

CASE REPORT

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# A rare case of renal thrombotic microangiopathy associated with Castleman's disease

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## Abstract

**Background:** Castleman's disease (CD) is an uncommon, heterogeneous lympho-proliferative disorder leading to high circulating levels of interleukin-6 (IL-6) and vascular endothelial growth factor (VEGF). Renal involvement has been only described in a limited number of small studies. Herein, we report a rare case of renal thrombotic microangiopathy (TMA) associated with CD and investigate the podocyte expression of VEGF in the renal biopsy prior to initiation of treatment.

**Case presentation:** An 18-year-old male presented with fever, diarrhea, diffuse lymphadenopathy, ascites and acute kidney injury. Laboratory tests for hemolytic uremic syndrome and thrombotic thrombocytopenic purpura were negative. The kidney biopsy showed TMA. An excisional lymph node biopsy was consistent with CD, plasma cell variant. Immunofluorescence staining showed suppressed podocyte VEGF expression. Chemotherapy that inhibits production of inflammatory mediators including IL-6 and VEGF led to complete recovery of renal function.

**Conclusions:** Our case illustrates a rare renal histological feature of CD. IL-6 and VEGF are postulated to suppress glomerular VEGF expression, thereby causing renal TMA. Therapy directed against these inflammatory mediators may have important therapeutic implications.

**Keywords:** Thrombotic microangiopathy, Castleman's disease, VEGF, Podocytes

## Background

Castleman's disease (CD), first described in 1956, is an uncommon lymphoproliferative disorder characterized by focal or generalized lymphadenopathy [1]. Clinically, this group of lymphoproliferative disorders is classified as unicentric CD (localized lymph node involvement, UCD), or multicentric CD (diffuse lymph node involvement, MCD). Systemic manifestations commonly associated with MCD include fever, weight loss, hepatosplenomegaly, ascites, edema, and anemia. Histologically, there are three different variants of CD: hyaline-vascular variant, plasma cell variant and mixed variant. The hyaline-vascular variant accounts for 90% of CD and is characterized by small hyaline vascular

follicles and interfollicular capillary proliferation. It is typically associated with UCD and most patients exhibit no symptoms. The plasma cell variant (9%) is characterized by hyperplastic follicles with interfollicular sheets of plasma cells and is often associated with MCD.

Thrombotic microangiopathy (TMA) is a histopathological term for microangiopathic hemolytic anemia, thrombocytopenia, and renal microvascular thrombosis. Diagnostic TMA features include endothelial swelling in glomerular capillaries and arterioles, mesangiolysis (dissolution or attenuation of mesangial matrix and degeneration of mesangial cells), and glomerular basement membrane double contours (a feature of glomerular basement membrane remodeling). The latter can be seen without thrombi, which suggests subacute or chronic TMA. Hemolytic uremic syndrome (HUS) and thrombotic thrombocytopenic purpura (TTP) are two major clinical entities comprising TMA with predominantly renal manifestations in the former whereas neurological and systemic manifestations in the latter, although

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overlap exists and differentiation of HUS from TTP is not always possible.

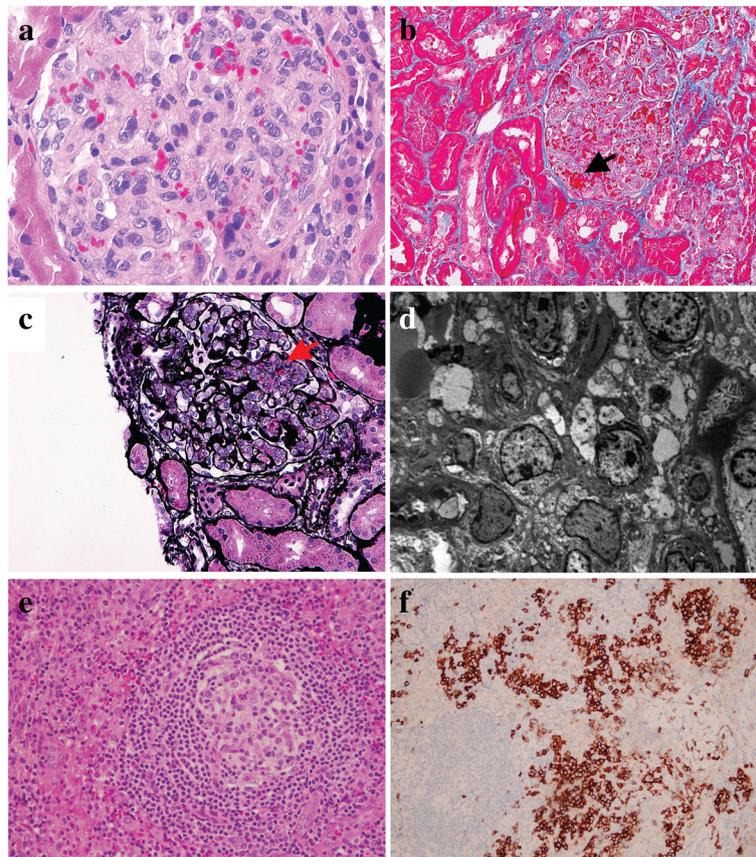
Here, we present a complicated case of renal TMA in a MCD patient in the absence of TTP/HUS. In the presented patient, decreased podocyte expression of vascular endothelial growth factor (VEGF) is linked to TMA associated with CD.

