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The Wolf at the Door

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CLINICAL PROBLEM-SOLVING

The Wolf at the Door

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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, sharing his or her reasoning with the reader (regular type). The authors' commentary follows.*

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A 29-year-old man presented to a local hospital with a 1-week history of intermittent fever, drenching night sweats, reduced appetite, and left upper abdominal pain exacerbated by inspiration. He reported no weight loss, cough, dyspnea, nausea, diarrhea, rash, mouth ulcers, arthralgias, or ocular or urinary symptoms.

This young patient presents with fever and abdominal pain. His prominent systemic symptoms and their short duration suggest infection until proved otherwise. Left upper abdominal pain that worsens on inspiration may be due to processes above or below the diaphragm. Bacterial and viral infections of the respiratory tract are common and may cause pleuritic pain, but the absence of dyspnea, chest pain, and cough makes these diagnoses less likely. Although more unusual on the left side than on the right, subphrenic abscess should be considered, as should inflammation, infarction, or infiltration of the spleen. On the basis of the information provided so far, a connective-tissue disorder or cancer seems unlikely, although Hodgkin's disease should be considered in a young person with fevers and sweats. At this point, I would want more information about the patient's medical history and any risk factors for infection.

Eight years previously, the patient had an episode of fever, with raised inflammatory markers that persisted for 12 weeks. He underwent evaluation for cancer and infection, including tuberculosis, but no cause was identified. Joint pains subsequently developed, and he had a positive antinuclear antibody test, at a low titer; he was treated with oral glucocorticoids over a period of 2 months, with resolution of his symptoms. He no longer took any medications. He was born in the United Kingdom to Indian parents, lived with his wife in London, and worked as a management consultant. He traveled to India occasionally; the last trip was 4 years earlier. He had never smoked, had minimal alcohol intake, and noted no risk factors for human immunodeficiency virus (HIV) infection. His father had died of an aggressive natural killer cell leukemia. There was no family history of autoimmune or clotting disorders.

It is unclear whether the patient's present illness represents a relapse of his prior condition or is unrelated. I am concerned about the possibility of relapsing inflammatory disorders, including systemic lupus erythematosus (SLE), antineutrophil cytoplasmic antibody–associated vasculitis, and adult-onset Still's disease. Important infections to consider include tuberculosis, malaria, and HIV infection. The incidence of tuberculosis is higher among patients of nonwhite race, and almost half of patients present with exclusively extrapulmonary disease. This patient's travel may have exposed him to infection with *Plasmodium vivax*, the most common cause of malaria in India, which frequently relapses months to years after the initial

presentation because of dormant hypnozoites in the liver. Infection with HIV must be considered in any young patient with a recurrent febrile illness. Previous acute HIV infection could be followed years later by acquired immunodeficiency syndrome–defining infections or lymphoma. Episodic fevers in a young person may also be caused by periodic fever syndromes such as familial Mediterranean fever and the tumor necrosis factor (TNF)–receptor–associated periodic syndrome (TRAPS), although in these cases, bouts of fever usually recur within weeks to months rather than years.

Clinical examination confirmed a temperature of 38.2°C, but the patient appeared well. The blood pressure was 125/64 mm Hg, and the pulse was 92 beats per minute and regular. Heart sounds were normal, and chest sounds were clear. There was no hepatosplenomegaly, lymphadenopathy, abdominal tenderness, or mass. He was alert and oriented, with no weakness or sensory deficits. There was no rash and no joint erythema or swelling.

The white-cell count was 2500 per cubic millimeter, with 62% (1540) neutrophils, 22% (560) lymphocytes, 15% (380) monocytes, <1% basophils, and <1% eosinophils. The hemoglobin level was 11.5 g per deciliter, and the platelet count 107,000 per cubic millimeter. The reticulocyte count was 0.3% (normal range, 0.5 to 1.5). The prothrombin time was 14.2 seconds (normal range, 9.6 to 11.6), and the activated partial-thromboplastin time was 75.4 seconds (normal range, 24 to 32), with a corrected value of 61.3 seconds on mixing with normal plasma. The serum sodium level was 127 mmol per liter, potassium 3.9 mmol per liter, blood urea nitrogen 8.1 mg per deciliter (2.9 mmol per liter), and creatinine 1.2 mg per deciliter (106 μmol per liter). Liver-function tests and the serum amylase level were normal. The erythrocyte sedimentation rate was 88 mm in the first hour, and the C-reactive protein was 0.8 mg per deciliter (normal value, <0.5). Blood cultures were obtained.

