CASE RECORDS of the MASSACHUSETTS GENERAL HOSPITAL

Case 26-2018: A 48-Year-Old Man with Fever, Chills, Myalgias, and Rash

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PRESENTATION OF CASE

Dr. William G. Tsiaras: A 48-year-old man was evaluated at this hospital because of fever, chills, myalgias, diarrhea, and a diffuse rash.

The patient had been in his usual state of good health until about 3 weeks before admission, in the late spring, when he noted the onset of fevers, chills, headache, and diffuse myalgias. He thought that he had influenza. Five days later, he noted an erythematous rash affecting his trunk, legs, feet, and hands. One day after that, mild, diffuse abdominal discomfort developed, along with anorexia and multiple episodes of nonbloody diarrhea. During the next 5 days, he had positional dizziness with syncope. Fourteen days before admission to this hospital, the patient sought medical attention at another hospital.

At the other hospital, examination revealed that the patient had fatigue and a diffuse erythematous rash. The temperature was 37.7°C. Laboratory evaluation was notable for an absolute eosinophil count of 600 per cubic millimeter (reference range at the other hospital, 0 to 200) and elevated levels on liver-function tests. Computed tomography (CT) of the chest, performed without the intravenous administration of contrast material, reportedly revealed mild, diffuse enlargement of lymph nodes, which were up to 9 mm in diameter in the mediastinum and up to 15 mm in diameter in the porta hepatis. A test of a nasopharyngeal swab for influenza A and B viruses, a rapid test of a throat swab for streptococcal antigen, and tests of the blood for babesia DNA, ehrlichia DNA, hepatitis A virus antibody, hepatitis B virus surface antibody and surface antigen, hepatitis C virus antibody, human immunodeficiency virus (HIV) p24 antigen and antibody, and Lyme disease IgM antibody were negative. The patient was treated with an unknown antibiotic agent, and after 5 days, he was discharged with prescriptions for cetirizine and hydroxyzine. He was scheduled for follow-up with his primary care physician.

The day before admission, the patient observed new mild swelling of the face and hands, with blisters on the palms. He was seen by his primary care physician the next day, and he reported persistent fevers, chills, rash with blistering, anorexia, and positional light-headedness. Laboratory test results are shown in Table 1. On

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Table 1. Laboratory Data.*

Variable	Reference Range, Adults, Office of Primary Care Physician	Morning of Admission, Office of Primary Care Physician	Reference Range, Adults, This Hospital†	On Admission, This Hospital	Day 3, This Hospital
Blood					
Hemoglobin (g/dl)	13.5–17.5	12.2	13.5–17.5	10.4	10.0
Hematocrit (%)	41.0–53.0	35.2	41.0–53.0	30.2	29.9
Red-cell count (per mm^3)	4,200,000–5,400,000	3,910,000	4,500,000–5,900,000	3,360,000	3,100,000
White-cell count (per mm^3)	4500–10,500	18,300	4500–11,000	11,000	6500
Differential count (%)					
Neutrophils	45.0–75.0	24.0	40–70	44	45
Lymphocytes	20.0–44.0	40.3	22–44	24	29
Atypical lymphocytes	0	4	0	4	13
Monocytes	2.0–12.0	10.6	4–11	2	5
Eosinophils	0–4	24	0–8	23	8
Bands			0–10	3	0
Platelet count (per mm^3)	130,000–400,000	90,000	150,000–400,000	111,000	107,000
Mean platelet volume (fl)	7.0–11.0	12.7	8.4–12.0		
Sodium (mmol/liter)	135–145	133	135–145	129	135
Potassium (mmol/liter)	3.5–5.5	3.2	3.4–4.8	4.0	3.5
Chloride (mmol/liter)	96–106	96	100–108	95	101
Carbon dioxide (mmol/liter)	21–32	26	23–32	22	23.7
Urea nitrogen (mg/dl)	6–23	15	8–25	17	17
Creatinine (mg/dl)	0.5–1.4	1.2	0.60–1.50	0.99	1.04
Glucose (mg/dl)	65–99	92	70–110	158	104
Calcium (mg/dl)	8.2–10.1	8.1	8.5–10.5	8.0	7.8
Total protein (g/dl)	6.4–8.2	8.3	6.0–8.3	7.5	5.8
Albumin (g/dl)	3.4–5.0	2.3	3.3–5.0	2.6	2.2
Globulin (g/dl)			2.3–4.1	4.9	3.8
Total bilirubin (mg/dl)	0.0–1.3	0.5	0.0–1.0	0.5	0.5
Aspartate aminotransferase (U/liter)	10–40	95	10–40	99	188
Alanine aminotransferase (U/liter)	20–60	153	10.55	116	160
Alkaline phosphatase (U/liter)	30–150	811	45–115	641	498
Erythrocyte sedimentation rate (mm/hr)	<10.0	74	0–15		
C-reactive protein (mg/liter)	0.10–15.00	41.33	<8		
Lactate dehydrogenase (U/liter)	85–227	725	110–210		490
γ-Glutamyltransferase (U/liter)			8–61	286	
C3 (mg/dl)			86–184	105	
C4 (mg/dl)			16–38	15	
Cryoprotein			None present	None present	
Heterophile antibody			Negative	Weakly positive	
EBV IgM antibody to viral capsid antigen			Negative	Negative	
EBV IgG antibody to viral capsid antigen			Negative	Positive	
EBV IgG antibody to nuclear antigen			Negative	Positive	

Table 1. (Continued.)

