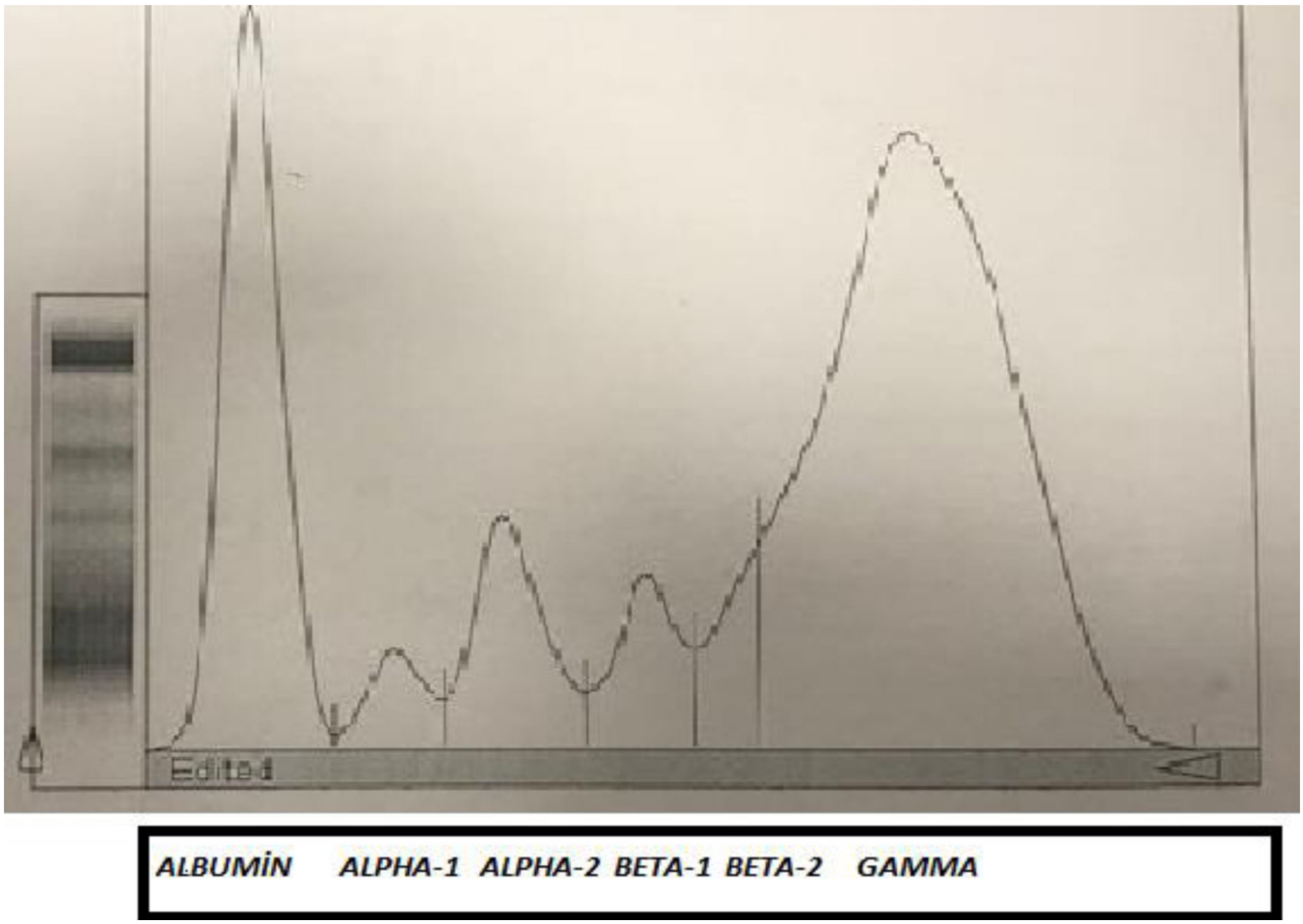

Figure 2 :
Graphed protein electrophoresis

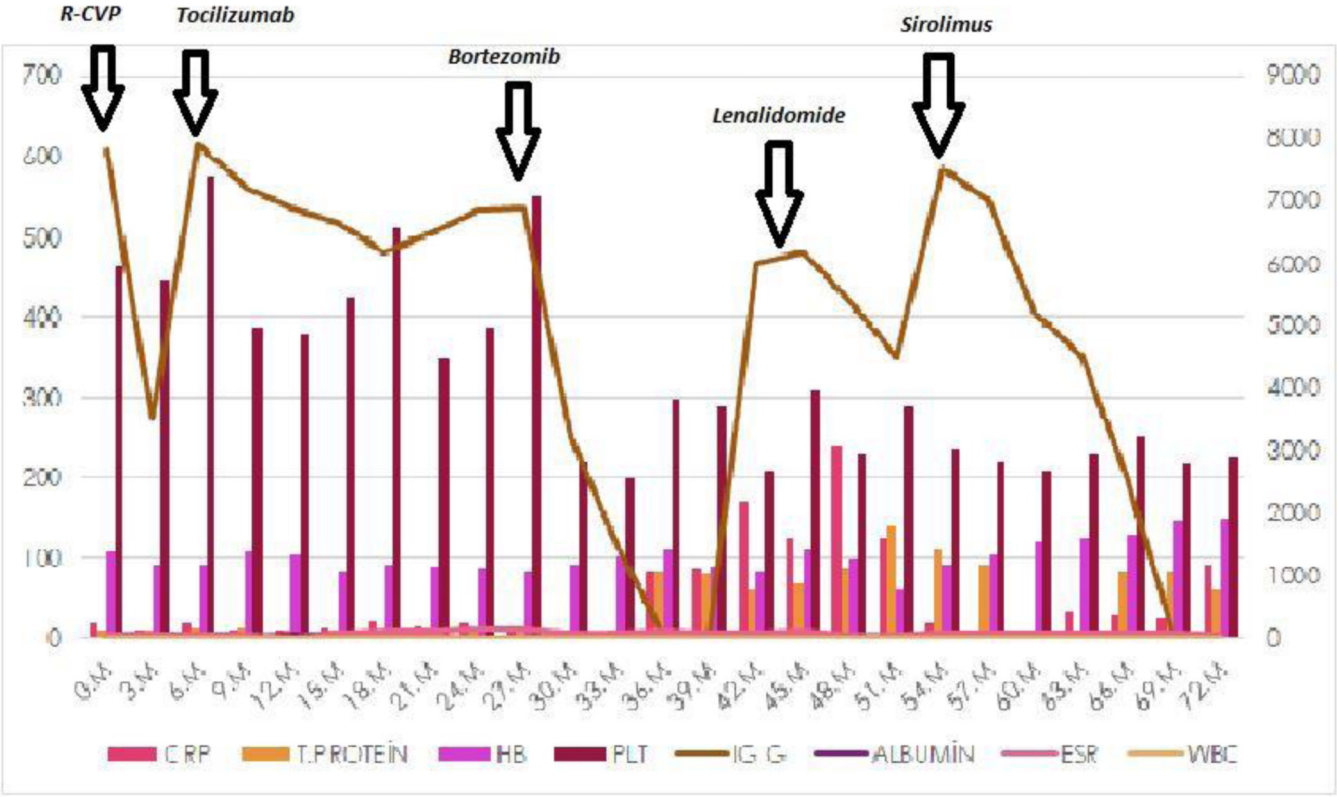

Figure 3 :
Treatments and responses

