Title: Bacille Calmette-Guérin lymphadenitis: a potential complication of immune reconstitution following haematopoietic stem cell transplant

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Case Report

An MHC class II deficient 2-year-old boy presented with fever and an enlarging left neck mass 100 days post-allogeneic haematopoietic stem cell transplant (HSCT). Fever persisted despite treatment with broad-spectrum β -lactam antibiotics. His Bacille-Calmette Guérin (BCG) vaccination site at presentation was quiescent. Ultrasound showed enlarged cervical lymph nodes. An incisional biopsy of the large nodal mass yielded acid-fast bacilli, identified as *Mycobacterium bovis* by genome sequencing. Treatment with rifampicin, isoniazid and pyridoxine was started. The mass suppurred (**Figure 1**), before healing concurrently with T-lymphocyte reconstitution at approximately day 130 post-HSCT.

BCG infection can complicate vaccination in patients with severe combined immunodeficiencies (SCID), including MHC II deficiency¹, causing a spectrum ranging from simple adenitis to disseminated disease. BCG immune reconstitution inflammatory syndrome, typically presenting as localised adenitis ipsilateral to vaccination site, is well-described after commencing antiretroviral therapy for human immunodeficiency virus and is recognised in patients post-HSCT^{2,3}. In this case, T-lymphocyte reconstitution restoring the T-lymphocyte mediated response in a previously BCG-vaccinated child, is likely to have precipitated both this presentation and its resolution.

Early identification of SCID through newborn screening might prevent vaccine administration to patients at risk of complications.

Question 1

How is MHC class II deficiency inherited?

- A. Autosomal dominant
- B. Autosomal recessive
- C. X-linked recessive
- D. Mitochondrial

Question 2

What role do MHC class II molecules have in the immune response?

- A. Co-stimulation of naïve CD4+ T-helper lymphocytes to prevent anergy
- B. Initiation of immunoglobulin class-switch recombination in B-lymphocytes
- C. Presentation of antigen to naïve CD4+ T-lymphocytes
- D. Presentation of antigen to naïve CD8+ T-lymphocytes

Question 3

Which method has been proposed for newborn screening for SCID in the UK?

- A. Absolute lymphocyte count
- B. Detection of T-lymphocyte receptor excision circles (TRECs)
- C. Tandem mass spectrometry to detect toxic metabolites
- D. Immunoassay for CD3 and CD45

Question 4

Which is the most appropriate treatment for localised BCG disease in immunocompromised children?

- A. Rifampicin and isoniazid
- B. Surgical resection
- C. Surgical resection and instillation of isoniazid
- D. Rifampicin, isoniazid, ethambutol and pyrazinamide

Question 5

What common side-effect should patients receiving isoniazid be counselled for?

- A. Peripheral neuropathy
- B. Increased seizure frequency
- C. Acute kidney injury
- D. Change in colour of urine

Answers

Question 1

Answer: B

Homozygous mutations in *CIITA*, *RFXANX*, *RFX5*, *RFXAP*, which all regulate transcription of MHC class II genes, cause MHC class II deficiency.⁴

Question 2

Answer: C

MHC class II molecules are expressed on antigen-presenting cells and present peptide to naïve CD4+ T-lymphocytes. Interaction between MHC class II-bound peptide and the T-lymphocyte receptor on the surface of T-lymphocytes leads to their activation, differentiation and proliferation.

Question 3

Answer: B

The proposed method for screening for SCID involves detection of TRECs, a marker of naïve T-lymphocytes in the Guthrie test, and is likely to detect SCID arising from any genetic defect. This will be evaluated in the future. Tandem mass spectrometry can detect metabolite abnormalities from adenosine deaminase or purine nucleoside phosphorylase deficiency.

Question 4

Answer: A

Literature on the treatment of BCG infection is limited⁵. It is unclear whether antimycobacterial medication is effective for the treatment of BCG adenitis. Typical

regimens in immunodeficient children consist of isoniazid monotherapy, or with rifampicin¹. *Mycobacterium bovis* is resistant to pyrazinamide.

Corticosteroids and surgical resection are used as adjuncts⁶. Most experience of excision is for non-tuberculous mycobacteria. This can be curative but risks temporary (or rarely permanent) cranial nerve palsies, particularly of the marginal mandibular nerve. Sinus formation and discharge may follow incomplete excision, even in immunocompetent children⁷⁻⁹.

Immune reconstitution post-HSCT may treat BCG complications in SCID patients, with or without antimycobacterial treatment¹, though some require immunomodulation to attenuate a life-threatening inflammatory response¹⁰.

Question 5

Answer: A

The most commonly associated side-effect of isoniazid is peripheral neurotoxicity; the risk of this may be reduced by administration of pyridoxine.

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Figure 1 Suppurative BCG lymphadenitis following spontaneous rupture.

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