CASE RECORDS of the MASSACHUSETTS GENERAL HOSPITAL

Case 20-2024: A 73-Year-Old Man with Recurrent Fever and Liver Lesions

Lakshmi Ganapathi, M.B., B.S., Rory L. Cochran, M.D., Ph.D.,
Gregory K. Robbins, M.D., Sara Barmettler, M.D., Steven M. Holland, M.D.,
and Emad I. Ababneh, M.D.

PRESENTATION OF CASE

Dr. Hayden S. Andrews (Medicine): A 73-year-old man was admitted to this hospital because of recurrent fever.

The patient had been in his usual state of health until 22 months before the current presentation, when 2 days of fever, cough, and fatigue developed. The patient sought evaluation at a primary care clinic affiliated with another hospital. Empirical oral antibiotic agents were administered to treat pneumonia. During the subsequent month, the cough resolved but fever recurred intermittently. The patient returned to the primary care clinic.

Dr. Rory L. Cochran: Computed tomography (CT) of the chest, abdomen, and pelvis, performed after the administration of intravenous contrast material, showed scattered solid pulmonary nodules, a few hepatic hemangiomas, and bilobar subcentimeter hepatic hypodensities (Fig. 1A). There was borderline splenomegaly, with the spleen measuring 13.0 cm in length (reference range, <13.2), and there was no lymphadenopathy.

One week later, magnetic resonance imaging (MRI) of the abdomen (Fig. 1B) revealed that the hepatic lesions, which appeared hyperintense on T2-weighted images with enhancement, had increased in number and size, measuring up to 2.4 cm in diameter. Some lesions were only enhanced peripherally, a finding that suggested central necrosis.

Dr. Andrews: A bone marrow biopsy and a liver biopsy were performed.

Dr. Emad I. Ababneh: Pathological examination of a bone marrow–biopsy specimen reportedly revealed normocellular bone marrow and rare nonnecrotizing granulomas. Pathological examination of the liver-biopsy specimen showed prominent portal histiocytosis and portal and lobular nonnecrotizing granulomas (Fig. 2A), with detached neutrophilic aggregates; a few of these foci were fibrin-ring granulomas (Fig. 2B). Special staining for acid-fast bacilli, Grocott's methenamine silver staining, and Brown–Hopps staining were negative for organisms. Immunohistochemical staining for cytomegalovirus, Epstein–Barr virus, and spirochetes was negative. Langerin staining for Langerhans' cells was negative.

From the Departments of Pediatrics (L.G.), Radiology (R.L.C.), Medicine (G.K.R., S.B.), and Pathology (E.I.A.), Massachusetts General Hospital, and the Departments of Pediatrics (L.G.), Radiology (R.L.C.), Medicine (G.K.R., S.B.), and Pathology (E.I.A.), Harvard Medical School — both in Boston; and the National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD (S.M.H.).

N Engl J Med 2024;390:2309-19.
DOI: 10.1056/NEJMcpc2309383

CME

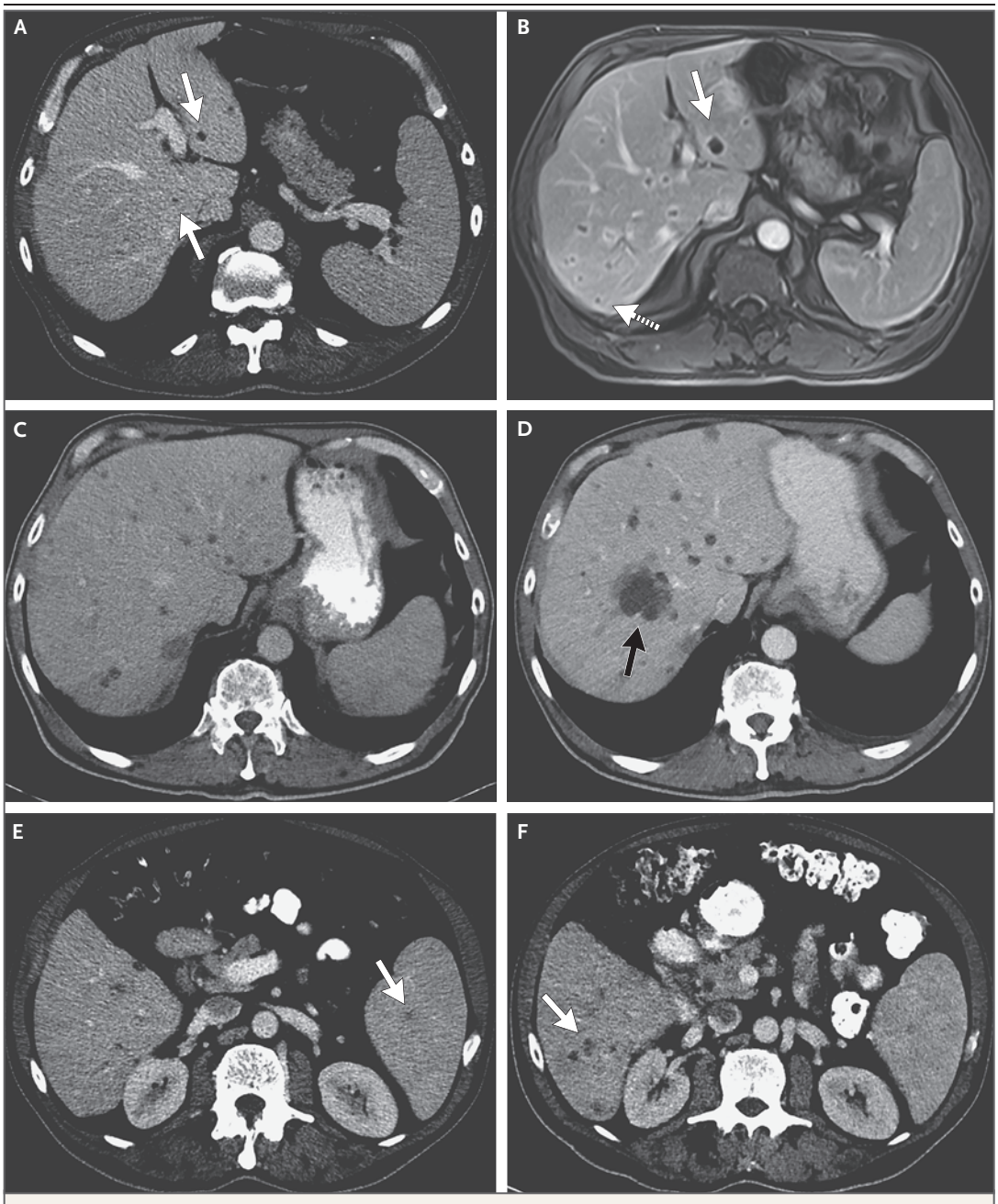

Figure 1. Imaging Studies.