The patient's pancytopenia with a low reticulocyte count indicates a low bone marrow output, rather than peripheral destruction of blood cells in the spleen or elsewhere. His fever and pancytopenia increase the possibility of an acute infection, especially with a virus such as parvovirus B19. Although primary infection with Epstein–Barr virus (EBV) or cytomegalovirus (CMV) is a common cause of febrile illness in young people, these infections are usually associated with reactive lymphocytes, which are absent in this patient. Infiltration of the bone marrow and spleen by carcinoma, leukemia, or non-Hodgkin's lymphoma is frequently accompanied by fever. The possibility of aplastic anemia with concurrent infection should also be considered.

The activated partial-thromboplastin time is markedly raised, and its failure to normalize with the addition of normal plasma suggests the presence of a clotting inhibitor such as the lupus anticoagulant. Fever may also occur with SLE. Whereas many connective-tissue diseases are associated with increases in both the erythrocyte sedimentation rate and the C-reactive protein level, SLE is often associated with an elevated erythrocyte sedimentation rate and a near-normal C-reactive protein level, such as this patient has. Further laboratory testing should include complement levels, antinuclear antibodies, antibodies to extractable nuclear antigens and double-stranded DNA (dsDNA; to screen for SLE), antineutrophil cytoplasmic antibodies (to screen for vasculitis), and tests for the antiphospholipid syndrome (anticardiolipin and anti–β_2-glycoprotein I antibodies and lupus anticoagulant). Blood smears should be examined for signs of malaria and marrow dysplasia or infiltration. Serologic testing is warranted for EBV, CMV, HIV, and parvovirus B19. At this point, computed tomographic (CT) imaging of the chest, abdomen, and pelvis is indicated to detect any lymphadenopathy, focus of infection, or organomegaly.

The patient was treated with intravenous amoxicillin and clavulanate but continued to have spiking fevers daily, with peak temperatures of more than 38.5°C. Over the next 2 days, headaches, confusion, and muscle cramps developed, as well as proteinuria (1.78 g of protein per liter), and he was transferred to a tertiary care hospital. Chest radiography and magnetic resonance imaging of the brain showed no abnormalities. A lumbar puncture revealed normal opening pressure. Cerebrospinal fluid protein and glucose levels were normal, and no cells were seen on microscopy. CT imaging of the chest, abdomen, and pelvis showed no abnormalities. The platelet count fell to 12,000 per cubic millimeter, and the neutrophil count to 290 per cubic millimeter.

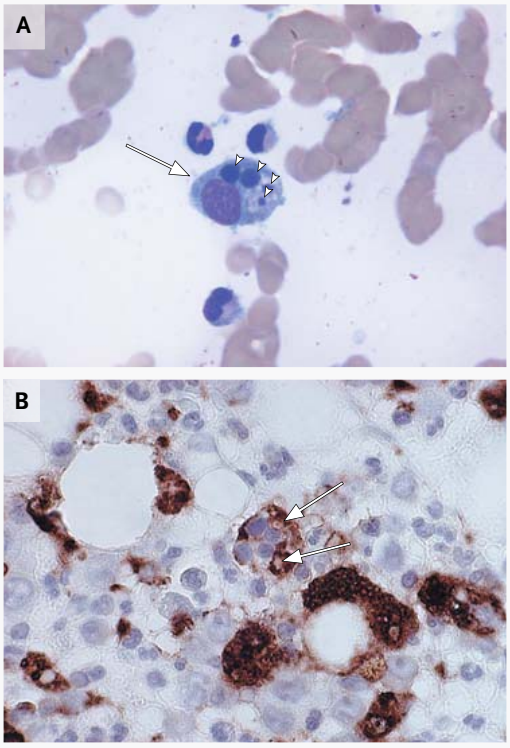

Figure 1. Bone Marrow Samples Obtained from the Patient.

