CASE REPORT

Severe Combined Immunodeficiency Disease with Features of Haemophagocytic Lymphohistiocytosis: A Case Report

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ABSTRACT

Severe combined immunodeficiency (SCID) is the foremost extreme frame of primary immunodeficiencies. We described a case report of a 23-month-old boy who presented with pyrexia of unknown origin (PUO) with initial findings suggestive of haemophagocytic lymphohistiocytosis. Physical examination showed unremarkable findings apart from hepatosplenomegaly. The diagnosis of SCID was established from lymphocyte enumeration testing by flow cytometry which revealed a phenotype of T(-), B(-), NK(-) and hypogammaglobulinaemia. The confirmatory genetic test was unable to be performed as the patient's condition rapidly deteriorated and he succumbed to the illness.

Keywords: SCID, HLH, Primary immunodeficiency

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INTRODUCTION

Severe combined immunodeficiency (SCID) exists as a group of inherited disorders characterised by impeded in T lymphocyte differentiation. Intact T cell function is essential in antibody production by B cells. The absence of T helper cells in SCID leads to defective B cells antibody responses, resulting in combined defects affecting both cellular and humoral immunity. SCID patients generally succumb to death in the first 12 months of life if they did not receive curative treatment. Hence, it is considered the foremost extreme types of primary immunodeficiency (PID).

Haemophagocytic lymphohistiocytosis (HLH) is classified as diseases of immune dysregulation by the International Union of Immunological Societies (IUIS) Expert Committee of Inborn Errors of Immunity. It is characterised by uncontrolled immune activation, especially macrophages and production of proinflammatory cytokines such as interferon-γ, interleukin (IL)-6 and IL-10 (1). The diagnosis of HLH is established using the HLH-2004 diagnostic criteria where a minimum of five out of eight criteria is required. The association between HLH and PID implies that impairment in T-cell functions is one of the contributing factors in the development of HLH. In infections, defect of T-cell functions in PID enhances HLH progression due to failure to control excessive inflammatory responses leading to cytokine storm. Previous studies reported several SCID mutations in HLH, for example defects in IL-2 receptor gamma, RAG1, IL-7 receptor alpha and CD3 epsilon (2).

In Malaysia, PID prevalence rate was 0.37 per 100,000 population which was lower than other countries (4.4–20.27 per 100,000 population) (3). This value might not indicate the actual prevalence in Malaysia as the PID cases were underdiagnosed and underreported. Most cases may fail to be detected in the primary healthcare setting as they often presented with common infections in childhood. Nevertheless, increasing awareness of this disease has led to an increase in the number of cases being reported recently. Study by Abd Hamid et al. on PID in Malaysia revealed SCID as the most commonly reported type of PID, with seven genetic mutations described; IL2RG, IL2RG c.270-2A>T, ADA, PNP, TTC7A and ZAP70 (3).

The major clinical manifestation in PID is increased susceptibility to infection. PID predisposes affected

patients to severe infection and immune dysregulation which led to conditions such as autoimmune disorder and malignancy. In this report, we describe a case of SCID presenting with PUO and features suggestive of HLH.

CASE REPORT

A 23-month-old boy with no history of prior hospitalisation presented with persistent fever of more than 38.5°C for one month duration. The fever which occurred especially at night was associated with chills and rigors. Other than that, there was no respiratory, gastrointestinal or urinary tract symptoms. The family denied any history of tuberculosis contact. The child also did not have history of recurrent ear infections, skin rashes, loss of weight or loss of appetite. He was otherwise growing well with normal developmental milestones. No family history of consanguinity was reported.

On physical examination, the child was active and not septic-looking. His development was appropriate for age, growing along 10th to 25th centile for both height and weight. However, hepatosplenomegaly was noted. Initial blood investigations showed anaemia (haemoglobin 6.9 g/dL), lymphopenia (lymphocyte absolute count 0.94 x 10^{9}/L), thrombocytopaenia (40x10^{9}/L) and deranged liver enzymes (AST 689 U/L, ALP 148 U/L, ALT 87). A full work up for PUO revealed no suggestive cause. However, patient fulfilled five out of eight criteria for HLH which include persistent fever of more than 38.5°C for more than one week, splenomegaly, high triglyceride (5.78 mmol/L), high serum ferritin (943.9 µg/L) with cytopaenias.

