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Review

Absent uvula and thrombocytopenia in an African infant with job's syndrome: Case report and review of literature

James Chipeta[1, 2], Jackie Banda[1], Mbinga Mbinga[1] and Somwe Wa-Somwe[1]

[1]University of Zambia School of Medicine, Department of Paediatrics and Child Health, P.0. Box 50110, Lusaka, Zambia.
[2]The School of Medicine and University Teaching Hospital Malaria Research Unit (SMUTH-MRU), C/O University teaching Hospital, Department of Paediatrics and Child Health, D-Block, P/B RW1X, Lusaka, Zambia.

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Job's syndrome, a subset of the Hyper-immunoglobulin E (IgE) recurrent Infection Syndrome (HIES), is a rare primary immunodeficiency disorder characterized by a classic clinical triad of recurrent staphylococcal abscesses, recurrent cyst-forming pneumonia, and markedly elevated serum IgE level. To date, slightly more than 200 cases have been published worldwide. Here we review HIES and report one case of Job's syndrome seen in an indigenous African infant at the University Teaching Hospital, Lusaka, Zambia, who presented with recurrent mandibular abscesses, pneumonia, *Pseudomonas aeruginosa* otitis media, markedly raised serum immunoglobulin E (IgE), thrombocytopenia and dysmorphic features (high-arched palate and absent uvula).

Key words: Absent uvula, Job's syndrome, thrombocytopaenia.

INTRODUCTION

Job's syndrome was first reported in 1966 by Davis (Davis et al., 1966). It is a rare primary immunodeficiency disorder and is a subset of the Hyper-immunoglobulin E (IgE) recurrent infection syndrome (HIES) characterized by a classic clinical triad of recurrent staphylococcal abscesses, recurrent cyst-forming pneumonia, and markedly elevated serum IgE level (Donabedian et al., 1983; Erlewyn-Lajeunesse, 2000). HIES is reported to occur in less than 1 per million population ($< 10^{-6}$) and though most cases are sporadic, both autosomal dominant (AD-HIES) and autosomal recessive (AR-HIES) types of the disease have been documented (Grimbacher et al., 1999a, b; Renner et al., 2004).

The autosomal dominant HIES, that is characteristic of Job's syndrome, is now increasingly recognized to be as a result of mainly Signal Transducer and Activators of Transcription type 3 (STAT3) gene mutations (Minegishi et al., 2007) and is a multisystem primary immune deficiency disorder characterized not only by the above-mentioned classic clinical triad but also by associated skeletal, facial, and ora-dental abnormalities including primary dentition, variations of oral mucosa and gingiva, osteopenia, minimal trauma fractures, scoliosis, a characteristic facial appearance, central nervous system abnormalities, and arterial aneurysms (Grimbacher et al., 1999b; Domingo et al., 2008; Freeman et al., 2007a; Ling et al., 2007). Here in this article, we present an African infant with Job's syndrome who besides the classic clinical triad of recurrent abscesses, pneumonia and elevated IgE, also had severe thrombocytopenia with dysmorphic features consisting of high-arched palate and absent uvula.

*Corresponding author. E-mail: Jameschipeta@smuth-mru.org.zm, damaseke@yahoo.com. Tel: 260-211-254965, 260-955-834198. Fax: 260-211-250305.

CASE

On December 27, 2008, a three-week old male indigenous African baby presented to the University Teaching

