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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

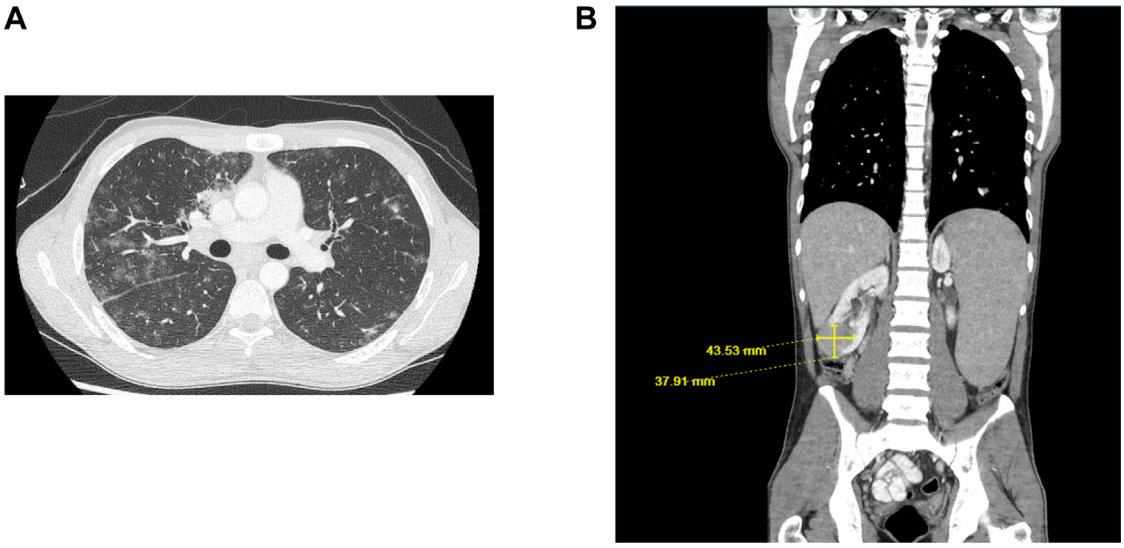

Figure 1. Computed tomogram showing ground-glass opacities consistent with granulomatous lymphocytic interstitial lung disease (A) and right kidney mass (B).

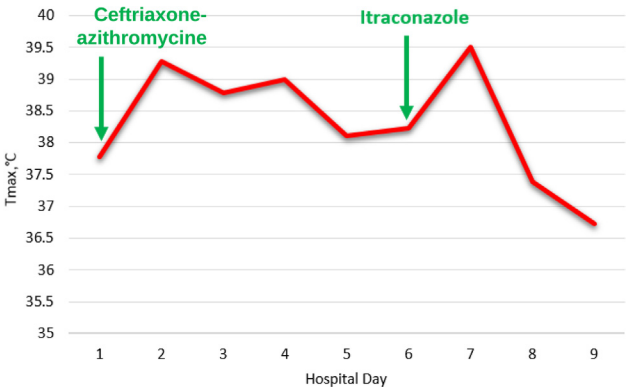

Figure 2. Fever curve during hospital admission.

no change in splenomegaly or retroperitoneal lymphadenopathy, and at 1 year after diagnosis, the renal mass was no longer seen on ultrasonography.

Discussion

CVID is a primary immunodeficiency disease that involves reduced serum concentrations of IgG, reduced IgA and/or IgM, and impaired production of specific antibodies in response to antigen (typically documented by poor response to vaccination). Decreased quantity and/or function of B cells typically causes the humoral deficit, although abnormal T-cell regulation of B cells can also be causative.[1] Recurrent sino-pulmonary tract infections are the main complication for most patients with CVID. Approximately half of patients with CVID have had at least one episode of pneumonia, and some patients with CVID have multiple episodes of pneumonia.[2] Other common infections include bronchitis, sinusitis, and otitis media. Immunoglobulin replacement is the standard of care for reducing frequency of infections. Patients with CVID are at increased risk for autoimmune disease, granulomatous disease, and malignant tumors, such as lymphoma.[3] Up to 15% of patients with CVID develop GLILD, which is a restrictive lung disease that is associated with greater morbidity and earlier mortality.[4] Lymphadenopathy and splenomegaly can be seen in one-quarter of patients with CVID,[5] with splenomegaly being associated with granulomatous disease and autoimmune disease.[6]

