25. USE OF RITUXIMAB IN REFRACTORY PRIMARY ANTIPHOSPHOLIPID SYNDROME WITH PULMONARY AND CEREBRAL MANIFESTATIONS

Asim Khan1, Ghazal Ansari1, Hoda Al-Koky1, Arla Mahto1, and Hasan Tahir3

1Rheumatology, Barts Health NHS Trust, London, United Kingdom

Introduction: We describe a 29-year-old gentleman with triple-antibody positive primary antiphospholipid syndrome (APS) who presented with recurrent cerebrovascular thrombotic events despite anticoagulation. He was escalated to rituximab. A pre-rituximab chest radiograph was abnormal resulting in a CT-chest which demonstrated bilateral widespread ground-glass opacities. Carbon monoxide transfer coefficient (KCO) was raised. Lung biopsy showed alveolar haemorrhage, alveolitis, capillaritis and a mixed inflammatory infiltrate consistent with APS. Alternative causes such as infection and malignancy were excluded. This case reflects a complex refractory APS with rare pulmonary manifestations. Management was multidisciplinary and included the use of rituximab to prevent further disease progression.

Case description: A previously well 29-year-old Asian gentleman presented in late 2015 with multiple right leg deep vein thromboses (DVTs). Rivaroxaban was commenced for six-months. A thrombophilia screen post-treatment demonstrated anti-cardiolipin IgG and IgM levels of > 420 kU/ml and 200 kU/ml respectively, anti-β2-glycoprotein-1 IgG and IgM levels of 163 kU/ml and 50 kU/ml respectively, and a strongly positive lupus anticoagulant. A follow-up US-Doppler revealed chronic DVTs; apixaban was initiated. Secondary causes of APS were excluded clinically and serologically. Repeat APS antibodies remained strongly positive.

In December 2016, he developed multiple APS-driven strokes affecting the occipital lobes, centrum semiovale and cerebellum. Other causes of stroke were excluded. Clopidogrel was commenced and apixaban was changed to warfarin with an INR target of 2.5–3.0. Despite consistently achieving this target he had an acute parietal lobe stroke in May 2017. Consequently, his INR target increased to 3.0–4.0. Hydroxychloroquine and high-dose atorvastatin were also added. In July 2018 he presented with recurrent transient ischaemic attacks. An MRI-head identified a previously unseen chronic temporal lobe infarct. Following a multidisciplinary discussion we changed warfarin to low molecular weight heparin and also planned to commence rituximab.
Pre-biologic, his T-spot was positive and his chest radiograph was abnormal. He had no chest symptoms. ACT-chest demonstrated multiple bilateral ground-glass opacities. Pulmonary function tests (PFTs) revealed an elevated KCO (130% predicted). A lung biopsy revealed alveolar haemorrhage, alveolitis, capillaritis and a mixed inflammatory infiltrate consistent with APS. Infection (including tuberculosis), malignancy and granulomatous disease were all excluded.

The patient was subsequently treated with high-dose corticosteroids and rituximab. His other treatment for APS remained unchanged. He was also treated for latent tuberculosis with isoniazid. Since this treatment the patient has had no further thrombotic episodes. Moreover, repeat CT-chest and PFTs have both shown significant improvements.

**Discussion:** Primary APS is an autoimmune thrombophilic disorder characterised by recurrent arterial and venous thromboembolism, and obstetric morbidity. Deep vein thrombosis and stroke are the most common venous and arterial thrombotic manifestations respectively. Treatment includes the use of anticoagulation such as warfarin. Refractory APS is associated with recurrent thrombotic episodes despite anticoagulation therapy. Our patient developed recurrent cerebral thrombosis despite warfarin and clopidogrel. This continued to occur even after increasing the INR target. Furthermore, prior to and during each thrombotic episode, our patient’s INR was always within the desired range. We also added secondary treatments for APS including atorvastatin and hydroxychloroquine and these also failed to prevent further cerebrovascular disease. We did not feel changing warfarin to low molecular weight heparin alone was sufficient to prevent further thromboses given the history of optimal INRs. We therefore opted to also add rituximab given its role in preventing further production of B-cell driven autoantibodies via CD20 binding. In addition, our patient had significant APS-driven pulmonary abnormalities which required addressing.

Pulmonary embolism and pulmonary hypertension are the most common respiratory pathologies of APS. Rarely APS can also cause pulmonary artery thrombosis and fibrosing alveolitis. Moreover and particular to our patient, it can cause alveolar haemorrhage, alveolitis and pulmonary capillaritis. This occurs via neutrophilic infiltration of the alveolar septum and pulmonary capillary wall, and microthrombi which results in inflammation. Necrosis and loss of capillary integrity then causes disruption of the alveolar-capillary basement membrane leading to haemorrhage. Remarkably despite the evident APS-driven lung disease in our patient, he was asymptomatic from a chest perspective.

Our patient has responded positively to rituximab with improvement in PFTs and CT-chest appearance. Moreover he has had no further thrombotic events. We aim to repeat brain imaging and recheck APS antibody titres to observe the effect of rituximab.

**Key learning points:** Excluding pulmonary embolism and pulmonary hypertension, pulmonary disease is an under-recognised manifestation of APS. Rarer lung sequelae include pulmonary capillaritis, alveolitis and alveolar haemorrhage which our patient exhibited. These pathologies require a combination of investigations to diagnose including imaging, PFTs and histopathological biopsy.

Most cases of APS respond to first-line treatment with anticoagulation such as warfarin provided INR targets are consistently achieved. Our patient continued to have recurrent thrombotic cerebrovascular events despite anticoagulation, antiplatelet therapy and other treatments. This case raises awareness of a complex refractory APS case which necessitated the introduction of biologic therapy in rituximab. Rituximab is already well-recognised in the treatment of catastrophic APS. We intend by this case to raise awareness of the effectiveness of rituximab in non-catastrophic APS, and its value in treating inflammatory APS-driven lung pathology. We await results for the effect of rituximab on APS-antibodies and whether this has any impact on prevention of disease progression.

This case also highlights the importance of a multidisciplinary approach in managing complex cases. We worked alongside other specialties including neurology, stroke medicine, haematology and respiratory medicine to achieve optimal patient care.

**Conflicts of interest:** The authors have declared no conflicts of interest.