CLINICAL PROBLEM-SOLVING

Closing the Gap

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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 31-year-old woman presented to the emergency department in October with a 10-day history of fever, sinus pressure, cough, nausea, and vomiting. Her husband and 1-year-old child, who attends day care, had similar symptoms.

In the preceding 5-month period, unlike her family members, she had had night sweats, fatigue, an unintentional 4.5-kg (10-lb) weight loss, and three episodes of coughing, nasal congestion, sinus pressure, nausea, and vomiting. Her sinonasal symptoms had been diagnosed as upper respiratory tract infections and had resolved with decongestants and cough suppressants.

Seasonal allergies are a frequent cause of nasal congestion, sinus pressure, and coughing. The patient's sick household contacts prompt consideration of an acute infectious process. Community-acquired viral infections such as influenza, enterovirus, and adenovirus are common in the fall and winter and can induce fever with sinopulmonary and gastrointestinal symptoms. However, the patient's constitutional symptoms and recurrent illnesses arouse concern for an insidious process. Important considerations include atypical infections (e.g., disseminated mycobacterial and endemic fungal disease), autoimmune conditions (including lupus and antineutrophil cytoplasmic antibody–associated vasculitis), malignant conditions (especially lymphoma), and primary immune deficiency. It is possible that the patient's sinonasal symptoms and constitutional symptoms have separate causes.

The patient was born in Florida and had lived in Baltimore most of her life. One week before her current illness, she had traveled to Chicago, where, at a petting zoo, she had direct contact with cows and sheep. She had not otherwise traveled in the preceding year. She owned two dogs and one cat and had no known bites, scratches, tick bites, or rodent exposure. She owned potted plants and did not garden. She worked in an office and reported drinking two alcoholic drinks weekly; she reported never having used tobacco or nonprescribed drugs. She noted no sexual partners other than her husband, took no medications, and had never been homeless or incarcerated.

At 14 years of age, she had been treated for immune thrombocytopenia with intravenous immune globulin, and the condition had not recurred. She was otherwise healthy as a child and adolescent.

Symptomatic histoplasmosis occurs in a small proportion of healthy persons infected with *Histoplasma capsulatum*, which could have been acquired in Illinois (where she traveled) or Maryland (place of residence). Q fever (*Coxiella burnetii*) and brucellosis

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(brucella species) merit consideration owing to her recent exposure to livestock; however, upper respiratory and gastrointestinal symptoms are not common with these infections. She has no exposures or risk factors for tuberculosis or nontuberculous mycobacterial infections.

Her history of immune thrombocytopenia may be unrelated but could suggest a primary or secondary immunologic disorder. Well-recognized triggers of immune thrombocytopenia are infections, including human immunodeficiency virus (HIV) and hepatitis C virus; lymphoma; autoimmune diseases, including lupus; medication use; and immune deficiency syndromes, such as common variable immunodeficiency (CVID) and autoimmune lymphoproliferative syndrome.

Her blood pressure was 120/68 mm Hg, heart rate 122 beats per minute, respiratory rate 16 breaths per minute, oxygen saturation 100% while she was breathing ambient air, and oral temperature 39.5°C (103.1°F). The body-mass index (the weight in kilograms divided by the square of the height in meters) was 22.5. Frontal and maxillary sinuses were tender to palpation. Dentition was intact; the oropharynx was pink without tonsillar enlargement, erythema, or exudate. Smooth, nontender cervical lymph nodes measuring approximately 2 cm in diameter were palpable. Lung fields were clear to auscultation. There was nontender hepatomegaly measuring 5 cm below the costal margin in the midclavicular line, and the spleen tip was palpable. The remainder of the physical examination was unremarkable.

