case report

# Successful treatment of steroid-refractory autoimmune thrombocytopenia associated with Castleman disease with anti-CD-20 antibody (rituximab)

Khalid Ibrahim,[a] Irfan Maghfoor,[b] Assem Elghazaly,[a] Nasir Bakshi,[c] Said Y. Mohamed,[a] Mahmoud Aljurf[a]

From the [a]Section of Adult Hematology/HSCT, [b]Section of Medical Oncology, [c]Department of Pathology and Lab Medicine, King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia

Correspondence: Mahmoud Aljurf, MD · Oncology Center, King Faisal Specialist Hospital and Research Centre, P.O. Box 3354, Riyadh 11211 Saudi Arabia · T: +9661 4424586, F: +9661 4423941 · maljurf@kfshrc.edu.sa · Accepted: June 2011

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Multicentric Castleman disease (MCD) is a lymphoproliferative disorder of incompletely understood etiology and with various clinical presentations. The best therapeutic option for this disease is not well established. MCD is known to be associated with autoimmune phenomena. A 70-year-old female patient of MCD with progressive nodal disease associated with autoimmune thrombocytopenia failed steroid treatment and showed a transient response to intravenous immunoglobulin. The patient achieved complete recovery of her platelet count and a very good response in nodal disease after 3 weekly doses of anti-CD-20 antibody (rituximab). Anti-CD20 antibody treatment could be a good therapeutic option for MCD, mainly when associated with immune-related disorders.

Castleman disease (CD), also referred to as angiofollicular lymph node hyperplasia, giant cell lymph node hyperplasia, benign giant lymphoma, lymphoid hamartoma, was first described by Caslteman and Towne in 1954.[1,2] CD is a heterogenous disorder and may present as a unicentric or multicentric type. Pathologically, three distinct varieties, hyaline vascular, plasmacytic and mixed, have been recognized.[2] CD is considered a non-clonal disorder, but clonal abnormalities have been detected in some patients with multicentric disease.[3]

Systemic CD is known to be associated with autoimmune phenomena, including immune thrombocytopenia.[4] Although optimal therapy for CD is not clearly defined, steroids have been used in the management with a reported response rate of 60%. The responses are short-lived, however.[5,6]

Recently several reports have appeared in support of the use of anti-CD20 antibody (rituximab) in the treatment of immune thrombocytopenia[7-10] as well as in multicentric CD.[11-13] However, there are no reports of anti-CD20 therapy in immune thrombocytopenia associated with CD. We report on a patient with mixed variant of multicentric Castleman disease associated with immune thrombocytopenia successfully treated with rituximab.

## CASE

A 70-year-old female presented with a 2-month history of bilateral neck and right axillary swelling at a private institution. A lymph node biopsy was suggestive of lymphoma and she was referred to our hospital for further care. Her pathology review documented the presence of mixed-variant Castleman disease (**Figure 1**). Staging work-up revealed bilateral cervical and right axillary lymphadenopathy. Her peripheral blood counts revealed a normal white blood cell count of $9.02\times10^9$/L, normal hemoglobin of 128 g/L and low platelets of $28\times10^9$/L. She was managed expectantly despite evidence of lymph node enlargement. In September 2009, she presented with significant progression of her adenopathy and marked thrombocytopenia ($2.0\times10^9$/L). Staging work-up revealed the presence of enlarged lymph nodes in the neck, axillae, mediastinum, abdomen and pelvis,

in addition to pleural effusions. A bone marrow aspiration revealed no evidence of tumor or infection in the marrow and an increased number of megakaryocytes. She was admitted with a diagnosis of progressive multicentric Castleman disease and immune thrombocytopenia. She was started on prednisone at the dose of 1mg/kg without improvement and was then given intravenous immune globulin at the dose of 1g/kg for two consecutive days. After an initial rise in platelet count, it decreased again to $17\times10^9$/L within 7 days (**Figure 2**). The patient was then started on rituximab 375 mg/m$^2$/week for 4 weeks. The platelet count recovered to $142\times10^9$/L after three doses and there was dramatic response with complete clinical disappearance of cervical and axillary adenopathy. The patient was discharged in stable condition and 6 months after rituximab therapy, had a stable platelet count and no evidence of progression of lymphadenopathy.

## DISCUSSION

The rarity and heterogeneity of CD have precluded properly designed trials of treatment and the majority of treatment recommendations are based on case reports, or case series. Unicentric CD, whether hyaline vascular or plasmacytic, is generally treated with surgical excision. When surgery is not feasible, irradiation may be considered and either treatment may be curative. Observation alone may be a valid option in some cases. Multicentric disease is rarely asymptomatic and surgical excision alone is rarely curative. These patients frequently require systemic therapy.[14] A number of therapies have been used for multicentric disease, including intravenous immunoglobulin, antiherpes drugs, e.g. aciclovir, (val) ganciclovir in HIV+ and HHV8+ disease, combination chemotherapy (e.g., CHOP) and in intractable cases even autologous stem cell transplantation. Other therapies include the antiangiogenesis therapy, thalidomide and anti-IL6 therapy. Surgery may also be useful in debulking disease. Our patient remained asymptomatic for more than one year and therefore, was managed expectantly. The first indication of symptomatic disease was presentation with severe thrombocytopenia.

