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Recurrent episodes of renal impairment with cytopaenias and lymphadenopathy

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Introduction

Thrombocytopaenia, anasarca, fever, reticulin fibrosis and organomegaly (TAFRO) syndrome is a recently described human herpes virus-8 negative subset of idiopathic multicentric Castleman's disease. Renal impairment is well described in patients with Castleman's disease with a spectrum of different histological features seen on kidney biopsy. This case report details a patient with acute kidney injury, volume overload and pancytopaenia as an index presentation of TAFRO syndrome. Further disease relapses were characterised by the development of nephrotic syndrome and obstructive uropathy. Initial treatment was with corticosteroids, intravenous immunoglobulin and plasma exchange. The use of cyclophosphamide and rituximab following relapses of disease led to sustained clinical improvement. Suppression of interleukin-6 with monoclonal antibody therapy has emerged as an additional therapeutic strategy for Castleman's disease and could be considered for this patient in the future if clinically appropriate.

Case report

A 46-year-old Caucasian man with no significant past medical history presented with a 6-month history of abdominal pain, fever and progressive peripheral oedema. On examination he was febrile and grossly volume overloaded with pitting oedema to the abdominal wall. He was found to be anuric with a serum creatinine level of 433 µmol/litre.

Abdominal ultrasound imaging showed enlarged kidneys with ascites. Three cavity computed tomography revealed widespread lymphadenopathy on both sides of the diaphragm and hepatosplenomegaly with bilateral pleural effusions and marked soft tissue oedema. A comprehensive intrinsic immunological and virological renal screen was unremarkable. A renal biopsy was performed (Figure 1) which, following evaluation under electron microscopy, revealed endothelial cell damage and electron lucent subendothelial deposits.

Supportive treatment with broad spectrum antibiotics, antifungal agents and intermittent haemodialysis was provided until native renal function recovered and he became independent of dialysis.

Subsequently, the patient developed profound anaemia (haemoglobin 38 g/litre) and thrombocytopaenia (platelets $2x10^9$/litre) with ongoing fever. Direct Coombs testing was positive, with elevated serum lactate dehydrogenase levels and reticulocyte counts although no erythrocyte fragmentation was seen on blood films. ADAMTS13 activity level was normal. Investigations for heparin-induced thrombocytopaenia and infections (human immunodeficiency virus, parvovirus B19, mycoplasma, Epstein–Barr virus and cytomegalovirus) were unremarkable. Packed red cell and platelet transfusions were administered. Treatment with prednisolone 60 mg, intravenous immunoglobulin and plasma exchange coincided with improvement in observed cytopaenias and clinical status. Investigations for an underlying periodic fever syndrome were negative. A left groin lymph node biopsy (Figure 2) and bone marrow biopsy (revealing megakaryocyte hyperplasia with grade 2–3 reticulin fibrosis) secured a diagnosis of idiopathic multicentric Castleman's disease.

Prednisolone was weaned to 5–10 mg daily with sustained remission and no evidence of substantial disease progression on serial imaging until anaemia and nephrotic syndrome (10 g proteinuria/day, hypoalbuminaemia and ascites) abruptly developed 3 years later. Serum creatinine level was normal (81µmol/litre). A repeat intrinsic renal screen was again unremarkable. A second renal biopsy was performed (Figure 3) which revealed features of a chronic glomerular thrombotic microangiopathy. His nephrotic syndrome spontaneously resolved without escalation of prednisolone above 10 mg daily.

Case report (continued)

Nine months later, genital oedema and acute kidney injury (serum creatinine 108 µmol/litre) developed without proteinuria or evidence of systemic volume overload. Ultrasound of the testes confirmed scrotal oedema in the absence of an underlying testicular lesion. Computed tomography showed disease progression with bilateral perinephric infiltrates and hydronephrosis secondary to external compression from new, extensive retroperitoneal lymphadenopathy.

Given the prolonged periods of clinical stability between relapses, cytotoxic therapy with was administered only following presentation with genital oedema, obstructive uropathy and significant retroperitoneal lymphadenopathy. Treatment with six cycles of dexamethasone, cyclophosphamide and rituximab chemotherapy resulted in clinical improvement with significant reduction in lymphadenopathy, resolution of hydronephrosis on interval imaging and improvement in renal function. There has been no subsequent evidence of disease relapse to date, now more than 18 months after completion of chemotherapy.