Palpable lymphadenopathy and hepatosplenomegaly arouse concern for cancer, particularly lymphoma, but can occur in infectious, autoimmune, and primary immune deficiency syndromes. Primary infection with Epstein–Barr virus or cytomegalovirus can cause infectious mononucleosis with lymphadenopathy, hepatosplenomegaly, and flulike symptoms. Acute HIV infection can mimic mononucleosis, although she does not have known risk factors for HIV. Tickborne illness such as Lyme disease, ehrlichiosis, or anaplasmosis is possible within the patient's geographic location, but cough and sinus tenderness are not characteristic of these infections. Cervical lymphadenopathy may represent either a localized reaction to upper respiratory tract infection or widespread lymphadenopathy.

The white-cell count was 2200 per cubic millimeter, with 62% neutrophils, 23% lymphocytes, 13% monocytes, and 0.4% eosinophils. The absolute neutrophil count was 1380 cells per cubic millimeter. The hemoglobin level was 10.7 g per deciliter, mean corpuscular volume 71.7 fl, and platelet count 88,000 per cubic millimeter. The absolute reticulocyte count was 16,700 per cubic millimeter (reference range, 24,100 to 87,700), and immature platelet fraction 8.2% (reference range, 0.1 to 6.3). The haptoglobin level was 187 mg per deciliter (reference range, 32 to 197), ferritin level 104 ng per milliliter (reference range, 30 to 400), and lactate dehydrogenase level 299 U per liter (reference range, 122 to 220). A peripheral-blood smear showed microcytic, hypochromic anemia, occasional pencil cells (rod-shaped red cells), lymphopenia, and thrombocytopenia. The aspartate aminotransferase level was 87 U per liter (reference range, 0 to 31), alanine aminotransferase level 79 U per liter (reference range, 0 to 31), alkaline phosphatase level 328 U per liter (reference range, 30 to 120), and total bilirubin level 0.8 mg per deciliter (13.7 μmol per liter) (reference value, <1.2 mg per deciliter [20.5 μmol per liter]). The total protein level was 5.5 g per deciliter (reference range, 6.0 to 8.2), and the albumin level 4.0 g per deciliter (reference range, 3.5 to 5.3). The erythrocyte sedimentation rate was 11 mm per hour (reference range, 4 to 25). The C-reactive protein level was 4.5 mg per deciliter (reference value, <0.5). Urinalysis was negative for leukocytes and red cells and showed trace protein.

Pancytopenia has a broad differential diagnosis, encompassing peripheral destruction of cells or impaired hematopoiesis from myelosuppression or bone marrow infiltration. The combination of mild pancytopenia (without severe neutropenia) and splenomegaly suggests splenic sequestration; the microcytic, hypochromic anemia and pencil cells suggest iron deficiency. Hematologic malignant conditions or infections (including Epstein–Barr virus, cytomegalovirus, HIV, hepatitis viruses, ehrlichiosis, and anaplasmosis) can cause pancytopenia, abnormal liver-associated enzymes, and constitutional symptoms. Autoimmune diseases, most notably systemic lupus erythematosus, may inflame the liver and induce pancytopenia (especially lymphopenia) through direct cellular destruction or bone marrow suppression. A normal serum ferritin level decreases the likelihood of hemophagocytic lymphohistiocytosis.

The gamma gap, calculated as the difference between the total serum protein level and the albumin level, was decreased. When the gamma gap is less than 1.8 g per deciliter, hypogammaglobulinemia is inferred. Hypogammaglobulinemia can be caused by primary immune deficiency syndromes or secondarily by malignant involvement, certain medications, chemotherapy, nephrotic syndrome, and protein-losing enteropathy; the normal serum albumin level is inconsistent with the latter two conditions. This patient was not taking any medications and had only trace protein on urinalysis. Most infectious causes of liver injury and splenomegaly are associated with polyclonal hypergammaglobulinemia, often reflected by an elevated gamma gap (>4 g per deciliter). Therefore, the low gamma gap in this case increases concern for primary immune deficiency or a malignant condition. Quantification of immunoglobulins is an important next step, along with imaging to define the extent of lymphadenopathy and identify targets for tissue sampling.

