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Challenging Clinical Cases

An unusual cause of fever in a patient with common variable immunodeficiency

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Case Presentation

The patient is a 22-year-old man with a history of common variable immunodeficiency (CVID) associated with a heterozygous mutation in TNFRSF13B (*TACI*), granulomatous lymphocytic interstitial lung disease (GLILD), massive splenomegaly, immune thrombocytopenia, and autoimmune hemolytic anemia. He presented with a 5-day history of fever with temperatures up to 38.9°C, malaise, sinus congestion, intermittent headaches, and loose stools. He had no cough, dyspnea, vomiting, abdominal pain, joint pain, or rash. He had been nonadherent with his weekly home dosing of subcutaneous immunoglobulin therapy for hypogammaglobulinemia because he reported only taking a total of 3 doses during the previous 3 months, with the most recent dose 4 days before presentation. He had been treated with immunoglobulin replacement since 10 years of age when CVID was diagnosed based on a clinical history of recurrent sinus and ear infections, low pretreatment immunoglobulin levels (IgG, 291 mg/dL; IgA, 18.7 mg/dL; and IgM, 31 mg/dL), and poor specific antibody response to vaccines. At 14 years of age he was treated with 4 weekly doses of rituximab with improvement in his chronic thrombocytopenia, reduction in splenomegaly, and radiographic resolution of his lung disease. By 7 months after rituximab treatment, the patient redeveloped thrombocytopenia, splenomegaly, and lung disease. At that time the patient and family were given the option to repeat rituximab therapy or consider bone marrow transplant, but they chose not to pursue these therapies because he was relatively asymptomatic at the time. Since then, he has had intermittent sinus and skin infections treated in the outpatient setting, with his last reported infection being an abscess on his thigh occurring 4 months earlier. The abscess was treated successfully in the emergency department with trimethoprim-sulfamethoxazole antibiotic therapy.

Additional history revealed bilateral chest pain during the preceding week that was attributed by the patient to muscle strain. Vital signs included a temperature of 37.8°C, slight tachycardia with a heart rate of 107/min, slight tachypnea with a respiratory rate of 24/min, blood pressure of 121/63 mm Hg, and normal oxygen saturation. His examination findings were notable for a nontoxic general appearance, 2 ulcers present on the base of his tongue, and massive splenomegaly. He did not have significant nasal congestion, and his lungs were clear to auscultation with no respiratory distress. The results of initial blood cell count studies are given in Table 1. The results of serum electrolyte measurement, liver function tests, and urinalysis were unremarkable. The results of a respiratory virus polymerase chain reaction (PCR) panel performed on a nasopharyngeal swab specimen were positive for rhinovirus and negative for influenza A, influenza B, parainfluenza, respiratory syncytial virus, human metapneumovirus, and coronavirus. The results of a rapid streptococcal antigen detection test performed on a throat swab specimen were negative. Chest radiography revealed possible right lower lobe pneumonia. Treatment with ceftriaxone and azithromycin was started, along with ibuprofen for headache. A dose of intravenous immunoglobulin was given. Serum IgG level before intravenous immunoglobulin therapy was 795 mg/dL. Though he was in no acute distress and currently afebrile, the decision was made to admit the patient that evening for close monitoring and intravenous antibiotic treatment of pneumonia.

The patient developed fever with temperatures to 39.1°C by noon the following day, and he continued to have fevers for 6 days with a peak temperature of 39.5°C. During this period, his workup was expanded in the context of continued fevers with lack of respiratory symptoms of cough, wheezing, or shortness of breath. Further history revealed that he cleaned windows and gutters for

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Table 1
Immunologic Findings

Component	Values 14 months prior	Present values	Reference range
Hemoglobin, g/dL	14.2	13.6	13.3–17.7
WBC, $\times 10^3/mm^3$	3.0	2.2	4.5–11
ANC, $/mm^3$	1,380	1,060	1,800–7,700
ALC, $/mm^3$	1,020	970	1,000–4,800
Monocyte count, $/mm^3$	420	110	0–600
Eosinophil count, $/mm^3$	170	40	0–600
Platelet count, $\times 10^3/mm^3$	70	36	135–466
Absolute CD19, $/mm^3$	78	67	100–500
Absolute CD16/56, $/mm^3$	31	3	90–600
Absolute CD3, $/mm^3$	936	1,542	71–2,100
Absolute CD4, $/mm^3$	613	566	300–1,400
Absolute CD8, $/mm^3$	303	953	200–900
$CD4^+CD45RA^+$, %	5	NA	10–67
$CD8^+CD45RA^+$, %	12	NA	10–71
Total serum IgG, mg/dL	1,120	795	600–1,500
Total serum IgA, mg/dL	<6.0	<6.0	68–378
Total serum IgM, mg/dL	12.9	5	60–263
Antigen stimulation			
Candida, cpm	2,886	NA	≥15,289
Tetanus, cpm	296	NA	≥4,761
Mitogen stimulation			
PHA	84,235	NA	≥135,190
ConA	79,982	NA	≥73,522
PWM	48,898	NA	≥26,677

Abbreviations: ANC, absolute neutrophil count; ALC, absolute lymphocyte count; $CD4^+CD45RA^+$, naive CD4 T cells; $CD8^+CD45RA^+$, naive CD8 T cells; cpm, counts per minute; NA, not applicable; PHA, phytohemagglutinin; ConA, concanavalin A; PWM, pokeweed mitogen; WBC, white blood cell count.

