CASE RECORDS of the MASSACHUSETTS GENERAL HOSPITAL

Case 35-2019: A 66-Year-Old Man with Pancytopenia and Rash

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PRESENTATION OF CASE

Dr. Joshua Salvi (Medicine): A 66-year-old man with a history of pancytopenia was transferred to this hospital in the winter for evaluation of pancytopenia and rash.

The patient had been well until 1 year before admission, when episodic fevers began to occur. Approximately 3 months before admission, fevers with a temperature of up to 38.3°C increased in frequency and severity and coincided with shaking chills. Scattered papules developed on the arms and legs; the lesions were initially deeply erythematous, but over a period of several days, the discoloration faded and the skin sloughed. There was no associated pruritus, and febrile episodes did not coincide with worsening of the skin lesions.

Two months before admission, episodes of orthostatic hypotension and dizziness developed. The patient was admitted to other hospitals on two occasions for recurrent lightheadedness. Laboratory evaluation reportedly revealed a normal level of corticotropin in the blood and a normal increase in the serum cortisol level after intravenous administration of cosyntropin. The white-cell count was 850 per microliter (reference range, 4200 to 9900), the hemoglobin level 9.2 g per deciliter (reference range, 13.0 to 17.4), the platelet count 61,000 per microliter (reference range, 140,000 to 440,000), and the mean corpuscular volume 89 fl (reference range, 82 to 100). The blood levels of aspartate aminotransferase and alanine aminotransferase were elevated. Serologic tests for hepatitis A, B, and C viruses and for human immunodeficiency virus (HIV) type 1 and type 2 were negative. The ferritin level was 12,620 ng per milliliter (reference range, 30 to 400), but subsequent testing for the *HFE* mutation most often associated with hemochromatosis was negative. Nineteen days before the ferritin level was measured, the iron level was 67 μg per deciliter (12 μmol per liter) (reference range, 45 to 182 μg per deciliter [8 to 33 μmol per liter]), the total iron-binding capacity 143 μg per deciliter (26 μmol per liter) (reference range, 261 to 478 μg per deciliter [47 to 86 μmol per liter]), the transferrin saturation 47% (reference range, 20 to 55), the folate level 18.3 ng per milliliter (41 nmol per liter) (reference range, 6 to 20 ng per milliliter [14 to

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N Engl J Med 2019;381:1951-60.
DOI: 10.1056/NEJMcpc1909627

Table 1. Laboratory Data.*

Variable	Reference Range, Other Hospital	8 Days before Admission, Other Hospital	Reference Range, This Hospital†	On Admission, This Hospital
Hemoglobin (g/dl)	13–17.4	9.2	13.5–17.5	9.8
Hematocrit (%)	38–50	26.1	41.0–53.0	28.2
Mean corpuscular volume (fl)	82–100	89.4	80.0–100.0	89.5
Platelet count (per μl)	140,000–440,000	58,000	150,000–400,000	51,000
White-cell count (per μl)	4200–9900	800	4500–11,000	940
Differential count (%)				
Neutrophils	47–80	56	40–70	65.5
Lymphocytes	14–46	28	22–44	22.0
Monocytes	5–13	14	4–11	9.9
Reactive lymphocytes	<1	2	0–8	
Immature granulocytes			0	1.3
Erythrocyte morphologic features		Presence of microcytes, macrocytes, ovalocytes, polychromasia, schistocytes, acanthocytes, and teardrop cells		Presence of burr cells and schistocytes
International normalized ratio	0.9–1.2	1.7	0.9–1.1	1.3
Partial-thromboplastin time (sec)	24–36	70		
Fibrinogen (mg/dl)	160–450	42	150–400	148
Thrombin time (sec)	11–15	38.8		
D-Dimer (ng/ml)	<230	712	<500	4165
Lactate dehydrogenase (U/liter)	94–250	1,106	110–210	1301
Ferritin (ng/ml)	30 –400	13,026	20–300	29,600
Triglycerides (mg/dl)	<150, fasting	378	40–150	685
Haptoglobin (mg/dl)	25–200	<20	30–200	<10
Sodium (mmol/liter)	133–145	127	135–145	127
Albumin (g/dl)	3.2–5.2	2.0	3.3–5.0	1.8
Globulin (g/dl)	2.0–3.5	2.6	1.9–4.1	3.2
Total bilirubin (mg/dl)	0–1	1.7	0.0–1.0	2.9
Alkaline phosphatase (U/liter)	39–117	500	45–115	604
Aspartate aminotransferase (U/liter)	0–37	316	10–40	399
Alanine aminotransferase (U/liter)	0–40	141	10–55	119
γ-Glutamyl transferase (U/liter)	7–51	615		

* To convert the values for triglycerides to millimoles per liter, multiply by 0.01129. 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.

