Western Australian Immunology Day
Clinical Grand Rounds (CGR) Abstracts

Saturday 14 November 2020

Harry Perkins Institute of Medical Research
McCusker Auditorium, 6 Verdun Street, Nedlands WA

Time	Clinical Grand Rounds (CGR)	Speakers
	Chairs: A/Professor Richard Loh, Dr Tiffany Hughes (SA)	
13.30 – 15.00	**CGR cases presented by advanced trainees** Each presenter has been allocated 10 minutes, including 7 minutes for the presentation and 3 minutes for questions.	Dr Nicola Benwell (WA) Dr Peter Bradhurst (NSW) Dr Luckshman Ganeshanandan (WA) Dr Alice Grey (NSW) Dr Lisa Horgan (NSW) Dr Adrian Lee (NSW) Dr Natasha Moseley (WA) Dr Claire Reynolds (SA) Dr Alex Stoyanov (NSW)

LOSING MY VOICE

Dr Nicola Benwell (WA)

Granulomatosis polyangiitis (GPA) is one of the ANCA positive small-vessel necrotising granulomatous vasculitides with diverse organ involvement most frequently involving the ear, nose, throat, lungs and kidneys. Severe stricturing disease of the tracheobronchial tree is an uncommon manifestation of this syndrome, characterised by its predilection towards young, female patients that may cause progression of stenosis that is discordant to apparent serological and clinical response in other affected organs to systemic immunosuppression.

We present the case of a young 19 year old university student with GPA whose original presentation included sinus and pulmonary disease with PR-3 seropositivity. Induction of remission with high dose corticosteroids and rituximab was followed by a brief period of remission over three months.

The following 2 months were characterised by fluctuating clinical course secondary to invasive pulmonary aspergillosis and rapid development of airway and life threatening tracheobronchial stenoses (TBS). This was in the absence of elevation in PR3 antibody level or reappearance of manifestations of her disease outside her tracheobronchial tree.

A combination of rapid escalation of anti fungal treatment, reinduction of remission with intravenous immunoglobulin, methylprednisolone and then cyclophosphamide, surgical interventions including tracheostomy and then multiple bronchial stents, and physiological/organ support in intensive care was required to save this patient's life and stabilise her clinical trajectory.

This case highlights a rare and severe phenotype of GPA and raises important educational points regarding multidisciplinary management, pathogenesis of TBS and prognostication in this small patient cohort.

ASCIA WA IMMUNOLOGY DAY CGR ABSTRACTS

THE TINY COMPLICATIONS OF B-CELL DEPLETION

Dr Peter Bradhurst (NSW)

The use of B-cell depleting therapy has become increasingly common with an increasing number of approved clinical indications across different specialties. Profound hypogammaglobulinaemia secondary to B-cell depletion has been recognised more frequently. Unusual and severe infections have now been reported in these patients.

This clinical grand rounds presentation focuses on two separate patients who underwent B-cell depleting therapy and presented with severe disseminated infection secondary to Ureaplasma urealyticum. U. urealyticum is a normal urogenital pathogen that may cause urogenital infection and chorioamnionitis.

Disseminated infection with U. urealyticum was first described in patients with primary immunodeficiency (CVID, XLA) but has been rarely described in recent years in the setting of secondary hypogammaglobulinaemia.

HETEROZYGOUS STAT1 GAIN-OF-FUNCTION MUTATION PRESENTING WITH CHRONIC HIDRADENITIS SUPPURATIVA

Dr Luckshman Ganeshanandan (WA)

Signal transducer and activator of transcription 1 gain-of-function (STAT1 GOF) mutations classically manifest as chronic mucocutaneous candidiasis (CMC). Additional diverse clinical presentations occur, including autoinflammation or autoimmunity in up to one third of cases.

We present a patient with a history of chronic and severe hidradenitis suppurativa, unsuccessfully treated with immune suppressive agents including anakinra, adalimumab and infliximab. The patient was ultimately diagnosed with a novel heterozygous mutation in STAT1, leading to elevated levels of phosphorylated STAT1 in peripheral blood mononuclear cells.

