IgG4-RD is defined by histopathological analysis of biopsy specimens showing lymphoplasmacytic infiltrate rich in IgG4+ plasma cells that is organized in a storiform pattern [1]. An IgG4+/IgG+ plasma cell ratio >40% is mandatory for histological diagnosis of IgG4-RD. In our observation, swelling parotids in a 60-year-old man suffering from xerostomia and the absence of anti-SSA and anti-SSB antibodies was suggestive of IgG4-RD [2].

In this case, renal PAN-like disease with microaneurysms and renal infarction was confirmed by arteriography. In the literature, IgG4-RD arterial lesions may occur, but are located in the thoracic aorta, abdominal aorta to iliac arteries, superior mesenteric artery, inferior mesenteric artery and splenic artery [3]. IgG4-RD may also manifest as idiopathic retroperitoneal fibrosis, inflammatory aortic aneurysm and inflammatory pericarditis [4]. Otherwise, tubulo-interstitial nephritis is the most dominant feature of IgG4-RD kidney involvement and may cause acute or chronic renal dysfunction, although some glomerular lesions such as membranous nephropathy are sometimes found [5, 6]. To our knowledge, PAN-like renal involvement has never been described in IgG4-RD. Interestingly, in a recent review, Saeki et al. [5] stated that most common findings of renal involvement are multiple low-density lesions seen on enhanced CT scans, but our observation is the first to describe micro-aneurysms confirmed by renal arteriography.

Moreover, our patient presented with polycythaemia probably due to non-adapted secretion of EPO, in the absence of JAK2 mutations. It is probable that this EPO abnormal secretion was due to IgG4-RD renal involvement, but this hypothesis could not be demonstrated since a renal biopsy was not performed because of the haemorrhagic risk. Normalization of the haemoglobin level with steroid therapy favours this hypothesis [7]. However, renal imaging favoured renal infiltration. We hypothesized that renal interstitial macrophages stimulated local renal EPO-producing cells. Interestingly, it was recently demonstrated that renal EPO-producing cells could also be responsible for fibrosis synthesis [8]. Therefore these cells could be responsible for both renal fibrosis, a key feature in renal IgG4-RD, and the increased EPO production found in our patient. IgG4-RD is a systemic disease with pleotropic manifestations, including renal PAN-like disease complicated by symptomatic secondary polycythaemia.

Funding: No specific funding was received from any funding bodies in the public, commercial or not-for-profit sectors to carry out the work described in this article.

Disclosure statement: The authors declare no conflict of interest.

François-Xavier Danlos1, Fadela Daoued-Keffi1, Julien Rohmer1, Guillaume Cluzel2, Estelle Blanc-Autran3, Hélène François4, Thierry Lazure5, Raphaele Seror6,* and Xavier Mariette1,* 

1 Service de rhumatologie and 2 Service de radiologie, Hôpital Bicêtre, Le Kremlin Bicêtre, 3 Service de médecine nucléaire, Centre Chirurgical Marie Lannelongue, Le Plessis-Robinson, 4 Service de néphrologie and 5 Service d’anatomopathologie, Hôpital Bicêtre, Le Kremlin Bicêtre, France

Revised version accepted 2 September 2015


E-mail: xavier.mariette@bct.aphp.fr

*Raphaele Seror and Xavier Mariette contributed equally to this study.

References


Rheumatology 2016;55:382–384

doi:10.1093/rheumatology/kev371

Advance Access publication 15 October 2015

A case of relapsing and refractory catastrophic anti-phospholipid syndrome successfully managed with eculizumab, a complement 5 inhibitor

In patients with refractory catastrophic APS, eculizumab may be a useful and cost-effective alternative.

Sir, Catastrophic anti-phospholipid syndrome (CAPS) is the most severe and rare form of APS, presenting with acute multiple-organ involvement, small-vessel thrombosis and visceral damage [1]. We present a case of CAPS that was refractory to conventional therapy. For the sake of clarity, our patient’s platelet counts over the years are represented in Fig. 1.
Our patient, a 43-year-old lady, was first diagnosed with APS in 2000, aged 32 years, and commenced on lifelong warfarin, following an episode of axillary vein thrombosis on a background of pregnancy morbidity, positive LA and IgG aPLs 114 GPL U/ml.

She presented in 2005 with acute hepatic illness, acute renal failure with significant proteinuria (1.6 g/24 h), thrombocytopaenia (64 × 10^9/l) and raised inflammatory markers [CRP 528.7 mg/l (normal < 10 mg/l)]. Infection screen was negative. Immunology revealed positive ANA (nucleolar) and elevated dsDNA at 35 U/l (normal < 25 U/l). Liver biopsy showed hepatitis with no evidence of microthrombi. Renal biopsy was deemed inappropriate due to thrombocytopaenia, increased APTT (75.6 s) and elevated fibrinogen levels. She improved on oral prednisolone and was discharged on aspirin, prednisolone and warfarin.