Serum immunoglobulin levels were decreased, with an IgG level of 336 mg per deciliter (reference range, 610 to 1616), an IgA level of 17 mg per deciliter (reference range, 61 to 348), and an IgM level of 28 mg per deciliter (reference range, 35 to 242). Contrasted computed tomography of the sinuses, chest, abdomen, and pelvis revealed bilateral frontal and maxillary sinusitis, numerous scattered irregular pulmonary nodules of varying sizes with lower lung predominance (Fig. 1A), several subcentimeter hyperdense liver nodules, liver enlargement measuring 20 cm in the craniocaudal dimension (reference value, <13 cm) (Fig. 1B), splenomegaly measuring 20.5 cm (reference value, <13), and diffuse intrathoracic and intraabdominal lymphadenopathy (many nodes >2 cm).

Lymphadenopathy with pulmonary and hepatic nodules arouses concern for disseminated granulomatous inflammation. This pattern can be seen with sarcoidosis, disseminated fungal or mycobacterial infections, lymphoma, and CVID. Sarcoidosis is unlikely to manifest with low immunoglobulin levels. The suggestion of granulomatous inflammation involving the lungs and liver warrants further consideration of histoplasmosis. Zoonotic infections, including Q fever (which can be acquired from livestock exposure) and leptospirosis (endemic in the rodent population in Baltimore), may cause hepatic and pulmonary inflammation but not characteristically sinusitis.

CVID is of particular concern. Establishing a diagnosis of CVID requires ruling out other causes of diffuse lymphadenopathy and hypogammaglobulinemia. Evaluation should also address potential complications of CVID, which include infection and malignant conditions. CVID itself can lead to diffuse granulomatous inflammation but should not be presumed to be the cause until other diagnoses are investigated.

The next steps should include testing serum and respiratory samples (including bronchoalveolar lavage [BAL]) for infection and obtaining tissue

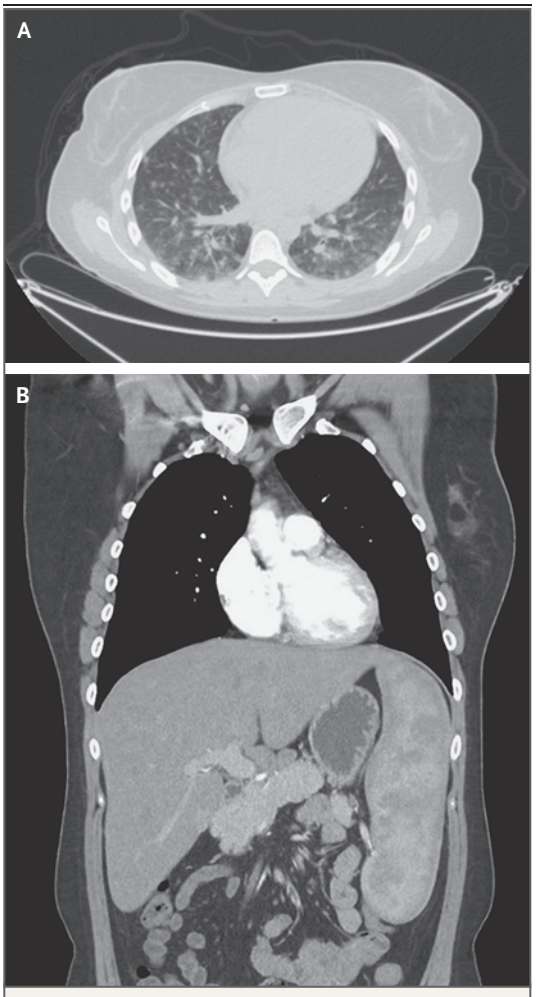

Figure 1. Imaging Studies of the Chest.
An axial computed tomographic scan of the chest shows bilateral pulmonary nodules of varying size in the perilymphatic and peribronchovascular distribution (Panel A); a coronal view shows hepatomegaly and splenomegaly (Panel B).

samples from a lymph node or accessible pulmonary or hepatic nodule for both microbiologic and histologic examination.

