

CLINICAL PROBLEM-SOLVING

Immune Interference

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In this Journal feature, information about a real patient is presented in stages (boldface type) to an expert clinician, who responds to the information by sharing relevant background and reasoning with the reader (regular type). The authors' commentary follows.

A 62-year-old man was admitted to the hospital for malaise, anorexia, rash, and diffuse lymphadenopathy. Fatigue and anorexia had begun 6 months earlier. Four months before admission, a pruritic rash developed on the back and during the next several days spread to the abdomen, arms, and legs. The rash did not resolve with topical glucocorticoids, antihistamines, or antibiotics (cephalosporin followed by fluoroquinolone). One month before admission, he completed a course of antibiotics and underwent a cervical-lymph-node biopsy at another hospital. The specimen showed granulation tissue with infiltration of lymphocytes, plasma cells, neutrophils, and a small population of atypical T cells but was inconclusive. No microbiologic studies were performed on the specimen.

Diffuse lymphadenopathy is usually caused by infection, autoimmunity, or cancer. Acute viral infections such as Epstein–Barr virus (EBV) and cytomegalovirus (CMV) are unlikely to persist for months unless the patient is immunocompromised. Other infections such as tuberculosis, fungi, syphilis, and human immunodeficiency virus (HIV) infection are more likely to cause chronic lymphadenopathy. Among cancers, lymphomas most characteristically cause diffuse lymphadenopathy. Autoimmune or inflammatory conditions that are associated with diffuse lymphadenopathy include systemic lupus erythematosus and sarcoidosis. A prominent rash and diffuse lymphadenopathy also arouse concern for syphilis, HIV infection, and hematologic cancers, such as human T-lymphotropic virus type 1 (HTLV-1)–mediated adult T-cell leukemia–lymphoma and T-cell lymphomas such as mycosis fungoides or Sézary syndrome.

The patient had lost 11 kg in the past 6 months. He reported no fever, night sweats, or cough. His medical history was notable only for coronavirus disease 2019 (Covid-19) 1 year earlier. He was taking no medications or herbal supplements. He had smoked one pack of cigarettes daily for 42 years and drank 12 ounces of beer twice per week. He was an office worker and enjoyed gardening. He was born in Kyushu, the southernmost of the four main islands of Japan, and later resided near Tokyo.

Previous Covid-19 infection can lead to a severe persistent immune activation that spans from long Covid to the more narrowly defined multisystem inflammatory syndrome (MIS), which can cause lymphadenopathy. However, MIS is more common in children and adolescents than in adults, generally develops within 6 weeks after infection, and typically manifests with persistent fever and other signs or symptoms (e.g., cardiovascular involvement) not present in this patient.

His history of smoking raises the possibility of metastatic carcinoma (e.g., lung or renal cancer). Gardening involves exposure to organisms in soil that can cause

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CME



chronic lymphadenopathy, including aspergillus, sporothrix, and mycobacteria. HTLV-1 is endemic in Kyushu; the atypical T cells could be a sign of HTLV-associated lymphoma, although they may also be reactive, in the context of infection or autoimmune disease.

He appeared fatigued. The axillary temperature was 36.8°C, the pulse 108 beats per minute, the blood pressure 112/66 mm Hg, the respiratory rate 12 breaths per minute, and the oxygen saturation 95% while he was breathing ambient air. Multiple tender lymph nodes, each between 1.0 and 1.5 cm in diameter, were noted, bilaterally in the cervical, axillary, and inguinal regions. Cardiopulmonary and abdominal examinations were normal; there was no hepatosplenomegaly. Erythematous papules and pustules were present on the trunk, arms, and legs, including the palms and soles (Fig. 1).

The white-cell count was 30,800 per microliter, with 83% neutrophils, 6% lymphocytes, 3% monocytes, and 5% eosinophils. The hemoglobin level was 9.7 g per deciliter with a platelet count of 676,000 per microliter. The erythrocyte sedimentation rate was 117 mm per hour (reference value, <10). The C-reactive protein (CRP) level was 11.3 mg per deciliter (reference value, <0.14). The aspartate aminotransferase level was 30 U per liter (reference

range, 13 to 30), the alanine aminotransferase level was 44 U per liter (reference range, 10 to 42), and the lactate dehydrogenase level was 190 U per liter (reference range, 124 to 222). These results were similar to those obtained 1 month earlier at the outside facility.