45 nmol per liter]), and the vitamin B_{12} level 861 pg per milliliter (635 pmol per liter) (reference range, 193 to 986 pg per milliliter [142 to 727 pmol per liter]). Magnetic resonance cholangiopancreatography revealed a small amount of pericholecystic fluid and mild edema in the right paracolic gutter that suggested an infiltrative process; the biliary ducts appeared normal, and no intrahe-

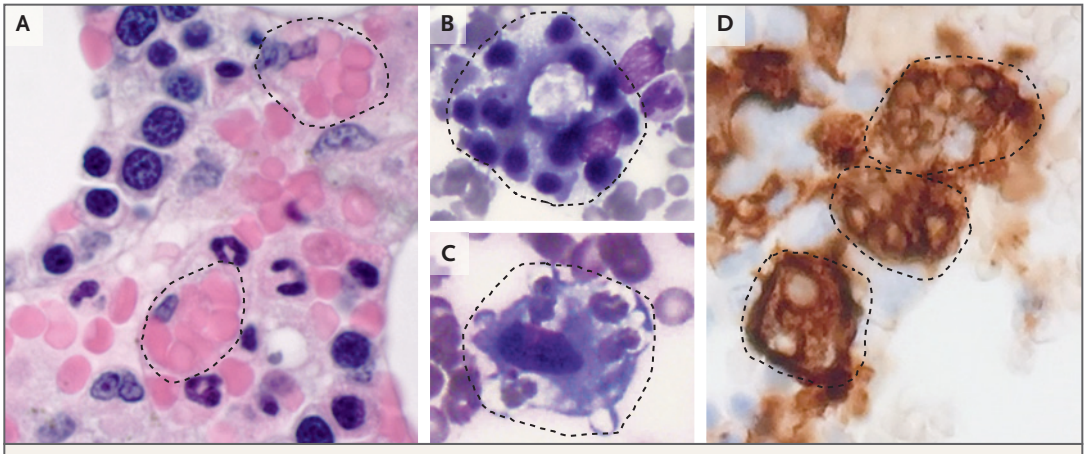

Figure 1. Bone Marrow Biopsy Specimen and Aspirate.

Hematoxylin and eosin staining of a core biopsy specimen (Panel A) and May–Grünwald–Giemsa staining of aspirate (Panels B and C) obtained at the other hospital show numerous histiocytes with engulfed erythroid elements (Panel B) and mature red cells (Panel C). Immunohistochemical staining for CD163 shows histiocytes filled with intracytoplasmic red cells (Panel D). Dashed lines outline hemophagocytic histiocytes.

patic iron deposition was seen. The orthostatic hypotension abated, but did not fully resolve, after the administration of intravenous fluids. The patient was discharged home and was instructed to follow up with his primary care physician.

Eight days before admission, orthostatic hypotension recurred. The patient was readmitted to one of the other hospitals, where he reported ongoing lightheadedness and generalized weakness. The temperature was 36.6°C, the pulse 91 beats per minute, the blood pressure 119/71 mm Hg while the patient was in the supine position (75/48 while he was standing), the respiratory rate 16 breaths per minute, the oxygen saturation 95% while he was breathing ambient air, and the weight 74.9 kg. He was pale, appeared ill, and had marked edema of the legs and periorbital region. Scattered nummular and erosive lesions with overlying eschar were noted on both feet, both forearms, and the medial right thigh; petechiae were also seen on the arms and chest. The remainder of the examination was normal. Laboratory test results are shown in Table 1. An antibody-based screening test for Lyme disease was negative, as were nucleic acid tests for babesia, ehrlichia, anaplasma, adenovirus, and cytomegalovirus. Histoplasma and aspergillus antigens were not detected in the blood. Cultures of the blood were negative.

A transthoracic echocardiogram was of technically poor quality but showed normal biventricular function; valvular dysfunction was not assessed. Radiography of the chest revealed atelectasis but was otherwise normal. Computed tomography (CT) of the chest, performed after the administration of intravenous contrast material, revealed small bilateral pleural effusions and no evidence of lymphadenopathy; CT of the abdomen and pelvis revealed normal hepatic parenchyma, a moderate amount of ascites, mild splenomegaly, and no evidence of lymphadenopathy. Positron-emission tomography (PET) from the skull base to the thighs, performed after the administration of intravenous ^{18}F-fluorodeoxyglucose (FDG) tracer, revealed homogeneous FDG uptake in the spleen, and there was no evidence of hypermetabolism in the abdominal or pelvic lymph nodes.

The patient was transferred to this hospital for further evaluation and management of possible hemophagocytic lymphohistiocytosis (HLH).

Dr. Valentina Nardi: Examination of a bone marrow biopsy specimen and aspirate that were obtained at the other hospital revealed maturing trilineage hematopoiesis and mildly hypercellular marrow with many histiocytes and numerous engulfed erythroid elements in the cytoplasm. The findings were consistent with hemophagocytosis, with no evidence of infection or lymphoma (Fig. 1).

Dr. Kristine M. Cornejo: A punch biopsy of an

erythematous lesion on the right thigh was performed at the other hospital. Microscopic examination of the specimen revealed focal epidermal erosion with impetiginized scale crust and a mild lymphohistiocytic infiltrate in the dermis and subcutaneous tissue; no fungal organisms were identified. The infiltrate lacked atypia, and there was no evidence of hemophagocytosis. The findings were nondiagnostic, and there was no evidence of lymphoma (Fig. 2).

Dr. Salvi: Intravenous fluids, cryoprecipitate, and empirical cefepime were administered.

