ASCIA 2014 Clinical Ground Rounds Abstracts

CGR1
THE MAN WITH THE DRAGON TATTOO
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Local and systemic sarcoidal reactions are rare but emerging phenomena following tattooing. Various aetiological mechanisms have been postulated, including systemic hypersensitivity to tattoo pigment or a Koebner phenomenon in a predisposed host. We describe one case from a small series with the manifestation of distant, organ-specific inflammation concomitant to tattoo involvement. This finding may provide new insights into understanding the conundrum of sarcoid pathogenesis.

A 22 year old professional tattoo artist presented in late 2013 with a 6 week history of blurred vision and bilateral ocular pain. He was extensively tattooed with a variety of pigments but had recently obtained a new black tattoo which, after initial healing, subsequently became raised and inflamed. Examination revealed bilateral panuveitis with associated disc oedema. However, serum angiotensin converting enzyme (ACE) was elevated and whole body gallium scan demonstrated increased uptake in both inguinal regions localising to lymph nodes. There was no radiological evidence of pulmonary involvement.

He was treated initially with cycloplegics and topical corticosteroids. However, there was progression of eye involvement and the development of inflammation in previously quiescent tattoos. He was commenced on high dose corticosteroids with resolution of cutaneous inflammation and partial remission of uveitis. There was ongoing flaring of eye involvement with attempted steroid weaning, despite introduction of methotrexate.

Although isolated inflammation of the uveal tract accompanying tattoo granulomas has previously been described as an entity distinct from sarcoid, this case, with associated elevations in serum ACE and evidence of nodal involvement, suggests that these phenomena may lie on the sarcoid continuum. Potential pathogenic mechanisms will be discussed.

CGR2
AUTOSOMAL RECESSIVE TRANSMISSION OF A NOVEL TNFRSF1A MUTATION IN TUMOUR NECROSIS FACTOR RECEPTOR ASSOCIATED PERIODIC FEVER SYNDROME
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Background: Autoinflammatory diseases are rare disorders characterised by inappropriate activation of antigen-independent inflammatory pathways. These include periodic fever syndromes such as Tumour Necrosis Factor Receptor Associated Periodic Fever Syndrome (TRAPS) and Familial Mediterranean Fever (FMF) which result from single-gene mutations.

Case: A 39-year-old man of Italian descent with symptoms of an autoinflammatory syndrome since age 8, with episodes of recurrent fever, arthritis, serositis and raised inflammatory markers. A clinical diagnosis of FMF had previously been made without genetic testing. Inflammatory episodes often extended beyond 2 weeks, with no response to colchicine.

Excellent response to interleukin-1 receptor-antagonist (Anakinra) therapy was observed.

One of his sisters experienced almost identical symptoms, although episodes were less frequent. His parents and other 3 sisters did not experience symptoms of periodic fever syndrome. His three children are all unaffected, as are the two daughters of his affected sister.

Genetic testing for FMF was performed in the patient, with no MEFV gene mutations identified. Further genetic testing for TRAPS revealed homozygosity for a novel missense mutation in the TNFRSF1A gene (Arg104Trp). Subsequent testing of other family members found that affected individuals were homozygous for the mutation, and heterozygote family members were unaffected. The parents of the affected siblings could not be tested, however both were unaffected and must also have been heterozygous for the mutation. The family was unaware of consanguinity; however a founder effect was thought to be possible in this case.

Conclusion: TRAPS is usually inherited in an autosomal dominant manner; however in this family inheritance appears to be autosomal recessive. The TNFRSF1A gene mutation identified has not previously been described in TRAPS. This demonstrates that the clinical manifestations and genetic mutations in TRAPS may be broader than previously realised. Furthermore, correct genetic diagnosis helps guide effective therapy, thereby helping prevent the complication of amyloidosis.

CGR3
TALE OF A HINDU PRIEST
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Background: The marking nut Semecarpus anacardium is used in Indian religious ceremony and Ayurvedic medicine. Like cashew nut, pistachio, mango and poison ivy, it belongs to the family Anacardiaceae. There are only a handful of reported cases of contact dermatitis caused by the marking nut. We report a case of anaphylaxis after marking nut ingestion. To the best of our knowledge this has never been reported before.