The patient received empirical treatment with ceftriaxone and doxycycline. Fever persisted daily, with a maximum oral temperature of 103.6°F (39.8°C). Sputum, urine, and blood cultures collected before antibiotic initiation were negative. Fungal and mycobacterial blood cultures were sent. An interferon-γ release assay for *Mycobacterium tuberculosis* was negative. Urine antigen tests for *Legionella pneumophila* and *Streptococcus pneumoniae* were negative. Nasopharyngeal polymerase-chain-reaction (PCR) testing for *Mycoplasma pneumoniae* and common respiratory viruses was negative. Antibodies against *Helicobacter pylori* and hepatitis A, B, and C viruses were nonreactive. Fourth-generation testing for HIV types 1 and 2 was negative. Serum PCR testing for Epstein–Barr virus, cytomegalovirus, HIV, human T-lymphotropic virus, human herpesvirus types 6 and 8, parvovirus B19, and leptospira was negative. Serologic tests for borrelia, ehrlichia, anaplasma, bartonella, and coxiella were nonreactive. No parasites were visualized on thick and thin blood smears. Serum PCR and IgG tests for *Toxoplasma gondii* were negative. Serum beta-D-glucan and galactomannan levels were within normal limits. Serologic testing for *Histoplasma capsulatum*, cryptococcus, coccidioides, and blastomyces was negative. Serum and urine antigen testing for histoplasma was negative.

Bronchoscopy with BAL revealed 78% lymphocytes, 14% monocytes, and 8% neutrophils; cytologic testing was negative for neoplastic cells. Bacterial, fungal, and mycobacterial cultures of the BAL fluid were negative. Testing for galactomannan was also negative, as were a respiratory viral panel and nucleic acid amplification tests for *Pneumocystis jirovecii*, *M. tuberculosis*, and cytomegalovirus.

Thorough diagnostic evaluation has not identified an infectious cause. Hypogammaglobulinemia, particularly if due to CVID, decreases the sensitivity of antibody-based assays; cultures are therefore of increased importance. Lymphoma remains a concern. At this point, tissue sampling, ideally an excisional lymph-node biopsy, is the most important next step to increase the sensitivity of detecting lymphoma. Tissue culture may occasionally identify disseminated infections (e.g., tuberculosis or endemic fungi) that are not detected in blood, sputum, or BAL samples.

Positron-emission tomography–computed tomography revealed bulky, intensely ^{18}F-fluorodeoxyglucose–avid lymphadenopathy in the neck, mediastinum, abdomen, and pelvis (Fig. 2). Excisional cervical lymph-node biopsy identified nonnecrotizing granulomas without malignant cells (Fig. 3). Peripheral-blood and lymph-node-tissue flow cytometry did not identify any clonal population of cells. Special stains were negative for bacterial, mycobacterial, and fungal organisms; cultures were sent.

Nausea and vomiting persisted. Esophagogastroduodenoscopy revealed edematous duodenal mucosa. Esophageal- and gastric-biopsy samples showed nonnecrotizing granulomas.

The absence of infectious organisms and malignant cells in a metabolically active lymph node reduces the likelihood of disseminated infection and a malignant hematologic condition, respectively. CVID is now the probable diagnosis and explains the patient's nonnecrotizing granulomatous inflammation, pulmonary and hepatic nodules, hepatosplenomegaly, pancytopenia, history of immune thrombocytopenia, and recurrent infections. Sarcoidosis also manifests with granulomatous inflammation, but low serum immunoglobulin levels and recurrent infections are uncharacteristic of this disease. The patient's humoral immune response to vaccination should be assessed to further evaluate the possibility of CVID.