DIFFERENTIAL DIAGNOSIS OF HLH

Dr. Marcela V. Maus: I am aware of the diagnosis in this case. This 66-year-old man has a 1-year history of fevers and a history of waxing and waning erythematous scaly lesions on his arms and legs, pancytopenia, and hyperferritinemia, with a ferritin level of greater than 10,000 ng per milliliter in the peripheral blood. The markedly elevated ferritin level leads us to consider the diagnosis of HLH syndrome. In a retrospective review of hyperferritinemia, which was defined by a ferritin level greater than 10,000 ng per milliliter, the most common diagnosis in children (occurring in 49% of cases) was HLH. However, in adults, the most common disorder was hematologic cancer (occurring in 26% of cases), and HLH was diagnosed in only 14% of cases.[1] In broad terms, the differential diagnosis for this patient's presentation includes infection, microangiopathic hemolytic anemia, DRESS (drug reaction with eosinophilia and systemic symptoms) syndrome, and macrophage activation syndrome. The 1-year time course would make infection unlikely, the low number of schistocytes on the peripheral-blood smear would make microangiopathic hemolytic anemia unlikely, the lack of exposure to drugs would make DRESS syndrome unlikely, and the absence of a history of autoimmune disease would make classic macrophage activation syndrome unlikely.

HLH is a life-threatening syndrome of hyperactive immune activation that is characterized by high levels of cytokines, which reflect activation of T cells and macrophages (Fig. 3). In fact, the pathophysiological features of macrophage activation syndrome are very similar to those of HLH, but macrophage activation syndrome manifests in the context of a preexisting rheumatologic disorder. The triggers for HLH are all associated with dysregulation of the immune system and include immunodeficiency syndromes (e.g., the Chédiak–Higashi syndrome or Griscelli's syndrome), rheumatologic disorders, HIV infection, Epstein–Barr virus (EBV) infection, and hematologic cancer. HLH is more common among infants and children than among adults, largely because primary HLH, which denotes the presence of an underlying genetic mutation, typically appears early in childhood on exposure to viral infections. Secondary HLH is triggered by infections that result in hyperactive immune responses. The distinction between primary and secondary HLH is not always useful, since both are often

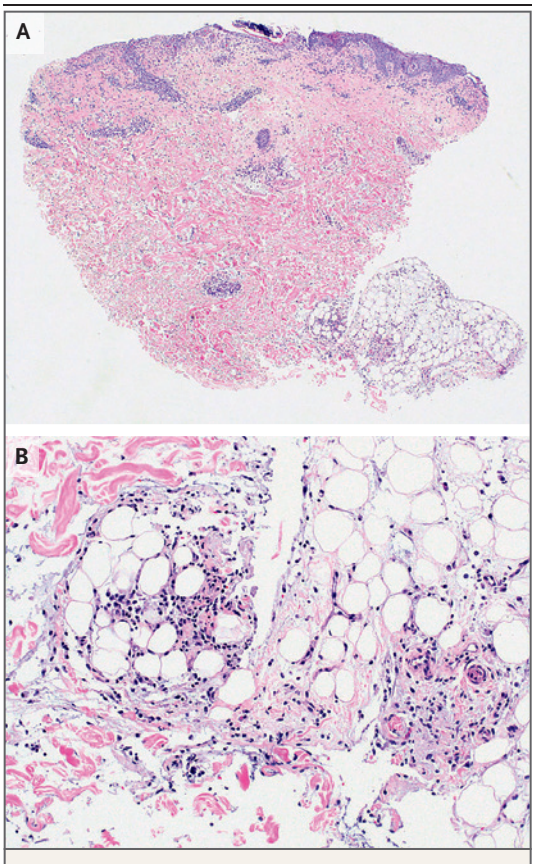

Figure 2. Initial Biopsy Specimen of the Skin, Obtained at the Other Hospital.

Hematoxylin and eosin staining of a biopsy specimen of a skin lesion on the right thigh is shown in Panel A; at higher magnification (Panel B), focal epidermal erosion overlying a mild lymphohistiocytic infiltrate within the dermis and subcutis that lacks atypia is shown.