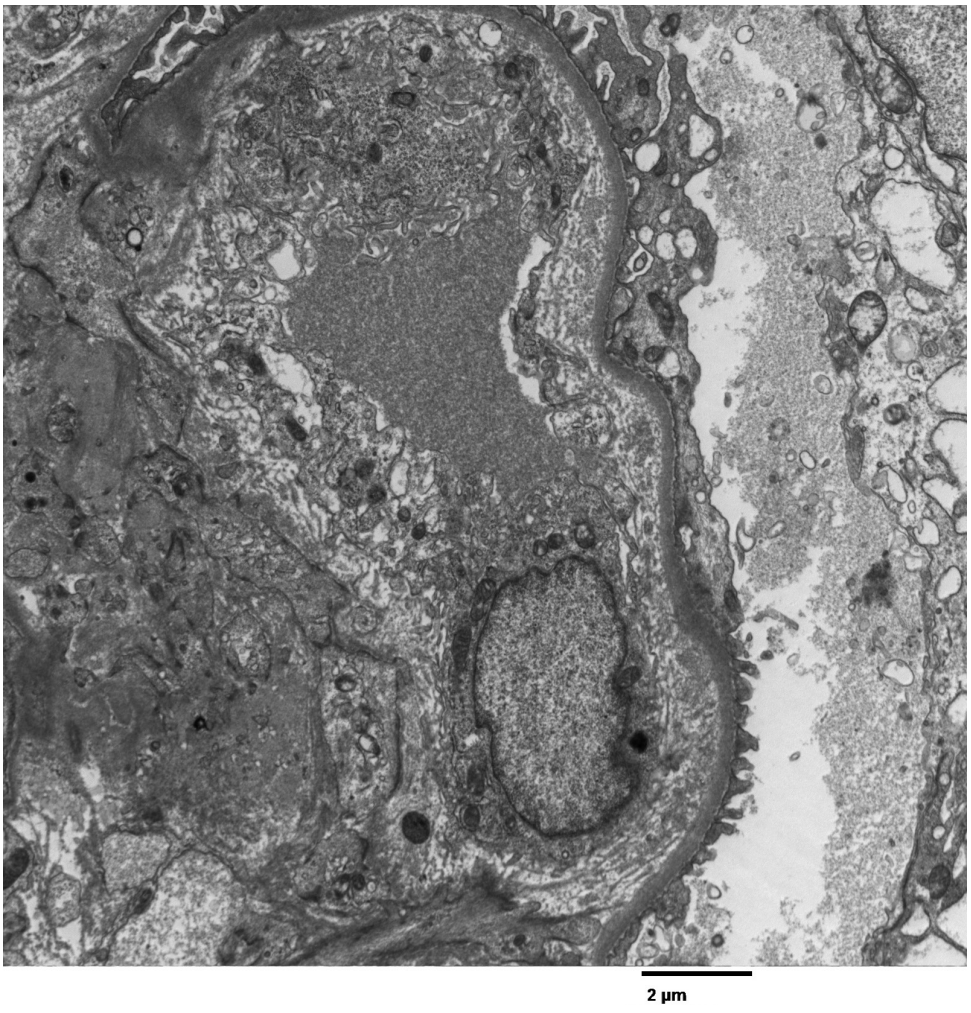

Figure 1. Renal biopsy showing endothelial cell injury and podocyte effacement, with electron lucent, granular material filling the subendothelial space, electron microscopy (magnification x8000).

Discussion

The diagnosis can be further refined to TAFRO syndrome, a subtype of idiopathic multicentric Castleman's disease (Masaki et al, 2013; Igawa and Sato, 2018).