The 20-valent pneumococcal conjugate vaccine was administered. Serologic testing 4 weeks later showed an antibody concentration of 0.4 μg per milliliter for serotype 57 and undetectable levels (<0.3 μg per milliliter) for the remaining 19 serotypes. Genome sequencing and single-nucleotide polymorphism array did not identify a monogenic or polygenic abnormality.

Immunologic studies showed abnormal B-cell subset quantitation and peripheral B-cell differentiation, with severe total CD19+ B-cell lymphopenia (4.6% [reference range, 6.3 to 20.0]; absolute count, 19 [reference range, 96 to 515]) and a relative absence of CD19+/CD27+ memory B cells (4% [reference range, 14 to 44]). The interleukin-18 level was 6332 pg per milliliter (reference value, <477), CXCL9 level 32,051 pg per milliliter (reference value, <647),

interferon-γ level 26.1 pg per milliliter (reference value, <4.2), soluble interleukin-2 receptor level 11,186.9 pg per milliliter (reference range, 175.3 to 858.2), and interleukin-10 level 34.8 pg per milliliter (reference value, <2.8). There were milder elevations in monocyte-derived cytokines: the interleukin-6 level was 7.7 pg per milliliter (reference value, <2.0), and the interleukin-13 level 2.5 pg per milliliter (reference value, <2.3).

The antibody response to vaccination is abnormal (the American Academy of Allergy, Asthma, and Immunology recommends a cutoff for a normal response of >1.3 μg per milliliter for at least 50% of tested antigens). This finding, combined with the hypogammaglobulinemia, is diagnostic of CVID. The elevated levels of serum cytokines indicate T-helper cell–mediated inflammation. The presence of pancytopenia, hepatosplenomegaly, diffuse granulomatous inflammation, and elevated markers of systemic immune activation are concordant with CVID; the history of recurrent sinopulmonary infections and immune thrombocytopenia supports the diagnosis.

Treatment with intravenous immune globulin and prednisone (20 mg daily) was initiated. Her fever, nausea, vomiting, cough, and malaise resolved within 1 week; pancytopenia and abnormal liver-associated enzymes resolved within 1 month, at which time she returned to work. All pending cultures were negative. During 18 months of follow-up, the severity of her hepatosplenomegaly and lymphadenopathy steadily abated.

COMMENTARY

This 31-year-old woman presented with recurrent episodes of fever, sinusitis, cough, nausea, and vomiting, with associated night sweats and