Therapy with high-dose corticosteroids is the mainstay of treatment for primary ITP. High-dose corticosteroids may also reduce bleeding by a direct effect on blood vessels, independent of platelet rise.[15-18] In addition, steroids have been used for symptomatic relief in CD with reduction in lymph node size, improvement of symptoms, and correction of blood count abnormalities.[5,6] The benefit is transient and symptoms usually recur soon upon discontinuation. Our patient did not respond to adequate doses of steroids and responded only transiently to IVIG.

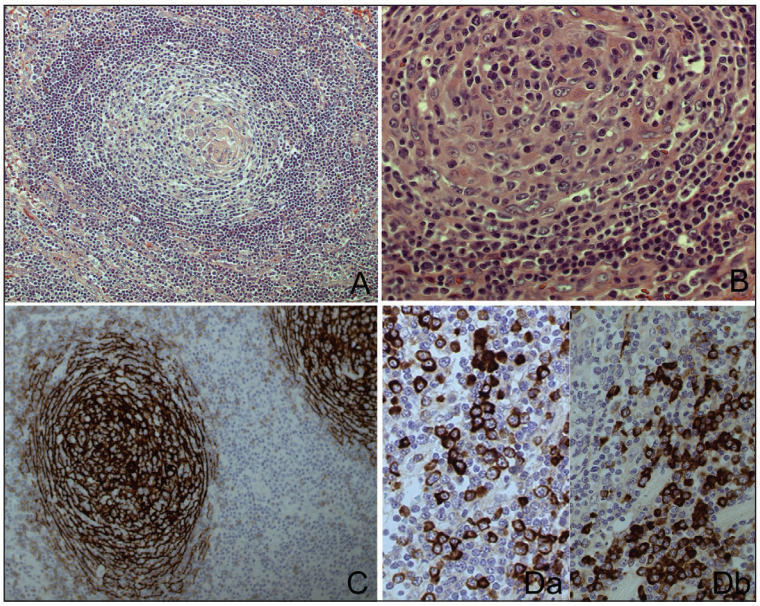


**Figure 1.** (A) Low power shows lymph node replaced by follicles with broad mantle zones ('onion skinning') and hyalinized blood vessels. H&E ×200. (B) A follicle with few scattered follicle-center cells and many large atypical follicular dendritic cells. H&E ×400. (C) Immunoperoxidase staining for CD21 demonstrating increased number of follicular dendritic cells and relative lack of follicle-center cells. ×400. (D)Large number of plasma cells present within the interfollicular region - polyclonal by light chain immunoperoxidase staining: Kappa (a) and lambda (b). ×400

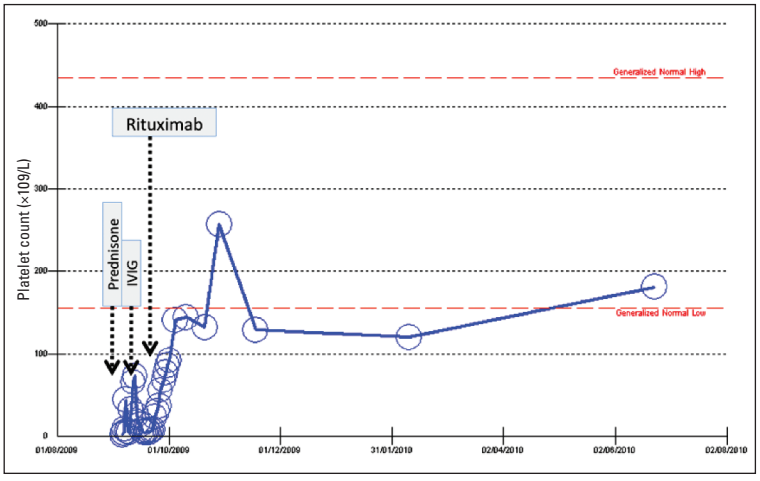


**Figure 2.** Platelet response to therapy.

Several studies have reported a response rate of up to 60% with anti-CD20 antibody therapy with complete remissions approaching 40% in chronic ITP.[7-10] These responses generally begin from 1 to 8 weeks after initiating anti-CD20 therapy[19,20] and may last from 2 months in partial responders to 5 years or longer in

15% to 20% of those who achieve complete remission.[7] Recent reports also suggest that rituximab may be an attractive option in systemic Castleman disease since follicular areas strongly express CD20 in MCD. Most of these are, however, associated with HIV+/HHV-8+.[11-13] Our patient tested negative for both HIV and HHV-8. To our knowledge, this is the first reported case where rituximab was tried in ITP associated with CD and both ITP and primary disease, i.e., Castleman disease showed good response.

In conclusion, anti-CD20 antibody therapy may be an attractive therapeutic option for Castleman disease, especially if associated with immune cytopenias, even in the absence of HIV or HHV-8.

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