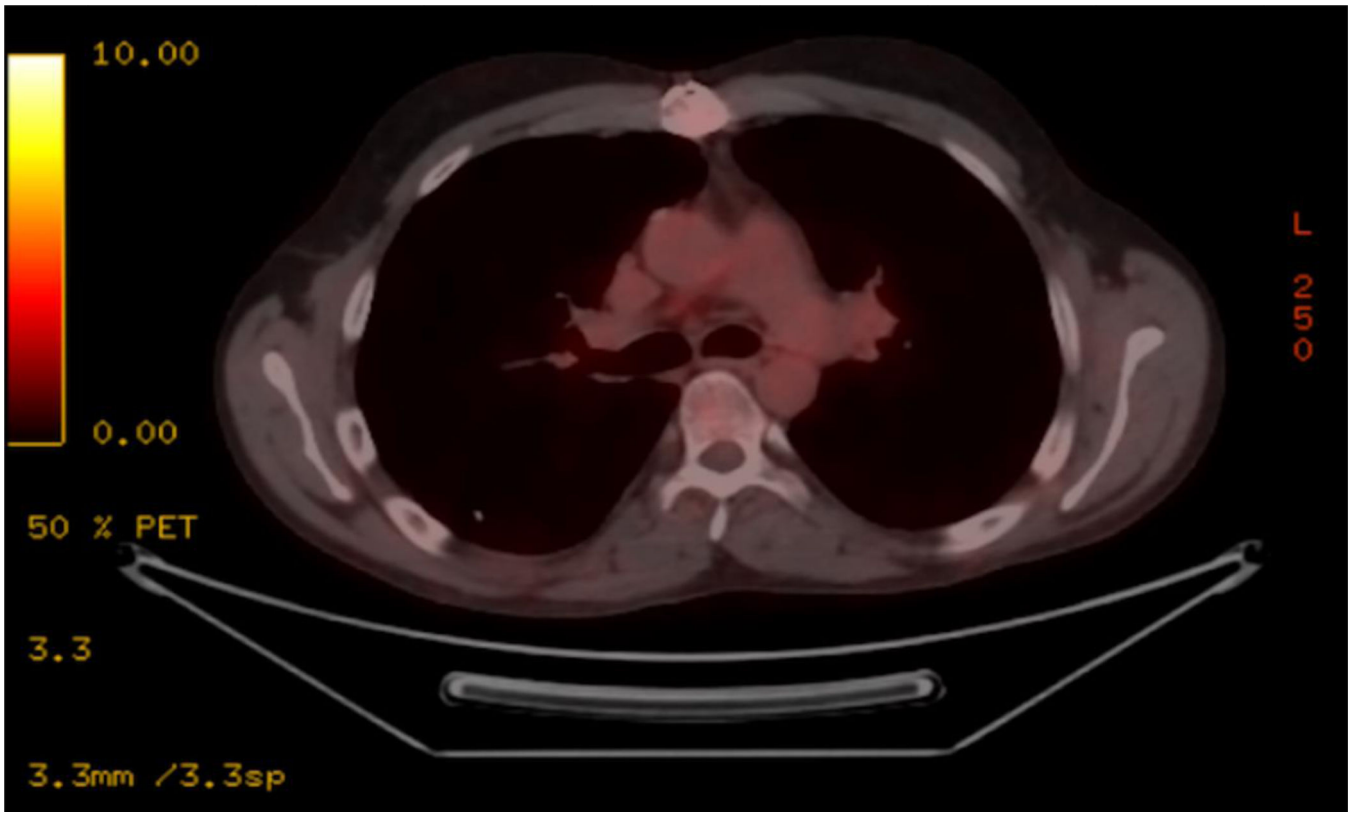

Figure 4:
Complete response was observed on control positron-electron tomography/computed tomography after sirolimus treatment.