The IgG, IgM, and IgA levels were normal. Testing for antinuclear antibodies was negative, as was testing for rapid plasma reagin and serum HIV antibodies. The CD4+ T-cell count was 1197 per microliter (reference range, 344 to 1290). Tests for EBV DNA in peripheral-blood mononuclear cells and CMV antigenemia were both negative. Testing for anti-HTLV-1 antibody was negative. The T-SPOT.TB (T-SPOT) interferon- γ release assay was negative. Acid-fast bacilli stains of the sputum were negative. Two sets of blood cultures were sterile. A chest radiograph was normal.

The size, tenderness, and distribution of lymphadenopathy are less characteristic of cancer and more consistent with an infection, although the discriminatory value of those criteria is limited. Disseminated grouped pustular rashes may reflect viruses (e.g., disseminated herpes simplex), bacteria (e.g., gonococcemia), fungi, or mycobacteria. Among autoimmune diseases, Behçet's syndrome and psoriasis are particularly likely to involve the

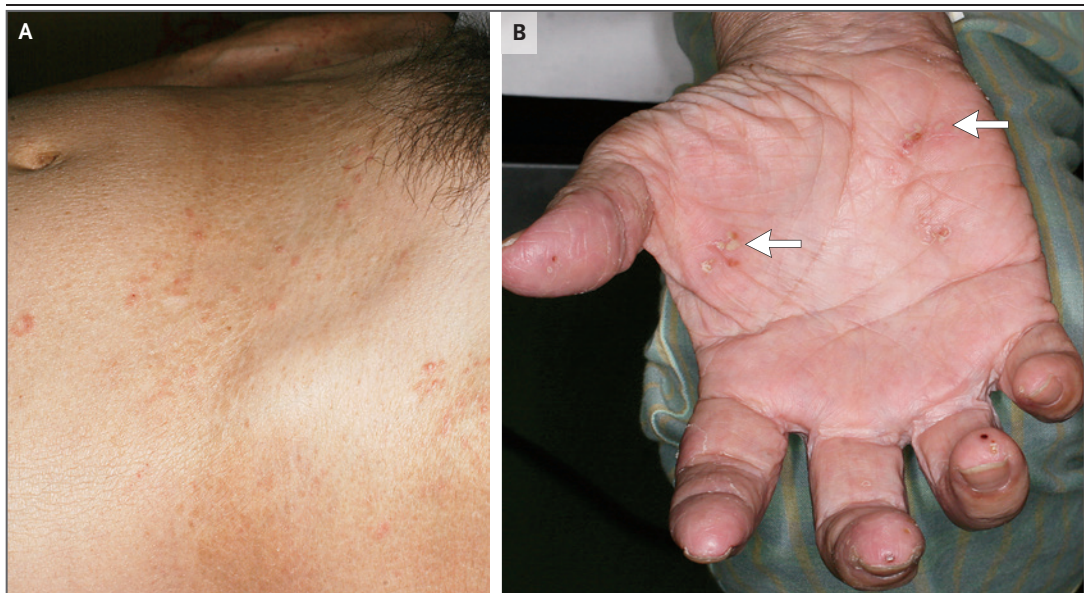


Figure 1. Skin Changes.

Panel A shows erythematous papules and pustules on the lower abdomen and right lateral side of the waist. Panel B shows pustules (arrows) and crust on the right palm.

formation of pustules. Drug reactions can also lead to pustular reactions, such as acute generalized exanthematous pustulosis, although the pustules are usually evenly distributed and resolve after drug withdrawal. The 4-month duration of the rash, its onset before antibiotic exposure, and the systemic symptoms collectively make an infectious cause for the pustular eruption most likely.

Leukocytosis, neutrophilia, anemia, thrombocytosis, and CRP elevation are all consistent with inflammation. The microbiologic tests rule out some common chronic infections. The negative interferon- γ release assay and negative acid-fast bacilli stains make tuberculosis less likely. The negative blood cultures make infectious endocarditis less likely but should be interpreted in the context of recent antibiotic treatment.

Contrast-enhanced computed tomography (CT) showed diffuse lymphadenopathy, with one left cervical lymph node having internal necrosis. Whole-body positron-emission tomography revealed hypermetabolic lymph nodes in cervical, supraclavicular, axillary, intrathoracic, mediastinal, periaortic, and mesenteric regions (Fig. 2 and Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). An excisional biopsy of a left supraclavicular lymph node revealed replacement of the lymph follicle by lymphocytes, plasma cells, and neutrophils, along with a small population of atypical plasma cells (Fig. S2).

