Case S2

A two year-old child who received standard immunizations (and not BCG\textsuperscript{1}) presented with fever, cough, hepatosplenomegaly\textsuperscript{2} (enlarged liver and spleen) and diffuse lymphadenopathy.\textsuperscript{3} A chest X-ray was read as consistent with pneumonia. He was treated with clarithromycin,\textsuperscript{4} but failed to improve. Further laboratory studies revealed a white blood count of 25,000.\textsuperscript{5} Quantitative immunoglobulins were normal, as was the reduction of nitroblue tetrazolium (NBT) by polymorphonuclear leukocytes.\textsuperscript{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)\textsuperscript{7} and cultures grew several atypical mycobacteria, as did blood cultures. Therapy with rifabutin, azithromycin, ciprofloxacin, ethambutol, and amikacin was begun,\textsuperscript{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).

\textsuperscript{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.

\textsuperscript{2}Enlarged liver and spleen

\textsuperscript{3}Enlargement of most lymph nodes

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

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

\textsuperscript{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.

\textsuperscript{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.

\textsuperscript{8}Broad-spectrum anti-mycobacterial therapy

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure1.png}
\caption{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.}
\end{figure}
Case S2, cont’d

Questions for Case S2:

(1) Describe the structure of the IFN-\(\gamma\) 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-\(\gamma\)? that responds to IFN-\(\gamma\)? What cytokines acts in concert with IFN-\(\gamma\) 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-\(\gamma\) 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?