API2016 Case Summary:

Rapamycin reduces splenomegaly and lymphadenopathy in Common Variable Immunodeficiency (CVID): A Case Report

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Case Report:

A 54 year old female was hospitalised with anti-microbial-sensitive H. influenza pneumonia, her first major infection. Past medical history included prior motor vehicle accident, 160 pack year history of smoking and a recent diagnosis of chronic obstructive pulmonary disease (COPD). Medications on admission were Budesonide-Efomoterol, terbinafine and bupropion. There was no history of allergy, recent travel, sick contacts, recreational drug use or pets in the home. The patient was treated with 1.2g of IV Benzylpenicillin QID and a weaning dose of oral prednisone beginning at 50mg PO OD. She failed to clinically improve by Day 10 prompting further investigations.

A progress chest X-ray showed bilateral lower zone infiltrates while computer tomography (CT) of the chest, abdomen and pelvis showed evidence of endobronchial infection as well as hepatosplenomegaly and widespread axillae, mediastinal and Para aortic lymphadenopathy. Differential diagnoses at this stage included underlying malignancy, sarcoidosis or connective tissue disease.

Laboratory investigations including FBC, EUC, LFT, autoimmune serology and investigations for infections including HIV, viral hepatitis, CMV, EBV, aspergillus, mycobacteria and pertussis were all unremarkable. The inflammatory markers CRP and ESR were elevated at 64 and 28, respectively. The most remarkable finding was of a panhypogammaglobulinemia with low levels of all IgG (0.3g/L) IgA (<0.3g/L) and IgM (0.5g/L). An axillae lymph node biopsy performed to investigate for sarcoidosis and malignancy showed reactive lymphoid hyperplasia.

A provisional diagnosis of common variable immunodeficiency (CVID) was made. The patient received 0.4mg/kg of intravenous immunoglobulin (IVIG) as an inpatient and was discharged with a plan for monthly outpatient IVIG. A bone marrow aspirate and trephine showed sparse plasma cells, which is consistent with CVID, and no evidence of malignancy.

Over the following twelve months the patient’s lymphadenopathy and splenomegaly worsened with splenic capsular pain becoming a major complaint. A positron electron tomography (PET) scan
showed wide-spread avid lesions above and below the diaphragm reported as consistent with sarcoidosis or lymphoma. A second axillae lymph node biopsy showed atypical lymphoid strictures and lymphoid hyperplasia with no evidence of malignancy. Immunophenotyping demonstrated a B+SMB+CD21low phenotype by EuroClass criteria, which has a higher association with splenomegaly and granulomatous disease¹. Additionally all of the patients CD4 and CD8 T-cells displayed a CD45RA-CCR7- activated/terminally differentiated phenotype.

The role of the mTOR pathway was investigated by using an HRP-conjugated antibody to pS6 (a protein downstream of mTOR) and immunohistochemistry on the previously obtained lymphoid tissue. Immunohistochemistry found up-regulated expression of pS6 in the patients follicular B and T-cells compared with normal tonsillar tissue. Additionally, there was minimal EBER staining (<10% of follicles).

Given this provisional evidence of up-regulated mTOR activity, the patient was commenced in a trail of rapamycin (an mTOR inhibitor) 6mg PO STAT followed by 2mg PO OD aiming for a trough of 5-10microg/L. After two months of treatment the patient displayed marked clinical improvement with reduction of lymphadenopathy and splenomegaly and associated pain. A progress PET scan confirmed decreased tracer uptake into lymph nodes, marked reduction in hepatosplenomegaly and decreased SUVmax of the spleen from 4.4 to 2.9.

**Summary and Discussion:**

This patient represents a late presentation and diagnosis of CVID in a patient whose clinical course was not characterised by recurrent infections. Patients with CVID have decreased survival compared with the general population over 40 years² and patients with the non-infectious complications of CVID have the highest mortality. Unfortunately good evidence for the treatment and management of such complications is lacking.

Rapamycin has been used successfully in autoimmune lymphoproliferative syndrome (ALPS)³ a condition that generally presents in the paediatric population. This condition is characterised by defective lymphocyte apoptosis, secondary to mutations in Fas/FasL, and lymphoid hyperproliferation mediated by the mTOR pathway. ALPS commonly presents with marked cervical lymphadenopathy. Histopathologically, ALPS is driven by Epstein Barr virus (EBV) and is associated

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¹ Wehr *et al* Blood 2008  
² Resnick *et al* Blood 2012  
³ Dragana *et al* Pediatric Blood Cancer 2009
with a characteristic expansion of CD4-8- double negative T-cells, which were not features in this case.

A number of single gene mutations have been associated with primary immunodeficiencies that may be relevant to this patient. Mutations in AID and UNG have been associated with autosomal recessive hyper-IgM syndrome\(^4\) with low IgG, IgA and enlarged lymph nodes and germinal centres. However in this condition serum IgM levels are generally normal to high and not low, as in this case.

PI3K gain of function mutations have been described in fourteen patients with sino-pulmonary infections, lymphadenopathy, nodular lymphoid hyperplasia and CMV or EBV viremia\(^5\). In these patients naïve and central memory T-cells were deficient and senescent T-cells were over-represented. Over-activation of the mTOR pathway was demonstrated in these patients and addition of rapamycin \textit{in vitro} partially restored T-cell defects.

Mutations in ICOS have been associated with variable age of onset recurrent bacterial infections, splenomegaly, autoimmunity, intestinal lymphoid hyperplasia and poor germinal centre formation\(^6\). Finally, polymorphisms in CTLA-4 have been associated with autoimmunity and granulomatous disease with or without lymphoid hyperplasia in approximately one third of patient\(^7\). Our patient is currently undergoing whole exome sequencing to investigate for these aforementioned mutations and polymorphisms and also to investigate for novel gene mutations.

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\(^4\) Lee \textit{et al} Blood 2005  
\(^5\) Lucas \textit{et al} Nature Immunology 2014  
\(^6\) Grimbacher \textit{et al} Nature Immunology 2003  
\(^7\) Knight \textit{et al} Journal of clinical Immunology 2007
Conclusions:

This case suggests the mTOR pathway may be up-regulated in some cases of CVID-associated splenomegaly and lymphadenopathy. In such cases mTOR inhibitors may be useful therapy, however the optimal duration of such therapy is unclear. Whole exome sequencing of this patient’s DNA is currently underway in the hope of identifying a previously reported or novel molecular diagnosis.

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