Histoplasmosis, caused by the organism *Histoplasma capsulatum*, is the most common endemic mycosis in the United States and inhabits the major river valleys of central and southern United States.[7] Fungal spores that can lead to infection are airborne and in higher concentrations in soil that contains bird or bat droppings.[8] Infections are generally asymptomatic, but disseminated disease can occur particularly in immunocompromised patients. Common clinical manifestations include fever, respiratory symptoms, hepatomegaly, splenomegaly, lymphadenopathy, gastrointestinal symptoms, and weight loss.[7] Oropharyngeal ulcers are common and can occur in up to two-thirds of patients with disseminated histoplasmosis.[8] Diagnostic laboratory testing for histoplasmosis includes cultures, fungal staining, antigen detection, and serologic tests, although rapid diagnosis can be attained through antigen testing of urine, with enzyme immunoassay of *Histoplasma* antigen in urine being detected in approximately 75% of non-immunocompromised patients and 95% of immunocompromised

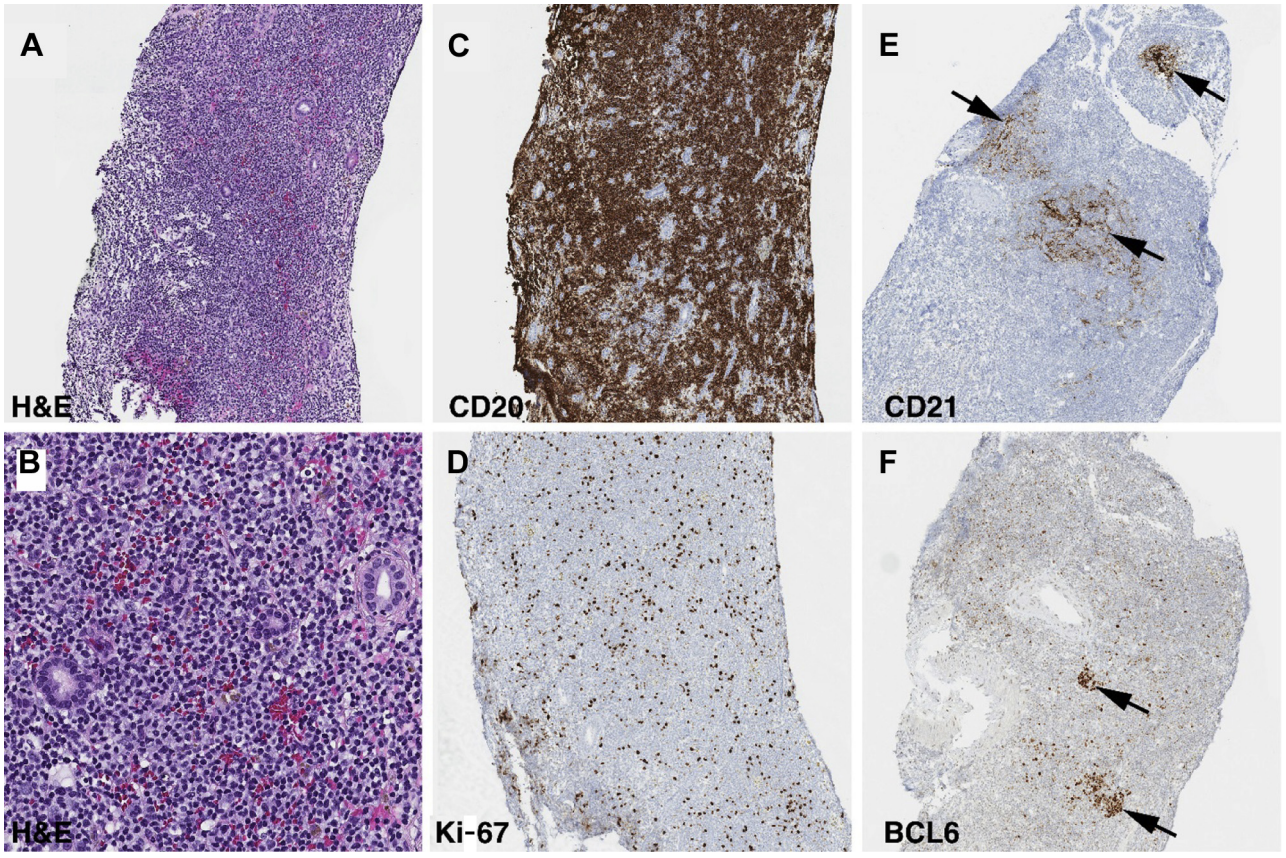

Figure 3. Needle biopsy specimen of the kidney. A and B, Dense infiltrate of lymphoid cells has replaced the renal parenchyma (hematoxylin-eosin [H&E] stain). C, CD20-positive B cells, stained brown, predominate. D, Ki-67 stain indicating low proliferative activity. E and F, Secondary lymphoid follicles (arrows) with CD21-positive follicular dendritic cells and BCL6-positive follicular center cells. Magnifications: ×10 for panels A, C, D, E, and F; ×40 for panel B.

