**STAT1 loss of function: a case series**

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**Background:** STAT1 is required for signalling of all the interferons (α, β, γ, ω, λ). Complete (recessive) loss of function (LOF) of STAT1 leads to early fatal infections with mycobacteria and viruses. Patients with AR complete STAT 1 deficiency carrying two loss-of-function alleles of STAT1 are vulnerable to intracellular bacterial and viral diseases. Heterozygosity for loss-of-function dominant-negative mutations in STAT1 is responsible for autosomal dominant (AD) Mendelian susceptibility to mycobacterial disease (MSMD), whereas heterozygosity for gain-of-function loss-of-dephosphorylation mutations causes AD chronic mucocutaneous candidiasis (CMC). We hereby describe 3 cases of STAT 1 deficiency; all of whom presented with BCGosis. Two patients succumbed to the illness and one patient is currently on treatment.

**Case Series:** Patients P1 and P2 were siblings born to a 3rd degree consanguineous parents. P1, a boy presented at the age of 6 months with failure to thrive and active BCGiosis with enlarged left axillary lymph node and isolated mycobacterium TB complex by Mycobacteria Growth Indicator Tube (MGIT) technique. Despite extensive anti-TB treatment (isoniazid, rifampicin, moxifloxacin and clarithromycin), the patient died at the age of 9 months with the complications of disseminated BCGosis. P2, the sister of P1 inadvertently received BCG vaccination and presented with BCGosis at 3 months of age. She was started on antituberculous treatment however she died of respiratory viral illness at the age of 4 months.

P3, a 6-month-old boy who received BCG shortly after birth presented to us with history of axillary swelling noticed by the mother at 3 months of age which gradually increased in size. He developed an erythematous maculo-papular rash all over the trunk and limbs. A biopsy of the skin lesions was suggestive of lichen scrofulosorum (figure 1). A fine needle aspiration cytology and MGIT isolated mycobacterium tuberculosis complex and was started on antituberculous drugs. He is currently well and thriving on anti-tuberculous therapy at last follow-up (9months of age).

Immunology investigations showed normal full blood counts, immunoglobulin levels, lymphocyte subsets in all 3 patients. Targeted next generation sequencing for MSMD genes revealed a homozygous mutation in STAT1 gene (c.769dup/769dup; p. Asp257Glyfs*22/Asp257Glyfs*) in P1 and P2. Parents were heterozygous for the same mutation. Functional analysis showed absent STAT1 phosphorylation on monocytes upon INF gamma stimulation by flowcytometry on all 3 patients. Genetic results are still awaited for P3. A family donor search for P3 is being activated for consideration of haematopoietic stem cell transplant (HSCT).
Conclusion: STAT1 deficiency (complete/partial) is associated mutation with increased propensity to viral infection and poor handling of mycobacterial infection. Early intervention with HSCT is mandated for cure and survival.

Figure 1: Disseminated BCG in patient P3

The photo on the left shows enlarged left axillary lymph node. Photo on the right showed maculopapular skin rash.