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The aggravating fury rituximab obliterated
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Author contributions

FC and HM were involved in the conception and design. HM was involved in the data acquisition and drafting of the article. AO and FC did critical revision for important intellectual content. All authors have given their final approval and agree to be accountable for all aspects of the work.

Running head: Rituximab for refractory MCD

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Multicentric castleman disease (MCD) is characterized by enlarged lymph nodes in 2 or more lymph node stations, characteristic features on microscopic analysis of enlarged lymph node tissue, and a variety of clinical symptoms. It is characterized into three subtypes – Human Herpes virus 8 (HHV8) associated MCD which usually occurs in HIV-positive individuals, POEMS-MCD (polyneuropathy, organomegaly, endocrinopathy, monoclonal plasma cell disorder, skin changes) and idiopathic MCD (iMCD). iMCD is subclassified into iMCD–TAFRO ((Thrombocytopenia, Anasarca, Fever, Reticulin fibrosis and Organomegaly) or iMCD–NOS (not otherwise specified). The histopathological spectrum of iMCD is delineated as regressed germinal centers and prominent vascularization on the hypervascular end of the spectrum, hyperplastic germinal centers with prominent plasmacytosis on the plasmacytic end of the spectrum and overlapping features of both would represent mixed histopathology.

IL-6 has been implicated in the pathophysiology of MCD especially if its levels are elevated. HHV8 can replicate in plasmablasts and produce the viral homolog of IL-6 which along with other cytokines produces symptoms and pathology found in HHV MCD. MCD usually occurs in HIV-positive patients. We hereby delineate an interesting case of severe idiopathic multicentric castleman disease which masqueraded as atypical hemolytic uremic syndrome (aHUS) and showed excellent response to rituximab after refractoriness to IL-6 antagonist therapy.

A 39-year-old female with no prior medical history initially presented with abdominal pain and body aches. Within a few days, her clinical status worsened, and she developed severe anemia, thrombocytopenia, and acute renal failure (ARF). Peripheral smear showed few
schistocytes (approximately 2% of 1000 red blood cells) and target cells. She had elevated 
LDH levels (1202 IU/L) and indirect hyperbilirubinemia (3.3 mg/dl). Retic count and 
haptoglobin were normal. She became unstable and was transferred to the ICU. She was 
intubated, required pressors for shock and was started on continuous renal replacement 
therapy (CRRT). She underwent daily plasma exchange for 5 days. However, her platelet 
count and hemoglobin continued to drop. Moreover, the ADAMTS13 level returned normal. 
The patient was started on eculizumab, an anti-complement C5 protein antibody for 
suspected aHUS. In addition, she received intravenous immunoglobulin and steroids. The 
platelet count improved with Eculizumab, climbing from $18 \times 10^3/\mu L$ to $92 \times 10^3/\mu L$ after 
two weeks of therapy. She improved clinically, was extubated and transferred out of the ICU.

The platelet counts subsequently started to decline. An aHUS panel was sent to an outside 
lab. It showed a modest increase in serum C5b-9 above reference intervals. Her dose of 
eculizumab was increased and she was restarted on steroids. Bone marrow biopsy was 
negative for leukemia, lymphoma, myelodysplasia, or hemophagocytosis and mutational 
analysis was unrevealing for BCR-ABL, JAK 2 mutations, MPL or CALR mutation. She 
received intermittent transfusions with platelets, pRBCs, and FFP. Her kidney function 
recovered after a few weeks, and she was eventually discharged with a platelet count of $23 \times 
10^3/\mu L$ and hemoglobin of 7.6 g/dL.

