Published in final edited form as:
Pediatr Blood Cancer. 2014 April ; 61(4): 737–739. doi:10.1002/pbc.24761.

Sustained Remission of Severe Multicentric Castleman Disease Following Multiagent Chemotherapy and Tocilizumab Maintenance

Lucie M. Turcotte, M.D., M.P.H.[1], **Colleen K. Correll, M.D.**[2], **Robyn C. Reed, M.D., Ph.D.**[3], and **Christopher L. Moertel, M.D.**[1]

[1]Division of Pediatric Hematology/Oncology, University of Minnesota, 420 Delaware Street SE, Minneapolis, MN 55455, USA

[2]Division of Pediatric Rheumatology, University of Minnesota, 2450 Riverside Avenue, 8952F, Minneapolis, MN 55454, USA

[3]Department of Laboratory Medicine and Pathology, University of Minnesota, 420 Delaware Street SE, Minneapolis, MN 55455, USA

Abstract

Castleman disease is a rare lymphoproliferative disorder, which presents in a unicentric or multicentric fashion. Multicentric Castleman disease (MCD) is associated with significant systemic symptoms, in part related to the underlying role of interleukin-6 in disease pathogenesis. Treatment for MCD has not been well established and prognosis has historically been poor. We present a case of severe MCD in a pediatric patient who has shown sustained remission following multi-agent chemotherapy and targeted maintenance therapy with the interleukin-6 receptor inhibitor, tocilizumab. This represents the first case report of sustained remission of MCD in a pediatric patient following discontinuation of tocilizumab therapy.

Keywords

Multicentric Castleman disease; tocilizumab; anakinra; CHOP

Introduction

Castleman disease is a rare nonclonal lymphoproliferative disorder, typically seen in adulthood. Clinically, Castleman disease can present either localized (unicentric) or as multisystem disease (multicentric). Underlying disease etiology is unclear, although it is often associated with concurrent human immunodeficiency virus (HIV) or human herpesvirus 8 (HHV-8) infections, particularly when presenting as multicentric disease. While not considered a neoplastic disorder, it is not purely reactive either. Histologically, the disease presents as three distinct variants: plasma cell, hyaline vascular, or mixed variant. Unicentric disease is typically the hyaline vascular type, with limited associated symptoms, and is often managed surgically. Multicentric Castleman disease (MCD) is usually plasma cell or mixed variant and involves symptoms, such as fevers, night sweats,

Corresponding Author: Lucie M. Turcotte, M.D., M.P.H., Division of Pediatric Hematology/Oncology, University of Minnesota, 420 Delaware Street SE, MMC 484, Minneapolis, MN 55455; Phone: 612-626-2778, Fax: 612-626-2815, turc0023@umn.edu.

Conflict of Interest Statement: Nothing to disclose.

fatigue, lymphadenopathy, hepatosplenomegaly, anemia, anorexia and multi-organ dysfunction. MCD requires systemic therapy, such as chemotherapy, for management.

Interleukin-6 (IL-6) is a multifunctional cytokine produced by macrophages, endothelial cells and tissue fibroblasts and has many proinflammatory functions, including stimulation of synthesis of acute-phase reactant proteins in the liver, fever, and activation of endothelial cells. Dysregulated IL-6 production by germinal center B-cells is considered to be the most important disease mediator in MCD [1]. Along with regulation of acute-phase response, IL-6 plays a role in T-cell function and terminal B-cell differentiation. Increased systemic levels leads to increased fibrinogen, stimulation of hepcidin production and anemia, B-cell growth, and increased lymph node vascularity and growth, accounting for many symptoms associated with MCD.

There is no standard approach to treatment of MCD and historically, the prognosis has been poor. Previous treatments have included corticosteroids and multi-agent chemotherapy [2], and recently have included targeted therapies, such as rituximab (anti-CD20 monoclonal antibody) [3], anakinra (IL-1 receptor antagonist) [4,5], and tocilizumab (IL-6 receptor antagonist) [6,7,8], but data are limited on the efficacy of these agents in the pediatric population or on follow-up after discontinuation. We present a pediatric patient with MCD, treated with multi-agent therapy with several months of follow-up.