There were no granulomas. Flow cytometry and immunostaining did not suggest lymphoma, Castleman's disease, or IgG4-related disease. Ziehl-Neelsen and Giemsa staining showed no microorganisms.

An abdominal skin biopsy revealed epidermal pustular dermatitis (neutrophilic infiltrate with spongiosis). No atypical cells were identified. Cultures of the biopsy specimens yielded no growth of bacteria or fungi.

The lymph-node biopsy shows findings compatible with inflammation (now with atypical plasma cells instead of atypical T cells) but is nondiagnostic. This excisional biopsy permits more confidence in ruling out granulomatous conditions and cancer. The neutrophilic infiltrate supports infection; the probability of a bacterial infection is low on the basis of the duration of illness, a lack of response to antibiotics, and sterile tissue and blood cultures. Those findings raise the possibility of more indolent infections such as mycobacteria or fungi. A negative acid-fast stain does not rule out mycobacterial infection owing to its low sensitivity.

After 6 days, acid-fast bacilli were detected on mycobacterial blood culture and were later identified as *Mycobacterium abscessus*. Culture from a biopsy of the left axillary lymph node subsequently grew *M. abscessus*. A second interferon- γ release assay,

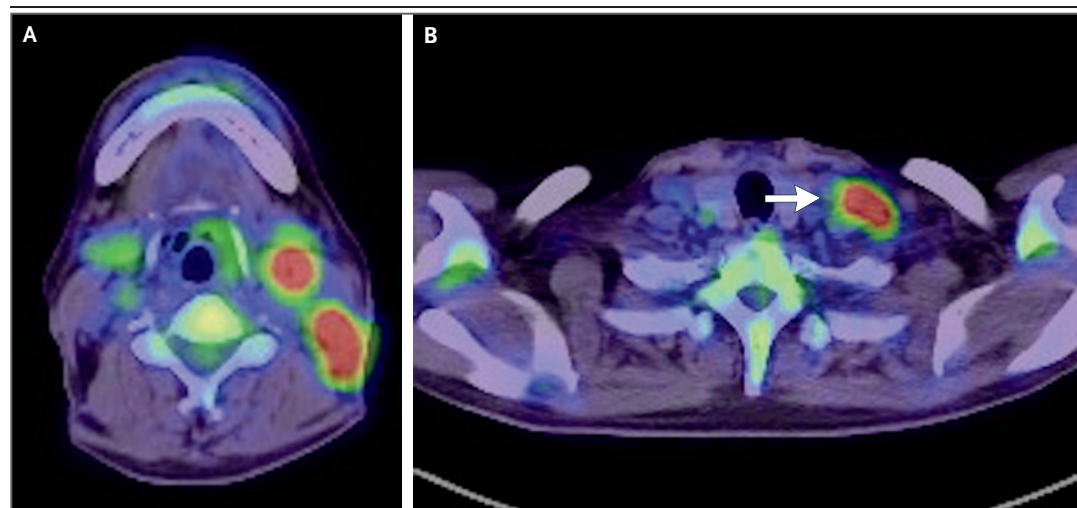


Figure 2. Whole-Body Positron-Emission Tomography (PET).

Whole-body PET showed hypermetabolic lymph nodes in the cervical (Panel A), supraclavicular (Panel B), axillary, intrathoracic, periaortic, and mesenteric regions. The arrow in Panel B indicates a biopsied lymph node.

QuantiFERON-TB Gold Plus (QFT), was indeterminate, owing to a lack of response in the mitogen tube (a positive control that confirms that the patient's immune system is capable of mounting an interferon- γ response).

The systemic inflammation, radiologic findings, and skin manifestations are explained by *M. abscessus* infection. *M. abscessus* is found in water and soil, so it is possible that the patient was exposed while gardening. His predisposition to severe extrapulmonary mycobacterial infection requires explanation. Disseminated mycobacterial disease usually occurs in the context of marked immunodeficiency, such as advanced HIV infection, primary immunodeficiencies (e.g., defects in the interleukin-12–interferon- γ axis), or immunosuppressive therapies (e.g., glucocorticoids). The results of the QFT assay point to another cause of immunodeficiency: autoantibodies to interferon- γ .