A contrast-enhanced CT image of the abdomen, obtained 21 months before the current presentation (Panel A), shows numerous scattered subcentimeter hypodensities (arrows) throughout the liver. A contrast-enhanced, T1-weighted, fat-saturated image from MRI, obtained 21 months before the current presentation (Panel B), shows new (dashed arrow) and enlarged (solid arrow) hepatic lesions, with some visible peripheral enhancement. A contrast-enhanced CT image of the abdomen, obtained 20 months before the current presentation (Panel C), shows numerous hepatic lesions. A contrast-enhanced CT image of the abdomen, obtained 18 months before the current presentation (Panel D), again shows numerous hepatic lesions; percutaneous drainage of the largest lesion (arrow) was subsequently performed. A contrast-enhanced CT image, obtained 1 month before the current presentation (Panel E), shows an enlarged spleen with new splenic hypodensities (arrow). A contrast-enhanced CT image, obtained on admission to this hospital (Panel F), shows new and enlarging hepatic lesions (arrow) and splenic lesions.

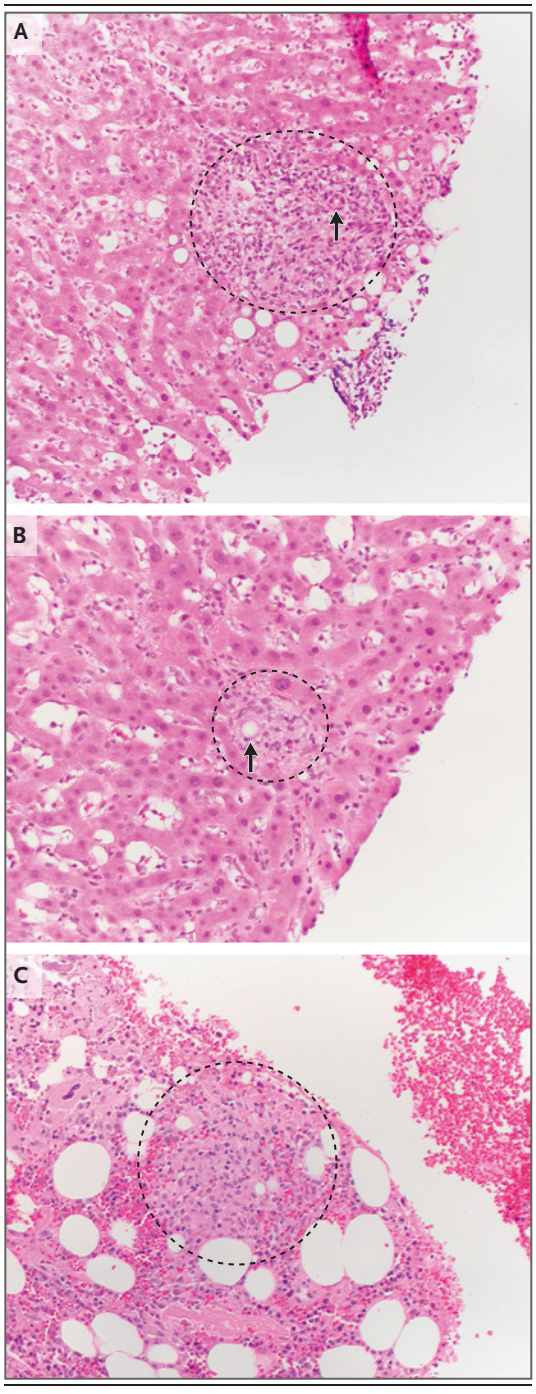

Figure 2. Specimens from Liver and Bone Marrow Biopsies.

Hematoxylin and eosin staining of a liver-biopsy specimen, obtained 21 months before the current presentation (Panels A and B), shows portal tracts expanded by a proliferation of epithelioid histiocytes that are forming a nonnecrotizing granuloma (Panel A, circle); a bile duct is visible (Panel A, arrow), which indicates the location in a portal tract. A small (micro) granuloma in liver lobules (Panel B, circle) shows a fibrin ring (Panel B, arrow); this finding is known as fibrin-ring granuloma. A bone marrow–biopsy specimen, obtained 19 months before the current presentation (Panel C), shows similar proliferation and granuloma formation (circle) in the clot section.

Dr. Andrews: Twenty months before the current presentation, the patient sought evaluation in the emergency department of this hospital because of 2 days of intermittent fever, which often occurred with chills, night sweats, and abdominal discomfort.

Before the onset of this illness, the patient had no history of recurrent fever or severe bacterial infections. He had hypertension, hyperlipidemia, and coronary artery disease that had led to percutaneous coronary intervention of three vessels 12 years before the current presentation. He also had a history of hiatal hernia, gastroesophageal reflux disease, and gallstone pancreatitis that had led to a cholecystectomy 9 years earlier. Medications included rosuvastatin, aspirin, ferrous sulfate, and a multivitamin. He had no known drug allergies.