Panel A shows a bone marrow aspirate with May–Grünwald and Giemsa stains. A macrophage (arrow) contains phagocytosed cellular elements (arrowheads). Panel B shows a trephine-biopsy sample of bone marrow with immunohistologic staining for CD68, showing abundant activated macrophages (brown) containing phagocytosed hematopoietic cells, including erythrocytes (arrows).

Blood and urine cultures were negative, as were serologic tests for HIV types 1 and 2, human T-cell lymphotrophic virus, hepatitis B virus, hepatitis C virus, varicella–zoster virus, herpes simplex virus, *Coxiella burnetii*, brucella, mycoplasma, *Chlamydophila psittaci*, legionella, and toxoplasma. Polymerase-chain-reaction assays for respiratory syncytial virus, influenza virus, parvovirus B19, CMV, EBV, human herpesvirus 6, and human herpesvirus 8 were negative, as was an enzyme-linked immunosorbent spot assay for tuberculosis.

Tests for antinuclear antibodies and anti-dsDNA antibodies were positive, both at a titer of 1:320. Tests for anti-Sm, anti-Ro, and anti-La antibodies were negative. The C3 level was 0.54 g per liter (normal value, >0.7), and the C4 level was 0.07 g per liter (normal value, >0.16). Testing for the lupus anticoagulant was positive. A test for anticardiolipin IgG antibodies was reported to be moderately positive, and a test for IgM antibodies was negative. Urine sediment and serum creatinine levels remained normal.

The patient has SLE, on the basis of positive tests for antinuclear and anti-dsDNA antibodies, pancytopenia, and proteinuria. Other features consistent with this diagnosis include fever and encephalopathy, as well as abdominal pain, which may indicate serositis. Lupus anticoagulant and anticardiolipin antibodies are commonly seen in SLE. Cytopenias are also frequent in SLE and reflect heterogeneous mechanisms that include anemia of chronic disease, peripheral immune-mediated destruction, primary bone marrow involvement, and therapy-related hematologic toxicity. However, the profound cytopenias in this patient raise the more serious possibility of a hemophagocytic syndrome, which warrants an urgent assessment of markers of macrophage activation, including ferritin, fasting triglyceride, and fibrinogen levels, as well as bone marrow examination.

The serum ferritin level was 105,506 μg per liter (normal range in men, 30 to 400), fasting triglycerides 494 mg per deciliter (5.58 mmol per liter; normal value, <177 [<2]), and fibrinogen 0.98 g per liter (normal range, 1.8 to 3.6). Repeated blood and urine cultures were sterile. Bone marrow aspiration and trephine biopsy revealed macrophage proliferation and phagocytosis of hematopoietic cells of erythroid, myeloid, and megakaryocytic lineages (Fig. 1A and 1B).

These findings of fever, pancytopenia, hypertriglyceridemia, hypofibrinogenemia, hyperferritinemia, and hemophagocytosis are indicative of the hemophagocytic syndrome, in this case due to SLE. I would immediately initiate treatment with intravenous glucocorticoids because of their rapid onset of action and efficacy as immunosuppressant agents, although the patient is likely to require subsequent treatment with glucocorticoid-sparing agents. Intravenous immune globulin is often used as an immunomodulatory agent in patients in whom infection is a concern. I would broaden