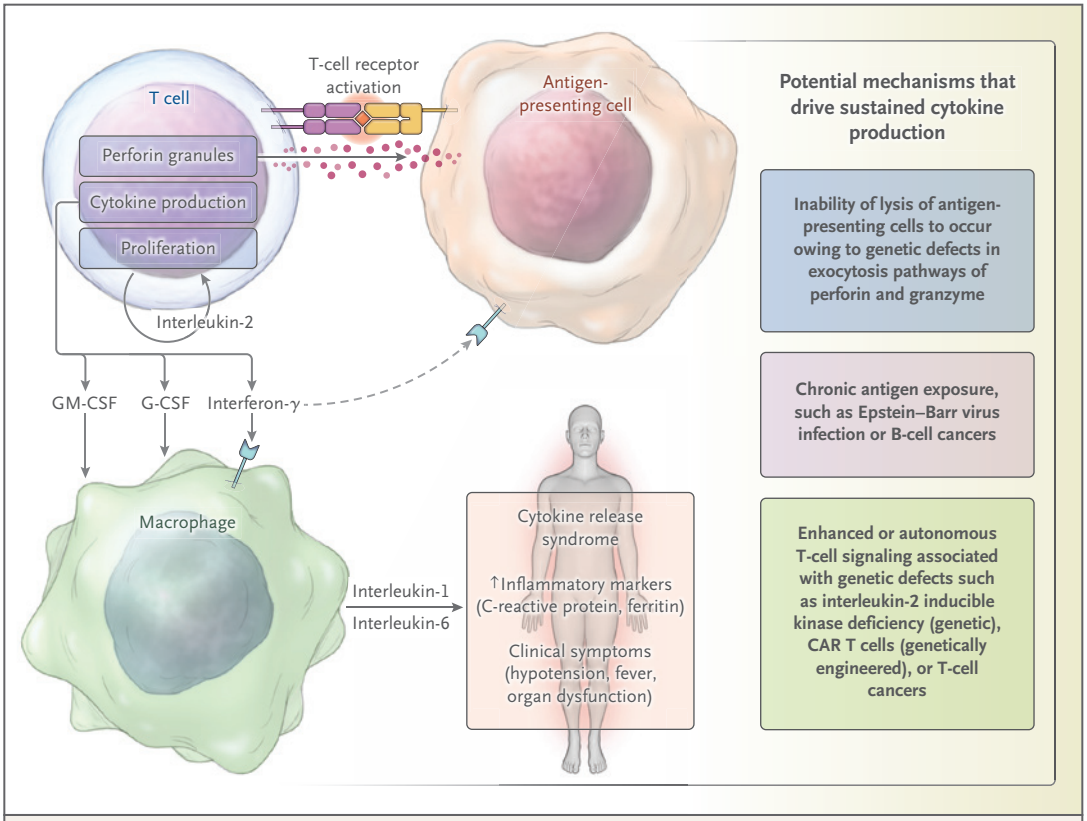

Figure 3. Pathophysiological Features of Sustained Cytokine Production in Hemophagocytic Lymphohistiocytosis Syndrome.

At the immunologic synapse, antigen-presenting cells (APCs) present antigens to T cells in the context of major histocompatibility complex (MHC) antigens. When a T-cell receptor recognizes the combination of MHC plus antigen, T-cell activation is triggered, which includes exocytosis of granules containing the cytolytic proteins perforin and granzyme and production of cytokines, such as interferon-γ, granulocyte colony-stimulating factor (G-CSF), granulocyte–macrophage colony-stimulating factor (GM-CSF), interleukin-2, and others. Normally, the release of cytolytic proteins results in lysis of the APCs, terminating T-cell activation; interleukin-2 production aids in T-cell proliferation, and interferon-γ triggers upregulation of MHC and programmed death ligand 1 (PD-L1) and activates macrophages to produce interleukin-1, interleukin-6, and other cytokines. The presence of interleukin-1 and interleukin-6 results in the clinical manifestation of the cytokine release syndrome, including fevers, hypotension, and organ dysfunction, and drives the upregulation of inflammatory markers such as C-reactive protein and ferritin. Potential disorders that drive sustained cytokine production include the inability of lysis of the APCs to occur owing to genetic defects in the exocytosis pathways of perforin and granzyme; chronic antigen exposure, such as in cases of Epstein–Barr virus infection or B-cell cancers; and enhanced or autonomous T-cell signaling, which can be associated with certain genetic defects (e.g., interleukin-2 inducible kinase deficiency), genetically engineered T cells (e.g., chimeric antigen receptor [CAR] T cells), or T-cell cancers.

triggered by infections and both often have underlying genetic mutations that can confer a predisposition to the syndrome.

Indeed, this patient meets six of the eight criteria for HLH that were described in a large study of patients with HLH.[2,3] The diagnostic criteria include fever (present in 95% of patients), splenomegaly (89%), bicytopenia (92%), hypertriglyceridemia or hypofibrinogenemia (90%), hemophagocytosis (82%), low or absent natural-killer (NK)–cell activity (71%), elevated soluble CD25 (interleukin-2 receptor α chain) level (71%), and a ferritin level greater than 500 ng per milliliter (94%). As is the case in this patient, most of these signs are evident with routine workup of an ill patient, but measurements of NK-cell activity and soluble CD25 are typically performed at reference laboratories as part of the

workup of HLH. The criteria for HLH reflect markers of immune hyperactivation and, in the case of diminished NK-cell activity, ineffective cytolytic pathways (most likely due to genetic mutations).

Because adults are less likely than infants and children to have primary HLH and more likely to have an underlying predisposing disease, alternative criteria for the diagnosis of HLH have been defined.[4] These criteria include fever, organomegaly, cytopenias, elevated ferritin levels, elevated lactate dehydrogenase levels, the presence of hemophagocytosis in the bone marrow aspirate, and most important, the presence of an underlying predisposing condition, such as a hematologic cancer or infection. In one study, the predisposing disease was hematologic cancer in 57% of the patients, and infections were present in 25% of the patients[4]; similar results were seen in a second study, which showed that, among 162 adult patients with HLH, 56% had non-Hodgkin's lymphoma.[5] This patient's disorder meets all the alternative criteria for a diagnosis of HLH, except that the underlying predisposing disease has not yet been elucidated.

HOSPITAL COURSE

Dr. Mark B. Leick: The patient had been healthy until 2 years before admission. On admission to this hospital, the patient reported ongoing swelling in the legs, forearms, and periorbital area, along with decreased appetite and poor oral intake. He had a history of coronary artery disease, hypertension, hyperlipidemia, hypothyroidism, and gastroesophageal reflux disease. He had received a diagnosis of pancytopenia 2 years earlier and had undergone an extensive evaluation 1 year after the diagnosis; results of serum protein electrophoresis and the serum free light-chain ratio had been normal, and examination of a biopsy specimen of the bone marrow had revealed no evidence of cancer. Medications included pantoprazole, levothyroxine, lisinopril, metoprolol, and aspirin; treatment with amoxicillin caused nausea, and treatment with simvastatin caused myalgia.

