

Case S2

A two year-old child who received standard immunizations (and not BCG¹) presented with fever, cough, hepatosplenomegaly² (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 anti-toxoid 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- γ (IFN- γ) receptor on the patient's peripheral blood monocytes was made using flow cytometry (Fig. 1).

¹Bacille 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.

²Enlarged liver and spleen

³Enlargement of most lymph nodes

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

⁵cells/ μ l

⁶Reduction 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.

⁷Acid-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.

⁸Broad-spectrum anti-mycobacterial therapy

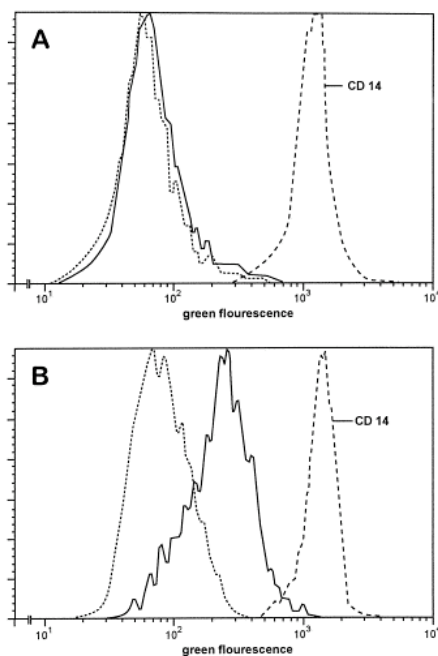


Fig. 1. Level of expression of the IFN- γ receptor on the surface of peripheral blood monocytes from the patient (A) and a healthy control (B). The solid line indicates binding of the specific antibody; the dotted line indicates binding of the appropriate isotype-matched control antibody, and the dashed line indicates the binding of anti-CD14 antibodies.

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?