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The Paediatric Immunology and Infectious Disease (PIID) Study Day and The 8th Annual Scientific Meeting of the Hong Kong Society of Paediatric Immunology and Infectious Diseases (HKSPIID)

11 July 2015

Trainee Session

Contradictory Immunological Test Results in a Baby with Suspected Disseminated BCG Disease. Is He Suffering from SCID?

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A 3-month-old boy presented with 2 left axillary nodules and multiple papular rash over 4 limbs. Disseminated BCG disease and thus primary immunodeficiency was suspected. He has unremarkable birth history and has been thriving well without any febrile illness or infections. Family history of primary immunodeficiency or childhood death was negative. Systemic examination did not show any dysmorphic features, hepatosplenomegaly, oral thrush or perianal abscesses. Chest X-ray showed the presence of thymus. Complete blood picture showed normal white cell count with lymphocyte count of 6.9 x 10^9/L. However, lymphocyte subset revealed reduced number of T cells (CD3/CD4/CD8), B cells (CD19) and NK cells (CD16/56). Is this child suffering from immunodeficiency?

Key issues for discussion

1. How to proceed when there is contradictory immunological test result.
2. Possible immunodeficiency for papulonecrotic tuberculid.

Discussion and suggestions raised by the expert panel:

- As part of the workup, ultrasound of the liver and spleen should be considered to exclude disseminated BCG.
- The initial lymphocyte subset showed a falsely low T-cell, B-cell and NK-cell counts. The first thing in interpreting lymphocyte subset is to add up the T-cells, B-cells and NK-cells to see if the sum is approximately equal to the absolute lymphocyte count.
- The overall clinical picture is likely to be hypersensitivity reactions to BCG vaccine, rather than BCG disease. The panel suggested that this might be a variant of immune response to BCG, thus representing another spectrum of clinical manifestations to BCG vaccination.

An Infant with Diffuse Maculopapular Rash and Ulcerated BCG Scar

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Our case is a Chinese boy who born from non-consanguineous parent at full term with BW 3.05 kg. His elder brother died of CMV hepatitis and multi-organ failure at 89 days old. Mother's maternal uncle died in early infancy.

He presented at 5.5 months old for one day fever and a week of coryzal. He also had worsening rash for 2.5 months characterised by pustular discharge then ulceration of BCG site followed by rash over left anterior chest, spreading to trunk, neck and limbs.

On examination, his growth was at 10th percentile. There was pallor, diffuse maculopapular rash with some pustules, scabbed BCG site and hepatosplenomegaly. Blood test showed marked hypochromic microcytic anaemia (Hb 4.7 g/dL), lymphopenia 0.4 x 10^9/L, neutrophil 7.7 x 10^9/L, platelet 156 x 10^9/L, blood smear with toxic granulation of neutrophils and no blast cell, elevated C-reactive protein 212 mg/L. Chest X-ray showed diffuse bilateral patchy infiltrates. Ultrasound abdomen revealed multiple hypo-echoic lesions in liver and spleen. He was covered with ceftriaxone, ganciclovir and transfused CMV negative blood.

Further investigations showed CMV pp65 antigen, urine

DEAFF test for CMV, measles and rubella IgM, blood PCR for parvovirus B19, EBV VCA polyvalent, anti-HIV 1 and 2 antibody, blood culture were all negative. Bone marrow sample was inadequate. CSF examination was normal. AFB smear of peripheral blood, bone marrow and BCG site were positive. PCRs for mycobacterium bovis from above sites were positive.

He deteriorated quickly with respiratory failure requiring mechanical ventilation. Anti-bacterials were escalated to vancomycin and meropenem. Isoniazid, rifampicin, ethambutol, amikacin, intravenous septrin were started. Further workup showed BAL AFB smear was positive while negative for PCP. Intravenous levofloxacin and empirical amphotericin were added. He further deteriorated with persistent high fever, pulmonary hypertension and multi-organ failure. He died of disseminated BCG disease 12 days after admission despite intensive care.

