Common variable immunodeficiency (CVID) is a heterogeneous group of immunodeficiency syndromes that involves defective production of specific antibodies and decreased serum concentrations of ≥1 immunoglobulin isotype. We describe a patient with an atypical case of CVID who had extensive granulomatous lesions that were partially attributable to mycobacterial infection. In the peripheral blood, there was a massive increase in the number of double-negative CD3^+ T cells that expressed the γδ T cell receptor.

Common variable immunodeficiency (CVID) is a heterogeneous group of immunodeficiency syndromes that involves defective production of specific antibodies and decreased serum concentrations of ≥1 immunoglobulin isotype. Clinically, affected patients present with recurrent bacterial infections of the respiratory and gastrointestinal tracts, and they have increased rates of autoimmune disease and lymphoproliferative disorders [1–4]. Moreover, subgroups of patients with caseating or non-caseating granulomatous lesions in lymphoid tissues, solid organs, or skin have occasionally been described [5–7]. In this setting, the finding of an increase in the number of double-negative CD3^+ T cells in the peripheral blood potentially indicates the presence of mycobacterial infection, as has been previously documented [for example, see [8]]. We describe a patient with an atypical case of CVID who had extensive granulomatous lesions that were partially attributable to mycobacterial infection. In the peripheral blood, there was a massive increase in the number of double-negative CD3^+ T cells that expressed the γδ T cell receptor (TCR).

**Case report.** A 31-year-old woman was referred to the Department of Infectious Diseases (Hôpital Haut-Lévêque; Pessac, France) in April 1996 for evaluation of recent weight loss (8 kg in 10 weeks) and progressive asthenia. CVID had been diagnosed in April 1995 when she was hospitalized for chronic diarrhea. The patient had been healthy until the age of 16 years, when she developed recurrent bronchitis and sinusitis and had several episodes of pneumonia, recurrent herpes stomatitis, and intermittent diarrhea. In 1995, she had hypogammaglobulinemia (IgG level, 1.27 g/L [normal range, 6.90–14.00 g/L]; IgA level, 0.4 g/L [normal range, 0.70–3.70 g/L]; and IgM level, 0.20 g/L [normal range, 0.40–2.40 g/L]). Since May 1995, she has received intravenous immunoglobulins every 3 weeks.

At the time of admission to the hospital (April 1996), the patient had no fever and complained of diarrhea (~8 stools daily). Physical examination revealed marked hepatosplenomegaly. Laboratory studies revealed the following values: WBC count, 4.2 × 10^9 cells/L (81% neutrophils and 10% lymphocytes); hemoglobin, 14.2 g/dL; platelet count, 5.02 × 10^10 platelets/L; erythrocyte sedimentation rate, 20 mm/first hour; C-reactive protein, 3 mg/L; and fibrinogen, 3.5 g/L (normal range, 2–4 g/L). She had profound hyphemoproteinemia (protein level, 40 g/L; normal range, 60–77 g/L) with an albumin level of 17 g/L (normal range, 32–50 g/L), but hepatic and renal functions were normal. Stool cultures did not yield microorganisms, and laboratory investigations revealed steatorrhea and protein-losing enteropathy. All blood cultures were negative for bacteria and fungi, and the results of serological tests were negative for cytomegalovirus, Epstein-Barr virus, HIV, and hepatitis A and C viruses. Cryoglobulins and antinuclear and anti-DNA antibodies were not detected. The results of a tuberculin skin test were negative.

The patient was lymphopenic (total lymphocyte count, 440 cells/mm^3). Flow cytometric quantification of T cell subsets [8] performed in April 1996 revealed the following values: CD3^+ T cells, 292 cells/mm^3 (66%); CD4^+ T cells, 14 cells/mm^3 (3.2%); CD8^+ T cells, 113 cells/mm^3 (25.4%); and CD3^+ CD4^- CD8^- T cells, 164 cells/mm^3 (37%) (figure 1). The ratio of CD4^+ T cells to CD8^+ T cells was 0.13 (normal range, 1–1.5). The percentage of double-negative T lymphocytes primarily expressing the γδ TCR that extensively used the variable-gene segments Vγ9 and Vδ2 (138 cells/mm^3; 38% of total peripheral...
lymphocytes) was highly elevated, compared with those of 57 healthy blood donors (median, 2.1%; range, 0.6%–8.2%) [8]. The B lymphocyte count was also decreased, to 64 cells/mm$^3$ (26.2% of total lymphocytes).

A CT scan of the abdomen revealed multiple mesenteric and retroperitoneal masses that were interpreted as lymphadenopathy. The findings of bone marrow biopsy and karyotype studies were normal, and there was not an increase in the large granular lymphocyte count in the blood. Histological examination of an intestinal lymph node biopsy specimen revealed epithelioid cell granulomas with polynucleated giant cells without caseous necrosis. Lymph node smears stained with Ziehl-Nielsen stain were positive for acid-fast bacilli; however, the cultures remained negative for tuberculous and nontuberculous mycobacteria. In addition, PCR of lymph node specimens for detection of tuberculous mycobacteria was performed with use of the commercially available Amplicor MTB kit (Roche Diagnostics); the results were also negative.

