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Susceptibility to mycobacterial infection in a young man with a hypoglossal nerve palsy: the hunt for an immunological defect

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This case report highlights the immunological considerations in patients who are diagnosed with disseminated infection due to BCG or environmental mycobacteria.

Case history

A 17-year-old boy presented with a four-week history of neck pain, difficulty chewing and deviation of his tongue to the right. On examination there was tenderness of the mid-cervical spine and a right XII nerve palsy. A 6 cm lesion was noted over the left deltoid (Figure 1). There was no lymphadenopathy or splenomegaly. Blood tests were normal apart from ESR 44 mm/h and CRP 83mg/L.

Cervical spine X-rays showed increased space between the odontoid peg and the arch of C1. CT of the neck revealed destruction of the basisphenoid, clivus and right occipital condyle, with craniocervical instability. The cervical spine was immobilized with a hard collar pending halo fixation. Gadolinium-enhanced MRI showed a T1 signal abnormality around the hypoglossal nerve and involving the anterior foramen magnum and the right side of the C1 vertebra. ^{99m}Tc bone scintigraphy revealed increased uptake in the sacrum, right iliac crest, right eighth rib and left acetabulum.

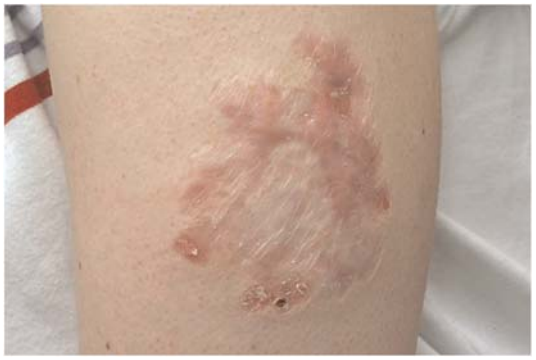
Following BCG vaccination four years previously the patient developed a chronic 6 cm discharging lesion at the inoculation site. This was biopsied one year prior to his presentation with neck pain. Histology demonstrated necrotizing granulomas and BCG was cultured. He defaulted follow-up and failed to complete antimycobacterial therapy.

The right iliac crest was biopsied and histology revealed non-caseating granulomatous inflammation. Although staining for AAFB was negative, rifampicin, isoniazid and ethambutol were commenced for presumed disseminated BCG. Culture confirmed BCG at 7 weeks, sensitive to rifampicin, isoniazid and ethambutol, resistant to pyrazinamide.

The patient's neck pain and XII nerve palsy resolved and his cutaneous lesion began to heal. A bone scan at 5 months showed reduced uptake in the right iliac crest and no additional abnormality. CT of the cervical spine at 9 months indicated fusion of the right occiput to C1. Triple therapy was continued for 1 year followed by rifampicin + isoniazid for a further year. Nuclear magnetic spectroscopy 1 year after discontinuing therapy showed improvement and the patient remains well.

He had no history of infection with bacteria, viruses or fungi, suggesting an isolated predisposition to mycobacteria. He was HIV-negative with normal immunoglobulin levels, IgG subclasses, complement levels and normal levels of specific antibodies to all the childhood vaccinations. Lymphocyte subsets showed generalized depression, attributed to disseminated infection, but normal percentages. Major histocompatibility complex class I & II expression was normal. He had normal adenosine deaminase and purine nucleoside phosphorylase levels, normal lymphocyte proliferative responses, normal neutrophil oxidative burst function and normal Toll-like receptor (TLR) 4 and TLR 7/9 screening by CD62L shedding assay.

Figure 1
BCG site, four years after inoculation



The patient's brother had also experienced an extensive cutaneous reaction to BCG and both were screened for defects in the IL-12/IFN-γ pathway, described below. Known defects were excluded. Anti-IFNγ autoantibodies were weakly positive but unlikely to be significant.