The control is expected to be positive in both interferon- γ release assays — T-SPOT and QFT. However, each assay shows the presence of an adequate interferon- γ response to stimulation with tuberculosis-specific antigens in different ways: QFT quantifies total secreted interferon- γ , whereas T-SPOT measures the number of interferon- γ –producing lymphocytes. Therefore, the discrepancy observed between the positive controls of QFT and T-SPOT suggests the presence of an interfering substance — namely, neutralizing autoantibodies against interferon- γ .

Neutralizing autoantibodies against interferon- γ were detected at a titer of 768 enzyme-linked immunosorbent assay (ELISA) units (EU) (reference range, 5 to 50; 1 EU = 1.0 μ g per milliliter) in a serum dilution of 1:1000. Anti-interferon- γ autoantibody syndrome was diagnosed.

The presence of anti-interferon- γ autoantibodies explains this patient's susceptibility to disseminated mycobacterial infection, because these neutralizing autoantibodies impair a key pathway in the immune response to intracellular pathogens. By blocking interferon- γ –mediated activation of macrophages and downstream interleukin-12 signaling, the defect specifically compromises control of organisms such as mycobacteria and salmonella while leaving defenses against most extracellular bacteria and viruses largely intact.

After 4 weeks of intravenous antibiotic therapy (azithromycin, amikacin, and imipenem), the rash and lymphadenopathy abated. On the basis of susceptibility testing, the regimen was switched to oral azithromycin and sitafloxacin.

One month later, the rash and lymphadenopathy recurred (Fig. 3). The patient was afebrile, and blood and skin mycobacterial cultures were negative. Cultures of a left axillary lymph node grew *M. abscessus* with an increase of four times in macrolide minimum inhibitory concentration (MIC) as compared with the original strain. After the administration of imipenem, tigecycline, and clarithromycin, the rash resolved, and the lymphadenopathy decreased.

Failure of an extended antimicrobial course to resolve an infection invites consideration of an incorrect original diagnosis, a supervening new illness, inadequate delivery of antimicrobial drugs, inadequate source control, or the development of antimicrobial resistance. The latter is most likely on the basis of the increase in macrolide MIC and clinical improvement with the new regimen.

Surveillance CT performed 4 weeks later showed regression of the lymphadenopathy but multiple new hepatic lesions. CT performed 2 weeks after the initial surveillance CT revealed further enlargement of these hepatic lesions (Fig. S3), despite further reductions in lymphadenopathy and in the rash and an increase in the energy level. A liver biopsy showed necrosis and clusters of epithelioid cells suggestive of granulomas (Fig. S4). Cultures from the specimen were negative.

The new hepatic masses could reflect recurrent infection with *M. abscessus* (or a new pathogen), but this is unlikely given the absence of fever and the clinical improvement. The sterile tissue culture further argues against infection, although previous antimicrobials may have reduced culture yield. A new metastatic cancer is improbable 2 months after imaging and biopsies that did not show a primary cancer.

Another consideration is a paradoxical reaction — that is, a clinical or radiologic worsening after the start of antimicrobial treatment. This typically arises when immune restoration (e.g., treatment of HIV infection) triggers an inflammatory response to residual mycobacterial antigens. The same phenomenon can occur when increased exposure to mycobacterial antigens from successful

antimicrobial treatment triggers a localized inflammatory response (sometimes at previously unrecognized sites of infection).

A paradoxical reaction to antimicrobial treatment was diagnosed. The antimicrobial regimen was continued without administration of glucocorticoids. After 6 weeks of intravenous therapy, the regimen was switched to oral treatment with clarithromycin, sitafloxacin, and clofazimine. At 2 months of follow-up, the liver lesions had resolved and the patient had gained 2 kg and returned to work.

COMMENTARY

This patient presented with rash, lymphadenopathy, and weight loss. The detection of *M. abscessus*, with evidence of disseminated disease, raised the question of what made him susceptible to a typically opportunistic infection. The discrepancy between the positive control results of two different interferon- γ release assays led to testing for neutralizing autoantibodies against interferon- γ and the diagnosis of anti-interferon- γ autoantibody syndrome.