He was referred to our tertiary centre for further investigations and management. In view of pancytopenia, full blood picture and bone marrow aspiration were performed. However, the results were not suggestive of leukaemia. Apart from that, an extensive infective screening including microbiology and virology investigations were done. However, all cultures came back as negative without positive isolate. His fever persisted despite given multiple courses of antibiotics. Acid fast bacilli smears were also negative. In short, all the investigations results were not suggestive of infections and a further workup and re-evaluation of the condition was required.

Considering the diagnosis of PID, he was then referred to a paediatric immunologist in our centre. Further immunological testing revealed reduced serum IgG, IgA and IgM levels (hypogammaglobulinaemia) (Table I) with T(-),B(-),NK(-) phenotype on flowcytometry (Table I). In view of possible SCID, he was scheduled for lymphocyte proliferation test and a confirmatory genetic testing. Unfortunately, his condition worsened, and he was admitted to the intensive care unit. Subsequent blood culture revealed Candida tropicalis septicaemia. He succumbed to death due to cardiorespiratory failure secondary to septicaemic shock and candidaemia.

DISCUSSION

SCID comprises a heterogenous group of disorders characterised by defective in number and function of both T and B lymphocytes. Occasionally it may involve the NK cells. All of them have an underlying genetic defect which subsequently results in the abnormality of the humoral and cell mediated immunity. Early in life, SCID patients may appear healthy as immune protection is accomplished by the available maternal antibodies thus delaying diagnosis.

The most common clinical presentations include pneumonia, chronic diarrhoea, gastrointestinal infection, oral candidiasis, systemic viral infections and opportunistic infections (4). However, patients are clinically indistinguishable and further investigations on the immunological workup and molecular investigations by Sanger sequencing or targeted next generation sequencing are required.

Infections have been the main presenting complaints and have been reported in majority of SCID patients. It is considered the hallmark of SCID. Although SCID is not apparent at birth, these patients are prone to severe bacterial, viral and fungal infections. Hence, in patients presenting with recurrent infections, a high index of suspicion regarding the diagnosis of PID is essential to aid early treatment and intervention. In our patient, the presenting complaint was only PUO with no associated respiratory, gastrointestinal and urinary tract symptoms. Thus, the diagnosis was difficult at that time due to atypical presentation of the patient.

Besides, the initial diagnosis in this case was misled by the patient's condition which fit into haemophagocytic lymphohistiocytosis (HLH) criteria. HLH is a heterogenous group of disorders characterised by symptoms and signs resulting from severe systemic inflammatory reaction following hypersecretion of proinflammatory cytokines and dysregulated immune homeostasis. In HLH, activation of lymphocytes is the main key feature of disease pathogenesis which is characterised by uncontrolled and excessive immune responses. Despite severe deficiency of T and NK cells in SCID, HLH can still occur in this group of patients. According to Bode et al., the development of HLH in SCID is due to the activation of macrophages and the release of cytokines which occur independently of lymphocytes counts.

Expert clinical judgement is crucial in establishing the diagnosis of HLH as not every patients who fulfill the criteria actually have HLH (5). Like in this case, even though the condition fit in the diagnosis of HLH, the exact

Table I: Relevant investigation results of the patient

Investigation		Result	Reference
Immunological			
Immunoglobulin levels	IgG	3.78	4.53-9.16 g/L
	IgA	<0.27	0.2-1.0 g/L
	IgM	<0.19	0.19-1.46 g/L
TBNK count	T cell	544	2100-6200 cells/µL
	T helper ($CD4^+$)	421	1300-3400 cells/µL
	T cytotoxic	108	620-2000 cells/µL
	($CD8^+$)	133	720-2600 cells/µL
	B cell	4	180-920 cells/µL
Complement C3	NK cell	2.1	0.9-1.8 g/L
Complement C4		0.9	0.1-0.4 g/L
ANA		Negative	
Infective			
Dengue serology	NS1	Negative	
	IgM/IgG	Negative	
Leptorapid test		Negative	
Blood C&S		No growth	
Mycoplasma Ab		Negative	
EBV IgM		Negative	
CMV IgM		Negative	
Parvovirus IgM		Negative	
Urine	FEME	Negative	
	C&S	Mixed growth	
Stool	FEME	Negative	
	C&S	No Enterohaemorrhagic *E. coli* O157 (EHEC), Enteropathogenic *E. coli* (EPEC*), Salmonella, Shigella*, Vibrio cholera, Vibrio parahaemolyticus isolated	
	Rotavirus	Negative	
ESR		30 mm/H	
C-reactive protein (x3)		Normal	
Hepatitis screening	Anti-HCV	Negative	
	HBsAg	Negative	
HIV I and II antigen		Negative	
Melioidosis serology		Negative	
Acid fast bacilli (x3)		Negative	
BFMP		Negative	
Biochemical			
Serum LDH		811.1	<480 U/L
Lipid profile	Cholesterol	4.93	0.0-5.2 mmol/L
	Triglycerides	5.78	0.0-1.71 mmol/L
	LDL-cholesterol	1.85	0.0-2.59 mmol/L
	HDL-cholesterol	0.45	1.04-1.5 mmol/L
Haematological			
Fibrinogen		3.8	2.0-4.0 g/L
Serum ferritin		943.9	23.9-336.2 ug/L
Full blood picture		Bicytopaenia with no abnormal mononuclear cells seen.	
Imaging			
Echocardiogram		Normal findings, no vegetation.	
Ultrasound abdomen		Hepatomegaly. No intra-abdominal collection or free fluid. No obvious intra-abdominal lymph node seen.	