Immunoglobulin pattern showed low IgA <0.15 g/L, IgG 0.79 g/L (2.05-9.48) and IgM <0.1g/L. Lymphocyte subset showed absence of T and NK cells with presence of low numbers of B cells: CD3 6/uL (1800-3300), CD4 4/uL (900-2300), CD8 4/uL (700-1500), NK cells (CD 16/56) 1/uL (300-800), CD19 226/uL (700-1700). Lymphocyte proliferation essay showed impaired lymphocyte proliferation: unstimulated 45913 cpm/10^6 cells (control 2287), PHA 7160 cpm/10^6 cells (control 114733), ConA <1 cpm/10^6 cells (control 67140), PWM 4447 cpm/10^6 cells (control 30193). Overall picture was compatible with T-B+ severe combined immunodeficiency. Genetic study confirmed mutation in IL2RG gene in the child and mother was a heterozygous carrier. Genetic counseling was offered.

Key issues for discussion

1. Differential diagnosis of diffuse maculopapular and pustular rash in suspected immunodeficient patient
2. Disseminated BCG disease and immunodeficiency

Discussion and suggestions raised by the expert panel:

- The elder brother died of CMV hepatitis, which is an unusual disease in normal children. This should prompt the consideration of an underlying primary immunodeficiency.
- Two opportunities for earlier diagnosis were possibly missed and lessons learnt: 1) careful history taking and proper investigations for the elder brother and 2) history taken upon the admission of the index patient, diagnosis of BCG disease, low absolute lymphocyte count, and absent thymic shadow on chest X-ray.
- By default, BCG is a test of the immune system. However, one can't rely on history taking before BCG vaccination which is a universal policy at newborn period.

A Down's Syndrome Child with Recurrent Respiratory Tract Infections

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WPS is a 2-year-old Down's syndrome boy with recurrent pneumonia at 4, 8 and 11 months old. At 11 months old, he suffered from severe Respiratory Syncytial Virus pneumonitis with hypoxia and ventilatory failure requiring PICU admission. Tracheal aspirate at that time isolated *Pseudomonas Aeruginosa* and *Stenotrophomonas Maltophilia*. Since then, he had been having recurrent rhinovirus/enterovirus respiratory tract infections at 15, 16 and 19 months. Repeated CT thorax showed that he had persistent bilateral extensive subpleural lung cysts suggestive of advanced honeycombing/fibrotic change. He previously required nocturnal oxygen supplement but was recently weaned off. Currently he still has recurrent wheeze, mainly viral induced, and has been put on flixotide and septrin.

Immunologic workup for this boy revealed normal immunoglobulin pattern, complement level and CBC profile. His lymphocyte subsets showed low CD19 level and NK cell level and slightly elevated CD3, CD4 and CD8 levels. His anti-HBs antibody level was low at 11-month old, and became negative at 20-month old. However, his anti-polio antibodies were initially at low level at 11-month old, but rose to a normal/high level at 20-month old, around 2 months after the booster vaccine was given. His ALT had been persistently elevated; however extensive workup was negative except for slightly elevated plasma cell-free EBV DNA level (level of 22).

In conclusion, WPS is a child with suspected common variable immunodeficiency/dysgammaglobulinaemia who presented with recurrent respiratory tract infections. He has persistent mildly abnormal lymphocyte subsets, but his antibody titers in response to vaccination were indeterminate. Our plan would be to start him on regular intravenous immunoglobulin infusion if he shows poor antibody response to a repeated booster dose of Hep B vaccine at a later stage.

Key issues for discussion

1. Diagnostic challenge
2. Possible further investigations to confirm diagnosis
3. Management plan to prevent recurrent infections

Discussion and suggestions raised by the expert panel:

- Prophylaxis with septrin or azithromycin can be considered for recurrent infections
- An easy rule on lymphocyte counts in neonate and infants:

total lymphocyte count is 2/3 of normal total white cell count; 2/3 of lymphocytes are T-cells; 2/3 of T-cells are CD4 T-helper cells.
- This patient has low B-cells: follow-up with serial lymphocyte subset is recommended.

