Case S2

A two year-old child who received standard immunizations (and not BCG)\(^1\) presented with fever, cough, hepatosplenomegaly\(^2\) (enlarged liver and spleen) and diffuse lymphadenopathy.\(^3\) A chest X-ray was read as consistent with pneumonia. He was treated with clarithromycin,\(^4\) but failed to improve. Further laboratory studies revealed a white blood count of 25,000.\(^5\) Quantitative immunoglobulins were normal, as was the reduction of nitroblue tetrazolium (NBT) by polymorphonuclear leukocytes.\(^6\) A test for HIV was negative. Serologic testing for tetanus antitoxoid antibody showed a normal post-vaccination titer. A biopsy of a cervical lymph node revealed mild inflammation with no distinct granulomas; however, the smear was positive for acid-fast bacilli (AFB)\(^7\) and cultures grew several atypical mycobacteria, as did blood cultures.

Therapy with rifabutin, azithromycin, ciprofloxacin, ethambutol, and amikacin was begun,\(^8\) which resulted in a modest improvement in fever and activity levels, and in weight gain. Due to the clinical presentation, an assessment for the presence of the interferon-\(\gamma\) (IFN-\(\gamma\)) receptor on the patient’s peripheral blood monocytes was made using flow cytometry (Fig. 1).

\(^{1}\)Bacille Calmette-Guerin, a vaccine used in most of the world (but not the US) to help prophylax against tuberculosis (TB). Preparations of BCG are rarely standardized and its effectiveness is questionable.

\(^{2}\)Enlarged liver and spleen

\(^{3}\)Enlargement of most lymph nodes

\(^{4}\)A macrolide antibiotic often used as empiric treatment for bacterial pneumonia (i.e., when the etiology of pneumonia is unknown)

\(^{5}\)cells/\(\mu\)l

\(^{6}\)Reduction of NBT results in the deposition of an insoluble colored product that is easily seen by light microscopy. It is a useful screening test for genetic defects in the NADPH oxidase.

\(^{7}\)Acid-fast bacilli refers to the appearance of Mycobacteria and a few other species, such as Nocardia, following a histochemical stain that appears red under light microscopy.

\(^{8}\)Broad-spectrum anti-mycobacterial therapy

![Fig. 1. Level of expression of the IFN-\(\gamma\) receptor on the surface of peripheral blood monocytes from the patient (A) and a healthy control (B). The solid line indicates binding of the specific antibody; the dotted line indicates binding of the appropriate isotype-matched control antibody, and the dashed line indicates the binding of anti-CD14 antibodies.](image-url)
Case S2, cont’d

Questions for Case S2:

1. Describe the structure of the IFN-γ receptor. How does it signal gene expression?

2. Describe the cellular components of a granuloma. Why did the lymph node biopsy grow atypical mycobacteria in the absence of granulomas?

3. What is the principal leukocyte(s) that secretes IFN-γ? that responds to IFN-γ? Which cytokine acts in concert with IFN-γ to promote macrophage activation?

4. In mice that lack the inducible form of nitric oxide synthase (iNOS or NOS-2), susceptibility to lethal mycobacterial infection is increased. This phenotype is similar to the one seen in this individual. Based on this observation, what is the likely relationship between IFN-γ receptor deficiency and iNOS expression?

5. Patients with AIDS develop a similar propensity to disseminated mycobacterial infections in the absence of mature granuloma formation. Why might this be the case?