



Abid, M. B., Peck, R., Abid, M. A., Al-Sakkaf, W., Zhang, Y., Dunnill, G. S., Staines, K., Sequeiros, I. M., & Lowry, L. (2018). Is tocilizumab a potential therapeutic option for refractory unicentric Castleman disease? *Hematological Oncology*, 36(1), 320-323.  
<https://doi.org/10.1002/hon.2420>

Peer reviewed version

Link to published version (if available):  
[10.1002/hon.2420](https://doi.org/10.1002/hon.2420)

[Link to publication record in Explore Bristol Research](#)  
PDF-document

This is the author accepted manuscript (AAM). The final published version (version of record) is available online via Wiley at <http://onlinelibrary.wiley.com/doi/10.1002/hon.2420/abstract>. Please refer to any applicable terms of use of the publisher.

## University of Bristol - Explore Bristol Research

### General rights

This document is made available in accordance with publisher policies. Please cite only the published version using the reference above. Full terms of use are available:  
<http://www.bristol.ac.uk/red/research-policy/pure/user-guides/ebr-terms/>

# Is Tocilizumab a Potential Therapeutic Option for Refractory Unicentric Castleman's Disease?

*Muhammad Bilal Abid\*<sup>1</sup>, Rachel Peck<sup>1</sup>, Muhammad Abbas Abid<sup>2</sup>, Wesam Al-Sakkaf<sup>1</sup>, Yuening Zhang<sup>3</sup>, Giles S Dunnill<sup>4</sup>, Konrad Staines<sup>5</sup>, Iara-Maria Sequeiros<sup>6</sup>, Lisa Lowry<sup>1</sup>*

1 Department of Haematology, University Hospitals of Bristol NHS Trust, United Kingdom

2 Division of Otorhinolaryngology and Head & Neck Surgery, John Hopkins School of Medicine, Baltimore MD USA

3 Department of Cellular Pathology, University Hospitals Bristol NHS Trust, United Kingdom

4 Department of Dermatology, University Hospitals of Bristol NHS Trust, United Kingdom

5 Department of Oral Medicine, University Hospitals of Bristol NHS Trust, United Kingdom

6 Department of Radiology, University Hospitals of Bristol NHS Trust, United Kingdom

## **KEYWORDS:**

Unicentric Castleman's Disease (UCD), Tocilizumab, Interleukin-6 (IL-6), Cytokine storm.

## **Abstract:**

Castleman's Disease is a rare lymphoproliferative disorder with two distinctly defined clinical forms. While multi-centric Castleman's disease (MCD) poses a potential therapeutic challenge, unicentric variant (UCD) has historically been considered curable with surgical resection. Hence, little is known to guide management of patients with UCD, refractory to surgical resection and combination chemotherapy. We present a case of a patient, negative for HIV and HHV-8, who had an unsuccessful surgical intervention and no response to radiotherapy and chemotherapy. He had severe paraneoplastic pemphigus and was treated with tocilizumab, an anti-interleukin-6 receptor monoclonal antibody that has demonstrated good response rates in MCD, but demonstrated no clinical response despite two months of treatment. Our report is the first to describe a lack of response to tocilizumab in the rare setting of refractory UCD and discuss potential for distinct disease biology.

## **CASE REPORT:**

### **Introduction:**

Castleman's disease (CD) is a rare lymphoproliferative disorder thought to be mediated via autoinflammation, cytokine release and viral co-infections<sup>1</sup>. CD represents a heterogeneous group of diseases and is stratified based on centricity and pathology. Two well-defined clinical subtypes include localized or unicentric CD (UCD) and systemic or multicentric CD (MCD) and three main histological variants consist of hyaline vascular type (80-90%), plasma cell type (10%-20%) and mixed type (<5%)<sup>2,3</sup>. MCD can further be subdivided by the presence or absence of viral co-infection with human herpes virus-8 (HHV-8) and human Immunodeficiency virus (HIV). Conventionally, the prognosis for UCD is excellent whereas the outlook for MCD is worse, typically when associated with HIV and HHV-8<sup>4</sup>.

The most common presenting complaint of UCD is isolated lymphadenopathy, although symptoms related to mass effects on surrounding structures may be present. A systematic review of 278 cases of UCD identified that the mean size of involved lymph nodes at baseline was 5.5 cm, compared to 3.8 cm for MCD cases<sup>5</sup>. The UCD case presented here had a baseline size of 6 cm. MCD commonly presents with systemic symptoms including traditional 'B symptoms' such as fever, night sweats and weight loss, along with generalized lymphadenopathy and splenomegaly.