In 2007, she presented with abdominal pain, fever and vasculitic lesions on fingers and toes. CRP was 447 mg/l, she had thrombocytopaenia (64 × 10^9/l) and International normalised ratio (INR) was 7.6. Repeat immunology was normal apart from positive IgG aPLs >100 GPL U/ml (normal < 9 GPL U/ml). Abdominal CT scan revealed a thickened aorta. For a presumed diagnosis of large vessel vasculitis, she received pulsed intravenous methylprednisolone (1000 mg × 3) and was discharged on oral prednisolone and AZA, which was subsequently changed to MMF due to patient intolerance and a minor flare in 2009.

In 2011, she was admitted with epigastric pain and elevated CRP of 469 mg/l. INR was > 15. She had reversal of the INR with intravenous vitamin K. There was a significant decline in her renal function (eGFR 10.5 ml/min), and she developed profound thrombocytopaenia (68 × 10^9/l). Proteinuria of 1 g/24 h was noted. Renal biopsy revealed microthrombi and no evidence of LN or Haemolytic Uraemic Syndrome. Neurological examination was unremarkable. Thrombotic Thrombocytopaenic Purpura was excluded as she had normal ADAMTS 13 levels. A diagnosis of CAPS was made.

She received three doses of 1 g i.v. methylprednisolone followed by three doses of two-weekly CYC (10 mg/kg). This was poorly tolerated and did not improve clinical or biochemical parameters. Daily plasma exchange was therefore commenced. Her course was complicated by uncontrolled hypertension and intracranial haemorrhage. Despite aggressive intravenous antihypertensive therapy and daily plasma exchange, her renal function continued to deteriorate (Cr 465 µmol/l; eGFR 7.3 ml/min) and platelets remained low (25–65 × 10^9/l). She had two further episodes of intracranial bleeding, one thrombotic stroke and one episode of status epilepticus.

The normal value for the platelets is 150–400 × 10^9/l. Note the improvement in platelet count after initiation of eculizumab.

---

**FIG. 1** This graph represents our patient’s platelet counts over the years.
Rituximab (1 g i.v. x 2) was tried without benefit, and a subsequent 5-day course of i.v. immunoglobulins (2 g/kg total dose) resulted in only a short-lived improvement in platelet count and no improvement in renal function.

Throughout her admission, our patient had rigid anticoagulation with low molecular weight heparin, with factor Xa and platelet monitoring. Despite documented therapeutic anticoagulant activity, she had recurrent episodes of thromboses (renal, ocular, CNS), and the IgG anti-phospholipid antibodies were still increased at >120 GPL U/ml. IgG anti-beta-2glycoprotein I-antibody was raised at 104 U/ml (normal <5 U/ml).

At this point, eculizumab (a humanized monoclonal antibody against complement C5) was commenced. She received meningococcal vaccination and antibiotic prophylaxis, and an induction dose of eculizumab 900 mg, followed by weekly doses of 1200 mg was given. Plasma exchange was stopped, and after 6 weeks, when the platelet count had stabilized, the frequency of eculizumab was reduced to 1200 mg two weekly, 900 mg two weekly and then 900 mg four weekly. She remains on this regime.

The patient’s platelets have improved from $31 \times 10^{9}$ to $136 \times 10^{9}$, eGFR has improved from 7.3 to 17.4 ml/min and she remains off dialysis. She has reduced her steroids to 10 mg once daily (a pituitary infarct and secondary Addison’s means this continues as replacement therapy). She lives a fully independent life, having made significant functional improvement following her strokes.

Eculizumab blocks cleavage of complement C5 and prevents generation of pro-thrombotic and pro-inflammatory molecules C5a and membrane attack complex C5b-9 [2]. Several case reports suggest its efficacy in the management of CAPS [1, 3]. Our case report adds support to this evidence base and demonstrates efficacy in the context of CAPS refractory to the usual treatments used, including immunosuppression, anticoagulation and plasma exchange [1].

While the unit cost of eculizumab is very high, we note that withdrawal of plasma exchange and avoidance of dialysis for >2 years to date suggest that, in these cases, it may be cost effective against the alternatives. More importantly, it has resulted in clinical stability for our patient, no new neurological deficits and marked improvement in her quality of life. We have also been able to reduce the dose and frequency of dosing with eculizumab while maintaining her stability.

We therefore conclude that, in patients with CAPS refractory to usual therapy, eculizumab may be an effective alternative, and its efficacy in cases such as ours supports its cost-effectiveness for this condition with high mortality and morbidity.

Funding: No specific funding was received from any funding bodies in the public, commercial or not-for-profit sectors to carry out the work described in this manuscript.

Disclosure statement: J.T. has received speaker honoraria and travel sponsorship from Alexion. All other authors have declared no conflicts of interest.

References