The patient was single and lived alone in a rural area of New England. He had previously worked in health care but had retired several years before admission. He smoked three cigars daily and did not drink alcohol or use illicit drugs. His father had died from coronary artery disease, and his brother had sarcoidosis and alpha$_1$-antitrypsin deficiency; an aunt and uncle had had cancer, but the types were unknown.

On examination, the patient appeared frail. The temperature was 36.4°C, the pulse 93 beats per minute, the blood pressure 119/74 mm Hg, the respiratory rate 16 breaths per minute, the weight 78.6 kg, and the oxygen saturation 97% while he was breathing ambient air. Periorbital edema and purpura were seen, along with well-circumscribed erosions and nodules on both legs, with overlying crust in various stages of healing. The abdomen was soft, with no tenderness or organomegaly. The remainder of the examination was normal. Laboratory test results are shown in Table 1. The ferritin level was 29,600 ng per milliliter. The soluble CD25 level in the blood was elevated, at 8635 pg per milliliter (reference range, 532 to 1891). The blood level of interferon-γ was high (>520 pg per milliliter). Nucleic acid testing of the blood for EBV DNA was positive, at 1340 IU per milliliter, and nucleic acid testing for human herpesvirus 6 and parvovirus was negative. An interferon-γ release assay for tuberculosis was negative, and antibodies to herpes simplex virus types 1 and 2 and to toxoplasma were not detected.

Given the finding of periorbital edema, a CT scan of the face, obtained without the administration of intravenous contrast material, showed ill-defined areas of increased attenuation along the preseptal soft tissues and within the inferior orbital areas bilaterally, with no signs of a focal drainable collection. Magnetic resonance imaging of the face and orbits was performed before and after the administration of intravenous contrast material. A T2-weighted image obtained with short-tau inversion recovery (STIR) parameters showed signal hyperintensity within the bilateral preseptal soft tissues, right lateral pterygoid and temporalis muscles with associated signal hyperintensity along the fascial planes of the extraocular muscles, and asymmetric mild enlargement and enhancement of the left superior oblique, medial, and lateral recti.

Two days after the patient's admission to this hospital, fine-needle aspiration biopsy of a fat pad was performed, and pathological examination of the specimen revealed no evidence of malignant cells; staining with Congo red was negative for amyloid. Results of serum protein electrophore-

sis were normal, and serum free light chains were not detected. Treatment with oral dexamethasone was initiated.

Eight days after the patient's admission, the ferritin level decreased to 15,846 ng per milliliter (reference range, 20 to 300), but pancytopenia persisted. Nine days after admission, ruxolitinib was administered. Ruxolitinib, a JAK1 and JAK2 inhibitor, has shown success in murine models of HLH, with decreased interferon-γ, interleukin-6, and interleukin-12 and decreased symptoms, and has been used successfully in humans. During the next 7 days, the patient noted increasing energy, decreased edema in the legs, and resolution of fever. The blood ferritin level further decreased to 2759 ng per milliliter, but pancytopenia and neutropenia persisted 3 weeks after the treatment course with dexamethasone and ruxolitinib had begun.

A repeat bone marrow biopsy was performed. The marrow was markedly hypocellular (cellularity <1% in the core specimen), with patchy serous atrophy; no hemophagocytic histiocytes were seen. Immunohistochemical examination revealed many scattered T cells and occasional B cells. Treatment with dexamethasone was continued, but ruxolitinib treatment was discontinued. The day after treatment with ruxolitinib was discontinued, fevers recurred, and the blood ferritin level had increased to 4188 ng per milliliter; the neutrophil count had not increased.

A diagnostic test was performed, and management decisions were made.

DIFFERENTIAL DIAGNOSIS OF HLH TRIGGERS

Dr. Maus: What triggered this patient's HLH syndrome? A standard workup for hematologic cancer, including imaging studies and bone marrow biopsy, was negative except for an increase in FDG uptake in the spleen, which was slightly enlarged. There are rare hematologic cancers that are characterized by an absence of lymphadenopathy or bone marrow involvement but may nevertheless trigger HLH.

EXTRANODAL LYMPHOMA

Approximately 10 to 35% of patients with non-Hodgkin's lymphoma present with extranodal disease at the time of diagnosis.[6] The most common sites of involvement are the gastrointestinal tract, skin, testes, bones, kidneys, and central nervous system. However, most extranodal lymphomas also have FDG avidity; the lymphomas without FDG avidity include chronic lymphocytic leukemia, Waldenström's macroglobulinemia, marginal-zone lymphoma, and some T-cell lymphomas.[7,8] Among these non-FDG–avid lymphomas, only splenic marginal-zone lymphoma and T-cell lymphomas typically manifest with extranodal disease. Splenic marginal-zone lymphoma involves the spleen, but the disease is indolent, is associated with autoimmune disease, and rarely causes B symptoms (i.e., weight loss, night sweats, and fever) or acute illness, characteristics that do not fit this patient's presentation. Therefore, the most likely underlying trigger is a T-cell lymphoma.