GMT Syndrome – Growth Hormone Deficiency with Selective IgM and T Cell Deficiency

GT CHUA

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Clinical presentation: We present a 5 year old boy with birth history of congenital pneumonia requiring ventilator support and intravenous antibiotics. He later developed recurrent acute bronchiolitis and pneumonia throughout infancy and childhood requiring hospitalisations. He was also found to have isolated low percentile in body length since 9 months old.

Investigations and results: Microbiological workup showed recurrent chest infections with encapsulated organisms including *Streptococcus pneumoniae* and *Haemophilus influenzae*. Repeated chest X-rays showed pneumonic changes in both lungs and CT thorax showed bronchiectasis with collapse consolidations of the right middle and left lingular lobes. Exhaled nasal nitric oxide (NO) test demonstrated decreased exhaled nasal NO. Immunological workup revealed selectively and persistently low levels of IgM; low CD3, CD4, CD8, NK cells levels; and impaired lymphocyte proliferation. Endocrinology investigations including clonidine stimulation test and glucagon stimulation tests confirmed growth hormone deficiency. Ongoing clinical observation and assessment also revealed soft dysmorphism, global developmental delay and autism spectrum disorder.

Management: Inhaled bronchodilators and corticosteroid were prescribed for his reactive airway, along with regular chest physiotherapy and nebulised saline to facilitate sputum clearance. Early and aggressive management of respiratory tract infections with oral antibiotics and prophylaxis with azithromycin have been given. However, antibiotic resistance was recently encountered requiring use of intravenous vancomycin against resistant strain *Streptococcus pneumonia* serotype 19A, and changing the prophylactic antibiotics to co-trimoxazole for *Haemophilus influenzae* prophylaxis. Regular intravenous immunoglobulin (IVIg) was also given resulting in reduced pulmonary infections and sputum production. However, he developed pneumonia towards the end of the course of IVIg requiring more frequent IVIg adminstration. Weekly subcutaneous growth hormone injections were given for his growth hormone deficiency with satisfactory improvement in growth velocity. Trainings were offered from allied health with regards to his global developmental delay and autism spectrum disorder.

Unresolved issues for discussion: This patient has an atypical presentation of T-cell dysfunction and selective IgM deficiency, in combination with growth hormone deficiency and neurodevelopmental problems. Apart from recurrent pneumonia caused by encapsulated organisms, there were no other recurrent serious infections caused by other organisms. Management of his condition became challenging as he required more frequent IVIg administration and development of chest infection caused by of resistant strain pneumococcus. Ongoing investigations will focus on establishing a definitive diagnosis and exploration of potential syndromal diagnosis by gene studies. So far, combination of growth hormone deficiency, T-cell and selective IgM deficiency has not been reported in the literature. We propose a potentially novel immunodeficiency syndrome – the GMT syndrome.

Key issues for discussion

1. How to investigate the underlying genetic cause of this GMT syndrome?
2. Why our patient with selective IgM and T cell deficiency had recurrent chest infections almost exclusively by encapsulated organisms?
3. What will be the next step of management?

Discussion and suggestions raised by the expert panel:

- Further investigations including IgG subclass was suggested, though might be difficult while on IVIG replacement.
- Growth hormone deficiency is a known, though uncommon association with X-linked agammaglobulinemia. The exact pathogenetic link between growth hormone deficiency and primary B-cell defect is unknown but might be relevant in this case.
- It is worthwhile to ask the radiologist to review the X-ray on long bones in this patients, and to watch out for possibility of immune-osseous syndromes such as cartilage hair hypoplasia.

A Case of Disseminated Aspergillosis in a Patient with Chronic Granulomatous Disease

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Chronic granulomatous disease is caused by an inherited defect of phagocyte nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, leading to defective intracellular killing of pathogens. It is characterised by recurrent bacterial and fungal infections. We present here a case of disseminated aspergillosis with uncommon involvement of brain and muscle.