The patient lived in a suburban area of New England with his wife and pet cats and finches. He was a veteran who had been stationed in Guam, Thailand, and Japan, as well as in Vietnam 5 decades before the current presentation. He had traveled to the Southwest and Southeast regions of the United States 2 years before the current presentation. The patient was retired and had previously worked in the food-services industry. He was a lifelong nonsmoker, and he did not use alcohol or illicit drugs. His family history included idiopathic thrombocytopenic purpura, psoriasis, granuloma annulare, and chronic pancreatitis in his siblings. His son had iritis. There was no family history of frequent infections or early childhood deaths.

The temporal temperature was 37.3°C, the pulse 79 beats per minute, the blood pressure 113/56 mm Hg, the respiratory rate 20 breaths per minute, and the oxygen saturation 99% while the patient was breathing ambient air. The lungs were clear on auscultation. He had mild tenderness in the epigastrium, as well as splenomegaly. Leukopenia and anemia were present. The levels of angiotensin-converting enzyme, 1,3-β-D-glucan, and galactomannan were normal. Testing for infection with *Mycobacterium tuberculosis*, human immunodeficiency virus, Epstein–Barr virus, cytomegalovirus, and hepatitis B and C viruses was negative. Testing for infection with *Chlamydia psittaci* and *Coxiella*

burnetii was also negative, as was testing for brucellosis, bartonellosis, listeriosis, histoplasmosis, coccidioidomycosis, cryptococcosis, blastomycosis, malaria, babesiosis, toxoplasmosis, syphilis, Lyme disease, anaplasmosis, and ehrlichiosis. Other laboratory test results are shown in Table 1.

Dr. Cochran: CT of the chest, abdomen, and pelvis revealed progressive increases in the number and size of the hepatic lesions (Fig. 1C), which measured up to 3.0 cm in diameter. There was also splenomegaly, with the spleen measuring 13.5 cm in length.

Dr. Ababneh: Pathological examination of a bone marrow–biopsy specimen (Fig. 2C) and of a specimen obtained on fine-needle aspiration of the liver showed nonnecrotizing granulomas like those seen on the previous liver biopsy. Cytologic examination of the specimens and flow cytometry of the peripheral blood were normal.

Dr. Andrews: Transthoracic echocardiography (TTE) showed no valvular vegetations. Empirical doxycycline therapy was started, and the patient was discharged home.

During the subsequent 19 months, the patient continued to have intermittent fever, chills, and epigastric pain, which led to additional admissions to this hospital and the other hospital. During the second admission to this hospital, 19 months before this admission, empirical doxycycline therapy was stopped, and empirical prednisone therapy was started, along with trimethoprim–sulfamethoxazole for prophylaxis against *Pneumocystis jirovecii* pneumonia.

Dr. Cochran: During the third admission, 18 months before this admission, CT of the chest, abdomen, and pelvis revealed worsening splenomegaly, with the spleen measuring 14.2 cm in length, and hepatic lesions that had increased in size and number. A percutaneous drain was placed in the largest hepatic lesion (Fig. 1D), which measured 4.0 cm in diameter.

Dr. Andrews: Bacterial, mycobacterial, and fungal cultures of the drained fluid did not grow organisms; however, culture of the blood showed growth of *Klebsiella pneumoniae*. The patient underwent esophagogastroduodenoscopy (EGD) and colonoscopy, which revealed gastritis, esophagitis, and diverticulosis. Treatment with prednisone and trimethoprim–sulfamethoxazole was stopped, intravenous ceftriaxone was started, and he was discharged home.

The patient's fourth and fifth admissions occurred at the other hospital 17 months and 16 months before this admission, respectively. During the fourth admission, another percutaneous drain was placed in a dominant hepatic lesion, and cultures reportedly resulted in no growth. The patient received a course of empirical broad-spectrum antibiotics. During the fifth admission, cultures again reportedly showed no growth. The patient received another course of empirical broad-spectrum antibiotics and was discharged home with instructions to restart empirical doxycycline therapy.

Dr. Cochran: The sixth admission also occurred at the other hospital, 1 month before this admission. CT of the abdomen revealed numerous new and enlarged hypodense hepatic lesions with new scattered subcentimeter splenic hypodensities (Fig. 1E).

Dr. Abahneh: Another liver biopsy was performed, which revealed liver parenchyma with abscess, acute inflammation and debris, and histiocytic and stromal reaction with histiocytic aggregates. Grocott's methenamine silver staining showed few bacteria, and a culture grew *Escherichia coli*; no acid-fast bacilli or fungal forms were detected.

Dr. Andrews: Treatment with doxycycline was stopped, intravenous ceftriaxone was started, and the patient was discharged home with instructions to start taking ciprofloxacin. During the subsequent month, fever did not abate. The patient returned to this hospital for a seventh admission.

Dr. Cochran: CT of the chest, abdomen, and pelvis showed stable scattered solid pulmonary nodules, new interstitial pulmonary edema, and increased splenomegaly, with the spleen measuring 15.0 cm in length. There was also an increase in the size and number of the hepatic and splenic hypodensities (Fig. 1F).

Dr. Andrews: The patient underwent EGD, which showed portal hypertensive gastropathy. TTE showed no vegetations. Aspiration of a hepatic lesion was performed, and a culture grew *Enterococcus faecalis*. Treatment with amoxicillin was started.

A diagnostic test was performed.

DIFFERENTIAL DIAGNOSIS

Dr. Lakshmi Ganapathi: This 73-year-old man presented with a 22-month illness that was notable for intermittent fever that had responded poorly to multiple courses of broad-spectrum antibiotics as well as recurrent invasive bacterial infec-