We propose treatment with a Janus Kinase 1 (JAK1) inhibitor which has been shown to downregulate STAT1 phosphorylation and reduce frequency and severity of CMC lesions.

A VEXING DIAGNOSIS

Dr Alice Grey[1], Dr Anthony Cheong[2], Dr Nicolás Urriola[1], Dr Frederick Lee[1] & A/Prof Stephen Adelstein[1]

1 Department of Clinical Immunology & Allergy, Royal Prince Alfred Hospital
2 Department of Medical Genomics, Royal Prince Alfred Hospital

A 74 year old previously well man presented in 2018 with auricular inflammation, hoarse voice and cough. He was diagnosed with relapsing polychondritis and commenced on prednisone. At around the same time, he developed superficial thrombophlebitis which recurred despite standard doses of anticoagulation.

These symptoms were followed by recurrent hospital admissions with bronchopneumonia, with no causative organism identified. He subsequently developed a pulmonary embolus, requiring recommencement of anticoagulation. Fatigue and persistent fevers were accompanied by progressive cytopenias, and he was diagnosed with Myelodysplastic Syndrome, ultimately becoming transfusion-dependant.

Finally, he also developed a lower limb rash that was histologically consistent with Sweet's Syndrome. Throughout the course of his illness, his symptoms have been refractory to all forms of immunosuppression with the exception of high dose corticosteroids. No unifying diagnosis could be found for his unusual constellation of symptoms, until a recent publication suggested a potential genetic cause.1

We have performed Sanger sequencing on our patient and confirmed this rare somatic mutation, making his case the first to be reported in Australia.

References: Beck at al, New England Journal of Medicine, 27 October 2020

ASCIA WA IMMUNOLOGY DAY CGR ABSTRACTS

AN UNEXPECTED CAUSE OF SEVERE ORAL ULCERATION

Dr Lisa Horgan (NSW)

Lisa Horgan[1], Sue-Ching Yeoh[1], Stephen Adelstein[1], Roger Garsia[1]

1. Department of Immunology, Royal Prince Alfred Hospital, NSW

Case presentation:

A previously well 83 year-old female of Vietnamese background, presented with a 5 month history of progressive severe oral ulceration extending to the vermillion borders of her lips. The provided drug history did not suggest SJS/TEN. Initial investigations did not reveal an infective aetiology (HSV, EBV, Enterovirus and syphilis) or an underlying primary or acquired immunodeficiency. PET imaging demonstrated distal oesophageal focal uptake however subsequent histology excluded malignancy. IIF on monkey oesophagus demonstrated weak basement membrane binding (titre 40) whereas IIF on rat bladder epithelium was negative. DIF undertaken on a lower lip biopsy was negative. However, there was an unexpected finding of cytoplasmic inclusions in endothelial and stromal cells confirmed as Cytomegalovirus (CMV) inclusions with immunohistochemistry. Additional findings of positive CMV IgG, negative CMV IgM and low positive CMV DNA suggested a novel case of primary CMV reactivation in an apparently immunocompetent patient. Clinical resolution of disease was achieved following the commencement of oral valganciclovir 900mg BD with complete sustained clinical remission at follow-up.

Discussion:

CMV is the dominant member of the virus family Herpesviridae and is an internationally ubiquitous virus with worldwide seroprevalence ranging from 45-100%.1 Primary CMV infection is typically asymptomatic or manifests with a self-limiting viraemic phase in healthy individuals. While the risk of invasive CMV infection is well recognised in immunocompromised patients2,3, relatively little attention has been given to severe CMV infection in the general population. We present a novel case of primary CMV reactivation manifesting with severe oral ulcerating disease in an apparently immunocompetent patient.

Conclusion:

This case outlines the diagnostic approach to severe oral ulceration and highlights primary CMV reactivation as a diagnostic consideration in cases of severe oral ulceration even in seemingly low-risk patients.