Discussion

Disseminated infection caused by BCG or environmental mycobacteria (EM) suggests a primary or acquired immunodeficiency, such as severe combined immunodeficiency, chronic granulomatous disease or HIV. A leaky cellular immunodeficiency was considered in the above case but immunological investigations were normal as listed. Given the isolated predisposition to BCG in two siblings, with no other demonstrable immune defect, an inherited deficiency in the IL-12/IFN-γ axis was considered most likely. Such disorders have been described relatively recently and are termed 'Mendelian susceptibility to mycobacterial disease' (MSMD). In addition to BCG and EM, affected individuals are prone to extra-intestinal disease caused by non-typhoidal *Salmonella*.[1] In this patient's case, screening excluded currently known deficiencies of the IL-12/IFN-γ axis, suggesting a novel defect.

The IL-12/IFN-γ pathway

Dendritic cells and macrophages act as antigen-presenting cells (APCs) which recognize invading mycobacteria through pattern recognition receptors. Signal transduction leads to activation of the APC and production of IL-12 and IL-23.[2] These cytokines bind to their receptors on T-helper and natural killer cells, inducing production of IFN-γ. The IL-12 receptor (IL-12R) is a complex of IL-12Rβ1 and IL-12Rβ2.[2] IL-12 consists of p40 and p35 subunits which bind to IL-12Rβ1 and IL-12Rβ2, respectively.

Secreted IFN-γ binds to its receptor (IFN-γR) on dendritic cells and macrophages, activating microbicidal mechanisms. The IFN-γR is composed of two chains, IFN-γR1 and IFN-γR2.[2]

Mendelian susceptibility to mycobacterial disease

Mutations have been identified in six genes: *IFNGR1* and *IFNGR2* (encoding IFN-γR1 and IFN-γR2), *STAT1* (encoding signal transducer and activator of transcription-1: Stat-1), *IL12P40* (encoding IL-12p40), *IL12RB1* (encoding IL-12Rβ1) and *NEMO* (encoding nuclear factor-κB-essential modulator: NEMO).[1,3] Mutations may be associated with partial or complete deficiency of the gene product.

IFN-γR1 and IFN-γR2 deficiency

Complete recessive deficiency of IFN-γR1 or IFN-γR2 presents with early severe, often fatal, infection with BCG and EM.[1] There is no cellular response to IFN-γ *in vitro*.[1] Haematopoietic stem cell transplantation has been curative in a few cases.[4]

Partial recessive IFN-γR1 deficiency diminishes the cellular response to IFN-γ.[5] Patients present with less severe mycobacterial infection which usually responds to antimicrobials +/− IFN-γ.[3]

Dominant *IFNGR1* mutations produce truncated receptors with a weak cellular response to IFN-γ.[1,3] Children develop moderately severe infection with BCG and EM.[6] *M. avium* osteomyelitis has been repeatedly described.[6] Outcome is generally good with antimicrobials +/− IFN-γ.[3]

Partial recessive IFN-γR2 deficiency has been reported in a child who presented with mild BCG and *M. abscessus* infection.[7] Partial dominant IFN-γR2 deficiency has been described in one family, causing *M. abscessus* osteomyelitis in one of two homozygous siblings, and disseminated CMV and *M. avium* infection in the other.[8]

Stat-1 deficiency

Stat-1 is a downstream signalling molecule for IFN-γ.[1] Dominant *STAT1* mutations cause a partial deficiency with a mild clinical phenotype.[1,9]

IL-12p40 and IL-12Rβ1 deficiency

Recessive mutations in *IL12B* result in complete deficiency with undetectable IL-12p40.[1] Recessive mutations in *IL12RB1* result in complete IL-12Rβ1 deficiency, with no cellular response to IL-12.[3] In both cases infection with BCG or *Salmonella* is common and usually responds to antimicrobials and IFN-γ.[1,3]

X-linked recessive MSMD: mutations in *NEMO*

NEMO is a regulatory subunit of the nuclear factor-κB (NFκB) inhibitor kinase complex which controls activation of the transcription factor NFκB, implicated in various immunological pathways.[2] Mutations in *NEMO* have been associated with predisposition to mycobacterial infection.[10]

Conclusion

We speculate that the case presented represents a novel variant of MSMD. Patients with disseminated or recurrent infection due to BCG or EM, with a severe persistent cutaneous reaction to BCG, or with extra-intestinal infection caused by non-typhoidal *Salmonella*, should be investigated for a defect in cell-mediated immunity. Consider screening for MSMD, after exclusion of HIV, particularly if family members are symptomatic.

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