Hospital Department of Paediatrics and Child Health, Lusaka, Zambia, with multiple pustular erythematous skin eruptions, a pre-auricular abscess and pneumonia. According to the mother, the skin eruptions characteristically started spontaneously as multiple small skin swellings on the face a week after birth and later developed into pustules that spread to other parts of the body. These were further complicated by a cough and a left pre-auricular abscess that the infant presented with at the time of admission to the hospital. Further history revealed the baby to have been born at term with a birth weight of 2900 g. He was a fifth child from a non- consanguineous marriage with all the other four siblings reported to be alive and healthy. Physical examination revealed an irritable baby weighing 3500 g with a temperature of 37.4℃. He had rather coarse faces with a relative micrognatha, high-arched palate and, peculiarly, with no uvula (Figure1a). He had multiple erythematous pustules with a left pre-auricular abscess. A complete blood count (CBC) done on admission showed Hb 11.5 g/dl, WBC 18,980 /µl, neutrophils 45.3%, lymphocytes 36.2%, eosinophils 1% (180 /µl), platelets 17,000 /µl. Peripheral smear was non-revealing and sickling test was negative. Serological tests for Human Immune deficiency Virus type 1 (HIV-1) as well as RPR on both the mother and baby were negative. Chest radiograph (Figure 1b) confirmed pneumonia with homogeneous opacity on the right mid and lower zones and an ill-defined patchy opacity in the left mid zone. Diagnosis of pneumonia and pre-auricular abscess was made. The baby was empirically put on intravenous cloxacillin. In the absence of platelet transfusion services at the institution (at the time), the infant was transfused with fresh whole blood. Incision and drainage of the pre-auricular abscess was also performed. A strong clinical suspicion of a primary immune deficiency with an autoimmune phenomenon was thought to be the underlying problem in the infant and so a laboratory request for immune profile of the baby was made. After ten days of intravenous antibiotics, the baby showed remarkable recovery and was discharged from hospital on oral antibiotics.

However, two weeks later, the infant was readmitted, at the age of one month and three weeks, with left submandibular abscess and suppurative otitis media. On examination the infant was pyretic (38.3℃), weighed 3800 g, had eczematous skin lesions, petechiae and purulent ear discharge. Three possible differential diagnoses of Wiskott-Aldrich syndrome, chronic granulomatous disease, and severe combined agammaglobulinaemia were considered at this time. However, the immune profile requested during the previous admission showed IgM and IgG to be within normal range (Table 1a) and thus further investigations were ordered including ear pus swab for microscopy, culture and sensitivity, serum IgE, serum complements 3 and 4 (C3 and C4), and a repeat CBC with T cell subsets analysis. ANA and the NBT, though considered, were unavailable. The re-

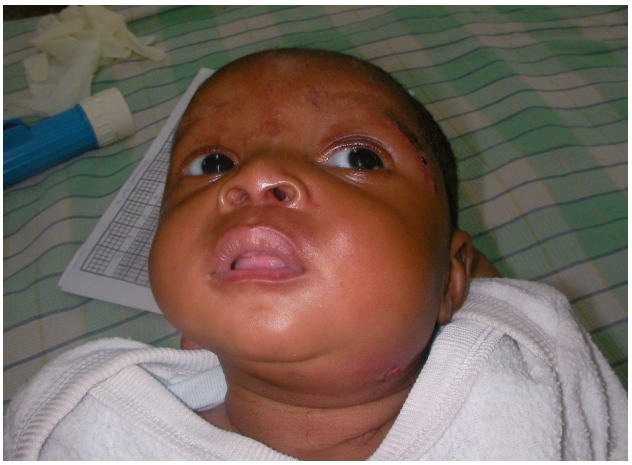

Figure 1a. Photograph of an Infant with Job's syndrome. Note the coarse facies with fleshy nasal tip, eczematous forehead and relative macroglossia. The infant had no uvula (not shown here).

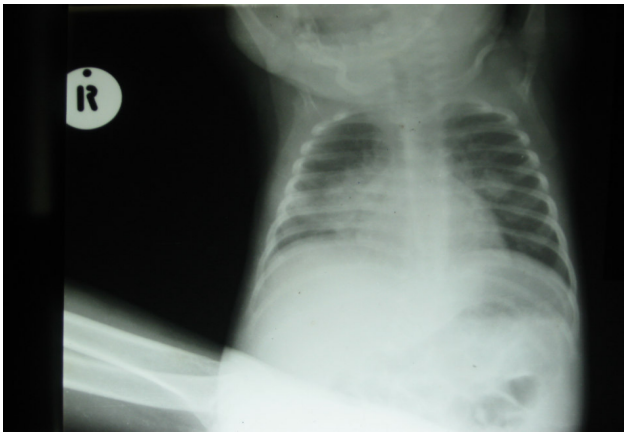

Figure 1b. Posterior-Anterior Chest radiograph of a three-week old infant with Job's syndrome showing a homogeneous opacity on the right mid and lower zones as well as an ill-defined patchy opacity of the left zone.