### Case presentation

A 19-year-old Caucasian male was transferred to Washington University Barnes-Jewish Hospital for evaluation of acute renal failure (ARF) and previously diagnosed TMA on renal biopsy. He presented with anasarca, mild proteinuria, and diffuse lymphadenopathy. He was initially admitted to a community hospital with diarrhea, nausea, vomiting, generalized swelling, and low grade fever for 3 weeks. There was no history of recent travel, medication use or change in his home environment. While in the community hospital, he was noted to have

new onset of thrombocytopenia and anemia without evidence of hemolysis or schistocytes. Stool *Shiga* toxin was negative, and stool cultures were negative for *E. coli* O157:H7, *Salmonella*, *Shigella*, and *Campylobacter*. Ascites was negative for peritonitis and malignancy, and an inguinal lymph node core biopsy was reported as nonspecific reactive hyperplasia.

Renal biopsy was performed and showed diffuse endothelial swelling, mesangiolytic and thrombi within capillary loops (Fig. 1, a-d). Occasional double contours were present (Fig. 1c). There were no crescents, fibrinoid necrosis, or significant fibrosis. Immunofluorescence (IF) was negative for immune complex deposits. TMA was diagnosed. ADAMTS 13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13) activity was decreased (20%; normal levels,  $\geq 67\%$ ). 10 sessions of plasmapheresis performed in the community hospital did not improve his anemia, thrombocytopenia and kidney dysfunction.



**Fig. 1** Histopathological findings in renal and the inguinal lymph node biopsies from the patient with MCD. Renal (a-d) and lymph node biopsies (e-f) at the onset of disease. **a** Diffuse endocapillary proliferation and endothelial swelling (Hematoxylin and eosin stain [H&E],  $\times 400$ ). **b** Thrombi within capillary loops (arrow; Masson trichrome,  $\times 200$ ). **c** Mesangiolytic (arrow) and double contour (Jones Methenamine Silver,  $\times 200$ ). **d** Transmission electron microscopy showed diffuse endothelial swelling with obliteration of capillary lumina and mesangial interposition ( $\times 4000$ ). **e** Hyalinization of the germinal center and concentric layering of peripheral lymphocytes (H&E,  $\times 200$ ). **f** Plasmacytosis highlighted with CD138 staining in the interfollicular space is characteristic of plasma cell CD type ( $\times 200$ )

On admission, tachycardia (109/min), hypertension (148/86 mmHg), and normal body temperature were observed. Conjunctivas were pale but not icteric. Respiratory sounds were decreased bilaterally. The abdomen was distended with free fluid. Lower extremities showed 1+ pedal edema, and lymph nodes were palpable in the axillary and inguinal regions.

Laboratory evaluation revealed microcytic anemia (hemoglobin 8.1 g/dL) and thrombocytopenia (platelets, 75,000/mm<sup>3</sup>) with lactate dehydrogenase and haptoglobin being within normal range. The repeated peripheral smear did not show schistocytes. Renal function had deteriorated (blood urea nitrogen [BUN], 27 mg/dL; serum creatinine [Cr], 2.18 mg/dL). The patient had normal liver function but with decreased total protein (6.2 g/dL) and albumin (3.0 g/dL). Complement levels were normal. Acute phase reactants including erythrocyte sedimentation rate (ESR, 59 mm/h; normal levels, <12 mm/h), C-reactive protein (CRP, 99.4 mg/L; normal levels, <9.9 mg/L) and ferritin (348 ng/ml; normal levels, <322 ng/ml) were elevated. An increased IgG of 1560 mg/dl (normal range: 700–1450 mg/dl) with normal levels of IgA and IgM was found. There was no monoclonal peak on immunoelectrophoresis in either serum or urine. Autoantibodies including antinuclear antibody (titer, 1:640) and anti-SS-A and anti-SS-B were positive. Additionally, serum lupus anticoagulant was positive, but  $\beta$ 2 glycoprotein and anti-cardiolipin antibody were negative. Test results for hepatitis virus A, B and C, human immunodeficiency virus, Epstein-Barr virus, and cytomegalovirus were negative. Urinalysis showed microhematuria without any casts and non-nephrotic range proteinuria (683 mg/24 h).