Case History: A 59-year-old Hindu temple priest ate a sweet at the end of a religious ceremony. Within 30 minutes he developed eye and lip swelling. He subsequently developed wheeze and stridor, which improved with adrenaline and salbutamol nebuliser. He required another dose of adrenaline-line and prednisolone at the hospital. There were no other likely allergens and no cofactors. Ingredients used to make the sweet were sought; skin prick testing was negative to cow’s milk, wheat flour, peanut, cashew, pistachio, almond, coconut, gum and watercress seed but positive with the marking nut (wheat 6 mm). He has been advised to avoid eating the marking nut in the future.

Discussion/Conclusion: Plants from Anacardiaceae have caused more contact allergy than all other plants combined. However in terms of type 1 hypersensitivity, while cashew nut allergy is common, marking nut allergy has not been described. Cross reactivity between cashew, pistachio and the marking nut might have been expected as they are phylogenetically related, but in this case the marking nut presented unique epitopes. We plan to carry out Western blotting to identify the allergenic proteins of the marking nut and compare this with known cashew and pistachio allergens. While this allergy is not expected to occur commonly in Australia, recognition is useful since it is likely to be seen in India and potentially amongst other Indian expatriates.
CGR4 CHRONIC GRANULOMATOUS DISEASE: A TWIST IN THE TAIL
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A term 2-month-old boy was admitted with history of one week of increasing neck swelling. On initial admission he was appropriately grown with low grade fever, a tender, fluctuant, erythematous right cervical mass, purulent ear discharge, oral thrush and hepatomegaly. Haemoglobin was 70 g/L, neutrophils 10.1 × 10^9/L, lymphocytes 6.2 × 10^9/L, and C-reactive protein 80 g/L. Haemoglobin fell to 53 g/L and the patient was transfused. Anti-staphylococcal antibiotics were commenced before the neck lesion discharged spontaneously, growing methicillin-sensitive Staphylococcus aureus. Abdominal ultrasound showed three hyperechoic liver lesions. Immunoglobulins were non-specifically elevated and T-cell subsets were normal. NBT and DHR were consistent with X-linked chronic granulomatous disease (CGD). Empiric antifungal therapy and oral prednisolone were commenced and the liver lesions gradually resolved, however the initial discharge he was receiving prophyactic Bactrim, itraconazole and IFN-gamma.

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CIPROFLOXACIN AN OXYMORONIC HYPERSENSITIVITY REACTION TO CIPROFLOXACIN
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We present the case of a 48-year-old man who experienced a reproducible, atypical hypersensitivity reaction following ciprofloxacin administration. The patient sustained a tibio-fibular fracture requiring surgical management with internal fixation, which was complicated by wound dehiscence and post-operative infection. Treatment included a course of intravenous tazocin and oral ciprofloxacin. He subsequently developed fever, generalised rash, arthralgia and deranged liver function tests on day five of therapy, and hence the antibiotics were ceased. The reaction was attributed to tazocin, and ciprofloxacin was reintroduced. One hour following ciprofloxacin administration, he developed fever, tongue swelling, pruritis, tachycardia and later significant hypotension, requiring intensive care unit admission. Serum tryptase was normal two hours after the onset of the reaction. He remained persistently febrile for five days, and these symptoms were attributed to sepsis in the setting of concurrent infection. Once recovered, a re-challenge with oral ciprofloxacin resulted in rapid onset of fever with rigors, generalised erythema and pruritis, thirty minutes following drug administration. A repeat serum tryptase level was again normal. He recovered within six hours with supportive therapy and administration of a single dose of steroid.

Drug hypersensitivity reactions may be classified according to their perceived mechanisms, with IgE-mediated drug hypersensitivity associated with specific clinical features with onset in the immediate phase following drug administration. Conversely, features of delayed drug hypersensitivity reactions occur several days following exposure, with a different constellation of clinical symptomatology. This case illustrates an interesting situation whereby typical features of a delayed hypersensitivity reaction occurred acutely following administration of the culprit drug: a notion which is an oxymoron in the face of currently held beliefs regarding mechanistic and typical clinical features of drug hypersensitivity reactions.

This patient’s clinical presentation, results of subsequent investigations and a discussion of possible mechanisms for this reaction will be presented.

