Transverse myelitis in a patient with activated phosphoinositide 3-kinase δ syndrome type 1

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Activated phosphoinositide 3-kinase (PI3K)δ syndrome (APDS) is a heterogenous primary immunodeficiency caused by autosomal dominant mutations in PIK3CD (APDS1) or P1K3R1 (APDS2), genes that code for the catalytic p110δ and regulatory p85 subunits of PI3Kδ respectively [1,2]. Both forms of APDS result in overactivation of PI3Kδ through gain-of-function mutations in p110δ or loss-of-function mutations in p85 and present with similar immunodeficiency. Over ninety percent of APDS patients present with recurrent ear, nose and throat or respiratory tract infections [1,2]. Both non-neoplastic and neoplastic lymphoproliferation are common, with lymphoma the most frequently experienced malignancy [1,2]. Almost 40% of patients with APDS1 and 20% of patients with APDS2 experience autoimmune or inflammatory disease such as cytopenias, chronic diarrhoea or autoimmune haemolytic anaemia. The majority of patients with APDS are treated supportively with antibiotic prophylaxis. Other therapeutic options include immunoglobulin replacement therapy (IGRT), immunosuppressive therapies and inhibitors of mTOR signalling such as rapamycin [3]. Rapamycin appears to be more effective at controlling non-neoplastic lymphoproliferation but less successful at modulating intestinal disease and cytopenias [3].

Our patient presented with lower respiratory tract infections in the first year of life and was diagnosed with hypogammaglobulinemia [4]. She was commenced on regular antibiotic prophylaxis and weekly IGRT. During childhood she developed bronchiectasis (Figure 1A), chronic rhino-sinusitis, persistent lymphadenopathy and non-infectious colitis. At 21 years of age genetic sequencing demonstrated that she carried the E1021K heterozygous mutation in PI3KCD, confirming a diagnosis of APDS1 . The same mutation was identified in her two siblings, both of whom had hypogammaglobulinemia and a

history of recurrent infections (Figure 1B). She continued to be managed conservatively with antibiotic prophylaxis, regular immunoglobulin replacement therapy and mesalazine without systemic immunosuppression. A year later, she presented to hospital with a short history of general malaise, nausea and vomiting. The following day she developed acute onset myelopathic symptoms and signs with rapidly progressive weakness of all four limbs over 24 hours, a C3 sensory level and significant sphincter dysfunction with urinary retention and faecal incontinence. At her nadir of weakness she was only able to shrug her shoulders and flicker toes of her right foot. She was afebrile and had no cranial nerve or bulbar deficits. She was transferred to intensive care for respiratory function monitoring. MRI brain was normal, but cervicothoracic spine MRI revealed a longitudinally extensive transverse myelitis between C2 to C6 with slight cord oedema (Figure 1C and Fig 1D). The lesion encompassed approximately 50% of the cross-sectional area of the spinal cord. CSF was acellular with normal protein and glucose levels. No oligoclonal bands were detected and viral PCR screen for HSV, VZV and enterovirus was negative. Autoantibodies, including ANA, dsDNA, ANCA, aquaporin-4 and anti-MOG, were negative. Serum ACE and calcium were within normal range and her CT chest, abdomen and pelvis revealed no evidence of underlying malignancy or infection. The initial impression was of a longitudinally extensive transverse myelitis and she was treated with a three-day course of IV methylprednisolone (1g per day), followed by a course of intravenous immunoglobulin (2g/kg for five days). Maintenance treatment with oral prednisolone was given for six months. She was also started on mycophenolate mofetil (MMF) 500mg bd, as mTOR inhibitors are not routinely used for management of neuromyelitis. There was an initial rapid improvement in lower limb power and a slower improvement in upper limb strength over six to twelve months. Bowel and bladder symptoms resolved over this period, but she has residual gastroparesis. She has since had an uneventful pregnancy, during which her MMF was paused and recommenced post-partum. She has been relapse-free over a three-year follow up period with no additional immunomodulatory medications required.

Autoimmune and inflammatory complications are seen frequently in APDS and encompass a broad range of clinical presentations, of which autoimmune cytopenias are the most common. Other organ-specific autoimmunity is also described including glomerulonephritis, exocrine pancreatic insufficiency, diabetes, autoantibody-positive thyroid disease, seronegative arthritis, sclerosing cholangitis, autoimmune hepatitis recurrent pericarditis and enteropathy [1,2]. This is the first described case of a neurological autoimmune complication in APDS. APDS is a combined immunodeficiency with impact on both T and B cell function reflecting the importance of PI3Kδ in haematopoietic lineages. While there is heterogeneity between patients, the most common immunological findings in peripheral blood are reduced numbers of naive CD4

and CD8 T-cells, B-cell lymphopenia with increased percentage of transitional B-cells, low levels of IgG and IgA with elevated IgM. At a cellular level, PI3Kδ acts at the plasma membrane to catalyse phosphorylation of the phospholipid phosphatidylinositol-4,5-biphosphate (PIP2), converting it to short-lived phosphatidylinositol-3,4,5-triphosphate (PIP3). PIP3 in turn activates downstream signalling pathways including AKT and mTOR pathways that regulate multiple cell processes such as cell metabolism, growth and survival. Functional studies in individual cell types from APDS patients and murine models have demonstrated important roles for PI3Kδ in multiple aspects of T- and B-cell biology and revealed a number of abnormalities that may contribute to the autoimmune phenotype [5]. Specifically, T-cell activation is enhanced with increased cytokine release in both Th1 and Th2 CD4 T-cells while impaired T-cell differentiation leads to reduced numbers of regulatory T-cells known to be important for peripheral tolerance. Although the major impact on B-cells appears to be reduced isotype switching and memory formation resulting in humoral deficiency, evidence is emerging that B-cell dysregulation results in production of autoreactive IgM and IgG that may represent an additional mechanism for also autoimmunity in patients with APDS. In support of this, increased PI3Kδ activity has been described in several autoimmune conditions known to be associated with autoantibodies, such as SLE and inflammatory arthritis. There is no consensus about optimal management of autoimmune complications in APDS. mTOR and specific inhibitors of PI3Kδ, which directly impact the overactive signalling pathway, make logical sense but evidence of efficacy for autoimmune complications in APDS is lacking and this is an area that needs further research. Our approach to date has been to select immunosuppressive agents known to be effective for a given specific autoimmune complication in non-APDS settings. Haematopoietic stem cell transplantation is currently the only curative option for patients with APDS but carries the risks of transplant-associated morbidity and mortality. In the future curative options may include gene editing approaches that are particularly attractive for conditions caused by gain of function mutations.

This case report demonstrates a previously undescribed autoimmune complication of APDS, demonstrating that further research is necessary to understand the relationship between the PI3Kδ pathway, autoimmunity and treatment [5].

References

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