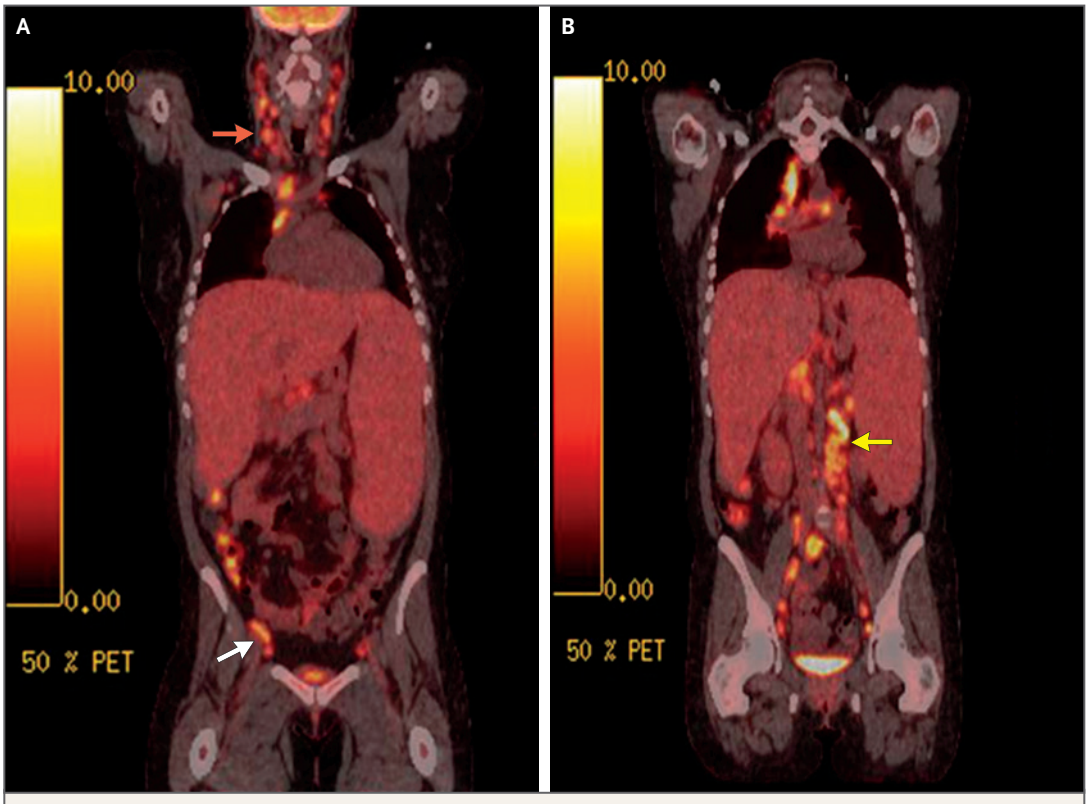

Figure 2. Imaging Studies from the Skull Base to Mid-Thigh.
A coronal positron-emission tomographic–computed tomographic scan shows bulky, ^{18}F-fluorodeoxyglucose–avid lymphadenopathy in the cervical (red arrow) and inguinal (white arrow) chains (Panel A), as well as the periaortic and retroperitoneal chains (Panel B, yellow arrow).

unintentional weight loss. She was found to have pancytopenia, hepatosplenomegaly, pulmonary and hepatic nodules, and nonnecrotizing granulomatous inflammation. Extensive evaluation for infectious and malignant causes was unrevealing. Ultimately, the additional combination of hypogammaglobulinemia and impaired vaccine response led to a diagnosis of CVID.

CVID is a group of primary immune disorders with impaired antibody production characterized by low serum immunoglobulin levels and inadequate antibody response to vaccines and infections. CVID is the most common symptomatic primary immunodeficiency, with a reported incidence of approximately 1 in 20,000 persons.[1] CVID affects both sexes equally and can manifest at any age. Most diagnoses occur between 20 and 40 years of age. The average delay to diagnosis is 6 to 7 years from the onset of cardinal symptoms.[2]

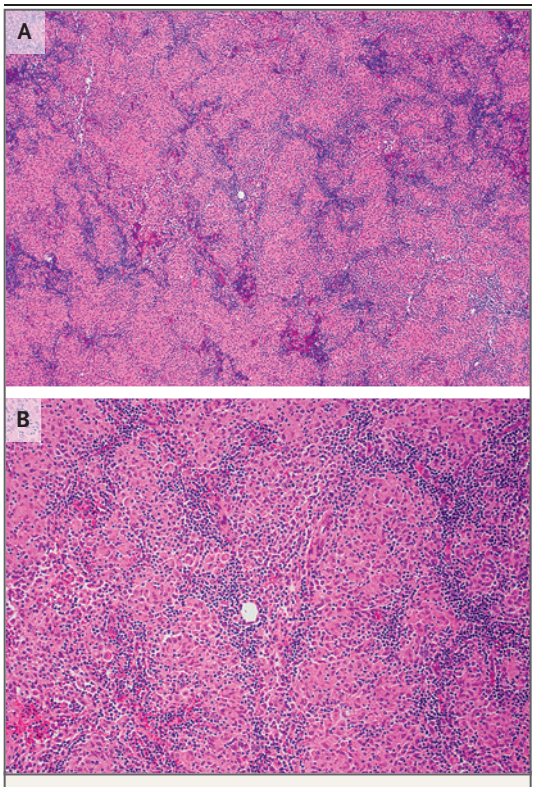

Figure 3. Histologic Examination of an Excisional Biopsy Sample of the Right Supraclavicular Lymph Node.