employment during the past few months, that he was around a pet bird at his girlfriend's house, that his father had died of metastatic colon cancer, and that his maternal grandmother had died of breast cancer. The spectrum of antimicrobial coverage was broadened by changing antibiotics to cefepime and levofloxacin. Blood test results were negative for human immunodeficiency virus, cytomegalovirus, Epstein-Barr virus, human herpesvirus 6, human herpesvirus 8, and parvovirus by PCR. Swab specimen of a tongue ulcer was negative for herpes simplex virus by PCR. A urine histoplasmosis antigen was tested. Computed tomography (CT) scans of his head, sinuses, chest, abdomen, and pelvis were performed, and a new lesion at the lower pole of the right kidney was noted, described as an ill-defined expansile lesion that was hypodense relative to the normal enhancing left kidney and without cysts, calcifications, or cavitations (Fig 1). Other CT findings included evidence of fluid in both maxillary sinuses suggestive of acute sinusitis with no intracranial abnormality, patchy and confluent ground-glass opacities throughout the lungs with multiple peripheral areas of consolidation that were increased compared with a CT performed 3 years earlier (Fig 1A), multiple enlarged mediastinal and abdominopelvic lymph nodes slightly increased in size from the prior CT, and massive splenomegaly, which had been noted previously. No fungal ball (mycetoma) signs were identified on the CT. In the context of his ongoing fevers, the right kidney mass was thought to be an infection vs a tumor. Cefepime was changed to doxycycline for additional staphylococcus coverage, given his history of skin abscesses. Given the concern for the possibility of lymphoma, lactate dehydrogenase and uric acid levels were measured and were normal. The urine histoplasmosis antigen test result was positive. This prompted initiation of a 12-week course of itraconazole, which led to defervescence by the second day of therapy (Fig 2). A bronchoalveolar lavage specimen was obtained and tested positive for cytomegalovirus; therefore, treatment with valganciclovir was initiated.

A percutaneous biopsy of the right kidney mass was performed. The biopsy revealed extensive infiltration and destruction of renal tissue by a lymphoproliferative lesion, which was composed mostly of small CD20-positive lymphoid cells with occasional large, transformed cells (Fig 3). Immunohistochemistry for Ki-67 revealed that the cells in the lesion had low proliferative activity. Flow cytometry detected an abnormal B-cell population with surface κ light chain restriction. The abnormal B cells were positive for CD19, CD20, CD22, CD24, CD38, CD52, CD74, FMC7, and HLA-DR. Most of them were negative for CD5, although there was possible expression of this marker on a small subset (<20%). All of them were negative for CD10. The morphologic testing and immunophenotyping results were consistent with an extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT). An attempt to obtain a G-banded karyotype was unsuccessful because of a failure of the cells to grow in culture, and molecular clonality testing was considered but not performed. For the renal MALT lymphoma, surgical resection, anti-CD20 immunotherapy, or watchful waiting were presented as initial options. Watchful waiting was selected by the patient. A surveillance program that involved CT and ultrasonography was initiated. Six months from diagnosis, there was slight decrease in size of the renal lesion, with

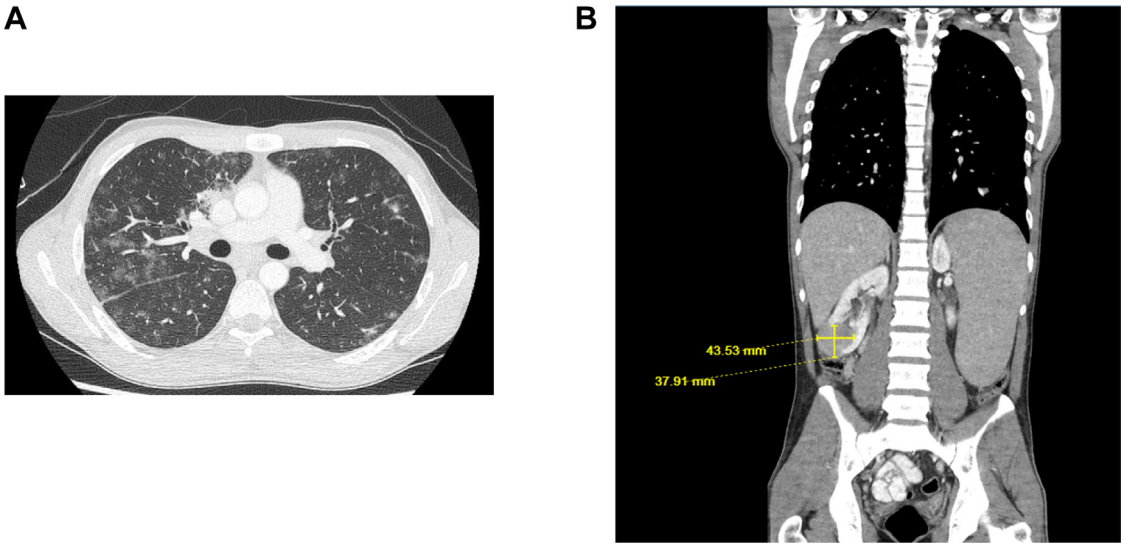

Figure 1. Computed tomogram showing ground-glass opacities consistent with granulomatous lymphocytic interstitial lung disease (A) and right kidney mass (B).