CGR6 SLE UNEXPECTEDLY COMPLEMENTED BY A DENSER DIAGNOSIS
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We present the case of a 45 year old Vietnamese man who was admitted with new onset fevers, a pleural effusion and pancytopenia with haemolytic anaemia. He had a preceding 6 month history of cytopenias, anorexia, 20 kg weight loss, alopecia, arthralgia and rash, as well as an episode of herpes zoster. Autoimmune serology initially demonstrated 1:1280 homogenous ANA with negative ENA, dsDNA level of 173 IU/mL, low complements, elevated rheumatoid factor, and high ferritin, ESR and CRP. Investigations for an underlying haematological malignancy with skin and bone marrow biopsies were non-diagnostic. During admission, serological evolution was demonstrated, with increased dsDNA levels to >800 IU/mL and detection of SS-A (Ro 60), Sm and ribonuclear protein antibodies. Diagnosis of SLE was made and treatment initiated with prednisone.

Throughout the admission, he had persisting pleural effusions, ascites and peripheral oedema with hypobulinamenaia of 19 g/L. Echocardiogram demonstrated normal left ventricular function. 24 hr urinary protein excretion was 1.7 g with bland microscopy and normal renal function. Renal biopsy unexpectedly revealed dense deposit disease. The results of further complement studies will be presented.

Dense deposit disease is a rare condition generally described in the paediatric population. It is associated with dysregulation of the alternative complement pathway, most commonly resulting from C3 nephritic factor and mutations in complement regulatory factor H. In contrast, deficiency of classical complement pathway components Clq/r/s, C2 and C4 is associated with increased susceptibility to SLE. We will discuss this unusual case of dense deposit disease in an adult with a new diagnosis of SLE, in relation to potential complement abnormalities.

CGR7 ANGIOEDEMA AND LOW C1 ESTERASE INHIBITOR FUNCTION DURING PREGNANCY
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Background: Acquired angioedema (AAE) is characterized by adult-onset, symptomatic angioedema with C1 esterase inhibitor (C1-INH) deficiency. Hereditary angioedema (HAE) type II is characterised by angioedema from early life with persistently low C1-INH function. We report a case of adult-onset, pregnancy-associated angioedema and low C1-INH function.

Case Report: A 29-year-old woman, without a family history of angioedema or autoimmune disease, presented with recurrent episodes of angioedema of the face and hands, and abdominal pain during her first pregnancy. Her condition was not responsive to antihistamines. Serial C1-INH testing showed persistently low function (27%, 40%) but normal concentrations (291 mg/L, 237 mg/L). Autoimmune disease and malignancy screens were negative. She was diagnosed as HAE type II and treated with C1-INH concentrate for major attacks, and subsequently delivered a...
healthy infant. After delivery, her symptoms subsided and she remained symptom-free for 24 months without treatment. She reported no symptoms with her menstrual cycles. Repeat C1-INH testing after 36 months showed normal C1-INH function (86%) and concentration (225 mg/L). However, during her second pregnancy (second trimester), symmetrical angioedema recurred and C1-INH testing again showed low function (64%) and normal concentration (181 mg/L). On reconsideration, HAE type II was unlikely based on adult onset and intermittency of low C1-INH function, and the diagnosis was revised to AAE.

**Conclusion:** We report an unusual case of intermittent C1-INH dysfunction associated with recurrent angioedema in pregnancy. Oestrogen is known to be a trigger of angioedema in Type III HAE, but is thought to act independently of C1-INH. AAE, sometimes associated with B-cell lymphoproliferative disorders, is characterised by consumption of C1-INH and the presence of C1-INH autoantibodies. Intermittent C1-INH dysfunction might be explained by fluctuating concentrations of C1-INH autoantibodies.

**CGR8**

**FAMILIAL CHILBLAIN LUPUS; A FAMILY OF FOUR**

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We present a case of a non-consanguineous NZ family with an autosomal dominant genetic condition which has features of familial chilblain lupus (FCL). A male aged 24 years (M24), his sister aged 22 years (F22), and her daughter aged 5 years (F5), have a vasculitis with onset in infancy, exacerbated by cold exposure, affecting acral sites, nose, cheeks, ears, hands and feet, with no neurological deficit or organ involvement, which has been refractory to immunosuppressive treatment, and demonstrates highly variable intrafamilial severity.