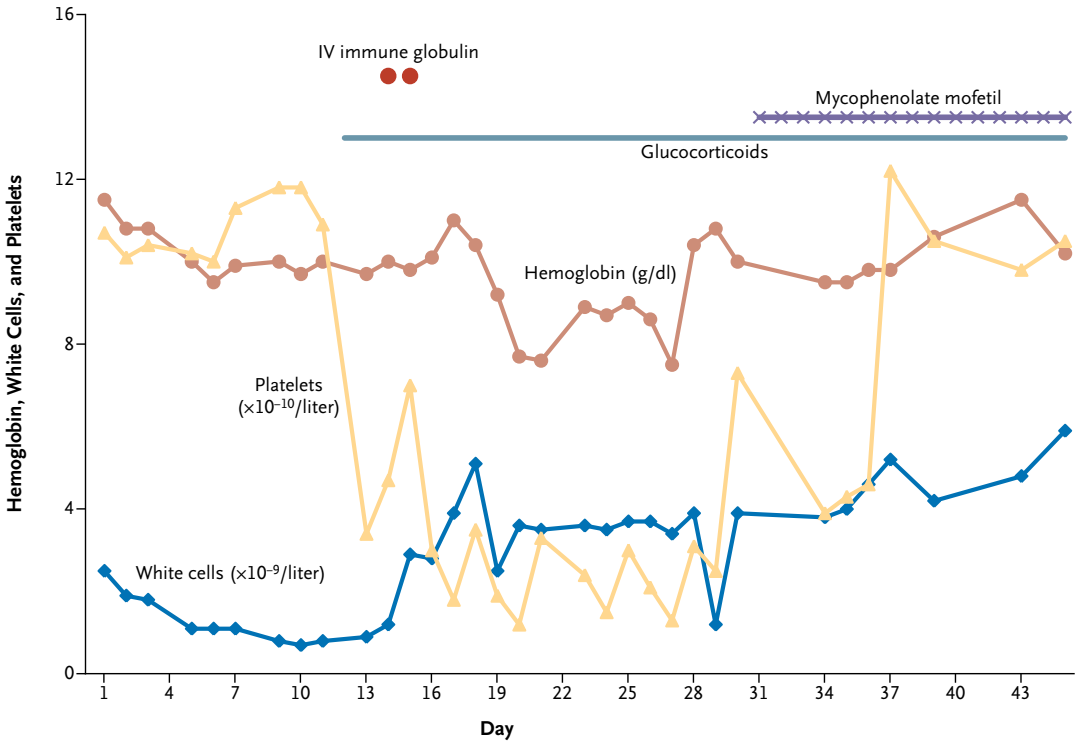

Figure 2. Response to Treatment.
Shown are hemoglobin levels and white-cell and platelet counts in response to treatment with intravenous (IV) immune globulin, mycophenolate mofetil, and glucocorticoids.

the antimicrobial coverage, given the need for immunosuppression in the context of ongoing fevers and severe neutropenia.

Treatment with intravenous methylprednisolone (1 g daily for 3 days) and intravenous immune globulin (2 g per kilogram of body weight over a period of 2 days) was initiated, and the antimicrobial regimen was broadened to include intravenous meropenem and acyclovir, with oral fluconazole as antifungal prophylaxis. The patient was given red-cell and platelet transfusions. The fever subsided, but the pancytopenia persisted, and he had ongoing difficulties with attention and short-term memory. Mycophenolate mofetil (1 g twice daily) was added, with subsequent improvement in his cytopenias and cognitive function (Fig. 2).

The patient's glucocorticoid treatment was gradually tapered, and he was discharged from the hospital while taking oral prednisolone and mycophenolate mofetil. At the time of discharge, his white-cell count and hematocrit were normal; he had mild thrombocytopenia, which resolved over the next 6 weeks. The patient's condition steadily improved, and all immunosuppressive treatment was progressively withdrawn over the next 2 years. He has resumed full-time work and remained well at a 3-year follow-up visit.

COMMENTARY

This case highlights two important and related causes of fever and pancytopenia: SLE and the hemophagocytic syndrome. The features that prompted consideration of SLE in this patient were fever, abdominal pain suggestive of serositis, proteinuria, and pancytopenia. The presence of antinuclear antibodies, anti-dsDNA antibodies, and the lupus anticoagulant confirmed the diagnosis.