Case

A 16-year old male presented to the hospital in acute renal failure with a four-week history of abdominal pain, fatigue, weakness, fever and night sweats. Laboratory studies showed: BUN 81 mg/dL, creatinine 4.1 mg/dL, and uric acid 15.6 mg/dL. Additionally, CBC revealed WBC 14.2/μL with mild absolute neutrophilia, hemoglobin 10.4 g/dL and platelets 105/ μL. Diffuse lymphadenopathy and hepatosplenomegaly were present on physical exam. CT imaging showed multiple enlarged cervical lymph nodes bilaterally, all >2.5 cm, as well as enlarged (2-3 cm) nodes in the mediastinum, axillae, mesentery and inguinal distributions. Ultrasound showed mild ascites and small bilateral pleural effusions, as well as nephromegaly and hepatosplenomegaly. Bone marrow studies showed no evidence of malignancy. An extensive infectious disease work-up was unrevealing. Renal and lymph node biopsies were performed (Figure 1). Histologic examination of the lymph node was significant for findings of atretic germinal centers, expanded mantle zone, prominent interfollicular vessels and interfollicular plasmacytosis, consistent with Castleman disease, mixed variant. Renal biopsy revealed glomerular basement membrane abnormalities and endocapillary proliferation, suggestive of thrombotic microangiopathy, which has been previously described in MCD [9,10,11].

During the early phase of illness, the patient's clinical status deteriorated quickly. He developed mental status changes, became anuric, requiring initiation of daily hemodialysis, required multi-agent inotropic support for hemodynamic instability, and developed acute respiratory failure secondary to fluid overload and pleural effusions, requiring intubation and mechanical ventilation. Further evaluation revealed that the patient was HIV and HHV-8 negative. The initial IL-6 level was 416.7 ρg/mL (normal = 0-3 ρg/mL). He also had elevated inflammatory markers (CRP and ESR) and low albumin.

Given the rarity of MCD in the pediatric population, particularly without an underlying viral risk factor, therapeutic decisions were difficult. On hospital day 11, treatment was initiated with methylprednisolone (1 g/day × 5 days) and weekly rituximab (375 mg/m^2/dose). Five days after initiating therapy, the patient's status continued to be tenuous without evidence of improvement of the significant inflammatory process, so tocilizumab (8 mg/kg/dose) was

initiated. The patient's clinical status showed some improvement, but he continued to require respiratory and hemodynamic support, so 6 days after initiating tocilizumab, anakinra (100 mg every other day) was also given. Over the next three weeks, the patient showed significant clinical improvement and after six weeks, he was discharged from the hospital. At the time of discharge he had received 4 doses of rituximab, 5 days of methylprednisolone, 2 doses of tocilizumab and 2 weeks of anakinra. He continued to require hemodialysis three times per week, but renal function was improving. Lymphadenopathy was mildly decreased in size, but still diffusely present. The decision was made to initiate treatment with CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) chemotherapy for 4 cycles and to continue tocilizumab for a total of 8 biweekly doses, followed by 8 monthly doses. Therapy was well tolerated. Renal function returned to baseline, endurance improved, organomegaly and lymphadenopathy improved, weight returned to baseline, and albumin, hemoglobin, platelets and inflammatory markers normalized by 75 days from initial presentation (Figure 2). Although IL-6 levels were not followed routinely, it had normalized at the completion of therapy and has remained normal. Lymphadenopathy was followed with CT imaging; serial imaging showed complete resolution of initially noted hilar, axillary, mesenteric and inguinal lymphadenopathy and cervical lymphadenopathy decreased to ≤1.5 cm (Supplemental Figure 1). At last follow-up, 13 months following completion of CHOP and 7 months following completion of tocilizumab, there is no evidence of disease recurrence.