TBNK: T, B and NK cell; ANA: antinuclear antibody; FEME: full examination and microscopic examination; C&S: culture and sensitivity; BFMP: blood film for malaria parasite; LDH: lactate dehydrogenase

diagnosis is not necessarily HLH. Establishing the correct diagnosis is important as the ultimate management depends on the genetic defect affecting this patient. Haematopoietic stem cell transplant (HSCT) remains the definite treatment in SCID and HLH. However, in HLH, the mainstay of treatment includes immunosuppressive agents and chemotherapeutic drugs as per HLH 2004 protocol which aim to eradicate activated T cell and ameliorate the cytokine storm followed by allogeneic HSCT (2).

In the case presented, there were some key points to distinguish SCID from other PIDs. Apart from prolonged fever, which is common in any PIDs, complete and differential white blood cell count shows low lymphocyte counts and subsequent lymphocyte immunophenotyping by flowcytometry revealed deficiencies in the T lymphocytes, B lymphocytes and NK cell counts. This points towards a T(-), B(-), NK(-) phenotype of SCID. This patient was scheduled for confirmatory genetic testing, which was unable to take

place because the patient died as a result of the illness. In this case, the possible genetic mutations associated with this T(-),B(-),NK(-) phenotype of SCID phenotypes are adenosine deaminase (ADA) deficiency and AK2 deficiency (Fig. 1) (4). Another important measure that could be useful is to measure ADA toxic metabolites (metabolite dATP) in erythrocytes, which would be markedly high in those with ADA SCID.

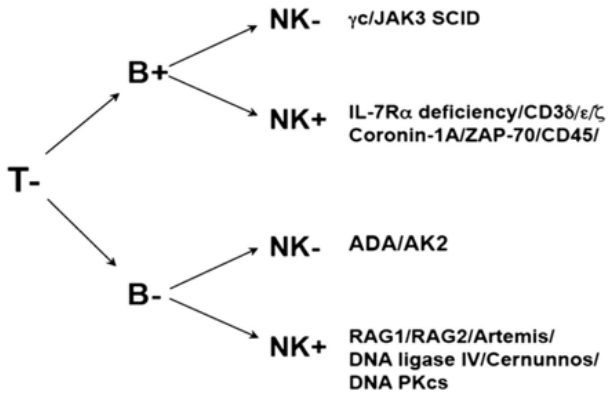

Figure 1: Summarised algorithms of possible genetic mutations in SCID patients adapted from (14). In this case, the patient shows deficiencies (-) in T lymphocytes (T), B lymphocytes (B) and NK cells which point towards a T(-)B(-)NK(-) phenotype of SCID. Hence, the possible genetic mutations are ADA deficiency and AK2 deficiency.

In case of SCID, it is important to emphasise on the early detection and diagnosis. Understanding the natural history and presentation will aid in early diagnosis of the patients. This will avoid delay in diagnosis which will lead to poor survival outcome. In this case, there might be delay in diagnosis since it was the first presentation of the patient. Apart from that, there was no history of consanguinity in the family which is an important diagnostic clue to suggest a hereditary illness.

CONCLUSION

SCID is a heterogenous group of disease with a wide range of clinical manifestations. Awareness and knowledge of this rare but life-threatening disease are important in detecting and establishing the diagnosis as PID can easily be mistaken by other diseases. In conclusion, early detection of SCID is crucial for early treatment and intervention. This in turn will improve the survival and prognosis of the patients.

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