She was admitted again 4 months later with abdominal pain and evaluation showed a right 
adnexal lesion. Diagnostic laparoscopy revealed intra-abdominal hemoperitoneum. She 
developed ARF requiring Hemodialysis (HD) and had persistent anemia and 
thrombocytopenia requiring multiple transfusions. Peripheral blood smear showed no
evidence of schistocytes. Haptoglobin and LDH were normal. She was eventually discharged with outpatient HD. She was kept on Eculizumab maintenance therapy every 2 weeks for around 2 months. She was again admitted with abdominal pain and was found to have a large left adnexal ovarian mass with a hemorrhagic component as well as pelvic lymphadenopathy. She underwent a left perirenal lymph node biopsy which showed non-specific findings like paracortical acute inflammatory infiltrates, hemorrhage, and rare fibrin thrombi. Bone marrow biopsy was repeated and showed only mildly hypercellular marrow with multilineage hematopoiesis. Flow cytometry on the marrow aspirate was unremarkable. In the interim, she was given romiplostim due to persistent severe thrombocytopenia. Given the suspicion of an autoimmune process of unknown etiology, she was also given rituximab 375 mg/m² weekly x 4 weeks. The patient stabilized over the next few weeks and was discharged. She received romiplostim 10 mcg/kg weekly for almost 3 months. Her platelet counts slowly rose while she was on the drug. She underwent an axillary lymph node biopsy 3 months later for evaluation of persistent lymphadenopathy which showed non-specific extramedullary hematopoiesis. She was once again admitted 6 months later with worsening anemia, thrombocytopenia and renal failure. She also had new cervical and supraclavicular lymphadenopathy. Parvovirus, EBV and CMV were negative. Repeat bone marrow biopsy showed only hypercellular marrow with myeloid and megakaryocytic hyperplasia. She underwent an excisional biopsy of an occipital lymph node which showed an enlarged lymph node with marked expansion of paracortex by sheets of plasma cells, hyaline vascular change, with regressed germinal centers, onion-skinning of mantle zones and vascular proliferation (Figures 1, 2 and 3). This was consistent with Castleman's disease, plasma cell variant. Interleukin-6 (IL-6) levels came back significantly elevated at 51.1 pg/mL (normal is 0 to 15.5 pg/mL). HIV and HHV8 testing were negative. Thus, she was diagnosed with idiopathic MCD. Based on the clinical findings, it was more inclined toward the idiopathic
TAFRO subtype. She was started on the IL-6 antagonist Siltuximab. She improved with normalization of creatinine and hemoglobin and partial recovery of platelet count and was discharged. The patient was admitted again 5 months later with chills, myalgias and right upper quadrant pain. Imaging of the chest, abdomen and pelvis showed no change in her existing lymphadenopathy and no new findings. PET/CT showed no evidence of highly FDG avid disease and no significant change in the size of the previously existing adenopathy. She developed increasing lethargy, rising uric acid, elevated CRP, and acute kidney injury consistent with Castleman's relapse. She was started on methylprednisolone and rituximab 375 mg/m² IV weekly. Methylprednisolone was later changed to prednisone. Her kidney function recovered. The hemoglobin and platelet count improved with a new baseline of 10.5-11.5 g/dL and 200-250 x 10³/µL respectively. The patient was thereafter continued on maintenance rituximab 375 mg/m² every 8 weeks. The patient has been relapse-free for over 2 years.

Our patient was diagnosed with iMCD as HHV8 and HIV were negative and clinical signs/symptoms were parallel with the TAFRO subtype. The initial suspicion of atypical HUS was made due to anemia, thrombocytopenia, renal dysfunction and signs of hemolysis like schistocytes on peripheral smear, increased LDH and indirect bilirubin. This suspicion was somewhat reinforced due to a partial response to eculizumab therapy. However, there was uncertainty as the patient continued developing repeated episodes of anemia, thrombocytopenia, and kidney failure despite being on eculizumab. Multiple bone marrow and lymph node biopsies were unrevealing. Lymph node biopsy for the third time finally showed characteristic features of MCD. In patients presenting with symptoms that could explain MCD with no alternate diagnosis, a single unremarkable lymph node cannot rule out MCD. Julie et al also described a case with idiopathic multicentric disease in which initial
lymph node biopsy showed only reactive changes and repeat biopsy discovered characteristic changes of MCD.5

In iMCD cases, IL-6 plays a significant role in driving symptoms and pathology in many cases of iMCD.4 A randomized clinical trial of IL-6 antagonist Siltuximab vs placebo showed durable responses with siltuximab in almost 1/3 of patients vs no response to placebo.6 However, not all iMCD patients have IL 6 elevation and many patients either may not respond to Siltuximab or may relapse after initial response.6

For iMCD, further treatment is based on severity.7 Rituximab is as an alternative first-line agent for more indolent cases of iMCD to avoid giving toxic chemotherapy to such patients.7 Rituximab eliminates CD20+ B-cells and plasmablasts.7 A very small number of case reports/series have described the use of rituximab in iMCD.7 One report described 25 cases of iMCD, who were treated with rituximab as first-line therapy and the CR and PR rates were 20% and 48%, respectively.8 In a study with 61 patients with histologically confirmed MCD, 49 patients were treated with rituximab. The overall survival was 94% at 2 years and 90% at 5 years with rituximab compared with 42% and 33% in patients who did not receive rituximab.9

For more severe cases, combination chemotherapy with/without rituximab is generally preferred.7,10 CHOP or CVAD (cyclophosphamide, vincristine, adriamycin, etoposide) regimens have shown good responses in patients with severe iMCD.7 One study showed sustained remission rates of 27% with combination chemotherapy in patients with severe iMCD.7 However, these chemotherapy regimens have serious side effects like bone marrow suppression.7 Our patient had severe iMCD manifestations and required several RBC and
platelet transfusions and CRRT/HD sessions. A rituximab-based regimen without chemotherapy was considered due to concerns for tolerability. The patient responded well with recovery of counts and kidney function. The response has been sustained with maintenance rituximab for over 2 years. Prospective studies evaluating the efficacy of rituximab in iMCD may be conducted to better comprehend its efficacy and safety.
References

Figure legends

**Figure 1: Characteristic histopathologic findings of Castleman Disease**
Hematoxylin and Eosin (H & E) image showing a regressed germinal center doublet with onion skinning and radially penetrating vessel

**Figure 2: Characteristic histopathologic findings of Castleman disease**
Hematoxylin and Eosin (H & E) image showing an expanded paracortex with hyaline vascular proliferation and increased plasma cells

**Figure 3: Immunostaining for plasma cells**
CD138 immunostaining highlighting the sheets of plasma cells