unavailable. The results of the repeat CBC showed Hb 7.1 g/dl, WBC 13130 /µl, neutrophils 46.9%, lymphocytes 29.2%, eosinophils 0.4% (53 /µl), platelets 30, 000/µl. Serum IgE was extremely high and more than 10 times the normal value at 374.0 kIU/ml (normal range 0.0 - 13.0 kIU/ml), while C3 was mildly raised but C4 was within normal range as were the T cell subset levels (Table 1a). Based on the clinical presentation of this infant and the available laboratory findings the diagnosis of HIES, Job's syndrome, was made.

Cultures from the ear pus swab were positive and isolated *Pseudomonas aeruginosa* sensitive to ciprofloxacillin and ceftaziolime but resistant to gentamycin. The infant had empirically been started on intravenous cefotaxime and cloxacillin therapy at the time of re-admission. How-

Table1a. Immunological profile for a Zambian infant with Job's syndrome.

Immunological Profile	Patient	Normal range
IgM	1.21 g/L	0.20 - 0.80
IgG	7.09 g/L	2.54 - 9.03
IgE	374.0 kIU/ml	0.0 - 13.0
C3	180 mg/dl	80 - 170
C4	33 mg/dl	14 - 44
IWBC Absolute count	13130	
% Lymphocytes	26.5	
% Neutrophils	65.8	
% Monocytes	7.7	
% Eosinophils	ND	
CD4 T cells Absolute Count	1700	410 - 1590
CD8 Absolute Count	414	
CD4/CD8 Ratio	4.1	

Table1b. USA's National Institute of Health (NIH) HIES Clinical Diagnostic Score status.

Clinical Feature	Findings in the patient	NIH HIES clinical diagnostic score
Highest serum IgE level (IU/ml)	374.0 kIU/ml	1
Skin Abscesses	>4	8
Pneumonia episodes	1	2
Characteristic face	Mildly present	2
Midline anomaly	Present	5
Newborn rash	Present	5
Eczema	Severe	4
Candidiasis	Absent	0
Fatal infections	Present	4
High palate	Present	2
Hyperextensibility	Absent	0
Young age correction	≤1year	7
Total score		40

ever, despite ten days of this intravenous antibiotics therapy, the infant's condition continued to deteriorate with persistent pyrexia and respiratory distress. Antibiotics were changed to ciprofloxacillin but the infant succumbed and died of septic shock on the 17th day of the readmission.

DISCUSSION

To date, over 200 cases of Job's syndrome have been reported worldwide but no case has been reported from Africa. A pubmed search conducted as we report this case using the phrase 'Job's syndrome and case report' yielded 218 entries. Limiting this search result to 'Africa' yielded no entries. We thus conclude that there is no documented case report of Job's syndrome from Africa in the available current online literature. Therefore, the case we report here may be the first documented case from Africa. Though the specific defect leading to HIES has now been discovered and clarified to be due to STAT3 gene mutations, diagnosis of Job's syndrome still largely relies on the clinically validated multi-component scoring system devised by Grimbacher (Grimbacher et al.,1999a). As recently updated by Paulson (Paulson et al., 2008), this scoring system comprises immunologic and non-immunologic clinical features. Our patient had five of the immunologic features namely a characteristic newborn rash, multiple recurrent abscesses, pneumonia, eczema and markedly raised serum IgE (Table 1b). Serum IgE is characteristically and normally virtually absent in the newborn and rises only to a maximum of 85 kIU/ml in boys in the first one year of life (Kulig et al., 1999). The IgE serum level of more than 10-fold normal in this infant at the perinatal age of three weeks was not only phenomenal but suggestive of HIES. Other causes of high serum IgE such as parasitic infestations, endemic in this area, are rare at this age and usually would have an accompanying marked peripheral eosinophilia which was not the case in this baby. The non-immunologic

