Miliary Tuberculosis with Indeterminate Interferon Gamma Release Assay Results

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Abstract

Recently, interferon gamma release assays (IGRAs) have become an important clinical tool for detecting latent tuberculosis. However, IGRA results may impede making a diagnosis. We herein present an interesting case of miliary tuberculosis with a nonspecific IGRA reaction due to hemophagocytosis.

Key words: miliary tuberculosis, hemophagocytosis, interferon gamma release assay (IGRA)

(Intern Med 52: 2583-2585, 2013)
(DOI: 10.2169/internalmedicine.52.0708)

Case Report

A 64-year-old man with advanced chronic kidney disease due to nephrosclerosis and ischemic heart disease was admitted to our hospital with an intermittent high-grade fever lasting for one week. The plan was to initiate hemodialysis therapy, and the patient underwent surgery for internal shunt ostomy in the left upper arm two months prior to admission. He was given neither steroids nor other immunosuppressants. On admission, he was free from respiratory symptoms, such as a productive cough. His laboratory data and radiological findings were evaluated. The clinical laboratory data obtained on admission confirmed a high alkaline phosphatase level (above 2,000 IU/mL) and a decreased hemoglobin (Hgb) level (below 10.0 g/dL). The serum C-reactive protein and procalcitonin levels were elevated, indicating an inflammatory reaction. The soluble interleukin-2 receptor (sIL-2R) level was elevated to 18,986 U/mL. Both anti-HIV and anti-human T-cell leukemia virus (HTLV) antibodies were negative. He had no history of hematological diseases. Chest roentgenography performed on admission showed no abnormalities, except cardiomegaly (Figure A).

We initially suspected a bloodstream infection, such as infectious endocarditis, and thus performed blood cultures and serological surveillance. However, these microbiological inspections yielded no useful data. On the other hand, chest computed tomography revealed slight density changes in both lung fields (Figure B); however, the patient had no respiratory symptoms. Although we recognized a slight density elevation in the pulmonary alveolar field, radiologists in our hospital did not mention these findings, and miliary tuberculosis was not suspected. The detection of a column appearance depends on the type of monitor used. We attempted to obtain respiratory samples to detect pulmonary infections, including tuberculosis. However, due to the lack of sputum production, we were unable to obtain respiratory samples. The interferon gamma release assay (IGRA, QuantiFERON-TB™ Gold In-tube (QFT-3G)) results showed values for both negative and positive controls as well as the patient’s samples exceeding 8.01 IU/mL. According to previous guidelines for using IGRAs (1), our patient’s results were invalid due to the nonspecific reaction of the negative control (a positive reaction in the negative control).

Despite conducting further studies, a final diagnosis was not reached, and the patient’s condition deteriorated. Hemo-

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Received for publication April 4, 2013; Accepted for publication July 10, 2013
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were identified to be Dickinson and Company, Sparks, MD, USA). The AFB Europe and Japan); and T-SPOT.TB (4).

The diagnosis of tuberculosis: QFT-3G, a form of the enzyme-linked immunosorbent assay (ELISA, licensed in the USA, Europe and Japan). Several previous reports have described the sensitivity of T-SPOT.TB™ as being higher than that of QFT-3G (4). In particular, in patients with HIV infection, the T-SPOT.TB™ has been reported to have improved sensitivity for the detection of latent tuberculosis compared to the QuantiFERON-TB™ Gold (QFT-2G) (5), the previous generation QFT. It is also noteworthy that there are fewer indeterminate results with T-SPOT.TB™ than with QFT (6). The QFT-3G represents an improvement in that another specific synthetic protein derived from M. tuberculosis, TB 7.7 (Rv2654) (7), has been added, and the stimulation of peripheral blood lymphocytes is possible beginning immediately after blood collection. Although the sensitivity of QFT-3G is improved compared to that of QFT-2G, a previous report described the sensitivity of T-SPOT.TB™ as being higher than that of both QFT-2G and -3G (4). Currently, IGRA are regarded as being good diagnostic tools for detecting activated or latent tuberculosis, not only by non-respiratory physicians, but also by pulmonologists. Indeed, IGRA have become essential for diagnosing tuberculosis in this decade. However, it is also important to assess indeterminate results. Indeterminate results show two patterns: an insignificant result typical of a sample assay (true indeterminate results), and an abnormal response in the control assay (rather than “no judgment”). Formerly, indeterminate results were interrupted considering the overall risk of tuberculosis. However, “no judgment” has been interpreted as the inability to judge the result due to the presence of a latent immunocompromised state. We suggest that rather than making a conclusion of “no judgment,” these results are important for diagnosing tuberculosis.

False control assay responses are divided into positive and negative findings. Positivity of a negative control is caused by a high level of IFN-γ in the sample serum. In patients with miliary tuberculosis, the pathological specimens show hemophagocytosis in the bone marrow. Previous reports...
have shown IFN-γ production to be accelerated in the hemophagocytic reaction (8-10). On the other hand, the baseline concentration of IFN-γ is high in patients with autoimmune diseases, such as systemic lupus erythematosus (11-13) and rheumatoid arthritis (13, 14). Moreover, some viral infections cause a high production of IFN-γ (15-17). Negative changes in a positive control are caused by individual background factors, such as an immunocompromised status, including acquired immunodeficiency syndrome or immunosuppressant intake. The level of anti-IFN-γ autoantibodies, as reported in severe infectious diseases, including sepsis caused by opportunistic pathogens (18) or disseminated non-tuberculous mycobacterium infection (19, 20), is also high in this situation.

In the present case, the “no judgment” IGRA result may have ended further investigations of tuberculosis, despite the presence of several clinical signs of tuberculosis. It appears that the present patient had miliary tuberculosis accompanied by hemophagocytosis. Therefore, we speculate that a high level of secretion of inflammatory cytokines, including IFN-γ, had occurred and that the IGRA results accounted for the control being negative for inappropriate secretion of cytokines. We recommend that respiratory physicians sufficiently assess IGRA results, including both indeterminate findings and the “no judgment” outcome. Miliary tuberculosis is usually associated with several abnormalities of the host immune response, including a high production of IFN-γ. In both patients with miliary tuberculosis and an immunocompromised state, the IGRA result of “no judgment” should be seen as the default. Beyond IGRA, further evaluations are required in patients suspected to have miliary tuberculosis.

The authors state that they have no Conflict of Interest (COI).

Acknowledgement

We thank Dr. Bierta Barford for editing the manuscript and Toshie Sekine for providing secretarial assistance. We also thank Dr. Takefumi Saito (National Hospital Organization, Ibaraki-higashi Hospital, Ibaraki, Japan) and Dr. Yuka Sasaki (Fukujuji Hospital, Tokyo, Japan) for their help with the present report.

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