All interferon- γ release assays use a positive control tube that confirms the patient's immune system is capable of mounting an interferon- γ response. The QFT assay quantifies total secreted interferon- γ , whereas the T-SPOT assay measures interferon- γ -producing lymphocytes. Neutralizing autoantibodies against interferon- γ can impair detection of interferon- γ levels in QFT but not the lymphocyte counts in T-SPOT.¹ Accordingly, in patients with anti-interferon- γ autoantibody syndrome, only the positive control tube in QFT shows no response.

Nontuberculous mycobacteria typically cause pneumonia and lymphadenitis and less often manifest as infections of the skin and soft tissues, osteoarticular structures, or intravascular catheters. *M. abscessus* complex is the most frequently isolated species among rapidly growing mycobacteria, which characteristically form colonies in culture within 7 days.² Disseminated *M. abscessus* disease manifests with fever, weight loss, lymphadenopathy, and skin lesions. Granulomas are frequently observed on histopathological analysis but may be absent in certain immunodeficiencies.³ Because tuberculosis, fungal infections, autoimmune diseases, and lymphoma may manifest



Figure 3. Skin Changes on the Second Admission.
Exanthematous pustulosis was observed on the palms.

similarly, mycobacteria-specific cultures are essential for diagnosis.

Major risk factors for disseminated nontuberculous mycobacterial infection in adults include advanced HIV infection, hairy-cell leukemia, idiopathic CD4 lymphocytopenia, and immunosuppressive therapy.^{2,4,5} Host defenses against mycobacteria rely on cell-mediated immunity involving T cells and natural killer (NK) cells. On recognition of pathogen components, macrophages and dendritic cells produce interleukin-12, which subsequently induces interferon- γ production by T cells and NK cells. Interferon- γ activates macrophages to eliminate intracellular pathogens (Fig. 4).⁶ Therefore, inherited or acquired defects in the interleukin-12–interferon- γ pathway should also be considered in patients with disseminated nontuberculous mycobacterial infections. In adults, the most common acquired impairment of this pathway is the occurrence of anti-interferon- γ autoantibodies, which neutralize interferon- γ .⁷

Anti-interferon- γ autoantibody syndrome occurs predominantly in persons of Southeast Asian or East Asian descent and is associated with specific HLA class II alleles, particularly HLA-DRB1*16:02 and DQB1*05:02.⁸⁻¹⁰ In studies conducted in Thailand and Taiwan, anti-interferon- γ autoantibodies were detected in 81 to 98% of adults without HIV infection, cancer, or other known immunodeficiencies who presented with disseminated nontuberculous mycobacterial infection.^{7,11} Persons with these neutralizing autoantibodies are