Our patient presented at 1 month of age with perianal abscess, pulmonary tuberculosis and aspergillosis required right lobectomy. He was given a long course of anti-fungal and anti-tuberculosis treatment. Bone marrow transplant with matched unrelated donor was performed twice but both failed engraftment. Subsequently, he was put on itraconazole, co-trimoxazole and gamma interferon prophylaxis. He had history of recurrent perianal abscess, lymphadenitis, peritonitis and ruptured appendicitis. At the age of 17, he presented with chest pain, shortness of breath and fever for 2 days. CT scan of thorax showed collapsed segment of right upper lobe, focal consolidation over right upper lobe and left lingula, small nodules over bilateral lung fields. Blood culture, Bronchoscopy and bronchoalveolar lavage microbiology did not reveal positive findings. MRI brain showed thickened pituitary stalk with uncertain significance. Fever went down with antibiotics but hypothermia and hypotension was noted while patient remained asymptomatic. His ESR remained elevated (~100).

Three months later, he presented with left thigh pain and a painful skin nodule over abdomen. Physical examination showed a 2 cm x 3 cm subcutaneous mass over right lower quadrant and vague swelling over left groin region. Empirical ceftriaxone was started. MRI showed inflammation of left iliacus and iliopsoas muscle. In view of possible tuberculosis spondylitis as a cause of iliopsoas and iliacus infection, anti-tuberculosis treatment with rifampicin, isoniazid, pyrazinamide and ethambutol were started. MRI spine came back to be normal. He subsequently developed headache with no neurological deficit. MRI showed multiple small abscess at left parietal and occipital region, with associated pachymeninges changes, gross vasogenic oedema causing mass effect. Vancomycin and dexamethasone was started. Incision and drainage of brain abscess was performed. Brain tissue, needle aspiration of abdominal nodule, iliacus and iliopsoas all grew aspergillus fumigatus. Acid-fast bacilli smear and bacterial were negative. CT thorax showed collapse consolidation in right upper lobe appeared increased in size compared with previous scan. Itraconazole was changed to voriconazole and Amibisome. Anti-tuberculosis treatment was stopped. He was transferred to tertiary centre for further management.

Key issues for discussion

1. Choice of anti-fungal agents in case of disseminated aspergillosis with central nervous system involvement and the use of steroid in this situation
2. The role of a third stem cell transplant for this patient
3. The role of long term interferon prophylaxis

Discussion and suggestions raised by the expert panel:

- The goal of management for this patient is to clear as much infection as possible. Double antifungals are needed. A combination regimen consisting of voriconazole (for its CNS penetration) and micafungin (clearance of fungal load) was suggested.
- To prepare for a definitive procedure with better environment for engraftment, inflammation should be controlled with a low dose prednisolone (0.5 mg/kg) and stopping interferon-gamma therapy was suggested.
- This patient definitely needs a definitive procedure with haematopoietic stem cell transplantation. A reduced intensity conditioning regimen with busulphan with pharmacokinetic monitoring, fludarabine and ATG was suggested. Granulocyte transfusion should be considered during the neutropenic period.

The Role of Nurse Practitioner in Educating Parents on Subcutaneous Immunoglobulin (SCIG) Administration – The First Experience of Home-Based Immunoglobulin Replacement in Hong Kong

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A baby boy was diagnosed to have X-linked agammaglobulinemia (XLA) at the age of 2 months, based on an extensive family history of XLA and known maternal carrier status. He was started on intravenous immunoglobulin (IVIG) replacement at 3 months. The option of subcutaneous immunoglobulin (SCIG) replacement with 20% human immunoglobulin preparation was offered to parents, and they