The understanding of the pathogenesis of CD remains limited. Albeit CD had been considered to originate from polyclonal sources, mainly HIV- and HHV-8- driven, recent evidence suggests that at least a proportion of cases have a monoclonal origin<sup>6-8</sup>. Based on recent therapeutic evidence, excessive cytokine release has gained attention as the key mechanism of pathogenesis as well as symptomatology. The dysregulation of interleukin-6 (IL-6) has been implicated in both UCD and MCD and hypersecretion of IL-6 by germinal center B-cells is considered to be responsible for systemic manifestations<sup>9</sup>. IL-6 regulates T-cell function, acute phase reaction and terminal B-cell differentiation<sup>10,11</sup>.

The optimal therapeutic strategy for MCD is unclear. A range of systemic therapies including steroids, cytotoxic chemotherapy-single agent or combination regimens such as CHOP, anti-CD20 monoclonal antibodies, bortezomib, antiviral agents and IL-6 inhibitors such as tocilizumab have been utilized with varying degrees of success<sup>4,12</sup>.

The standard of care for UCD is surgical resection, with 10-year OS rates exceeding 95%<sup>5</sup>. Data remains scarce where complete surgical resection is not possible or remains unsuccessful.

Alternative treatments include debulking surgery, neoadjuvant systemic chemotherapy or rituximab. Radiotherapy remains an option for unresectable cases, but with mixed results<sup>13,14</sup>.

### **Case presentation:**

A 46-year-old African male, with no past medical history of significance, presented to another hospital with an 18 months history of worsening right-sided chest pain, malaise and B-symptoms. Physical examination did not reveal any anemia, pallor, jaundice, lymphadenopathy or hepatosplenomegaly. The respiratory examination was remarkable for decreased breath sounds in the right apex with minimal tracheal deviation to the ipsilateral side. Full blood count, liver and renal function tests and ferritin were normal. CRP level was elevated at 39 mg/L and LDH 339 IU/L. Serum albumin was 31 g/L and paraproteins were normal. A computed tomography (CT) scan showed a 6x6x7 cm right upper lobe mass **[Figure 1]** and a CT-guided biopsy revealed the diagnosis of unicentric Castleman's disease (UCD) of hyaline vascular variant **[Figure 2]**. HIV and HHV-8 were negative and no paraprotein was detected. Four cycles of weekly rituximab were given, primarily to debulk the mass. At that point, the patient moved to our area and presented to our service.

A repeat CT scan did not show any interval decrease in the size of the mass. A right-sided thoracotomy, with attempted curative resection of the mass, was abandoned due to massive hemorrhage necessitating a salvage angioembolization of the feeding vessels. Following a case review, further cardiothoracic surgery was deemed high risk; radical radiotherapy (40Gy in 20 fractions) was therefore administered. One month after completion of radiotherapy, there was only modest reduction in tumor size and his chest discomfort persisted. No further active therapy was planned at that point.

Three months after completion of radiotherapy, the patient was admitted with progressive, painful blistering of oral mucous membranes and lip vermillion, requiring nutritional support and parenteral pain relief. Paraneoplastic pemphigus (PNP) was diagnosed, based on clinical grounds, and he was treated with high dose pulsed steroids and Mycophenolate Mofetil, up to 1.5 gram/day, without response. The condition progressed with severe involvement of oral, pharyngeal and genital mucous membranes, hair loss, spreading lichenoid and blistering eruption of the skin, eventually affecting >75% of the total skin surface.

Further discussions regarding potentially curative surgery were held but he was deemed unfit for such major and risky surgery. He was therefore given a trial of combination chemotherapy with R-CHOP (Rituximab, Cyclophosphamide, Doxorubicin, Vincristine and Prednisolone). The

first cycle was complicated by significant sepsis, with no clinical or radiologic improvement in the underlying UCD or PNP.

Given his primary refractory disease and poor state of health due to progressive pemphigus, he was deemed unsuitable for further chemotherapy. Evidence from tocilizumab activity in MCD was extrapolated and he received four cycles of tocilizumab at a dose of 8mg/kg every two weeks. He demonstrated no clinical or radiological response after two months of treatment and remained as an inpatient through the course for pain relief and parenteral nutrition. The decision was made to switch to palliative management and he died a week later.