References:

1. Cannon MJ, Schmid DS, Hyde TB. Review of cytomegalovirus seroprevalence and demographic characteristics associated with infection. Rev Med Virol 2010; 20: 202-213.
2. Winston DJ, Ho WG, Champlin RE. Cytomegalovirus infections after allogeneic bone marrow transplantation. Rev. Infect. Dis. 1990;12(Suppl 7):S776–S792.
3. Jacobson MA, Mills J. Serious cytomegalovirus disease in the acquired immunodeficiency syndrome (AIDS) Clinical findings, diagnosis, and treatment. Ann. Intern. Med. 1988;108(4):585–594.

DYSFUNCTIONAL ADENOSINE DEAMINASE 2 (ADA2) PRESENTING WITH IMMUNE DYSREGULATION

Dr Adrian Lee (NSW)

A 44 year-old female, born to consanguineous parents, was referred to Immunology for evaluation of an immunodeficiency after suffering from recurrent sinopulmonary infections and otitis media since childhood. In more recent years, she developed a constellation of symptoms including daily non-infectious watery diarrhoea, alopecia, Raynaud's phenomena, sicca symptoms and arthralgias. After pancytopaenia was noted and developing unintentional weight loss, a bone marrow biopsy was performed which was unremarkable. Whole-body imaging revealed splenomegaly but no solid-organ malignancy.

Investigations revealed a panhypogammaglobulinaemia with an IgG of 3.2 g/L, proportionally reduced peripheral blood total and class-switched memory B cells, and suboptimal functional antibody responses to vaccines. Her autoantibody investigations were non-contributory. She was commenced on antibody replacement to good improvement of her recurrent infections. Sanger sequencing revealed a likely pathogenic homozygous frameshift mutation in adenosine deaminase 2 (ADA2) and she had undetectable serum ADA2 enzymatic levels. Both her parents were heterozygous carriers for the mutation. Extended functional studies are currently underway.

In summary, we present a rare case of ADA2 dysfunction that provides valuable insights into the complexity of the immune system.

IF THE VUS FITS… A CASE OF RECURRENT, SELF-LIMITING HLH-LIKE DISEASE

Dr Natasha Moseley (WA)

Natasha Moseley[1], Jovanka King[2] and Andrew McLean-Tooke[1,3].

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3. Pathwest, QEII, Nedlands, Perth, Western Australia

Background:

X-linked lymphoproliferative disorders (XLP), XLP1 (SAP deficiency) and XLP2 (XIAP deficiency) are relatively newly described inborn errors of immunity (IEI) which are typically associated with Epstein-Barr virus (EBV)-driven haemophagocytic lymphohistiocytosis (HLH). A clinical picture of intermittent splenomegaly, cytopenia, and fever is seen more commonly in XLP2, which occurs due to deficiency of the X chromosome-linked inhibitor of apoptosis (XIAP) protein.

Case presentation:
A 14-year old boy presented with fever, hyperferritinaemia, pancytopenia, and hepatosplenomegaly. Two similar episodes were reported previously. At 5 years of age, he presented with prolonged fever, raised ferritin, pancytopenia, splenomegaly and prominent haemophagocytosis on bone marrow biopsy. A diagnosis of HLH was not made at this stage, but the retrospective application of a H-score calculation yielded a value of 259, suggesting a 99% probability of HLH. This episode was self-resolving, managed only with intravenous antibiotics for a presumed infectious aetiology. He continued to have persistent splenomegaly with mild liver function derangement. At 12 years of age, he had a second episode of prolonged fever. No medical attention was sought, and his symptoms self-resolved after several weeks. His third episode of protracted fever and inflammatory marker elevation again resolved spontaneously after 14 days; however, on this occasion, he developed acute, progressive hepatitis with marked icterus and predominant transaminitis, responding to oral prednisolone. In addition, he developed hepatomegaly, pancytopenia, raised ferritin and mild haemophagocytosis on bone marrow biopsy, with a H-score of 195 (85% probability of HLH).
Initial immunological testing was remarkable for reduced NK cell cytotoxicity, with normal CD107a degranulation, and normal expression of perforin, SAP and XIAP by flow cytometry. However, given a high index of clinical suspicion of an underlying IEI; whole exome sequencing was initiated. A hemizygous missense mutation in XIAP was identified, which has not been previously reported in the literature, and is classified as a variant of unknown significance. Additional functional studies to support the pathogenicity of this variant are in progress.