Discussion

This case represents successful treatment of a rare disease in pediatrics. The early, critical nature of this patient's illness necessitated aggressive, multi-agent management. Initial treatment with rituximab and methylprednisolone was selected because of the low toxicity profile and previously demonstrated efficacy in MCD with associated renal thrombotic microangiopathy [3]; however, given the progressive nature of the illness, tocilizumab and anakinra, were added to quiet the underlying aggressive inflammatory process. Combination therapy with tocilizumab and anakinra has not been described in MCD, but risks associated with both agents include infection and hepatic toxicity, and concerns were raised among treating physicians that these side effects may be potentiated when using these agents concurrently. Once stabilized, the patient was managed with lymphoma-type therapy (CHOP) [2], along with tocilizumab; anakinra was discontinued to minimize toxicity. Treating physicians felt strongly that aggressive management was warranted, despite risks of prolonged immune suppression and infection, given the associated high rates of disease-related morbidity and mortality, and persistent lymphadenopathy and elevated inflammatory markers at the time of hospital discharge. While it is impossible to determine what ultimately improved the clinical course of our patient or what has led to continued remission, particularly given the long half-life of tocilizumab and the rapid succession of employed therapies, we believe the early combination of tocilizumab and anakinra, as well as the use of combination chemotherapy with tocilizumab are important contributors. Previous reports of tocilizumab in MCD have not offered guidelines for duration of therapy and have not described duration of remission upon discontinuation. This case report describes early combination therapy with anakinra and tocilizumab, as well as successful discontinuation of tocilizumab with several months of disease-free follow-up. We propose tocilizumab be considered front-line therapy for this aggressive, cytokine-mediated disease.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Supported by NIH T32 CA099936 and Children's Cancer Research Fund, Minneapolis, MN.

References

1. Yoshizaki K, Matsuda T, Nishimoto N, et al. Pathogenic significance of interleukin-6 (IL-6/BSF-2) in Castleman's disease. Blood. 1989; 74:1360–1367. [PubMed: 2788466]
2. Seo HY, Kim EB, Kim JW, et al. Complete remission in a patient with human herpesvirus-8 negative multicentric Castleman disease using CHOP chemotherapy. Cancer Res Treat. 2009; 41:104–107. [PubMed: 19707509]
3. Lee JP, Kim DK, Oh DY, Paik JH, Moon KC, Kim S, Kim YS. Successfully treated multicentric Castleman's disease with renal thrombotic microangiopathy using rituximab and corticosteroid. Clin Nephrol. 2011; 75:165–170. [PubMed: 21255547]
4. Galeotti C, Tran TA, Franchi-Abella S, Fabre M, Pariente D, Kone-Paut I. IL-1RA agonist (anakinra) in the treatment of multifocal castleman disease: case report. J Pediatr Hematol Oncol. 2008; 30:920–924. [PubMed: 19131781]
5. El-Osta H, Janku F, Kurzrock R. Successful treatment of Castleman's disease with interleukin-1 receptor antagonist (anakinra). Mol Cancer Ther. 2010; 9:1485–1488. [PubMed: 20501803]
6. Nishimoto N, Sasai M, Shima Y, et al. Improvement in Castleman's disease by humanized anti-interleukin-6 receptor antibody therapy. Blood. 2000; 95:56–61. [PubMed: 10607684]
7. Nishimoto N, Kanakura Y, Aozasa K, et al. Humanized anti-interleukin-6 receptor antibody treatment of multicentric Castleman disease. Blood. 2005; 106:2627–2632. [PubMed: 15998837]
8. Galeotti C, Boucheron A, Guillaume S, Kone-Paut I. Sustained remission of multicentric Castleman disease in children treated with tocilizumab, an anti-interleukin-6 receptor antibody. Mol Cancer Ther. 2012; 11:1623–1626. [PubMed: 22638145]
9. Lajoie G, Kumar S, Min KW, Silva FG. Renal thrombotic microangiopathy associated with multicentric Castleman's disease. Am J Surg Pathol. 1995; 19:1021–1028. [PubMed: 7661275]
10. El Karoui K, Vuiblet V, Dion D, et al. Renal involvement in Castleman disease. Nephrol Dial Transplant. 2011; 26:599–609. [PubMed: 20656751]
11. Xu D, Lv J, Dong Y, et al. Renal involvement in a large cohort of Chinese patients with Castleman disease. Nephrol Dial Transplant. 2012; 27:iii119–iii125. [PubMed: 21602182]