T-CELL LYMPHOMA

Peripheral T-cell lymphomas are a heterogeneous group of rare but generally aggressive cancers. The most common peripheral T-cell lymphoma is a "not otherwise specified" subtype, but multiple subtypes exist, including anaplastic large-cell lymphoma; angioimmunoblastic T-cell lymphoma; hepatosplenic T-cell lymphoma; enteropathy-associated T-cell lymphoma; extranodal NK T-cell lymphoma, nasal type; subcutaneous panniculitis-like T-cell lymphoma; and primary cutaneous gamma–delta T-cell lymphoma. The potential diagnosis of extranodal NK T-cell lymphoma, nasal type, should be considered in this patient because it is an EBV-associated lymphoma that is characterized by germline T-cell–receptor T cells that express CD56 and lack CD8, with positive staining for EBV-encoded RNA in the tumor cells. Scans obtained in this patient did show abnormal signal intensity in the nasal cavity, and this disease can also involve the skin; however, the disease typically manifests with a symptomatic midfacial mass. Approximately 3% of patients who have NK T-cell lymphoma, nasal type, also present with HLH. However, this subtype of lymphoma typically has FDG avidity on PET, and the patient had neither a symptomatic nasal mass nor clinically significant FDG-avid disease.

One of the patient's primary symptoms was a scaling erythematous rash on the legs, so cutaneous T-cell lymphoma seems quite likely, despite the rarity of this disease. Subcutaneous panniculitis-like T-cell lymphoma manifests with painless subcutaneous nodules or plaques involving

the legs (occurring in 71% of patients), arms (62%), trunk (56%), and face (25%).[9,10] A waxing and waning course is typical, with lesions in various stages of growth and remission. Approximately 20% of patients have a history of autoimmune disease. In patients with subcutaneous panniculitis-like T-cell lymphoma, it is unusual for the lymphoma to be present in areas other than the skin, although the bone marrow can harbor hemophagocytes. Pathological examination of skin lesions typically reveals cellular infiltrates composed of T cells and histiocytes in the subcutaneous fat. The tumorigenic cells associated with subcutaneous panniculitis-like T-cell lymphoma arise from a mature cytotoxic T cell. The World Health Organization originally characterized the tumorigenic T cells as having clonal rearrangements of either the alpha–beta or the gamma–delta T-cell receptor, but subcutaneous panniculitis-like T-cell lymphoma has now been redefined such that the disease is restricted to primary cutaneous T-cell lymphomas that have clonal rearrangements of the alpha–beta T-cell receptor.[9] The other immunophenotypic features of subcutaneous panniculitis-like T-cell lymphoma tumors include CD3+, CD8+, CD4–, and CD56–, as well as positivity for granzyme B, perforin, T-cell receptor alpha–beta, and T-cell intracellular antigen. The in situ hybridization analysis for EBV-encoded RNA is negative. Approximately 17% of patients with subcutaneous panniculitis-like T-cell lymphoma present with secondary HLH, and these patients have a worse prognosis than those who do not present with secondary HLH.[9]

In patients with subcutaneous panniculitis-like T-cell lymphoma, the lesions typically involve only the subcutaneous fat. The erythematous scaling of the nodules in this patient suggests that his lesions involved the dermis and epidermis and not just the subcutaneous fat. This characteristic is commonly seen in primary cutaneous gamma–delta T-cell lymphoma, which represents less than 1% of all cases of cutaneous lymphomas. Gamma–delta T cells arise from double-negative thymocytes early in T-cell development and form part of the innate immune system. Unlike alpha–beta T-cell receptors, gamma–delta T-cell receptors are not restricted by the HLA; instead, they recognize lipid antigens or microbial compounds. Gamma–delta T cells make up less than 5% of circulating lymphocytes but are abundant in the skin and gut. They may proliferate in response to infections, such as tuberculosis, listeria, and malaria.

In a series of 20 patients with confirmed primary cutaneous gamma–delta T-cell lymphoma, 70% presented with HLH symptoms. I suspect that in the case of primary cutaneous gamma–delta T-cell lymphoma, it is the autonomous T-cell proliferation and aberrant cytokine production that drive the HLH symptomatology, including macrophage activation (Fig. 3). This disease is very aggressive and portends a poor prognosis, regardless of the presence of HLH symptoms.[9] Aside from the clonal gamma–delta T-cell receptor gene rearrangements, no characteristic mutations in primary cutaneous gamma–delta T-cell lymphoma have been defined, although complex cytogenetic features have been reported.

Given the combination of the patient's HLH symptoms and laboratory findings, the absence of lymphadenopathy, and the presence of cutaneous lesions, I favor the diagnosis of primary cutaneous gamma–delta T-cell lymphoma manifesting with HLH syndrome. I would recommend a biopsy of a nodule on the left thigh that would include the subcutaneous fat, and I would perform immunohistochemical testing for CD3, CD4, CD8, CD56, and T-cell receptors alpha–beta and gamma–delta, along with T-cell receptor clonality and genetic testing of both the germline and the tumor.

DR. MARCELA V. MAUS'S DIAGNOSIS

Primary cutaneous gamma–delta T-cell lymphoma that triggered hemophagocytic lymphohistiocytosis syndrome.

PATHOLOGICAL DISCUSSION

Dr. Cornejo: A skin biopsy specimen obtained at this hospital from the medial left thigh showed an atypical proliferation of medium-to-large pleomorphic cells in the dermis and subcutaneous tissue that was associated with prominent karyorrhexis (Fig. 4A). Mild interface changes of the epidermis with ulceration were also identified. The infiltrate was angiocentric and angiodestructive; it surrounded and infiltrated the vessel walls and was associated with fibrin thrombi (Fig. 4B and 4C). There was no evidence of hemophagocytosis.