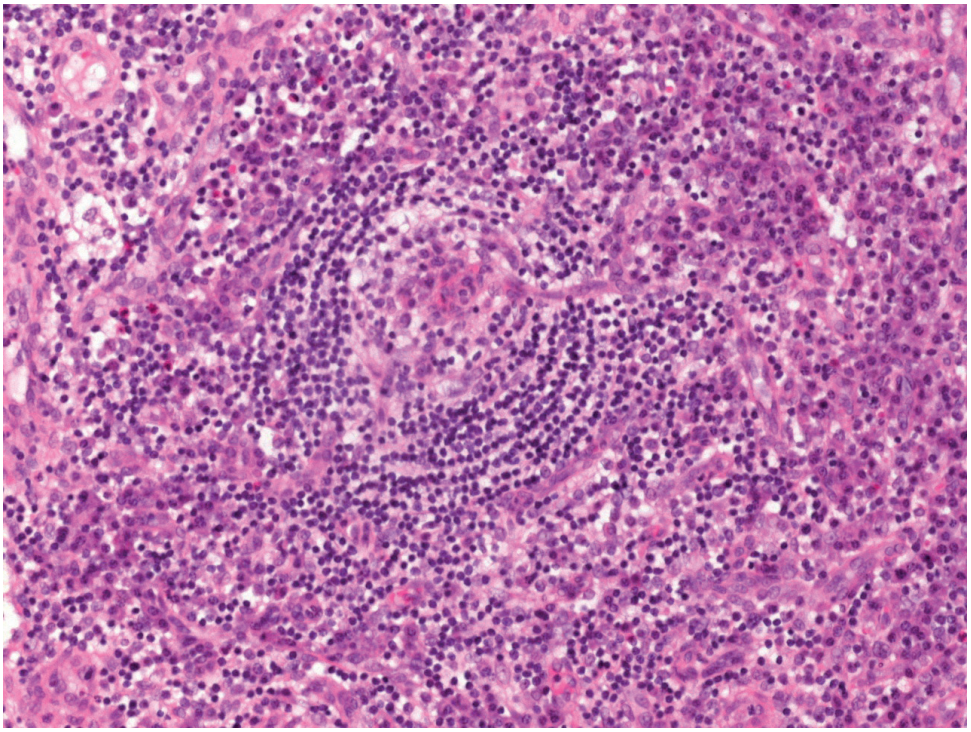

Figure 2. Left groin lymph node biopsy showing a lymphoid follicle with an atrophic germinal centre, onion skinning of the mantle zone lymphocytes and penetration of a vessel from the paracortex through the mantle zone into the germinal centre, haematoxylin and eosin stain, light microscopy, magnification x200. Staining for human herpes virus-8 (not shown) was negative.