Table 1. Laboratory Data.*

Variable	Reference Range, This Hospital†	On First Admission, 21 Mo before This Admission	On This Admission
White-cell count (per μl)	4500–11,000	2970	5200
Differential count (per μl)			
Neutrophils	1800–7700	2160	4250
Lymphocytes	1000–4800	580	480
Monocytes	200–1200	210	430
Eosinophils	0–900	0	0
Basophils	0–300	10	20
Hemoglobin (g/dl)	13.5–17.5	10.0	11.4
Hematocrit (%)	41.0–53.0	29.9	37.2
Platelet count (per μl)	150,000–400,000	160,000	238,000
Sodium (mmol/liter)	135–145	135	134
Potassium (mmol/liter)	3.4–5.0	4.0	4.6
Chloride (mmol/liter)	98–108	99	99
Carbon dioxide (mmol/liter)	23–32	23	19
Urea nitrogen (mg/dl)	8–25	18	12
Creatinine (mg/dl)	0.60–1.50	1.01	0.87
Glucose (mg/dl)	70–110	115	104
Aspartate aminotransferase (U/liter)	10–40	46	26
Alanine aminotransferase (U/liter)	10–55	46	27
Alkaline phosphatase (U/liter)	45–115	439	577
Total bilirubin (mg/dl)	0.0–1.0	0.5	0.7
Albumin (g/dl)	3.3–5.0	3.4	3.5
Total protein (g/dl)	6.0–8.3	5.9	6.8
C-reactive protein (mg/liter)	0.0–8.0	64.4	—
Erythrocyte sedimentation rate (mm/hr)	0–13	29	—
Angiotensin-converting enzyme (U/liter)	8–53	17	30
Prothrombin time (sec)	11.5–14.5	13.4	12.9
Prothrombin-time international normalized ratio	0.9–1.1	1.0	1.0

* To convert the values for urea nitrogen to millimoles per liter, multiply by 0.357. To convert the values for creatinine to micromoles per liter, multiply by 88.4. To convert the values for glucose to millimoles per liter, multiply by 0.05551. To convert the values for bilirubin to micromoles per liter, multiply by 17.1.

† Reference values are affected by many variables, including the patient population and the laboratory methods used. The ranges used at Massachusetts General Hospital are for adults who are not pregnant and do not have medical conditions that could affect the results. They may therefore not be appropriate for all patients.

tions that had required prolonged administration of antibiotics for resolution. The patient also had persistent lymphopenia, an elevated level of alkaline phosphatase, progressive hypodensities in the liver and spleen, and multiple pulmonary nodules. Splenomegaly had worsened over time, and portal hypertension had developed. Histopathological examination of bone marrow and liver tissue had revealed nonnecrotizing granulomas. Presumably, the pulmonary and splenic nodules also indicate granulomatous inflammation. In formulating a differential diagnosis, I will focus on indolent disease processes that could lead to the development of nonnecrotizing granulomas in multiple organs.

INFECTIONS

The differential diagnosis for systemic granulomatous disease is broad and includes bacterial, myco-

bacterial, fungal, and parasitic infections. Examples of nonmycobacterial bacterial infections include brucellosis, bartonellosis, and *C. burnetii* infection; the patient underwent tests for each of these infections, and all were negative. He also underwent an evaluation that was nonrevealing for fungal infections, including histoplasmosis, coccidioidomycosis, cryptococcosis, and blastomycosis.

The patient had previously lived in both Vietnam and Thailand. This history raises the possibility of melioidosis, a disease that is caused by the gram-negative bacterium *Burkholderia pseudomallei*, which is endemic in countries in Southeast Asia.[1,2] The organism is found in the soil and water, and transmission occurs primarily by inoculation through the skin and aerosol inhalation. Although acute manifestations of melioidosis have been described in people living in regions where the disease is endemic,[3-5] including military personnel during the Vietnam War,[6,7] the initial infection can be asymptomatic or subclinical. In addition, melioidosis can have a long period of latency, recrudescing with severe disease manifestations decades after the initial infection.[8] Melioidosis lesions can manifest acutely as abscesses or chronically as localized or systemic granulomas. Although melioidosis has more commonly been described in those who have coexisting conditions (e.g., heavy alcohol use, renal impairment, immunocompromise, and advanced diabetes), it has also been described in otherwise immunocompetent persons.[9,10] In addition, recrudescent disease has been described in persons older than 60 years of age.[8] However, *B. pseudomallei* is not difficult to grow in culture, and multiple specimens obtained from the granulomatous lesions in this patient did not yield growth of this organism.

In this patient with systemic granulomatous disease, it is also important to consider diseases caused by mycobacteria, including *M. tuberculosis*, and nontuberculous mycobacteria. However, no acid-fast bacilli were visible on multiple acid-fast stain evaluations, an interferon-γ release assay for *M. tuberculosis* was negative, and repeated mycobacterial cultures did not yield growth.

SARCOIDOSIS

The presence of nonnecrotizing granulomas in multiple organs also suggests the possibility of sarcoidosis. Although this patient did not have hilar lymphadenopathy or reticular opacities that were consistent with sarcoidosis on chest imaging, the spectrum of clinical features of sarcoidosis is highly variable and can include pulmonary and extrapulmonary manifestations, including hepatic involvement.[11] Sarcoidosis can also be associated with various hematologic abnormalities, including lymphopenia, as was seen in this patient.[11] A normal level of angiotensin-converting enzyme does not rule out sarcoidosis, given the poor sensitivity and specificity of this test. However, a diagnosis of sarcoidosis would not explain this patient's recurrent invasive bacterial infections.

IMMUNODEFICIENCY SYNDROMES

In addition to the presence of nonnecrotizing granulomas in multiple organs, this patient had recurrent episodes of invasive bacterial infections, some of which required prolonged courses of antimicrobial therapy for clearance. This suggests the possibility of an underlying immunodeficiency. A thorough evaluation ruled out secondary causes of immunodeficiency, including cancer and human immunodeficiency virus infection. Therefore, a primary immunodeficiency is a strong consideration.

Primary immunodeficiencies are classified according to the component of the immune system that is primarily disrupted — either innate or adaptive immunity.[12] Primary immunodeficiencies also include syndromes associated with autoimmunity or immune dysregulation as a predominant feature.[12] The age at the onset of primary immunodeficiencies is dependent on the severity of genetic defects. In persons who have severe genetic defects, symptoms develop in early life; in those with milder or partial defects, symptoms may not develop until adulthood. Susceptibility of the patient to specific pathogens and the presence of associated clinical features can offer additional clues about underlying immune defects.