F22 has relatively mild lipoatrophy of the face, and lower limb and hand vasculitis which have resulted in fixed PIPJ contractures and recurrent lower limb vasculitis in winter. Her brother, the most severely affected person in this family, has severe facial disfigurement affecting ears and nose, and amputations of all four limbs precipitated by peripheral limb ischaemia and deep infection. F6 has similar features to her mother with small joint involvement of the hands and feet which has progressed despite treatment with prednisone, standard DMARDS, anti-TNF and anti-B cell therapy.

The affected individuals have no clinical or laboratory features of connective tissue disease, and normal levels of all complement factors. They do, however, demonstrate an upregulation of interferon stimulated genes, consistent with a type I interferon driven disease. No mutations were identified in any of the currently known Aicardi-Goutières syndrome/FCL genes.

The phenotype in this family may therefore be caused by a presumed heterozygous, likely gain of function, mutation in a novel gene. The case will be presented for discussion of the difficult management problem it has posed to a range of specialties.

**CGR9**

**A RAG OF A JOURNEY: A CASE OF UNCONDITIONED HSCT FOR SCID**

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**Background:** Curative treatment for severe combined immunodeficiency (SCID) is hematopoietic stem cell transplantation (HSCT). Recent data for SCID due to VDJ recombination defects (e.g. RAG1/2) suggest a poorer outcome following unconditioned (vs conditioned) HSCT, with many such patients requiring a second (conditioned) HSCT. This case highlights critical clinical decision making with respect to type of HSCT when immediate survival of the patient is paramount.

**Case History:** We describe a 7 month old boy diagnosed with RAG1 SCID (compound heterozygote mutations) with Omenn’s syndrome phenotype who received an unconditioned matched sibling HSCT at 9 months of age. He presented with respiratory distress, erythroderma, peripheral oedema and failure to thrive. Investigations demonstrated disseminated adenovirus infection (stool, blood, BAL), PJP pneumonia (BAL) and picornavirus infection (NPA). His immune function investigations revealed a T low B-NK+ phenotype; undetectable naïve T cells, poor lymphocyte proliferation to phytohemagglutinin (PHA) stimulation, oligoclonal CD4+ T and CD8+ T cells and elevated IgE levels.

Pre-HSCT, he developed liver dysfunction secondary to adenovirus infection and autoimmune hepatitis. Due to the patient’s worsening adenovirus hepatitis despite cidofovir treatment and the fact that his matched sibling donor was adenovirus IgG positive, an unconditioned HSCT was performed. Post-HSCT, clearance of adenovirus was achieved but immune recovery was slow. As he remained clinically well, a conservative approach was adopted and immune reconstitution monitored regularly. Nine months post-BMT, he has normal T cell numbers, and increasing numbers of naïve T cells. Lymphocyte proliferation to PHA is normal. However, B cell recovery has been poor and he remains on immunoglobulin replacement therapy. T cell donor chimerism nine months post-HSCT was 90%. At present, he is off all antimicrobial therapy and immunosuppression and remains well.

**Discussion:** The journey has just begun for our patient and we continue to await with anticipation on his remarkable recovery.
CGR11
PURINE NUCLEOSIDE PHOSPHORYLASE (PNP) DEFICIENCY
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Background: Purine nucleoside phosphorylase (PNP) deficiency is a rare cause of severe combined immunodeficiency (SCID). Diagnosis can be challenging and may be delayed, resulting in significant morbidity and mortality for affected patients. Here we report a case of PNP deficiency in which diagnosis was facilitated by a urine metabolic screen inclusive of PNP substrates.

Case Report: A 23-month old boy born to non-consanguineous parents of Asian descent was diagnosed with PNP deficiency SCID at 14 months of age. This diagnosis was made following investigation of gross motor developmental delay by means of a urine metabolic screen that demonstrated the presence of increased substrates for PNP, suggestive of an enzyme deficiency. Subsequent investigations demonstrated undetectable red blood cell PNP enzyme levels and genetic testing confirmed compound heterozygous mutations of the PNP gene. Further immunological investigations were consistent with a diagnosis of PNP deficiency SCID. At the time of diagnosis, the patient was clinically well and thriving, with no significant infections. He underwent a matched unrelated bone marrow haematopoietic stem cell transplant (HSCT) at 20 months of age with a non-myeloablative conditioning regimen. Immunological investigations at day 100 post-transplant demonstrate evidence of early immune reconstitution.