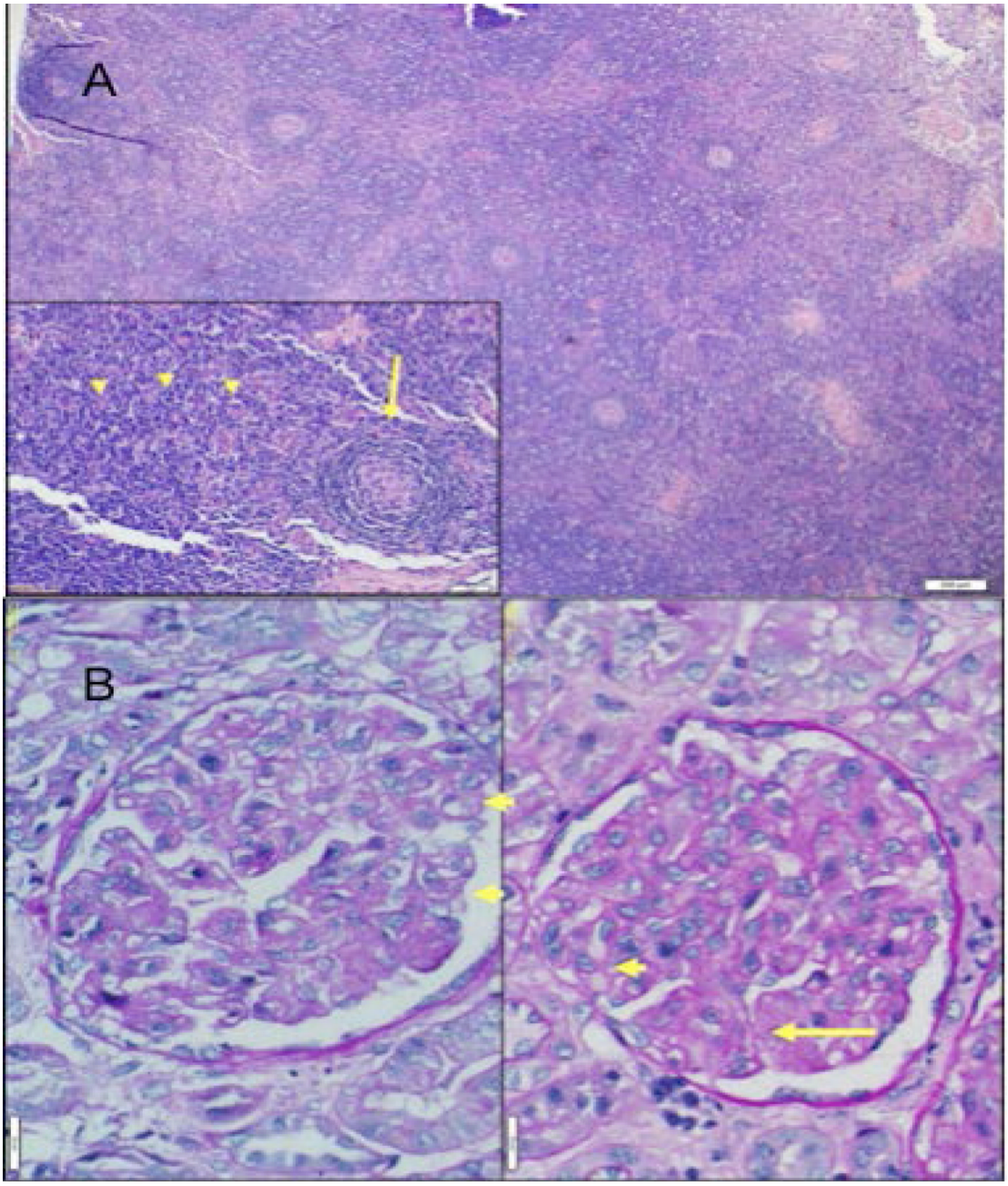

Figure 1.

A. Lymph node biopsy disclosed atretic germinal centers with an expanded mantle zone. At higher magnification (box), atretic germinal centers were surrounded by lymphocytes in a prominent “onionskin” mantle pattern (arrow). In some interfollicular areas, there were aggregates of plasma cells (arrowhead). H&E stain, 40x and 400x. B. Kidney biopsy demonstrated glomerular basement membrane splitting and duplication (arrowheads) and segmental endocapillary proliferation (arrow). Immunofluorescence microscopy of a single glomerulus was negative for immune complex deposition (not shown). PAS stain, 400x.