Renal ultrasound showed normal size and echogenicity of both kidneys. Computed tomography (CT) of the

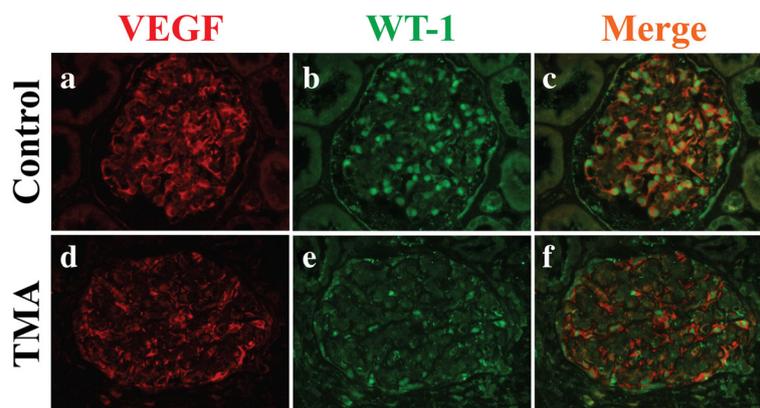
chest, abdomen and pelvis showed retroperitoneal, mesenteric, pelvic, axillary and mediastinal lymphadenopathy as well as hepatosplenomegaly, moderate ascites and small bilateral pleural effusions.

An excisional lymph node biopsy performed in our hospital showed follicular hyperplasia and diffuse interfollicular plasma cell infiltrate (Fig. 1 e–f). Some of the lymphoid follicles showed hyalinization of germinal centers and concentric layering of peripheral lymphocytes (onion-skinning) in the mantle area (Fig. 1e). Immunohistochemistry revealed interfollicular plasmacytosis demonstrated by CD138 staining (Fig. 1f). HHV-8 immunostaining was negative. The patient's diagnosis was consistent with MCD, plasma cell variant. High circulating level of VEGF (343 pg/ml; normal levels, <86 pg/ml) was detected in this patient, a characteristic feature of CD. Notably, double IF staining for VEGF and the podocyte nucleus marker WT-1 showed that podocyte VEGF expression was reduced in this patient compared to healthy control (Fig. 2).

The patient was started on chemotherapy with Rituximab, Etoposide, Cyclophosphamide, Vincristine and Prednisone for 6 cycles. Within a week of initiation of chemotherapy, his renal function normalized. His clinical symptoms such as fever, ascites and lymphadenopathy started improving. Anemia and thrombocytopenia resolved, and markers of inflammation such as ESR and CRP normalized within the first few weeks. The patient has been free of symptoms for 2 years without taking any medication.

## Discussion

CD is a rare lymphoproliferative disorder. Renal involvement has been only described in a limited number of small studies. Based on a study conducted in a large CD



**Fig. 2** Podocyte VEGF expression in healthy control kidney and renal biopsy from the CD-associated TMA patient. Formalin-fixed paraffin kidney sections from control (a–c) and patient (d–f) were examined by dual IF staining of VEGF (red, a and d) and podocyte nucleus marker WT-1 (green, b and e). Merged images for VEGF and WT-1 in c and f. Note the decreased podocyte VEGF expression in CD-associated renal TMA. Original magnifications:  $\times 400$

cohort of Chinese patients, renal involvement in CD is about 25% [2], particularly seen in patients with MCD plasma cell or mixed variant [2, 3]. ARF represents the most common renal presentation, and glomerular pathologies majorly include AA amyloidosis [3, 4], TMA [2, 3, 5] and membranoproliferative glomerulonephritis [6]. Other renal pathological findings include mesangio-proliferative glomerulonephritis, interstitial nephritis [7], membranous nephropathy [8], crescentic glomerulonephritis [2, 9, 10], minimal change disease [2] and focal segmental glomerulosclerosis [3]. Consistent with previous studies, our patient developed renal TMA in MCD plasma cell variant, the aggressive type of CD.

The dysregulated production of VEGF and interleukin-6 (IL-6) is implicated to play a central role in the pathogenesis of CD. Proliferating plasma cells in lymph nodes cause overproduction of both cytokines leading to elevated systemic levels [11, 12]. VEGF exerts potent pro-inflammatory effect and increases blood vessel permeability, which explains pleural effusion, ascites, and generalized edema in our patient. IL-6 has pleotropic effects, such as promoting B-cell differentiation to immunoglobulin-producing plasma cells, stimulating hepatocyte to synthesize acute-phase proteins, and inducing dominance of Th17 cells over Tregs to disrupt immune tolerance [13]. It has been shown that mice overexpressing IL-6 produce a syndrome resembling CD [14]. In our patient, IL-6 accounts for a variety of clinical symptoms including generalized lymphadenopathy and hepatosplenomegaly, polyclonal hypergammaglobulinemia, increased levels of ESR, CRP and ferritin, anemia, and overproduction of autoantibodies.