agreed to proceed with this form of treatment on a self-financed basis. The medication was imported on a named-patient basis and at the age of 4.5 months, the patient received the first dose of SCIG infusion in the hospital day care unit. The infusion (1 gram, in 5 mL) was administered to the anterior thigh uneventfully. Subsequently, parents were trained by an Advanced Practice Nurse (APN) for home SCIG therapy, using a step-by-step guidance note providing clear instructions on preparations (the child, the environment and collecting the equipment and consumables), handwashing and clean technique, checking and drawing up the immunoglobulin solution, inserting and securing the needle, monitoring and completion of infusion. Parents were educated on recognising adverse reactions and how to manage such a situation. After demonstration, parents are observed to perform each step closely with immediate feedback given. Comments were written down on the training log, which is compiled into a patient-held record including a calendar of infusion dates, adverse events, blood test results, growth charts, correspondence with primary care paediatricians and emergency contact numbers. Parents attained competence in knowledge and competence, which remained highly satisfactory on follow-up review. The patient is now 26 months, and comes to the hospital for clinical review once every 3-4 months. Currently, he is receiving 2 grams (10 mL) of SCIG every 10 days, equivalent to a requirement of 0.4 gram/kg every month. Apart from one episode of influenza A, he is free from infections and his pre-dose serum IgG has been well maintained at 0.8-0.9 g/L. He attends pre-school and makes excellent progress. His parents and extended relatives perceived a much better quality of life and health status compared to his uncles who need to travel to the hospital every month for IVIG infusion and suffer from breakthrough infections. This is the first case of home-based SCIG replacement in Hong Kong and we demonstrate success in educating and empowering parents to manage their child with a major primary immunodeficiency, right from early infancy.

Key issues for discussion

1. Is 2-weekly administration of SCIG recommended for school-aged children? Should weekly administration be always regarded as the standard?
2. Now that the SCIG infusion was administered by parents during sleep time without the notice of the patient, how should we make the transition to empower him to participate and take charge of his own SCIG infusion as he grows older?

Discussion and suggestions raised by the expert panel:

- In the UK, 87% of patients requiring immunoglobulin replacement are using SCIG
- There is good evidence to support the use of SCIG for better therapeutic efficacy and lifestyle adjustment
- The production of educational video is very helpful to demonstrate the steps in administration of SCIG.

Pyrexia of Unknown Origin in a 1-year-old Girl

H MAO

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In November 2014, a 1-year-old girl presented to us with recurrent fever for 3 months. The patient had lymphopenia (ALC 800/ul with 12.6% CD3T, 5.95% CD3CD4T, 1.82% CD3CD8T, 54.26% CD19B and 35.5% CD56 NK cells) and low immunoglobulin level. Lymphocyte subset analysis showed T-B+NK+ phenotype. Target gene IL7Ra sequencing was performed while no mutation was identified. Exome sequencing of customerised PID-related genes was offered and in progress. The working diagnosis was combined immunodeficiency. Extensive microbiology workups were done with no positive result, except high copies of EBV DNA load were detected in the blood and nasopharyngeal aspirate. Inflammatory markers including CRP and PCT were mildly increased. Serial CXR and CT thorax suggested inflammatory infiltration and progressive space-occupying opacities. Lung biopsy was offered but refused by the parents. Broad-spectrum antibiotics and antifungals were initiated. Isoniazid and rifampicin were also started as the patient received BCG vaccination. However the fever persisted. She developed left-sided convulsion. MRI brain showed cerebellar lesion. Finally lung biopsy was performed and histology indicated the presence of AFB, while immunohistochemistry staining revealed EBV-associated B cell lymphoproliferation, and features of progression to diffuse large cell lymphoma. Antibiotics and anti-fungal drugs were stopped. Instead, ethambutol and clarithromycin were added. The fever came down gradually. Chemotherapy with rituximab plus COP was further started for the treatment of lymphoproliferative disease. After three cycles of chemotherapy, EBV was not detected and repeated CT thorax showed the size of lung lesion was reduced. Bone marrow transplantation option was offered to the parents and a full matched sibling was identified. Now the patient is stable, and waiting for the transplantation after completion of chemotherapy.

Key issues for discussion

1. Would she need any conditioning for the transplantation?
2. What is the nature of the cerebellar lesion, mycobacterial disease or B cell lymphoproliferative disease, or both?

