Retinal vasculopathy in STING-Associated Vasculitis of Infancy (SAVI).

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Rheumatology Key Message: Retinal vasculopathy is a newly recognised feature of SAVI

SIR, STING associated vasculopathy with onset in infancy (SAVI) is an autoinflammatory disease caused by autosomal dominant gain-of-function mutations in *STING*, encoding the stimulator of interferon genes protein [1, 2]. It is a rare type I interferonopathy that typically presents with neonatal-onset systemic inflammation, cutaneous vasculopathy, extensive tissue loss and interstitial lung disease. Here we describe two patients presenting with severe retinal vasculopathy, the first description of this phenotype in SAVI.

Case 1, a 6-year-old boy, presented in early infancy with a persistent cough and tachypnoea with perihilar changes on chest x-ray, diffuse maculopapular rash, nail-clubbing and failure to thrive (FTT). He was referred for respiratory assessment at 7 months and found to have persistently abnormal acute phase reactants, an abnormal interferon gene signature and interstitial lung disease (ILD) on CT-chest. Genetic analysis by Sanger sequencing confirmed a heterozygous somatic mutation in *STING* (c. 463 G.A, p.V155M), confirming SAVI [3]. Treatment with corticosteroids and monthly-IVIG was ineffective. At age 29 months he was started on the Janus kinase inhibitor baricitinib (8mg/day). This improved systemic inflammation and allowed weaning of glucocorticoids. His respiratory status remained stable. Age 5-years he presented with gradual visual loss in his left eye with perception of hand movements only; fundoscopy revealed retinal vessel telangiectasia, tortuosity and dilatation, with extensive intra- and subretinal exudates (Fig. 1A&B). This was managed conservatively and is under surveillance.

Case 2, a 3-year-old boy, was born at 32 weeks by elective caesarean section due to intrauterine growth retardation. TORCH screen was negative and karyotype testing was normal. Postnatally a ventricular septal defect (VSD), and patent ductus arteriosus (PDA) were detected, and he had FTT. Aged 2 months, he developed a painful swelling of the thigh following routine intramuscular vaccination, requiring intravenous antibiotics; blood cultures grew group B streptococcus. Investigations revealed persistent neutropaenia (0.9 $x10^9$/L), anaemia (haemoglobin 68 g/L), thrombocytopaenia (platelets 56 x 10^9/L); and raised inflammatory markers (CRP 165 mg/L). Tests for breakage syndromes including Fanconi anaemia and Nijmegen breakage syndrome were negative. Bone marrow aspirate showed absent neutrophils and precursors, reduced megakaryocytes and dyserythropoeisis. Genetic testing revealed a pathogenic mutation in *STING* (p.Phe279Leu), previously described in SAVI [4]. However, this was initially considered not to explain the phenotype. Based on this, and despite a definitive cause for this marrow suppression, he underwent a CD19-depleted haploidentical allogeneic haemaotpoietic stem cell transplant (allo-HSCT), aged 7-months. Donor engraftment was 100%, with no graft versus host disease (GvHD), normalisation of cell counts and subsequent normal vaccine responses. VSD closure for worsening cardiac function was required at 8-months of age. Persistent pulmonary hypertension was observed post-operatively, not explained

by any residual VSD shunt, and required treatment with sildenafil. There were no radiological features of ILD. At 18 months of age he presented with encephalopathy, and seizures: MRI of the brain showed bilateral patchy parieto-occipital cortical, subcortical and deep white matter hyperintensities, with cerebral and cerebellar microhaemorrhages. Global developmental delay and speech regression ensued. At 23 months, there were concerns regarding vision, although visual evoked potentials were intact. At 34 months, following another seizure, MRI orbits suggested bilateral ocular vitreous opacifications, subsequently confirmed as haemorrhages with bilateral tractional retinal detachment (Fig. 1C-F). Surgical management of the eyes unfortunately did not restore vision. Subsequently, typical vasculitic and autoinflammatory features of SAVI developed: vasculitic skin rash, saddle nose, and pathergic reaction to immunisations (Fig. 1G&H). Aged 36 months, he commenced baricitinib 6 mg/day, with relief of cutaneous vasculitis features. Three months after starting baricitinib therapy, he remains clinically with normal acute phase reactants remain normal (CRP <5 mg/L; ESR 14 mmHg). However, he remains blind in both eyes.

We describe retinal vasculopathy as a novel phenotype of SAVI. Although eye involvement has not been previously described in SAVI, it has been described in other interferonopathies such as autosomal dominant retinal vasculopathy, and Aicardi Goutières syndrome related to mutations in the DNA exonuclease TREX1 [5, 6]. Retinal pathology also features in other monogenic autoinflammatory conditions such as retinal vasculitis is described in haploinsufficiency A20 (HA20) [5]. In neonatal-onset multisystem inflammatory disease (NOMID)/chronic infantile neurologic cutaneous articular (CINCA) syndrome, eye pathology mainly includes optic disc oedema, pseudopapilloedema, and optic atrophy, although retinal vasculitis has also been described [7].

Although the diagnostic utility of a fluorescein angiography for screening in this condition is unknown, if performed early, it may permit detection of vascular leak secondary to vasculitis, neovascularisation, haemorrhage and tractional retinal detachment. Early detection would facilitate laser therapy together with systemic treatment with baricitinib that may help to prevent sight loss.

The exact pathogenesis remains to be fully elucidated but is likely to be due to a vasculitic thrombotic microangiopathy in retinal vessels secondary to unregulated excess of type I interferon (IFN)-inducible gene products and downstream inflammatory cytokines. Microvascular angiopathy has been observed in cerebral microvasculature in transgenic mice secreting excess type I IFNs in the brain as well as adults receiving IFN-α or IFN-β therapy [8]. Retinal vasculopathy is frequently reported as a toxic side effect of type I IFN therapy [9]. In conclusion, we report that severe sight-threatening retinal vasculopathy is a novel phenotypic manifestation of SAVI. Early screening for retinal pathology may is now thus recommended as part of routine follow up of SAVI.

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Declaration

The authors declare no conflict of interest.

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