ANTI–INTERFERON-γ AUTOANTIBODIES

Anti–interferon-γ autoantibodies cause an adult-onset immunodeficiency that can occur in persons older than 50 years of age. Persons with anti–interferon-γ autoantibodies have increased susceptibility to disseminated infections by intracellular organisms, but nontuberculous mycobacteria are by far the most common pathogen.[13] In addition, cases of anti–interferon-γ autoantibodies have primarily been described in persons of Asian descent,[14] making this an unlikely diagnosis in this patient.

CHRONIC GRANULOMATOUS DISEASE

Chronic granulomatous disease could explain this patient's recurrent liver abscesses, in addition to the noncaseating granulomas. Any pathologic mutation within the six genes that encode the subunits of the NADPH oxidase system can lead to the development of chronic granulomatous disease, which is characterized by the disruption of superoxide production (i.e., "respiratory burst") in phagocytes and impaired phagocyte function.[15,16] In addition to the development of noncaseating granulomas, persons with chronic granulomatous disease have increased susceptibility to infections with catalase-positive organisms (including klebsiella species). In persons who have partial protein expression and residual superoxide production, symptoms may develop in adulthood. However, reports of symptoms first developing in patients beyond the sixth decade of life are rare,[17] making chronic granulomatous disease an unlikely diagnosis in this patient.

COMMON VARIABLE IMMUNODEFICIENCY

Common variable immunodeficiency (CVID) is the most prevalent symptomatic primary immunodeficiency in adults, and it can occur at any age without sex predominance.[18] Although CVID comprises a heterogeneous group of disorders, one key feature is the low levels of circulating immunoglobulins that are caused by defects in B-cell differentiation.[18] Low immunoglobulin levels are primarily associated with recurrent sinopulmonary and gastrointestinal bacterial infections, including infections with encapsulated bacteria.[18] The clinical presentation can vary but may include the development of noncaseating granulomas, autoimmune cytopenias, lymphoproliferation, and cancers.[18] The elevated level of alkaline phosphatase and the development of portal hypertension in this patient also support a diagnosis of CVID, since some patients with CVID have liver involvement.[19,20] A common cause of noncirrhotic portal hypertension in patients with CVID is nodular regenerative hyperplasia (NRH).[19,20]

To evaluate for CVID, I would measure serum immunoglobulin levels and the response to vaccine challenges. I would also recommend a liver biopsy to evaluate for NRH.

DR. LAKSHMI GANAPATHI'S DIAGNOSIS

Common variable immunodeficiency.

DIAGNOSTIC TESTING

Dr. Sara Barmettler: Measurement of the serum immunoglobulin levels revealed hypogammaglobulinemia with a low level of IgG (419 mg per deciliter; reference range, 614 to 1295) and a low level of IgM (30 mg per deciliter; reference range, 53 to 334). The IgA level was normal. The serum free light chain ratio and the results of serum protein electrophoresis were normal. Functional antibody testing revealed a protective level of IgG against tetanus, but an inadequately protective level of serotype-specific IgG against *Streptococcus pneumoniae* (only 8 of 23 serotypes, or 35% protective), despite vaccination challenge with 23-valent pneumococcal polysaccharide. The inadequate response to vaccination challenge suggested a lack of functional antibody production. Treatment with immunoglobulin replacement therapy was started while additional testing was performed.

The international consensus document for CVID includes the following diagnostic criteria: one of the characteristic clinical manifestations (infection, autoimmunity, or lymphoproliferation); reduced serum concentrations of IgG in combination with decreased levels of IgA or IgM (or both); poor or no response to immunizations; the absence of another defined immunodeficiency; and an age older than 4 years.[21,22] The next step in this case was to rule out other defined immunodeficiencies.

Classic X-linked and autosomal chronic granulomatous disease was ruled out with the use of dihydrorhodamine testing, which showed normal neutrophil oxidative burst. The classic immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome was ruled out by means of regulatory T-cell testing. Toll-like receptor testing ruled out toll-like receptor deficiency. Testing of the interferon-γ and interleukin-12 pathway was performed to evaluate for certain causes of Mendelian susceptibility to mycobacterial disease. This testing showed normal expression of interferon-γ receptor 1 (CD119) on monocytes, normal activation of interferon-γ–stimulated phosphorylated signal transducer and activator of transcription 1 (pSTAT1) in monocytes, normal expression of interleukin-12RB1 (CD212) on lymphocytes, and normal interleukin-12–induced pSTAT4. Testing for anti–interferon-γ autoantibodies was negative.

Genetic testing was performed initially with a panel of 407 primary immunodeficiency genes.