Despite the failure to identify any microorganisms, on the basis of the lymph node smear findings, combination antituberculous therapy (isoniazid, rifampicin, and ethambutol) was initiated in June 1996. Six months later, the patient’s clinical status had not improved, and the double-negative CD3$^+$ CD4$^+$ CD8$^-$ T cell count had not decreased (figure 1). A CT scan of the abdomen showed the same masses. Therefore, in December 1996, a new therapeutic regimen (clarithromycin, ethambutol, and rifabutin) directed against atypical mycobacteria was introduced. Three months later, the patient had gained 3 kg, diarrhea was attenuated but had not disappeared, and the double-negative γδ T lymphocyte count had begun to decrease (figure 1). However, 12 months of this treatment did not lead to further clinical and biological improvement, and a CT scan of the abdomen showed persistence of multiple lymphadenopathies.

In February 1998, cervical condylomatosis induced by human papillomavirus was diagnosed, which led to the prescription of IFN-α (9 × 10$^6$ IU 3 times per week) while antituberculous therapy was continued. Three months later, the patient’s general condition had improved: she had gained 3 kg, the diarrhea had abated, and a CT scan showed a one-third reduction of the lymphadenopathies. Moreover, the double-negative γδ T lymphocyte count had decreased dramatically (figure 1). This therapy was continued for 9 months, until December 1998. Since that time, the patient has been healthy, despite having 3 loose stools daily and persistent granulomatous disease noted on CT scans of the abdomen. The double-negative γδ T lymphocyte count is within the normal range and is stable.

Figure 1. Total CD3$^+$ (■) and CD3$^+$ CD4$^+$ CD8$^-$ (○) lymphocyte counts in the blood noted during follow-up in a patient with common variable immunodeficiency. Dates are month, day, year.
Discussion. The occurrence of noncaseating granulomatous lesions in patients with CVID is a well-recognized feature usually described as a “sarcoid-like” syndrome [5–7]. However, although T cell abnormalities have been observed in patients with CVID [2, 3, 9–11], mycobacterial infections have rarely been described in such patients [12]. The present observations suggest that, in patients with CVID, Mycobacterium infections can develop, can generate a marked increase in the γδ T cell count, and may be involved in granulomatous disease.

Although the results of culture and PCR for mycobacteria were negative for our patient, infection with a Mycobacterium species is likely to have occurred: the Ziehl-Nielsen reaction was clearly positive and the patient improved while receiving specific antitymocobacterial treatment, particularly when IFN-α was added. So far, γδ T lymphocytosis has been reported in 1 patient with CVID whose T lymphocytes bore the Vδ1 segment [13]. γδ T cells are normally a minor component of total peripheral blood lymphocytes, averaging ~5% [14], but they are predominant within the epithelia of the skin, gut, and airways [15]. It is generally assumed that they participate with αβ T cells in protection against intracellular bacteria, as has been shown with transgenic mouse models that lack one or the other TCR [16]. Indeed, γδ T cells recognize a wide range of mycobacterial proteins in vitro, including low-molecular-weight proteins and nonprotein ligands, without the need for prior antigen processing and presentation [12]. We previously found that the γδ T cell count was increased in patients with HIV and Mycobacterium avium coinfection but not in those with HIV and Mycobacterium tuberculosis coinfection, which suggests that γδ T cells play a role in the response to mycobacterial infection in immunocompromised patients [17]. Therefore, it is possible that our patient, who had a very low CD4⁺ T cell count and an altered immune system, had an exacerbated increase in the γδ T cell count because of an attempt to replace the missing αβ T cells in the immune response against the mycobacterial agent, as has been demonstrated in patients with cytomegalovirus infection who have undergone kidney allograft-transplantation [18]. Therefore, Vβ2Vγ9 T lymphocytosis was likely secondary to antigenic stimulation; it was probably due to infection with an atypical Mycobacterium species and was not a direct consequence of CVID.

Our observation suggests that IFN-α can be used to treat infections with intracellular microorganisms. While our patient was receiving quadruple antibiotic therapy, her symptoms were only slightly attenuated, and the elevated double-negative T cell count persisted; when IFN-α was coadministered, all signs of mycobacterial infection disappeared, and the γδ lymphocyte count decreased. Data are available concerning the involvement of the type II interferon system in susceptibility to mycobacterial infection [19]; however, the effect of type I interferon, which was used here, is not yet clear. Because of the pivotal role of the dendritic cells in antigenic presentation to T lymphocytes, and because of their ability to secrete and respond to IFN-α, it is possible that therapeutic administration of the latter may improve dendritic cell functions and foster a better T lymphocyte–dependent response [20]. Administration of granulocyte-macrophage colony-stimulating factor may also be beneficial not only because such therapy differentiates between operational dendritic cells and precursor cells, but also because it acts at the level of the bone marrow compartment.

References


17. Pellegrin JL, Taupin JL, Dupon M, et al. γδ T-cells increase with My-