Conclusion: The diagnosis of rare forms of atypical SCID can be difficult, with subsequent delay in treatment of affected patients. Here we present a case of PNP deficiency SCID in whom the diagnosis was initially suspected based on results of a urine metabolic screen. Following from this, we propose that a urine metabolic screen inclusive of PNP substrates is useful in the early identification of these children, at the time of their first presentation with developmental delay and/or neurological symptoms. This timely diagnosis, before the children become unwell with infections, facilitates earlier treatment with potentially curative HSCT.

CGR12
MONOCLONAL B-CELL POPULATION OF INDETERMINANT MALIGNANT POTENTIAL IN THE SETTING OF ATYPICAL CVID ASSOCIATED WITH LYMPHADENOPATHY AND SPLENOMEGALY
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Background: Common variable immunodeficiency disorder (CVID) is characterised by antibody production failure and classically presents by the third decade with recurrent infections. A subset of CVID patients do not suffer recurrent infections and have high rates of inflammatory, autoimmune, lymphoproliferative disorders and lymphoma. This second group faces diagnostic and management challenges and a higher mortality rate.

Case Report: A 53F was hospitalised with H. influenza pneumonia, her first major infection. Examination found lymphadenopathy and investigations revealed panhypogammaglobulinaemia. CT demonstrated endobronchial infection and hepatosplenomegaly. An axillary lymph-node (LN) biopsy found reactive hyperplasia. Investigations for autoimmune, infective and malignant causes of lymphadenopathy and/or hypogammaglobulinaemia were unremarkable. The patient was treated with intravenous immunoglobulins (IVIG), antibiotics and steroids and recovered. She was discharged and received monthly outpatient IVIG. Over a year her splenomegaly and lymphadenopathy worsened. PET scanning showed widespread metabolically active LNs consistent with lymphoma. Left axillary LN FNA cytology was suggestive of follicular lymphoma and a monoclonal B-cell population consistent with Non-Hodgkin’s Lymphoma (B-NHL) was demonstrated by flow-cytometry. Subsequent left axillary LN excision demonstrated enlarged atypical reactive follicular structures that were Bcl-2-negative. The previously described B-NHL population could not be found. Peripheral blood and bone-marrow immunophenotyping were normal. The monoclonal B-cell population described presented a management problem for the treating physicians.

Discussion: Patients with atypical CVID present with pathologies not addressed by replacement of immunoglobulins. Abnormal monoclonal populations detected by cytology and flow-cytometry may be secondary to sampling bias in atypical LNs with hyperplasia. These populations may be transient and/or of uncertain malignant potential.

Conclusion: Atypical CVID may present with significant lymphoproliferative disease and transient monoclonal B-cell populations of indeterminate malignant potential. These patients are at a high risk for lymphoma. Treatment with chemotherapy (or Rituximab monotherapy) should be weighed against careful monitoring and a ‘watch and wait’ approach.

CGR13
A CASE OF OMALIZUMAB-ASSOCIATED ANAPHYLAXIS
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We describe the case of a 46-year-old nurse with a history of severe atopy as evidenced by very high serum IgE, difficult-to-control asthma, and frequent episodes of anaphylaxis requiring adrenaline. Her triggers of anaphylaxis have included trace amounts of fish and latex protein, intravenous contrast, parental iron, and influenza vaccination, and she has also experienced episodes of idiopathic anaphylaxis. Systemic mast cell disorder was excluded with a normal bone marrow examination and baseline mast cell tryptase (MCT) levels.

Since October 2008 our patient has received omalizumab 450 mg fortnightly, with dramatic reduction in the frequency of episodes of anaphylaxis and marked improvement in asthma control. Interruptions to therapy have consistently resulted in worsening of asthma control. However, she has experienced iatrogenic anaphylaxis with every dose of omalizumab. The reaction is stereotypical, characterised by restlessness, itch, nausea and vomiting, stridor and wheeze, which are apparent 20 minutes post injection and maximal at 40 minutes. Her episodes of omalizumab-associated anaphylaxis are not associated with hypotension, elevated MCT, or complement consumption. Desensitisation was attempted but abandoned due to critical worsening of asthma control. Her reactions are now so severe that omalizumab is routinely administered with a prophylactic adrenaline infusion in the Intensive Care Unit. The pathogenesis of her reactions is unknown but there is evidence for omalizumab-specific IgE with positive skin prick testing and omalizumab specific T cells were detected by Enzyme-Linked ImmunoSpot.