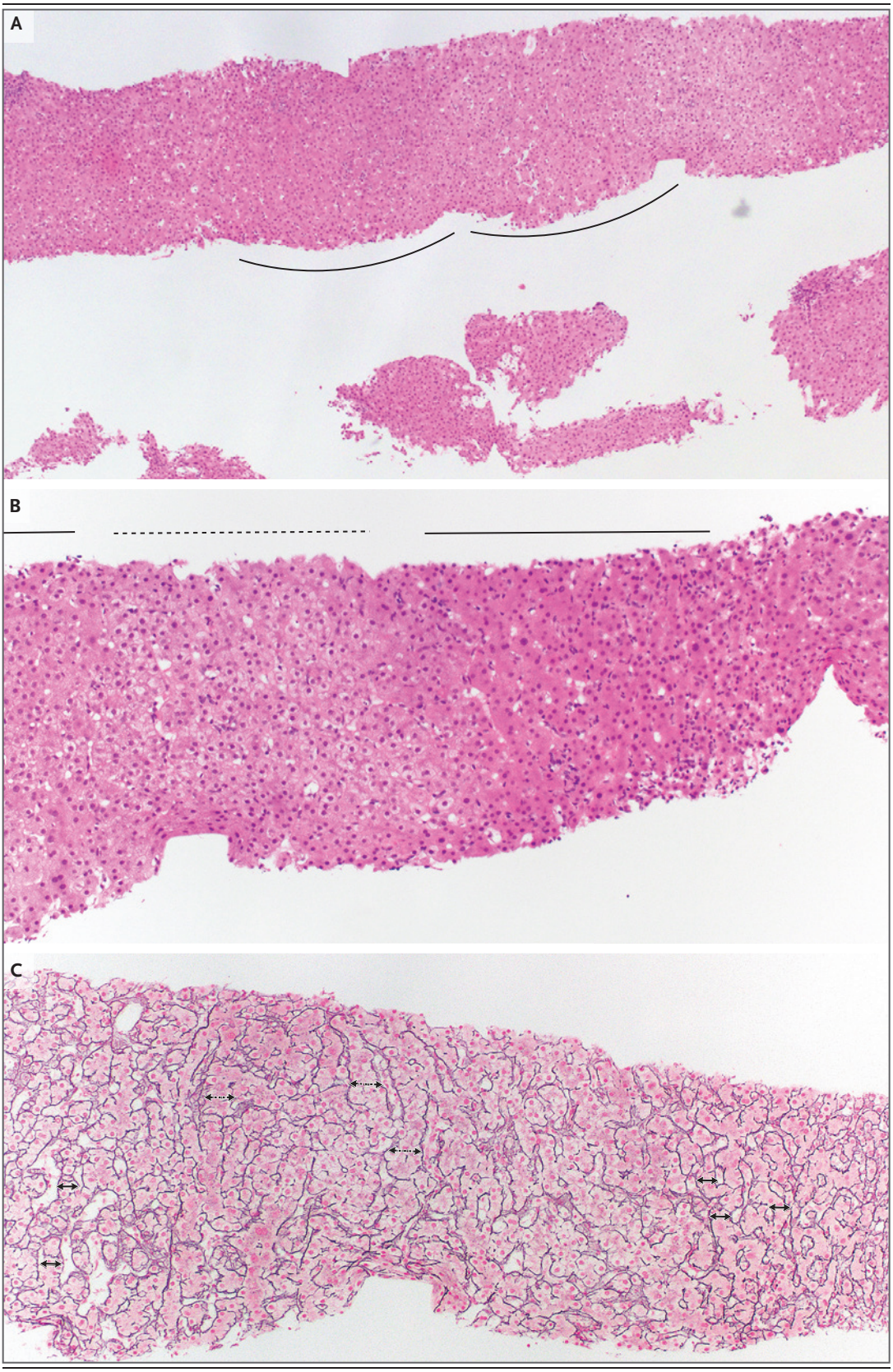

Figure 3 (facing page). Specimen from a Repeat Liver Biopsy.

On hematoxylin and eosin staining of slides from a core needle–biopsy specimen (Panels A and B), the edges show humps (Panel A, curved lines) that are indicative of possible nodularity. A vague zonation of compact hepatic trabeculae (Panel B, solid lines), as compared with spread out and wide trabeculae (Panel B, dashed line), is present. Reticulin staining (Panel C) also shows the narrower trabeculae (solid arrows) and wider trabeculae (dashed arrows), highlighting the distinction between these different areas. These findings are subtle, and although they are not specific, in the context of the patient's presentation, they are consistent with vascular remodeling in the form of nodular regenerative hyperplasia.

This genetic testing identified three variants of unknown significance: one variant in *ATM*, which is associated with autosomal recessive ataxia–telangiectasia; one in *FANCI*, which is associated with autosomal recessive Fanconi's anemia; and one in *SEMA3E*, which has a preliminary association with chronic kidney disease, seizures, and hypothyroidism. The *ATM* and *FANCI* variants were not thought to be relevant in this case because of both the inheritance patterns of the genes and the mismatch between the clinical phenotype of the patient and the reported disease associations. Similarly, with the *SEMA3E* variant, the patient did not have the associated clinical features. Whole-exome sequencing was performed but did not reveal any pathogenic variants.

Flow cytometry showed lymphopenia with very low levels of total absolute CD3+ T cells, CD4+ T cells (77 cells per microliter), CD8+ T cells, and CD19+ B cells. Lymphocyte proliferation testing, which was performed to evaluate function of the T cells, was normal. Advanced flow cytometry showed low levels of memory B cells and a low level of switched memory B cells (a finding that has been associated with an increased risk of autoimmunity, splenomegaly, and lymphoproliferative disease in patients with CVID), as well as a low naïve CD4 T-cell compartment.

Historically, patients with CVID were identified on the basis of the increased risk of infections.[23] However, there is a subgroup of patients with additional autoimmune and lymphoproliferative complications, including conditions with liver involvement, such as NRH.[24-26] Patients with NRH often first present with an elevated level of alkaline phosphatase, with or without changes in the levels of aspartate aminotransferase and alanine aminotransferase. This finding can be followed by the development of portal hypertension, varices, and jaundice.[27,28] The preferred test for the diagnosis of NRH is liver biopsy.

Given the clinical presentation of this patient and the results of the laboratory tests, a clinical diagnosis of CVID was made. A liver biopsy was performed to evaluate for NRH.

PATHOLOGICAL DISCUSSION

Dr. Ababneh: On a repeat liver biopsy, multiple needle cores showed liver parenchyma with nodular edges (Fig. 3). No pathologically significant inflammation or granulomas were present. The parenchyma had a subtle nodular appearance. The nodularity was highlighted by reticulin staining to delineate the hepatic plates and show areas of atrophic hepatic plates adjacent to areas of modestly thickened ones. These findings were subtle but consistent with vascular remodeling in the form of NRH.

PATHOLOGICAL DIAGNOSIS

Common variable immunodeficiency with nodular regenerative hyperplasia.

DISCUSSION OF MANAGEMENT

Dr. Steven M. Holland: This case reflects the lack of certainty that syndromic diagnoses entail and the accompanying lack of prognostic clarity. Immunoglobulin failure in a patient with multisystem granulomatous disease is consistent with the complicated form of CVID. CVID that occurs with a CD4 T-cell count of less than 200 cells per microliter is associated with a combination of B-cell and T-cell defects and has been called late-onset combined immunodeficiency.