Discussion:
This case highlights the challenges of identifying variants of unknown significance, even in patients with a compatible clinical history. We discuss the approach to seeking additional familial and functional data that may assist in confirming the pathogenicity of this VUS in XIAP.

CAPTURING THE CASTLE

Dr Claire Reynolds (SA)

Castleman's disease refers to a group of rare lymphoproliferative conditions with distinct clinical syndromes and histological patterns. These can be divided into unicentric disease and multicentric disease. Unicentric disease refers to disease limited to a single, or region, of lymph nodes, and is curable with surgical resection. On the other end of the spectrum, multicentric disease refers to systemic disease, a potentially fatal condition with extensive lymph node involvement and constitutional symptoms. Significantly elevated IL-6 levels have been demonstrated in this condition, which has allowed use of targeted anti-IL-6 therapy as a steroid-sparing agent.

We describe the case of a 54 year old female presenting with a three month history of constitutional symptoms, nephrotic syndrome, arthralgias, retroperitoneal fibrosis and widespread lymphadenopathy with initial suspicion of IgG4-related disease. Initial core lymph node biopsy was positive for plasma cells with no evidence of monoclonality. IgG4 stain was not performed, but given severity of her weight loss and night sweats, she commenced a trial of oral high-dose prednisolone, with partial response. Subsequent PET scan showed FDG avid lymphadenopathy both above and below the diaphragm with uptake also in the thyroid, bone marrow and retroperitoneal region. Excisional lymph node biopsy showed plasma cell infiltrate with no evidence of lymphoproliferative disease, and no increase in the IgG4:IgG ratio. This supported the diagnosis of multicentric Castleman's disease and she has had an excellent clinical response to IV tocilizumab and weaning steroids.

PLASMA CELLS – TOO MUCH OF A GOOD THING?

Dr Alex Stoyanov (NSW)

A 46 year old Samoan female was referred to our service with a three year history of constitutional symptoms, weight loss, arthralgia and right flank pain. Initial investigations demonstrated anaemia, polyclonal hypergammaglobulinaemia and significantly elevated inflammatory markers with an ESR of 140mm/hr and CRP of 130mg/L. Soft tissue thickening along the ureters extending around the aorta as well as mildly FDG avid para-aortic, iliac and axillary lymphadenopathy was seen on imaging. Core and subsequently excisional lymph node biopsies both demonstrated marked plasma cell proliferation but there were no architectural changes consistent with Castleman disease and staining for both human herpes virus (HHV8) and IgG4 was negative. No evidence of infection or malignancy was found. Tapering corticosteroids were initially introduced without improvement but the patient remained stable over the next twelve months with no evidence of end organ dysfunction or progression on imaging.

Unfortunately, the patient then developed progressive renal dysfunction with a rise in the creatinine to 132µmol/L associated with proteinuria and worsening anaemia. Renal biopsy demonstrated membranoproliferative glomerulonephritis with negative immunofluorescence and no evidence of amyloidosis. We suspected the patient's disease may be due to IL-6 driven polyclonal lymphoproliferation, consistent with a variant of multicentric Castleman disease or rarely described systemic plasmacytosis. Monthly tocilizumab was initiated with marked improvement in the patient's constitutional symptoms, inflammatory markers and anaemia as well as complete resolution of the renal dysfunction within four months.

Our case highlights an unusual clinical presentation and demonstrates the spectrum of polyclonal plasma cell disorders, their features and organ involvement. We discuss the diagnostic and therapeutic challenges in assessing these patients.