### **Discussion/Conclusion:**

Tocilizumab is a recombinant, humanized monoclonal antibody that blocks the IL-6 receptors, both soluble and membrane-bound, and hence blocks downstream intracellular signalling<sup>15, 16</sup>. Promising results have been reported with the use of tocilizumab in patients with MCD. A major, multi-centre trial of 28 patients reported that tocilizumab, given at a dose of 8mg/kg fortnightly, resulted in a significant reduction in lymphadenopathy for 52% of patients after one year of treatment and a median follow-up of 15 months. Biochemical improvement in inflammatory markers was also noted<sup>17</sup>. Three small case series, using the same regimen of tocilizumab and each including 2-3 patients, reported an overall response rate of 100% with a follow-up ranging up to four years<sup>18-20</sup>. Tocilizumab has also been reported to be beneficial in PNP associated with MCD<sup>10</sup>.

The case presented here had refractory UCD, an entity with an extreme paucity of data, owing to its rarity. The refractory UCD was not amenable to surgery at the outset and did not respond to neoadjuvant rituximab, radiotherapy and systemic chemotherapy with R-CHOP. The effectiveness of tocilizumab in treating MCD coupled with the pre-existing knowledge that IL-6 is dysregulated universally in MCD made the prospect of using it for UCD enticing. However, tocilizumab did not result in clinical benefit in this case. Disappointingly, there was also no clinical response of his PNP to tocilizumab. PNP has been reported as an independent adverse prognostic factor in a large single-center review of CD including 114 patients of which 62 (54%) had UCD. Of the 37 patients with PNP, 32 had UCD<sup>21</sup>.

Though cases of refractory course of UCD have occasionally been reported<sup>22-23</sup>, this report is the first of refractory UCD treated with tocilizumab, to the best of our knowledge. Since the success rate for complete surgical resection has been remarkable in UCD, data is lacking on alternate therapies for disease not amenable to resection. In this patient, tocilizumab was not effective in treating refractory UCD. Whether association with PNP or lack of clinically significant follow-up confounded

delineation of its true efficacy, it would be worthwhile exploring if IL-6 pathway plays as fundamental a role in UCD as is reported in MCD. This report further highlights a need for in-depth understanding of UCD and its clonal derivation and hints that some of the cases may be neoplastic right from outset.

**Acknowledgements:**

We acknowledge the invaluable guidance of Dr. Muhammed Sohail (Department of Pathology, University Hospitals Bristol NHS Trust, United Kingdom) through the course of this study.

**Authors' Contributions:**

MBA conceived of the study and wrote the manuscript. RP co-wrote the manuscript. LL, KS and GSD rendered patient care and performed a critical review of the manuscript. WAS, MAA, YZ and I-MS performed a critical review of the manuscript. YZ provided the histopathology images and descriptions and I-MS provided radiology images. All authors read and approved the final manuscript.

**Informed Consent:**

Informed consent was obtained from patient prior to publication.

**Disclosure:**

The authors declare no conflict of interest.

## REFERENCES:

1. Castleman B, Iverson L, Menendez VP. Localized mediastinal lymph-node hyperplasia resembling thymoma. *Cancer* 1956; 9:822-830.
2. Herrada J, Cabanillas F, Rice L, Manning J, and Pugh W. The clinical behaviour of localized and multicentric Castleman disease. *Annals of Internal Medicine* 1998; 128(8):657-662.
3. Bowne WB, Lewis JJ, Filippa DA, et al. The management of unicentric and multicentric Castleman's disease. *Cancer* 1999; 85(3):706-717.
4. Dong Y, Na J, Lv J, et al. Clinical and laboratory characterization of a large cohort of patients with Castleman disease retrospectively collected from a single center. *Leukaemia & Lymphoma* 2009; 50:1308–1317.
5. Talat N, Belgaumkar AP and Schulte KM. Surgery in Castleman's disease: a systematic review of 404 published cases. *Annals of surgery* 2012; 255(4):677-684.
6. Chang KC, Wang YC, Hung LY, et al. Monoclonality and cytogenetic abnormalities in hyaline vascular Castleman disease. *Modern Pathology* 2014; 27; 823–831.
7. Wang L, Bu DF, Yang Y, Chen XX and Zhu XJ. Castleman's tumours and production of autoantibody in paraneoplastic pemphigus. *Lancet* 2004; 363:525–531.
8. Reichard KK, Robinett S and Foucar MK. Clonal cytogenetic abnormalities in the plasma cell variant of Castleman disease. *Cancer Genet* 2011; 204(6):323-7.
9. Muskardin TW, Peterson BA and Molitor JA. Castleman disease and associated autoimmune disease. *Current opinion in rheumatology* 2012; 24(1):76-83.
10. Musters A, Assaf A, Gerlag DM, Tak PP and Tas SW. Discovery of Innovative Therapies for Rare Immune-Mediated Inflammatory Diseases via Off-Label Prescription of Biologics: The Case of IL-6 Receptor Blockade in Castleman's Disease. *Frontiers in immunology* 2015; 6:625.
11. Hirano T. Interleukin 6 in autoimmune and inflammatory diseases: a personal memoir. *Proceedings of the Japan Academy. Series B, Physical and biological sciences* 2010; 86(7):717-30.
12. Chan KL, Lade S, Prince HM and Harrison SJ. Update and new approaches in the treatment of Castleman disease. *J Blood Med.* 2016; 7:145-58.