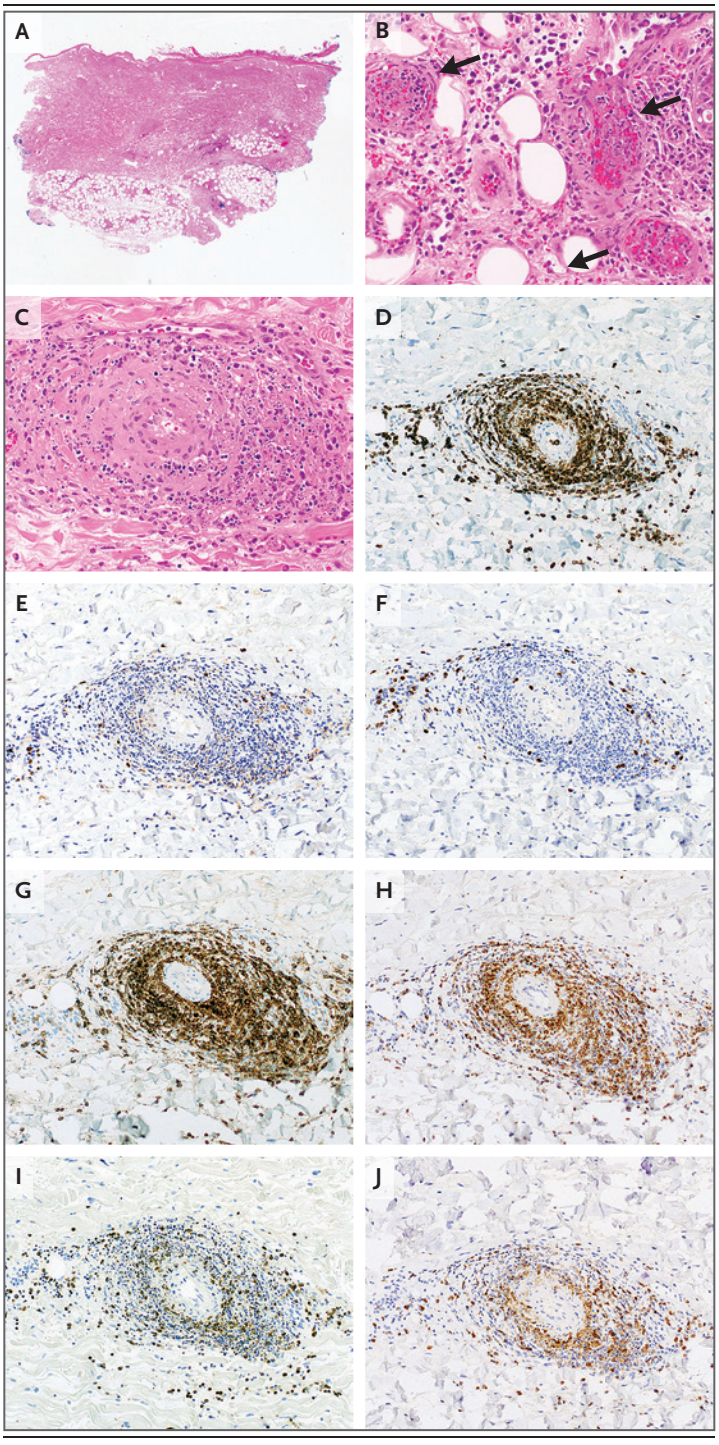

Figure 4. Subsequent Biopsy Specimen of the Skin, Obtained at This Hospital.

Hematoxylin and eosin staining of a biopsy specimen of a skin lesion on the left thigh shows a denser proliferation of atypical medium to large lymphocytes in the dermis and subcutis than was seen in the initial biopsy specimen (Panel A), with evidence of karyorrhectic debris, fibrin thrombi (Panel B, arrows), and angioinvasion and angiodestruction (Panel C). Immunohistochemical stains show that the neoplastic cells are CD3+ T cells (Panel D), with loss of CD4 (Panel E), CD8 (Panel F), and CD5 (not shown). The atypical lymphocytes also express CD56 (Panel G), perforin (Panel H), and granzyme B (not shown). Beta F1 (Panel I) and T-cell receptor delta (Panel J) are coexpressed.

Immunohistochemical stains showed that the neoplastic cells were CD3+ T cells, with retained coexpression of CD2, and with loss of CD4, CD8, and CD5 (Fig. 4D, 4E, and 4F). Rare scattered CD20+ B cells were also seen. The lymphocytes expressed CD56, as well as cytotoxic proteins granzyme B and perforin (Fig. 4G and 4H). Immunohistochemical staining for CD68 identified scattered intermixed histiocytes, and staining for CD30 highlighted rare inflammatory cells. In situ hybridization was negative for EBV-encoded RNA. Beta F1 (an antibody for the T-cell beta chain antigen receptor) and T-cell receptor delta staining were both positive in the atypical lymphocytes (Fig. 4I and 4J). Molecular studies showed the presence of a clonal T-cell receptor gamma chain gene rearrangement. The morphologic features and immunophenotype in conjunction with the molecular findings were consistent with primary cutaneous gamma–delta T-cell lymphoma. Coexpression of beta F1 and T-cell receptor delta on immunohistochemical testing has been previously reported.[11]