features, had a characteristic coarse facies, high-arched palate with a peculiar oral feature of an absent uvula. He scored 40 points on the NIH HIES clinical scoring system (Table 1b) making Job's syndrome to be the most likely diagnosis in the infant. The closest differential diagnosis in this patient especially with the presentation of petechiae and thrombocytopenia was Wiskott - Aldrich syndrome (WAS). The most invariable abnormality in WAS is thrombocytopenia with small platelet volume and this thrombocytopathy is responsible for the typical bleeding complications such as intracranial hemorrhage after vaginal delivery and bloody diarrhea in the perinatal period (Sullivan et al., 1994). Eczema and petechiae are usually also present at diagnosis in WAS. Our patient did have severe thrombocytopenia and petechiae throughout his illness and ended up receiving one platelet and multiple whole blood transfusions before he died. However, as already highlighted in the birth history, his immediate postnatal history was uneventful and only developed the rash at one week of age. There was neither history of bloody diarrhea nor signs of intracranial hemorrhage postnatally. Like in Job's syndrome infectious complications are the most frequent cause of death in WAS and the immune dysregulation may also manifest as autoimmune disease, including hemolytic anaemia, vasculitis, inflammatory polyarthritis, and inflammatory bowel disease (Krivit and Good, 1954). Furthermore, both cellular and humoral immunity are impaired in WAS. Over time progressive depletion of T cells is observed in WAS patients with eventual lymphopenia. There is also impairment of immunoglobulin levels typically consisting of low levels of IgM, normal levels of IgG, and increased levels of IgA, IgD, and IgE (Krivit et al., 1959 and Berglund et al., 1968). Despite having marked thrombocytopenia and petechiae, laboratory investigations done in our patient did not show the WAS afore-described typical cell-mediated and humoral immune impairments (Table 1a). On the contrary, the infant had slightly raised serum IgM while IgG was within normal range with a markedly raised IgE. The CBC revealed no lymphopenia with a normal CD4/CD8 count ratio. These observations made showed "WAS" to be an unlikely diagnosis in this infant. We thus postulate that thrombocytopenia exhibited in our patient is part of HIES autoimmune phenomenon as has also been reported elsewhere (Yamazaki-Nakashimada et al., 2006). Though we did not perform NBT in this patient, chronic granulomatous disease was unlikely from both the clinical presentation and the relatively normal serum immunoglobin profile levels.

The major and critical component of the complement system that participates in all three pathways of immune activation is the complement component 3(C3) and C3 deficiencies are reportedly associated with higher susceptibility to severe infections and in some cases with autoimmune diseases such as systemic lupus erythematosus (Reis et al., 2006). Thus we assessed whether there was complement deficiency in our patient. As can be seen by the laboratory results serum C3 was slightly higher than normal while C4 was within normal range. There was thus neither C3 nor C4 deficiency in this infant.

At the time of death, our patient had a culture confirmed *P. aeruginosa* otitis media and died of septic shock that we attributed to the same isolated organism. Fungal and Pseudomonas infections have been reported and highlighted by Freeman AF (Freeman et al., 2007b) to be the major cause of morbidity and mortality in patients with HIES. We suspect that the infant did not fully recover from the pneumonia during his first admission. This was later complicated by the *P. aeruginosa* otitis media and a submandibular abscess during the second admission with the resultant septic shock. As we conclude this case report we bemoan the limitations to comprehensive clinical work up and effective management of patients with rare conditions in resource poor countries as we look at the protracted time it took us to investigate and come up with a diagnosis in this infant. However, our case report illustrates the fact that, even under limited resources, diagnosis of rare conditions can be made.

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