Discussion and suggestions raised by the expert panel:

- One message from this case was that an aggressive approach to obtain biopsy for pathology and pathogen identification should be adopted early in the investigation
- The use of next generation sequencing is an increasing challenge in the clinical setting: one thinks that technology can help life to be sorted out but actually it makes life more difficult, as it is difficult to ascertain what variants mean. In silico prediction is one way to help, but in the end, functional assays in the biological system are the ultimate way to prove or disprove, thus coming back to the clinicians to do more work!

A Case of Preterm Newborn with Haemophagocytic Lymphohistiocytosis and Complicated Maternal History

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A 35 week preterm newborn, with birth weight 2.445 kg, had 4 episodes of severe sepsis on day 7, day 15, day 34 and day 50 of life. She presented with fever, skin rash, and hepatosplenomegaly. The septic episodes were complicated with septic shock, respiratory failure and liver function impairment, which required multiple prolonged antibiotics use, inotropic support, repeated blood products transfusion, ventilator support and prolonged intensive care. Investigations showed a picture of pancytopenia, very high ferritin and hypofibrinogenemia. Diagnosis of haemophagocytic lymphohistiocytosis (HLH) was made on day 19 and treatment was initiated on day 20 according to protocol HLH-2004.

Mother has past history of pulmonary tuberculosis, presented with left pleural effusion, and completed treatment in 4 years ago. She is a known hepatitis B carrier. She had pyrexia of unknown origin, rash and arthritis since 32 weeks of gestation. Fever persisted after delivery and extensive workup was performed. A clinical diagnosis of maternal Still's disease was made by rheumatologist. Subsequently, NSAID and steroid were given after delivery and had a good response. However, on day 35 of life of patient, mother was reported to have tuberculosis. PET scan that performed during the extensive investigations showed a pancreatic nodule. Fine needle aspiration of the nodule yielded acid fast bacilli under microscopy. Anti-tuberculosis treatment was initiated after the diagnosis of reactivation or re-infection of tuberculosis made.

To look for any congenital infection for patient, various investigations were performed and shown no evidence of tuberculosis infection. These included placental histology, cerebrospinal fluid, early morning urine, gastric aspirate and bone marrow for acid fast bacilli, CT thorax, abdomen and pelvis. Immunity checked up was performed. Lymphocyte subset were taken on day 19 (during septic shock), day 40 (just recover from sepsis) and day 82 (1 month after septic episode) and all reported B cell (CD19=0%) and NK cell (0.4-3.8%) were low.

After reviewing the patient's condition with microbiologist, intensive care team and respiratory team, anti-tuberculosis treatment commenced as there was a possibility of acquiring tuberculosis from mother. Currently, patient has recovered from the severe septic episodes. She is receiving HLH and anti-tuberculosis treatment and condition has been stabilised.

Key issues for discussion

1. Is the HLH triggered by the "TB infection" or familial?
2. Any underlying immunodeficiency syndrome serves as trigger of HLH?

Discussion and suggestions raised by the expert panel:

- Certainly HLH can be triggered by TB
- Suggested anti-TB regimen when there is deranged liver enzymes: ethambutol, quinolones and aminoglycosides. These drugs do not affect liver enzymes, and can be continued till ALT returns to normal, then gradually re-introduce isoniazid, then rifampicin.
- It is very unusual to have HLH in neonates. For the moment, treatment is the same whether it's primary or secondary HLH.
- Follow-up with serial lymphocyte subset is needed for absent B-cell count.

An Unusual Presentation of Severe T-cell Immunodeficiency

KN Cheong (PIID Trainee)

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A 15-year-old Indian boy born to consanguineous parents, presented to us initially at the age of 10 years for work up of chronic lymphopenia (0.2-0.25 x 10^9/L).

He had been born full term, not small-for-age, with uneventful postnatal course. Congenital hydronephrosis on antenatal scan resolved without sequelae. There was no family history of immunodeficiency or sudden death, and he had 2 healthy brothers aged 17y and 3y. Vaccinations had been given uneventfully according to the HK schedule.