patients.[9] Treatment of disseminated histoplasmosis depends on severity of illness and includes amphotericin B formulations for moderate to severe disease and itraconazole for mild to moderate disease.[10]

Our patient had fever, splenomegaly, and tongue ulcers as physical findings consistent with disseminated histoplasmosis, along with a history of being near a pet bird and cleaning of windows and gutters, which would have increased his risk of exposure to *Histoplasma* spores. His splenomegaly, however, was not a new discovery and was actually a previously known clinical finding associated with his CVID and GLILD. The patient may be more susceptible to histoplasmosis because of the dysregulation of cell-mediated immunity associated with his CVID, as evidenced by his low response on antigen and mitogen stimulation assays performed 14 months before presentation (Table 1). His increases in lung ground-glass opacities and mediastinal and abdominopelvic lymphadenopathy were possibly a lymphocytic response to infection, although there were no lung or lymph node biopsy specimens to prove this. He responded well to itraconazole therapy, with resolution of fever within 48 hours of treatment initiation.

Disseminated histoplasmosis in immunodeficient patients has primarily been reported in patients with AIDS and less so in patients with primary immunodeficiency, such as those with CVID.[11] Reactivation of latent infection has been reported in patients with chronic immunosuppression, such as with chemotherapy, long-term steroid use, or AIDS,[12] although our patient had last received his only immunosuppressive therapy, rituximab, 8 years ago, and a medical record review of our patient yielded no documentation of a prior histoplasmosis infection. We found 3 case reports of *Histoplasma* infection in patients with CVID: (1) a 66-year-old man who initially presented with dizziness, tinnitus, and confusion who was diagnosed with *Histoplasma* meningitis[13]; (2) a 49-year-old woman who presented with lower gastrointestinal tract bleeding and was diagnosed with disseminated histoplasmosis with findings of a cecal ulcer[14]; and (3) a 29-year-old man who presented with chronic diarrhea and weight loss, along with "whitish, necrotic lesions on the tongue," who was ultimately diagnosed with disseminated histoplasmosis.[15] Our patient differs from these other case reports in that he did not have any neurologic or gastrointestinal symptoms, but he did have tongue lesions similar to the case report of the 29-year-old male patient.

The patient's MALT lymphoma in the kidney is likely related to the history of CVID and autoimmunity. MALT lymphoma is a rare cancer, is especially rare in CVID, and is believed to form in lymphoid tissues secondary to chronic inflammatory or autoimmune stimulation. A 2006 review of MALT lymphoma in patients with CVID mentioned 9 published cases at the time, with primary sites of involvement being the lung in 5 cases, the parotid gland in 2 cases, the paranasal sinuses in 1 case, and the orbital cavity in 1 case.[16] Our patient is unique in that his MALT lymphoma is located in the kidney, which is a rare site of involvement that has not previously been reported in patients with CVID.[17] MALT lymphoma overall is an indolent malignant tumor with a good prognosis. The 5-year survival rate is greater than 90%, and the 10-year survival rate is 75% to 80%, although recurrences can occur a median of 5 years after treatment.[18] The prognosis of MALT lymphoma in the specific setting of CVID has not been systematically studied or reported. Our patient's MALT lymphoma spontaneously regressed without intervention and was no longer detectable by ultrasonography within 1 year of initial diagnosis. This is an interesting finding because there have only been some anecdotal reports of spontaneous remission in adult patients with ocular and pulmonary MALT lymphomas.[18,19] The temporal association of the discovery and resolution of the lesion to the histoplasmosis infection in our patient raises the question of whether the infection could have influenced the formation of the MALT lymphoma through fungal modulation of the immune system because there is evidence that *Histoplasma* can subvert the innate immune system by "hiding" its β-glucan from phagocyte dectin-1 receptor recognition using a layer of α-linked glucan in combination with glucanase to reduce levels of exposed β-glucan.[20] We were not able to find evidence of such tactics influencing the adaptive immune system in a way that would increase the risk of malignant tumors, and we are not aware of any previously reported associations to support suggesting a direct association between histoplasmosis and MALT lymphoma. Therapy for MALT lymphoma can include watchful waiting, localized radiotherapy vs surgical resection, antibiotics (in the case of gastric MALT lymphoma associated with *Helicobacter pylori*), and systemic treatments, such as chemotherapy and immunomodulatory agents.[18] Of note, some of the treatment modalities for CVID-GLILD and MALT lymphoma can be similar, such as rituximab, which highlights the potential dual benefit of such treatments for the patient.[16]

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