Hematoxylin and eosin staining showed effaced lymph-node architecture by nonnecrotizing granulomatous inflammation (Panel A); the granulomas were small, compact, and comprised epithelioid histiocytes (Panel B, higher magnification). The histologic images were provided by Caroline Early, M.D.

One hallmark of CVID is frequent sinopulmonary or enteric infections, often with encapsulated bacteria. However, only a third of patients with CVID have infections as the sole manifestation, whereas one or more autoimmune, inflammatory, or malignant complications may develop in the rest.[3,4] These complications include immune thrombocytopenia (as seen in our patient), autoimmune hemolytic anemia, nonnecrotizing granulomatous inflammation, noninfectious pulmonary and gastrointestinal disease, benign lymphoproliferation, and malignant conditions (especially lymphoma).[4] Infectious complications tend to occur early in the disease course, whereas malignant conditions are most often late complications. Autoimmune complications may occur at any time.[5]

The pathogenesis of autoimmunity and granulomatous inflammation in CVID is poorly defined. Current research suggests an intrinsic immunologic defect leading to dysregulation of cellular immunity, in addition to impaired humoral immunity. Along with impaired B-cell function, many patients with CVID have systemic immune activation, especially persistent T-cell activation or serum cytokine elevation.[6]

Granulomatous inflammation in CVID can mimic sarcoidosis. Distinguishing features include recurrent infections and immunologic phenomena, which are common with CVID but not with sarcoidosis. Hypogammaglobulinemia is characteristic of CVID, whereas hypergammaglobulinemia is often observed with sarcoidosis.[7] Granulomas in CVID are often less well-formed, less fibrotic, and more lymphoid-rich than sarcoidosis granulomas.[8]

The diagnosis of CVID involves measurement of a reduced serum level of IgG and a reduced level of either IgA or IgM; the ruling out of secondary causes of hypogammaglobulinemia; and evidence of impaired antibody response to antigenic challenge with vaccination.[9] Peripheral flow cytometry is a useful adjunct but not required for the diagnosis and not commonly used. Quantification of B-cell subsets can help both identify and classify the disease.[9-11] Several genetic variants associated with CVID have been identified, but a molecular diagnosis is not identified in most cases.[1,12] No genetic abnormalities were identified from genome sequencing or single-nucleotide polymorphism array in our patient.

The comprehensive metabolic panel may provide an important clue to the diagnosis. A protein

gap less than 1.8 g per deciliter, as was present in this case, indicates hypogammaglobulinemia.[13] Another finding suggestive of hypogammaglobulinemia is a normal erythrocyte sedimentation rate with an elevated C-reactive protein level; the erythrocyte sedimentation rate measures the time it takes for red cells to settle at the bottom of a test tube, and this is reduced when circulating protein levels are low.

Intravenous immune globulin is the cornerstone of therapy and has been shown in trials to reduce infections[4]; observational data show that its use is associated with improved survival.[3] When there is evidence of autoimmunity or granulomatous inflammation, immune suppression with glucocorticoids is also warranted in some patients. Both were used in the current patient. Although data from randomized trials are lacking to guide treatment, observational data show that 66 to 86% of patients with granulomatous inflammation attain remission with glucocorticoids alone.[14] If there is severe or persistent inflammation, glucocorticoid-sparing agents (most commonly rituximab, azathioprine, or inhibitors of tumor necrosis factor α) are added, with a response occurring in more than 90% of patients in case series.[14,15]

This case highlights the importance of including CVID in the differential diagnosis of multisystem granulomatous disease. In this patient, abnormalities in humoral and cellular immunity from CVID led to recurrent infections and granulomatous inflammation. Identifying the diagnosis led to effective treatment with immune globulins and glucocorticoids.

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

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