On reviewing his previous tests, lymphopenia had been present since infancy (0.8 x 10^9/L at 7 months and 0.7 x 10^9/L at 14 months). Asthma had been diagnosed since 6 months of age, which was poorly controlled on Becotide and Singulair. At 10 years old he had an uncomplicated course of chickenpox, but developed frequent asthmatic exacerbations due to recurrent pneumonia (usually sputum positive for *H. influenzae*). CT Thorax showed no features of bronchiectasis, but lung function tests showed mild restrictive pattern. He also developed warts in his right little and middle fingers. Growth was satisfactory with body weight along the 25th percentile and height along the 10th percentile. He had normal development and unremarkable systemic examination.

Bone marrow examination and microbiological workup (including HIV) were negative. Serum Immunoglobulins and functional antibody levels (polio and hepatitis B) were within normal range. Lymphocyte subset showed severe T cell lymphopenia - CD3+ 80/μL (1100-2000), CD4+ 55/μL (600-1600), CD8+ 9/μL (500-1200); with low B cells 60/μL (200-600) and NK cells 73/μL (300-600). Genetic study for STK4 was negative.

Whole exome sequencing found the patient to have homozygous mutation c. G95C, p.G32A for PNP deficiency. Enzyme assays done in the UK with healthy controls found low RBC PNP for the index patient, his younger brother, and mother (lowest in the index patient, although around 10% residual enzyme activity compared to normal controls). Platelet PNP activity was also low in him and his younger brother. Purine metabolites inosine, deoxyinosine, guanosine, and deoxyguanosine were detected in the patient's urine indicating a blockade in convsersion to xanthine and hypoxanthine; although urinary xanthine, hypoxanthine and uric acid were also present. The patient had normal serum urate 292 μmol/L (ref: 135-430 μmol/L).

The patient was started on septrin prophylaxis and continued to run a stable clinical course, with only mild viral respiratory infections and 2 uncomplicated episodes of *H. influenzae* pneumonia treated with oral antibiotics since.

Key issues or discussion

1. The patient had a relatively mild disease phenotype with no evidence of frequent severe infections, neurological abnormality, or autoimmune phenomenon (e.g. vasculitis) usually seen in PNP deficiency (T-B+NK+). He also had a normal serum urate level and an estimated 10% residual PNP enzymatic activity compared with normal controls, suggesting a hypomorphic mutation.
   To compare with clinical and immunophenotypes of other reported cases of partial PNP deficiency in current literature.
2. What would be the natural course and prognosis for this patient, and the implications on management?
3. Approach to workup of suspected immunodeficiencies presenting with lymphopenia.

Discussion and suggestions raised by the expert panel:

- Long-term prognosis is probably uncertain in this case, a wait and watch approach is appropriate for the moment
- The immunological abnormalities are relative mild in this case, and continuation of prophylactic antibiotic treatment is appropriate
- Neurological abnormalities in PNP deficiency are usually not progressive, and the indication for haematopoietic stem cell transplant is for immune reconstitution and not for rescue of neurology
- The decision for transplant should be guided by the clinical picture, not the numbers in immune tests!

Annual Scientific Meeting

The Roland Levinsky Memorial Lecture: 'SCID: from 100% Mortality to 100% Survival in 50 Years?'

HB Gaspar

Professor in Paediatric Immunology, Institute of Child Health, University College London, UK

Severe combined immunodeficiency (SCID) is a devastating condition characterised by the complete lack of adaptive immunity. Affected children are susceptible to recurrent severe infections and without intervention the outcome is uniformly fatal. Prior to 1968, the condition had a 100% mortality. The advent of bone marrow transplantation transformed the outcome for these children and over the decades the survival rates have improved progressively with greater than 90% survival in some SCID forms if a matched sibling donor is used. The increasing understanding of the genetic basis of the SCID type has also allowed the development of novel gene therapies, whereby vector mediated genetic correction of autologous bone marrow progenitors can allow recovery of lymphoid development. IN some forms of SCID, gene therapy has now led to 100% survival with very high rates of efficacy. Another major development has been the introduction of newborn screening which means that babies are now identified at birth and protected and then undergo an early transplant or gene therapy.