13. Bandera B, Ainsworth C, Shikle J, Rupard E and Roach M. Treatment of unicentric Castleman disease with neoadjuvant rituximab. *CHEST Journal* 2010;138(5):1239-1241.
14. Matthiesen C, Ramgopal R, Seavey J, Ahmad S and Herman T. Intensity modulated radiation therapy (IMRT) for the treatment of unicentric Castleman's disease: a case report and review of the use of radiotherapy in the literature. *Radiol Oncol* 2012;46(3):265–270.
15. Brandt SJ, Bodine DM, Dunbar CE and Nienhuis AW. Dysregulated interleukin 6 expression produces a syndrome resembling Castleman's disease in mice. *J Clin Invest* 1990;86(2):592–599.
16. Suthaus J, Stuhlmann-Laeisz C, Tompkins VS, et al. HHV-8-encoded viral IL-6 collaborates with mouse IL-6 in the development of multicentric Castleman disease in mice. *Blood* 2012; 119(22):5173–5181.
17. Nishimoto N, Kanakura Y, Aozasa K, et al. Humanized anti-interleukin-6 receptor antibody treatment of multicentric Castleman disease. *Blood* 2005; 106(8):2627-2632.
18. Matsuyama M, Suzuki T, Tsuboi H, et al. Anti-interleukin-6 receptor antibody (tocilizumab) treatment of multicentric Castleman's disease. *Internal Medicine* 2007; 46(11):771-774.
19. Galeotti C, Boucheron A, Guillaume S and Koné-Paut I. Sustained remission of multicentric Castleman disease in children treated with tocilizumab, an anti-interleukin-6 receptor antibody. *Molecular cancer therapeutics* 2012; 11(8):1623-1626.
20. Nagao A, Nakazawa S and Hanabusa H. Short-term efficacy of the IL6 receptor antibody tocilizumab in patients with HIV-associated multicentric Castleman disease: report of two cases. *J Hematol Oncol.* 2014; 7:10.
21. Dong Y, Wang M, Nong L, et al. Clinical and laboratory characterization of 114 cases of Castleman disease patients from a single centre: paraneoplastic pemphigus is an unfavourable prognostic factor. *Br J Haematol* 2015; 169(6):834-42.
22. Baek HJ, Kook H, Han DK, Shin MG, Kim HS, Hwang TJ. Unicentric Castleman disease relapsed after rituximab-CHOP chemotherapy or radiation therapy in an adolescent. *J Pediatr Hematol Oncol* 2012;34(5):e206-8.
23. de Vries IA, van Acht MM, Demeyere T, Lybeert ML, de Zoete JP, Nieuwenhuijzen GA. Neoadjuvant radiotherapy of primary irresectable unicentric Castleman's disease: a case report and review of the literature. *Radiat Oncol* 2010;5:7.



**Figure Legends:**

**Figure 1: Chest Computed Tomography, A) Coronal view B) Axial view.**

CT scan of the chest shows a right apical, vascular mass measuring 6x6x7cm, with no accompanying mediastinal lymphadenopathy.

**Figure 2: Hyaline vascular variant of Castleman's disease (CD)**

- A) Hyaline vascular variant (H+E x200): Hyalinised germinal centre containing atypical follicular dendritic cells with 'onion-skinning' by surrounding lymphocytes.
- B) Immunohistochemical staining of lung mass (X 200) for CD23 highlights follicular dendritic cell clusters within an expanded mantle zone of CD23-positive cells.

**Figure 3: Paraneoplastic pemphigus (PNP)**

Photomicrographs show involvement of mucous membranes, hair loss, spreading lichenoid and blistering eruption of the skin.

Abbreviations: Castleman's disease (CD), Paraneoplastic pemphigus (PNP)