Diffuse endothelial swelling, mesangiolytic and capillary loop thrombi in combination with podocyte VEGF downregulation in our patient resemble renal TMA seen in cancer patients treated with VEGF inhibitors [15] or preeclampsia patients with increased circulating level of soluble fms-like tyrosine kinase 1 (sFlt1), a soluble VEGF receptor and an antagonist of VEGF [16]. VEGF is a vascular growth factor for vasculogenesis and angiogenesis during development and in disease through regulation of vascular permeability, endothelial cell migration, proliferation, and cell survival [17]. VEGF released by podocytes binds to VEGF receptors on glomerular endothelial cells, resulting in receptor tyrosine phosphorylation and signal transduction. It has been demonstrated that tight regulation of glomerular VEGF signaling is critical for establishment and maintenance of the glomerular filtration barrier. Moreover, it has been shown that podocyte VEGF deletion in adult mice is sufficient to trigger TMA by utilizing podocyte-specific VEGF knockout mice [15, 18]. Previously, Karoui et al. reported decreased glomerular VEGF expression in a MCD patient with renal TMA [3]. However, co-

localization staining of glomerular VEGF with any glomerular cell-specific marker was not performed. The serum level of VEGF from the same affected patient was also not examined. For the first time, we performed dual IF staining of VEGF with the podocyte nucleus marker WT-1 in the kidney biopsy and correlated with serum VEGF level in our patient. Our study showed podocyte VEGF downregulation associated with markedly elevated serum VEGF before chemotherapy. The question of how persistent VEGF and IL-6 overproduction leads to deficient podocyte VEGF expression remains unresolved.

It is of note that not every CD patient develops renal TMA. Genetic or acquired dysregulation of ADAMTS13 or the complement alternative pathway can predispose patients to develop TMA. Deficiency of ADAMTS13, owing to mutations in the *ADAMTS13* gene or autoantibodies that inhibit ADAMTS13 activity, can cause idiopathic TTP. It is not unusual for ADAMTS13 to be decreased in TMA without TTP. In TTP, ADAMTS13 activity is typically <5% [19]. Therefore the TMA in our patient does not appear to be caused by TTP, particularly in the absence of hemolysis, schistocytes and neurological symptoms. Dysfunction of the complement alternative pathway, caused by mutations in complement factor H, I, B, or membrane cofactor protein or by autoantibodies against factor H, can result in complement-mediated TMA [20, 21]. The presented patient may have mild complement abnormalities that increase his susceptibility to develop renal TMA associated with CD.

In summary, we discuss a rare case of MCD patient presenting with ARF, mild proteinuria and renal TMA. The renal injury is associated with inhibited expression of podocyte VEGF. In this patient, an excellent renal response to chemotherapy was achieved. Reagents that suppress overproduction of IL-6 and VEGF may lead to highly-targeted treatments in CD. In addition, further investigation to delineate the mechanism(s) involved in podocyte VEGF downregulation will lead to discovery of specific target molecules for the treatment of renal TMA seen in CD.

#### Abbreviations

ADAMTS 13: A disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; ARF: Acute renal failure; BUN: Blood urea nitrogen; CD: Castleman's disease; Cr: Creatinine; CRP: C-reactive protein; CT: Computed tomography; ESR: Erythrocyte sedimentation rate; H&E: Hematoxylin and eosin stain; HUS: Hemolytic uremic syndrome; IF: Immunofluorescence; IL-6: Interleukin-6; MCD: Multicentric CD; sFlt1: Soluble fms-like tyrosine kinase 1; TMA: Thrombotic microangiopathy; TTP: Thrombotic thrombocytopenic purpura; UCD: Unicentric CD; VEGF: Vascular endothelial growth factor

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**Availability of data and materials**

All data and material were presented in this manuscript.

**Authors' contributions**

AM and YMC wrote the manuscript and were treating physicians for the patient. LNC and HL performed pathological analysis and interpretation and contributed to writing the manuscript. All authors read and approved the final manuscript.

**Competing interests**

The authors declare that they have no competing interests.

**Consent for publication**

Written informed consent was obtained from the patient for publication of this case report and images in it. A copy of the written consent is available for review by the Editor of this journal.

**Ethics approval and consent to participate**

Not applicable.

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