Together these developments have the potential to transform a previously uniformly fatal condition into one where all children have a very high chance of a life-long cure.

The Bill Marshall Memorial Lecture: 'Vaccination: Successes, Hurdles and Failures'

S Plotkin

Emeritus Professor of Paediatrics, The University of Pennsylvania, USA

Vaccines have generally been highly successful in eliminating the infections against which they are developed, but today we face the need to develop vaccines against complex disease and to improve partially successful licensed vaccine.

Influenza – Vaccines against influenza are moderately protective in children and young adults but poorly protective in the elderly. Efforts are being made to add conserved antigens to the classical hemagglutinin-based vaccines in order to augment protection.

Pertussis – Immunity against acellular vaccines wanes with time and adolescents and adults have considerable breakthroughs. Even whole cell vaccines do not give permanent immunity. Thought is being given to reformulating pertussis vaccines with stronger adjuvants or additional pertussis antigens.

HIV – A vaccine trial in Thailand gave a low level of protection but importantly showed the importance of antibody-dependent cellular cytotoxic antibodies. Efforts are directed at improving ADCC responses but also to elicit broadly neutralising antibodies and effector CD8+ T cells.

Rotavirus – Live rotavirus vaccines have had extraordinary success in developed countries, where individual protection and herd immunity are induced. However, efficacy in developing countries has been lower and efforts are being directed towards identification of the inhibitory factors in those countries.

Dengue – Dengue infection occurs in large parts of the world. Multiple vaccines are being tested to prevent disease and hospitalisation. One vaccine has already shown considerable protection against the latter but there are yet unexplained variation in protection against different serotypes.

Respiratory syncytial virus – Much effort is directed against this virus prevalent in infancy, but held back by the disastrous results of a trial conducted in the 1960s. The recent discovery of an unappreciated structure of the Fusion protein of the virus has reawakened interest.

Meningococcal – We now have vaccines against all the major serogroups of these bacteria, thanks to the strategy called reverse vaccinology. Control of meningococcal disease is now possible if the vaccines are properly used.

Group B streptococcus – A vaccine that would be given to mothers late in pregnancy is now in advanced development.

Ebola – In response to the devastating epidemic in West Africa, numerous candidate vaccines are now available based on the viral glycoprotein.

Despite progress, there are numerous unsolved problems in vaccinology that are retarding development of effective vaccines against HIV, tuberculosis and malaria.

Patient Advocacy: Making a Difference – Patient Advocacy for Primary Immunodeficiency Disorders

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A disease is defined as rare by the European Commission on Public Health when it is life threatening, chronically debilitating and affects fewer than 1 in 2,000 population. The minimal prevalence of primary immunodeficiency disorders (PIDs) is estimated to be 2-5 per 100,000 population. As PIDs are so rare, the probability for clinicians to meet a patient with PID during their medical training and clinical practice is quite low. The chance of encountering a case of PID in graduate and professional examination is slim, which is also in part related to the fact that PIDs are given low priority in the undergraduate medical curriculum and training at the postgraduate level. Raising awareness on PIDs among the healthcare professionals, policy makers and the general public remain the most critical issue to ensure early diagnosis, timely treatment and optimal outcome of these patients. As PIDs are chronic disorders which require lifelong treatment unless the underlying defect is corrected, the needs and interests of patients should be recognised. Patient organisation provides them with the visibility and voice, and constitutes a platform for key stakeholders (patients and families, healthcare professionals, industry and policy makers) to work for better service provision and delivery of care. This year, we celebrate the birth of PID League, a territory-wide patient organisation in Hong Kong, which is a fruit of nearly 30 years of efforts in building up a specialist service for PID. We witness the motivation and determination of patients and their families not just in coping with their illness, but also on mutual support, experience sharing and striving for better therapies that they need to live a more productive life. The main challenges ahead for improving PID care in Hong Kong include funding for orphan drugs, central diagnostic facilities and transitional care. Achieving these goals will be in the best interests of patients, for healthcare systems and society as a whole.