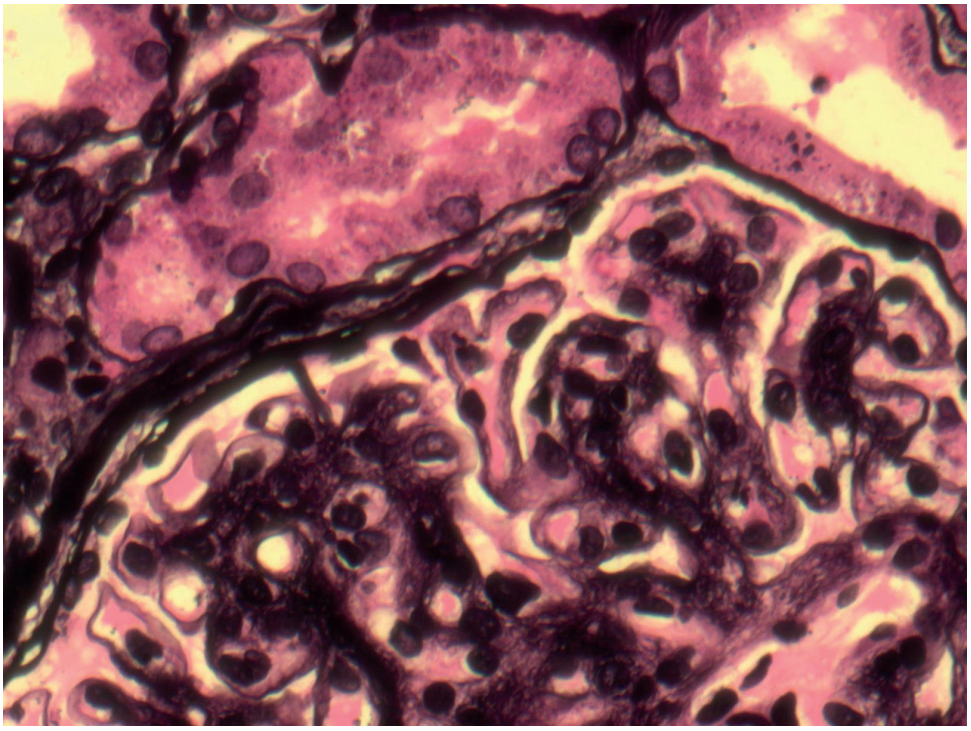

Figure 3. Renal biopsy showing features of a chronic glomerular thrombotic microangiopathy with double contouring of the glomerular capillary walls, silver stain, light microscopy, magnification x60. Thrombi within the capillary lumens consistent with an acute thrombotic microangiopathy were not visualised. Immunohistochemistry (not shown) had granular, patchy positivity for IgG4, IgM and C1q in both the capillary walls and the mesangium. Plasma cell staining for kappa and lambda on this biopsy was equal.

The diagnostic criteria for TAFRO syndrome (Iwaki et al, 2016) are as follows:

- Lymph node histopathological criteria: atrophic germinal centres with enlarged endothelial cell nuclei and endothelial venule proliferation with small numbers of plasma cells and negative human herpes virus-8 status
- Three out of five major 'TAFRO' criteria:
  1. Thrombocytopaenia
  2. Anasarca (which refers to severe generalised oedema of any aetiology)
  3. Fever
  4. Reticulin fibrosis
  5. Organomegaly
- One out of two minor criteria:
  1. Megakaryocyte hyperplasia
  2. Raised alkaline phosphatase levels without transaminitis.

The features of other subtypes of Castleman's disease are outlined in a review by Dispenzieri and Fajgenbaum (2020).

The main differential diagnoses for idiopathic multicentric Castleman's disease-TAFRO are idiopathic multicentric Castleman's disease-not otherwise specified, POEMS-(polyneuropathy, organomegaly, endocrinopathy, monoclonal plasma cell disorder, skin changes) associated multicentric Castleman's disease and human herpes virus-8-associated multicentric Castleman's disease. In this case, investigations for a plasma cell dyscrasia and human herpes virus-8 were negative.

Renal involvement in multicentric Castleman's disease has been previously documented (Xu et al, 2012). A retrospective study of 19 patients who underwent renal biopsy identified small vessel renal lesions (similar to those observed in this case) with superimposed glomerular or arteriolar thrombi in 47% of patients (El Karoui et al, 2011) with amorphous electron lucent subendothelial deposits seen on electron microscopy. Other biopsy findings (described more commonly with co-existent human immunodeficiency virus infection) included AA amyloidosis, tubulointerstitial disease and focal segmental glomerulosclerosis.

Dysregulation of interleukin-6 production is key in the pathogenesis of Castleman's disease. Siltuximab, a chimeric monoclonal antibody against interleukin-6, has demonstrated benefit in patients with idiopathic multicentric Castleman's disease (van Rhee et al, 2014). It is a potential treatment option should this patient relapse in the future, especially if serum interleukin-6 levels are raised.

Most of the initial cases of TAFRO syndrome have been reported in Japanese-born patients (Dispenzieri and Fajgenbaum, 2020), which makes this patient unusual. This case is also notable for highlighting the myriad of ways in which Castleman's disease can cause renal dysfunction.

Learning points

- Castleman's disease describes a rare group of disorders that share certain histopathological features but have a very wide spectrum of clinical presentations.
- TAFRO (thrombocytopaenia, anasarca, fever, reticulin fibrosis and organomegaly) syndrome is a recently described subset of idiopathic multicentric Castleman's disease that typically runs a very aggressive clinical course.
- Renal involvement in Castleman's disease (including TAFRO syndrome) is well recognised and may present with renal dysfunction (acute kidney injury, nephrotic syndrome or abnormal urinalysis).
- Systemic immunosuppression with corticosteroids, followed by cyclophosphamide and rituximab led to clinical and radiological improvement in this case.
- Monoclonal antibody therapy against interleukin-6 is emerging as a promising treatment strategy, especially in patients with elevated serum interleukin-6 levels.

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