DISCUSSION OF TREATMENT

Dr. Leick: Because the patient's malignant T cells expressed low levels of CD30, treatment with cyclophosphamide, doxorubicin, dexamethasone, and brentuximab vedotin was initiated. This regimen was administered, rather than the standard cyclophosphamide, doxorubicin, vincristine, and dexamethasone (CHOP) regimen, given emerging evidence that suggests the superiority of this regimen in peripheral T-cell lymphomas expressing CD30.[12]

Four days after the initiation of chemotherapy, the patient's cutaneous lymphomatous lesions were less indurated. However, the next day, rapidly progressive respiratory failure developed, which resulted in intubation, initiation of pressors, and transfer to the intensive care unit. The most likely diagnosis was diffuse alveolar hemor-

rhage, given that, at the time of intubation, the patient had had epistaxis and clots were removed from his trachea. A bronchoscopy was negative. Other possible diagnoses included volume overload (volume overloaded, with multifocal interstitial opacities), and aspiration pneumonia. Subsequently, the patient was noted to have fixed and dilated pupils; an urgent CT scan of the head showed a large intraparenchymal hemorrhage in the left cerebellar hemisphere with mass effect on the brain stem and fourth ventricle, as well as transtentorial and tonsillar herniation. In consultation with the patient's brother and sister-in-law, comfort measures were initiated, and the patient died peacefully on hospital day 57.

After the patient's death, a familial HLH germline genetic analysis performed at Cincinnati Children's Hospital was negative for germline mutations. However, targeted gene sequencing of the patient's skin biopsy specimen for hematologic cancers revealed a nonsense mutation with a 34.6% allele frequency in *TNFAIP3* (the gene encoding NF-κB negative regulator A20) that was predicted to be a pathogenic variant (TNFAIP3 ENST00000237289.4:c.1694C←A, ENSP00000237289.4:p.Ser565Ter). Recent testing of the patient's bone marrow specimen in which the same gene sequencing panel was used had been negative. Therefore, the patient was believed to have a tumor-specific mutation. Dysfunction of *TNFAIP3* has been associated with autoinflammatory disease in humans and increased production of interferon-γ and tumor necrosis factor α by T cells during in vitro stimulation.[13,14]

ANATOMICAL DIAGNOSIS

Skin involvement associated with peripheral T-cell lymphoma most consistent with primary cutaneous gamma–delta T-cell lymphoma.

This case was presented at the Massachusetts General Hospital Cancer Center Rounds.

No potential conflict of interest relevant to this article was reported.

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

REFERENCES

1. Otrock ZK, Hock KG, Riley SB, de Witte T, Eby CS, Scott MG. Elevated serum ferritin is not specific for hemophagocytic lymphohistiocytosis. Ann Hematol 2017;96:1667-72.
2. Bergsten E, Horne A, Aricó M, et al. Confirmed efficacy of etoposide and dexamethasone in HLH treatment: long-term results of the cooperative HLH-2004 study. Blood 2017;130:2728-38.
3. Henter J-I, Horne A, Aricó M, et al. HLH-2004: diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. Pediatr Blood Cancer 2007;48:124-31.
4. Hejblum G, Lambotte O, Galicier L, et al. A Web-based Delphi study for eliciting helpful criteria in the positive diagnosis of hemophagocytic syndrome in adult patients. PLoS One 2014;9(4):e94024.
5. Rivière S, Galicier L, Coppo P, et al. Reactive hemophagocytic syndrome in adults: a retrospective analysis of 162 patients. Am J Med 2014;127:1118-25.
6. Anderson T, Chabner BA, Young RC, et al. Malignant lymphoma. 1. The histology and staging of 473 patients at the National Cancer Institute. Cancer 1982;50:2699-707.
7. Elstrom R, Guan L, Baker G, et al. Utility of FDG-PET scanning in lymphoma by WHO classification. Blood 2003;101:3875-6.
8. Weiler-Sagie M, Bushelev O, Epelbaum R, et al. (18)F-FDG avidity in lymphoma readdressed: a study of 766 patients. J Nucl Med 2010;51:25-30.
9. Willemze R, Jansen PM, Cerroni L, et al. Subcutaneous panniculitis-like T-cell lymphoma: definition, classification, and prognostic factors: an EORTC Cutaneous Lymphoma Group Study of 83 cases. Blood 2008;111:838-45.
10. Gallardo F, Pujol RM. Subcutaneous panniculitic-like T-cell lymphoma and other primary cutaneous lymphomas with prominent subcutaneous tissue involvement. Dermatol Clin 2008;26:529-40.
11. Rodríguez-Pinilla SM, Ortiz-Romero PL, Monsalvez V, et al. TCR-γ expression in primary cutaneous T-cell lymphomas. Am J Surg Pathol 2013;37:375-84.
12. Horwitz S, O'Connor OA, Pro B, et al. Brentuximab vedotin with chemotherapy for CD30-positive peripheral T-cell lymphoma (ECHELON-2): a global, double-blind, randomised, phase 3 trial. Lancet 2019;393:229-40.
13. Giordano M, Roncagalli R, Bourdely P, et al. The tumor necrosis factor alpha-induced protein 3 (TNFAIP3, A20) imposes a brake on antitumor activity of CD8 T cells. Proc Natl Acad Sci U S A 2014;111:11115-20.
14. Zhou Q, Wang H, Schwartz DM, et al. Loss-of-function mutations in TNFAIP3 leading to A20 haploinsufficiency cause an early-onset autoinflammatory disease. Nat Genet 2016;48:67-73.