In 1971, the World Health Organization codified the term "common variable immunodeficiency."[29] Even then, CVID was recognized as a predominantly B-cell disorder, but some patients had T-cell dysfunction and others had lymphoid cancers. Now, more than 50 years later, disease-causing gene mutations have been associated with CVID. In one study involving patients with CVID, such mutations were identified in 31%, 36%, and 54% of patients from cohorts in the United States, Sweden, and Iran, respectively.[30]

Although the specific genetic causes differ between countries, the identification of underlying genes is only somewhat more likely in patients with complicated CVID than in those with uncomplicated disease. Uncomplicated CVID, which occurs with antibody failure, bronchiectasis, splenectomy, or cancers other than lymphoma, is associated with relatively normal survival (if treatment with immunoglobulin replacement therapy is provided). In sharp contrast, complicated CVID, which may be characterized by autoimmunity, gastrointestinal disease, liver disease, lymphoma, or severe lung disease, is associated with markedly shorter survival than uncomplicated CVID.[31] Complications such as granulomatous–lymphocytic interstitial lung disease, nodular lymphoid hyperplasia of the gastrointestinal tract, and symptoms resembling inflammatory bowel disease of the gastrointestinal tract have been difficult to manage.[32]

Among the most insidious complications is NRH, which is associated with portal hypertension and granulomatous complications.[28] NRH occurs in 5 to 10% of patients with CVID. The resulting portal hypertension drives hypersplenism, splenic sequestration–related cytopenias, infections, and sequelae such as ascites.[27] Other complications related to progressive NRH in patients with CVID include pulmonary arterial hypertension and hepatopulmonary syndrome. NRH has recurred in transplanted livers, a finding consistent with NRH being driven primarily by a host immune process.[33] It is now clear that NRH occurs in the context of many immunodeficiencies, including complicated CVID (as was seen in this patient), as well as other combined immunodeficiencies, phagocyte defects such as chronic granulomatous disease, and STAT defects.[20]

What is behind NRH and its associated adverse outcomes? As compared with uncomplicated CVID, CVID that occurs with inflammatory complications is associated with increased levels of circulating bacterial DNA, soluble CD14, and circulating interferon-γ, all of which augment inflammation.[34] Immune modulation and immune suppression are often used to control complicated CVID. B-cell and T-cell counts have a prognostic value (lower is worse), as do serum bacterial DNA levels and interferon-γ activity (higher is worse).

Intravenous or subcutaneous immunoglobulin replacement therapy is administered monthly with a target trough concentration of approximately 900 mg per deciliter, but there can be individual variation. Levels can be affected by protein-losing enteropathy, nephropathy, and catabolism. Prophylactic antibiotics may help in preventing bronchiectasis and sinusitis.

In patients with CVID, it is sensible to monitor blood counts, liver and kidney function, trough IgG concentration, and pulmonary function on a yearly or more frequent basis. Monitoring for liver disease involves assessments for splenomegaly, a low platelet count, and an elevated alkaline phosphatase level, as well as fibroscans and imaging. Monitoring for lung disease involves pulmonary-function tests and CT of the chest, performed every 3 to 4 years or as needed. Upper and lower endoscopy may need to be performed to investigate for bowel disease. Measurement of bone density and assessments for other consequences of malabsorption should be considered.[32]

Granulomatous–lymphocytic interstitial lung disease is treated with glucocorticoids, rituximab, and an antimetabolite.[35] Inflammatory bowel disease is often treated with glucocorticoids and biologic agents (e.g., tumor necrosis factor inhibitors, vedolizumab, ustekinumab, or possibly Janus kinase inhibitors).[36] NRH treatment includes the administration of glucocorticoids for granulomatous involvement, as well as the management of portal hypertension and consideration of hematopoietic stem-cell transplantation and liver transplantation.[20,37]

FOLLOW-UP

Dr. Gregory K. Robbins: The patient's condition initially improved with immunoglobulin replacement therapy. He continued to have intermittent fever and rigors; however, the episodes were much less severe, and he received outpatient treatment with oral antibiotics. Treatment with glucocorticoids and biologics to target NRH was considered, but this approach was determined to be too risky in this patient.

Two years later, new small-volume ascites had developed, and by the following year, he had received a diagnosis of esophageal varices. Over the course of the following year, progressive weight loss occurred, and pancytopenia, multifocal small hepatic and splenic lesions, worsening splenomegaly, and large-volume ascites developed. He was admitted to this hospital after a variceal banding with melena, hypotension, and multiorgan failure. The goals of care were changed to comfort, and the patient died in the hospital.

FINAL DIAGNOSIS

Common variable immunodeficiency.

This case was presented at the 2023 Harvard Medical School course "Infectious Disease in Adults," directed by Drs. Nesli Basgoz, Ruanne V. Barnabas, Rajesh T. Gandhi, and Sandra B. Nelson.