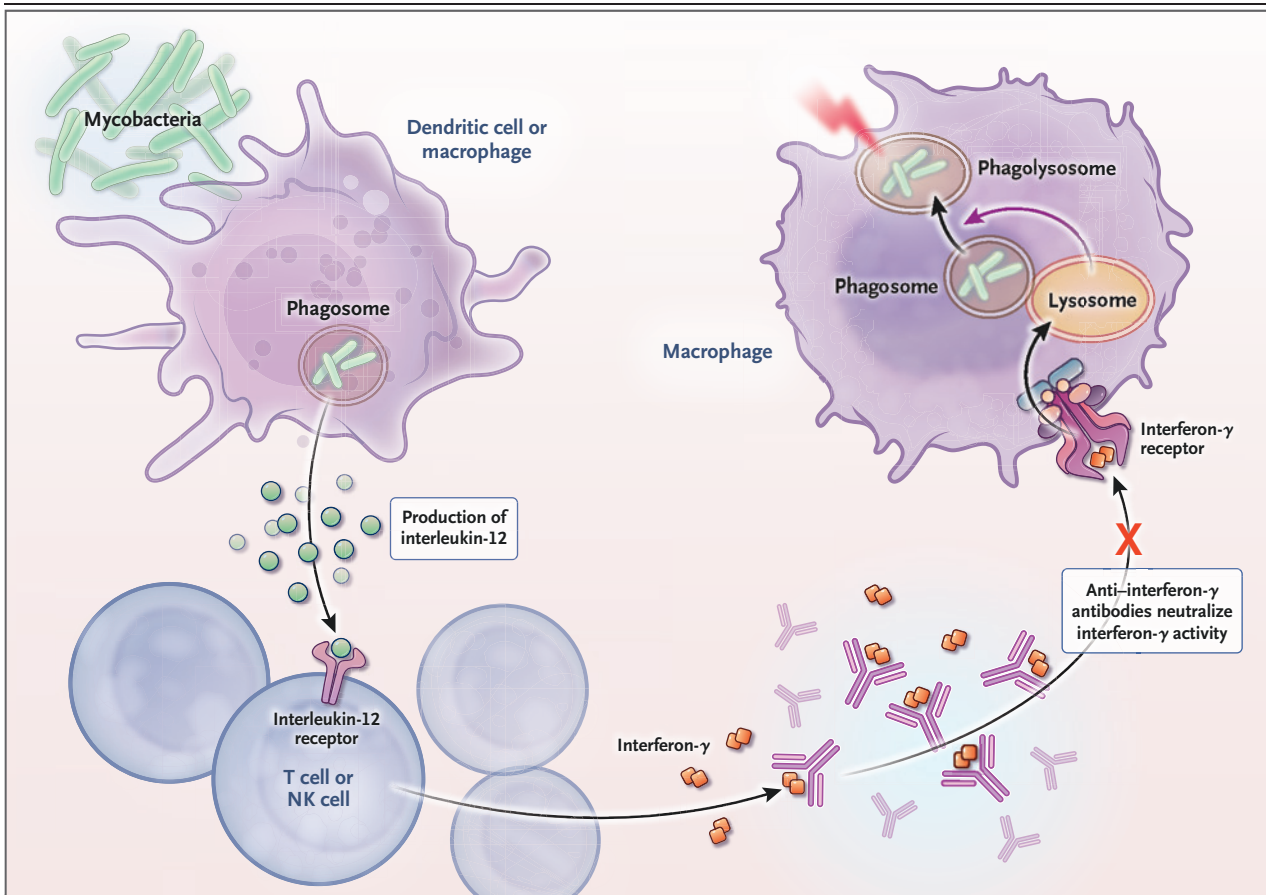


Figure 4. Cell-Mediated Defense Mechanism against Mycobacteria.

After the recognition and internalization of nontuberculous mycobacteria, macrophages and dendritic cells form a phagosome and produce interleukin-12. Interleukin-12 subsequently induces interferon- γ production by T cells and natural killer (NK) cells. Interferon- γ activates macrophages, promoting the fusion of phagosomes with lysosomes to form phagolysosomes, which enables them to kill and degrade the pathogen. Anti-interferon- γ autoantibodies neutralize interferon- γ activity, thereby disrupting the interleukin-12–interferon- γ axis.

also susceptible to salmonella, burkholderia, histoplasma, cryptococcus, talaromyces, cytomegalovirus, and herpes zoster reactivation.^{3,6} Case reports and series have described reductions in autoantibody titers with the use of rituximab or cyclophosphamide in persons with anti-interferon- γ autoantibody syndrome,^{8,12,13} but randomized trials establishing their efficacy in reducing the frequency or severity of associated infections are lacking.

This patient's development of new liver lesions on a revised antibiotic regimen, in the context of otherwise improving clinical status and negative liver-biopsy cultures, led to the diagnosis of a paradoxical reaction. Paradoxical reactions in mycobacterial infections are thought to result from a hypersensitivity immune response to antigens released

from killed mycobacteria and typically occur between 3 and 22 weeks after treatment initiation.¹⁴

Paradoxical reactions commonly emerge or intensify during immune reconstitution in immunocompromised patients but can also occur in persons who are immunocompetent. This patient had impaired interferon- γ responsiveness but intact cell-mediated immunity, including CD4+ T cells, which were capable of reacting to the increased quantity of mycobacterial antigens. Treatment failure, including drug resistance, must be ruled out before diagnosis of a paradoxical reaction. Clinical improvement often occurs with observation alone. In patients with severe symptoms, glucocorticoids or tumor necrosis factor α antagonists may be considered.^{14,15}

This case illustrates how the discovery of a particular infection (in this case, *M. abscessus* in a patient without known immunocompromise) can point to a specific immunodeficiency syndrome (in this case, anti-interferon- γ autoantibody syndrome). It also highlights that clinical worsening in the context of treatment does not necessarily imply treatment failure but rather may indicate a paradoxical reaction, which reflects the dynamic interplay between mycobacteria and the immune system. These two manifestations illustrate both interference with the immune system and its overzealous response.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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