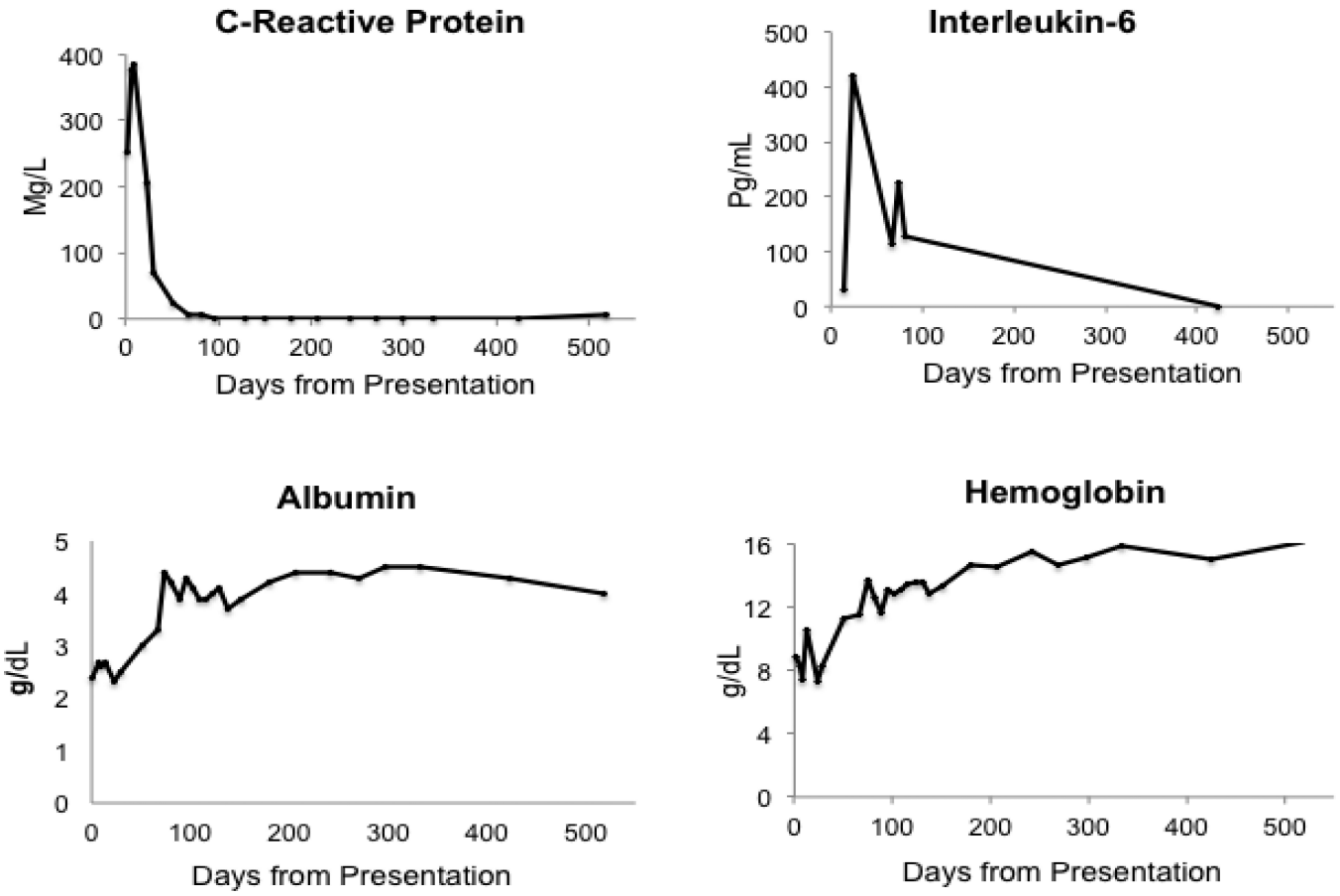

Figure 2.

Laboratory value trnds over treatment course. Treatment initiated with methylprednisolone and rituximab on day 11, tocilizumab on day 16, anakinra on day 22 and CHOP on day 60. Last course of CHOP completed day 134 and last dose of tocilizumab given on day 298.