Omalizumab is a humanised monoclonal IgG1 anti-IgE that binds free, but not receptor bound IgE. The reported rate of anaphylaxis to omalizumab is low at 0.09%. The mechanism by which omalizumab causes anaphylaxis is unclear; it does not cross-link IgE bound to Fc-epsilon receptors on mast cells, nor does it activate complement. We postulate a role for IgG-omalizumab complexes and are investigating the role of platelet activating factor.
**CGR14**

**PINNING DOWN THE CAUSE: AN UNUSUAL CASE OF CHRONIC EOSINOPHILIA**

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We describe the unusual case of a 25 year old female who presented with severe abdominal pain associated with marked peripheral eosinophilia (peaking at an eosinophil count of $6.05 \times 10^9/L$). This was on a background of intermittent abdominal pain for 7 years.

Gastroscopy and flexible sigmoidoscopy showed the presence of an eosinophilic infiltrate within the antral, duodenal and sigmoid biopsies. Apart from the elevated peripheral eosinophilia, other biochemical markers including celiac serology were unremarkable, and stool microscopy for ova, cysts and parasites were negative. A diagnosis was made of allergic/eosinophilic oesophagogastrenteritis and the Allergy and Clinical Immunology team was involved in her care for advice on further testing prior to her embarking on an elimination diet.

The patient described symptoms consistent with pinworm infestation. Given her rising eosinophil count, our recommendations included empirical treatment for parasites. She was prescribed albendazole and ivermectin and her eosinophilia rapidly improved. A month post her hospital admission, her abdominal symptoms and peripheral eosinophilia had completely resolved.

Repeat gastroscopy and biopsies of her stomach and duodenum showed complete resolution of the previous eosinophilic infiltrate.

This case highlights the importance of full consideration of a broad differential diagnosis, prior to embarking on a restrictive elimination diet, or considering other therapies, of eosinophilic oesophagogastrenteritis and peripheral eosinophilia.

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**CGR15**

**IPEX SYNDROME – NOT JUST A PAEDIATRIC CONDITION**

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Immune dysregulation, polyendocrinopathy, enteropathy, X linked syndrome (IPEX syndrome) is a rare life threatening disorder caused by mutations in forkhead box p3 gene (FOXP3) a key transcription factor in regulatory T cell function.

IPEX traditionally has a severe and early onset with enteritis, failure to thrive, eczema, immunodeficiency and autoimmune phenomena particularly neonatal diabetes. Without treatment IPEX is universally fatal. The only curative treatment is haemopoietic stem cell transplantation which is thought to give the best outcomes, preventing organ damage and side effects of immunosuppressive therapies.

There is significant diversity in clinical presentation and outcomes of IPEX patients with little correlation between clinical phenotypes and FOXP3 expression, T regulatory cell functional assays and genotype. The oldest survivor of this condition reported in the literature to date is 22 yrs.

We describe a case of a 61 yr old gentleman with IPEX syndrome. Our patient suffered with asthma and eczema from 6 weeks, enteropathy from 6 yrs requiring a colectomy at 15 yrs, recurrent pneumonia and oral and ocular herpes simplex. Despite this he describes having lived a full and active life. His more recent medical problems have been autoimmune haemolytic anaemia, massive splenomegaly and recurrent intestinal variceal haemorrhages.

It was not until his grandson was diagnosed with IPEX syndrome after he presented with neonatal diabetes that he was diagnosed. He was found to have FOXP3 mutation R347H with normal numbers of T regulatory cells (CD4+ CD25+ 127 low) on flow cytometry.

This case illustrates the heterogeneity in clinical manifestations of this condition, the lack of genotype phenotype correlation and should increase our awareness about IPEX syndrome in milder phenotypes and prompt testing in a wider group of patients. Given this diversity it would be valuable to find a biomarker to predict disease severity and help guide management including the need for stem cell transplantation.