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

REFERENCES

1. Birnie E, Virk HS, Savelkoel J, et al. Global burden of melioidosis in 2015: a systematic review and data synthesis. Lancet Infect Dis 2019;19:892-902.
2. Nasner-Posso KM, Cruz-Calderón S, Montúfar-Andrade FE, Dance DAB, Rodriguez-Morales AJ. Human melioidosis reported by ProMED. Int J Infect Dis 2015; 35:103-6.
3. Tran QTL, Phan PH, Bui LNH, et al. Child melioidosis deaths caused by Burkholderia pseudomallei-contaminated borehole water, Vietnam, 2019. Emerg Infect Dis 2022;28:1689-93.
4. Meumann EM, Cheng AC, Ward L, Currie BJ. Clinical features and epidemiology of melioidosis pneumonia: results from a 21-year study and review of the literature. Clin Infect Dis 2012;54:362-9.
5. Sia TLL, Mohan A, Ooi MH, et al. Epidemiological and clinical characteristics of melioidosis caused by gentamicin-susceptible *Burkholderia pseudomallei* in Sarawak, Malaysia. Open Forum Infect Dis 2021;8(10):ofab460.
6. Weber DR, Douglass LE, Brundage WG, Stallkamp TC. Acute varieties of melioidosis occurring in U.S. soldiers in Vietnam. Am J Med 1969;46:234-44.
7. Brundage WG, Thuss CJ Jr, Walden DC. Four fatal cases of melioidosis in U.S. soldiers in Vietnam. Bacteriologic and pathologic characteristics. Am J Trop Med Hyg 1968;17:183-91.
8. Koponen MA, Zlock D, Palmer DL, Merlin TL. Melioidosis. Forgotten, but not gone! Arch Intern Med 1991;151:605-8.
9. Le Tohic S, Montana M, Koch L, Curti C, Vanelle P. A review of melioidosis cases imported into Europe. Eur J Clin Microbiol Infect Dis 2019;38:1395-408.
10. Gauthier J, Gérôme P, Defez M, et al. Melioidosis in travelers returning from Vietnam to France. Emerg Infect Dis 2016; 22:1671-3.
11. Crouser ED, Maier LA, Wilson KC, et al. Diagnosis and detection of sarcoidosis: an official American Thoracic Society clinical practice guideline. Am J Respir Crit Care Med 2020;201(8):e26-e51.
12. McCusker C, Upton J, Warrington R. Primary immunodeficiency. Allergy Asthma Clin Immunol 2018;14:Suppl 2:61.
13. Koizumi Y, Mikamo H. Anti-interferon gamma autoantibody and disseminated nontuberculous mycobacteria infection: what should be done to improve its clinical outcome? Clin Infect Dis 2021;72: 2209-11.
14. Hong GH, Ortega-Villa AM, Hunsberger S, et al. Natural history and evolution of anti-interferon-γ autoantibody-associated immunodeficiency syndrome in Thailand and the United States. Clin Infect Dis 2020;71:53-62.
15. Holland SM. Chronic granulomatous disease. Hematol Oncol Clin North Am 2013;27:89-99, viii.
16. Rider NL, Jameson MB, Creech CB. Chronic granulomatous disease: epidemiology, pathophysiology, and genetic basis of disease. J Pediatric Infect Dis Soc 2018; 7:Suppl 2:S2-S5.
17. Schapiro BL, Newburger PE, Klempner MS, Dinauer MC. Chronic granulomatous disease presenting in a 69-year-old man. N Engl J Med 1991;325:1786-90.
18. Ameratunga R, Allan C, Woon S-T. Defining common variable immunodeficiency disorders in 2020. Immunol Allergy Clin North Am 2020;40:403-20.
19. Song J, Lleo A, Yang GX, et al. Common variable immunodeficiency and liver involvement. Clin Rev Allergy Immunol 2018;55:340-51.
20. Sharma D, Ben Yakov G, Kapuria D, et al. Tip of the iceberg: a comprehensive review of liver disease in Inborn errors of immunity. Hepatology 2022;76:1845-61.
21. Bonilla FA, Barlan I, Chapel H, et al. International consensus document (ICON): common variable immunodeficiency disorders. J Allergy Clin Immunol Pract 2016; 4:38-59.
22. Chapel H, Cunningham-Rundles C. Update in understanding common variable immunodeficiency disorders (CVIDs) and the management of patients with these conditions. Br J Haematol 2009;145:709-27.
23. Cunningham-Rundles C, Bodian C. Common variable immunodeficiency: clinical and immunological features of 248 patients. Clin Immunol 1999;92:34-48.
24. Farmer JR, Ong M-S, Barmettler S, et al. Common variable immunodeficiency non-infectious disease endotypes redefined using unbiased network clustering in large electronic datasets. Front Immunol 2018;8:1740.
25. Ho H-E, Cunningham-Rundles C. Non-infectious complications of common variable immunodeficiency: updated clinical spectrum, sequelae, and insights to pathogenesis. Front Immunol 2020;11:149.
26. Lee TK, Gereige JD, Maglione PJ. State-of-the-art diagnostic evaluation of common variable immunodeficiency. Ann Allergy Asthma Immunol 2021;127:19-27.
27. Fuss IJ, Friend J, Yang Z, et al. Nodular regenerative hyperplasia in common variable immunodeficiency. J Clin Immunol 2013;33:748-58.
28. Malamut G, Ziol M, Suarez F, et al. Nodular regenerative hyperplasia: the main liver disease in patients with primary hypogammaglobulinemia and hepatic abnormalities. J Hepatol 2008;48:74-82.
29. Fudenberg H, Good RA, Goodman HC, et al. Primary immunodeficiencies: report of a World Health Organization committee. Pediatrics 1971;47:927-46.
30. Abolhassani H, Hammarström L, Cunningham-Rundles C. Current genetic landscape in common variable immune deficiency. Blood 2020;135:656-67.
31. Resnick ES, Moshier EL, Godbold JH, Cunningham-Rundles C. Morbidity and mortality in common variable immune deficiency over 4 decades. Blood 2012;119:1650-7.
32. Cunningham-Rundles C. How I treat common variable immune deficiency. Blood 2010;116:7-15.
33. Hercun J, Parikh E, Kleiner DE, et al. Recurrent nodular regenerative hyperplasia following liver transplantation in common variable immunodeficiency. Hepatology 2021;74:1698-701.
34. Ho H-E, Radigan L, Bongers G, El-Shamy A, Cunningham-Rundles C. Circulating bioactive bacterial DNA is associated with immune activation and complications in common variable immunodeficiency. JCI Insight 2021;6(19):e144777.
35. Lamers OAC, Smits BM, Leavis HL, et al. Treatment strategies for GLILD in common variable immunodeficiency: a systematic review. Front Immunol 2021;12: 606099.
36. Hashash JG, Squire J, Francis FF, Binion DG, Cross RK, Farraye FA. An expert opinion/approach: clinical presentations, diagnostic considerations, and therapeutic options for gastrointestinal manifestations of common variable immune deficiency. Am J Gastroenterol 2022;117:1743-52.
37. van Stigt AC, Dik WA, Kamphuis LSJ, et al. What works when treating granulomatous disease in genetically undefined CVID? A systematic review. Front Immunol 2020;11:606389.