SLE is frequently associated with fever and with cytopenias. Both findings may reflect underlying disease activity, but additional causes should be

considered if these manifestations are severe or prolonged. In this patient, the combination of relentless fever and severe, rapidly progressive pancytopenia suggested overwhelming infection or secondary hemophagocytic syndrome. The poor response to antimicrobial agents and the very high ferritin levels prompted bone marrow examination, which confirmed secondary hemophagocytic syndrome.

Secondary hemophagocytic syndrome, sometimes known as the macrophage activation syndrome, can present at any age and is a rare complication of infection, hematologic cancer, drug exposure (particularly exposure to immunomodulatory drugs), and autoimmune disease. The most common infectious trigger is EBV, but HIV is increasingly implicated, and many other viral, bacterial, and protozoal infections have also been associated with secondary hemophagocytic syndrome.[1,2]

Of the autoimmune diseases associated with the hemophagocytic syndrome in adults, SLE is by far the most common, accounting for about 60% of cases; the estimated prevalence of the hemophagocytic syndrome among patients with SLE is up to 2.4%.[3,4] Adult-onset Still's disease is responsible for 10 to 15% of cases.[4,5] There is considerable overlap between the features of adult-onset Still's disease and those of secondary hemophagocytic syndrome, and the possibility of hemophagocytosis should be considered in any patient with adult-onset Still's disease in whom cytopenias develop.[6]

The mechanisms underlying secondary hemophagocytic syndrome are poorly understood. However, studies indicate that some cases are associated with heterozygous mutations and polymorphisms in the genes responsible for familial hemophagocytic lymphohistiocytosis, a primary disorder that usually presents in infancy.[7-9] The identified mutations are associated with defective killing by cytotoxic lymphocytes and natural killer cells, and it is postulated that defective clearance of antigen or antigen-presenting cells leads to persistent stimulation of the immune response and a consequent cytokine storm, resulting in many of the manifestations of this condition.[10] High levels of interleukin-1, interleukin-6, TNF, and interferon-γ cause fever, up-regulate ferritin transcription and secretion, and induce cytopenias through myelosuppression rather than through the phagocytosis that is the morphologic hallmark of the disorder.[11]

There are no validated diagnostic criteria for secondary hemophagocytic syndrome, but suggestive features include high temperatures, organomegaly, cytopenias and coagulopathy, markedly elevated ferritin levels, hypertriglyceridemia, and hypofibrinogenemia. Bone marrow examination usually shows hemophagocytosis, but this finding may initially be absent or confined to other organs, such as the spleen or lymph nodes.[12]

Data from clinical trials are lacking to guide decisions about specific therapy in adults, and management of secondary hemophagocytic syndrome is based on control of the cytokine storm, treatment of possible triggers, and supportive care. In patients with associated autoimmune diseases, immunosuppression may be indicated. Reports on case series have described good outcomes in patients treated with a variety of immunosuppressive agents, including glucocorticoids (the most commonly used agents for this condition), cyclophosphamide, cyclosporine, and intravenous immune globulin[3,13]; the use of etoposide, biologic agents, and plasmapheresis has been reported in refractory cases.[11] Caution must be exercised in prescribing immunosuppressive therapy, since infectious triggers are identified in more than 50% of these patients,[5] and concurrent antimicrobial therapy should be considered.

In three case series of adults with autoimmune diseases and secondary hemophagocytic syndrome, mortality rates ranged from 7 to 38%.[3-5] Reported predictors of death included a C-reactive protein level greater than 5 mg per deciliter, a platelet count below 50,000 per cubic millimeter, the presence of infection, and prior use of glucocorticoids. Our patient had severe thrombocytopenia but did not have other features associated with a poor prognosis.

This case highlights the importance of considering additional possibilities when findings are atypical for an established condition. Once a diagnosis of SLE had been made, the crucial next step was to recognize that the ongoing fevers and pancytopenia indicated another diagnosis, secondary hemophagocytic syndrome. Rapid identification of this life-threatening complication of SLE facilitated early aggressive management and resulted in a good clinical outcome.

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

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