Variable	Reference Range, Adults, Office of Primary Care Physician	Morning of Admission, Office of Primary Care Physician	Reference Range, Adults, This Hospital†	On Admission, This Hospital	Day 3, This Hospital
Cytomegalovirus antigenemia assay			Negative	Negative	
Antitreponemal antibody			Negative	Negative	
HIV-1 and HIV-2 antibody and HIV-1 p24 antigen			Negative	Negative	
HIV-1 on PCR assay			Not detected		Not detected
Hepatitis A virus total antibody			Negative		Negative
Hepatitis A virus IgM antibody			Negative		Negative
Hepatitis B virus surface antigen			Negative		Negative
Hepatitis B virus surface antibody, qualitative			Negative		Negative
Hepatitis B virus core antibody			Negative		Negative
Hepatitis C virus antibody			Negative		Negative
Tryptase (ng/ml)			<11.5		14.5
Antinuclear antibody			Negative at 1:40 and 1:160		Positive at 1:40 and 1:160, speckled
Urine					
Color		Yellow	Yellow		Yellow
pH		6.0	5.0–9.0		5.5
Specific gravity		1.025	1.001–1.035		1.008
Glucose		Negative	Negative		Negative
Ketones		Negative	Negative		Negative
Protein		Trace	Negative		Negative
Leukocytes		Negative	Negative		Negative
Blood		Negative	Negative		Negative

* EBV denotes Epstein–Barr virus, HIV-1 human immunodeficiency virus type 1, HIV-2 HIV type 2, and PCR polymerase chain reaction. 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 calcium to millimoles per liter, multiply by 0.250. 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.

the basis of advice from a rheumatologist located in the same office, the patient was given one dose of oral prednisone and was referred to the emergency department of this hospital.

Additional history was obtained in the emergency department. The patient reported pruritus in the areas of the previous leg rash, fatigue, chronic pain in the cervical spine and low back, and a mostly intentional weight loss of 11 kg over the previous 15 weeks. He had had no known exposures to animals or insects. He had a history of hyperlipidemia, depression, and gastroesophageal reflux disease. Medications included aspirin, mirtazapine, rosuvastatin, omeprazole, and cetirizine, as well as hydroxyzine as needed for pruritus. He reported that he had started to take a new over-the-counter medication for the treatment of pain approximately 5 weeks before admission but had stopped taking it at the onset of his presenting symptoms. He could not recall the name of this new medication. He had had no adverse reactions to medications. His family history was notable for lung cancer in his mother and diabetes and coronary artery disease in his father;

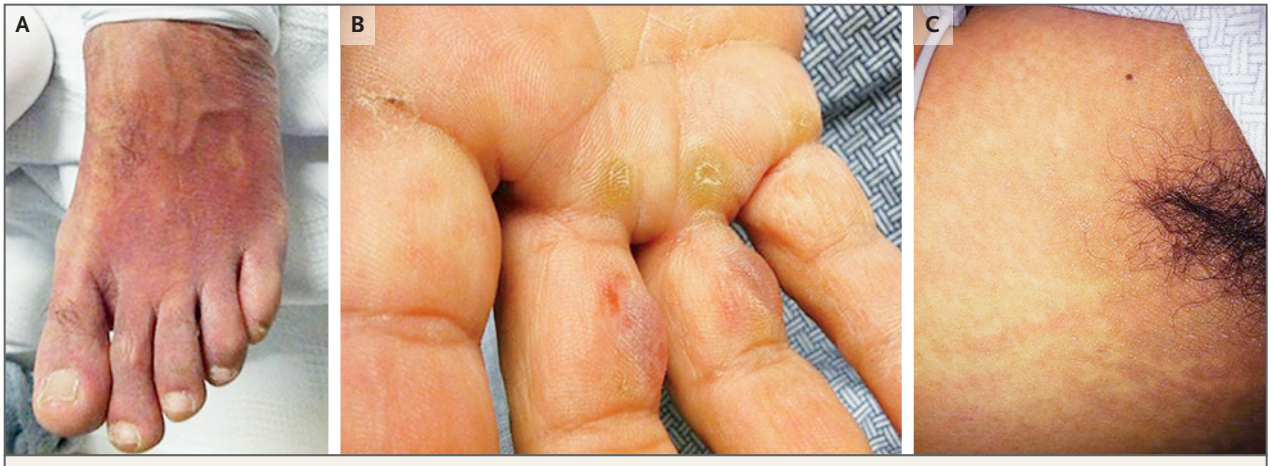

Figure 1. Clinical Photographs of the Rash.

The patient presented with a polymorphous eruption, including violaceous plaques with exfoliative scale on the dorsal feet (Panel A), flaccid bullae on the palms (Panel B), and a blanching, maculopapular rash on the trunk (Panel C).

there was no history of autoimmune or dermatologic disorders. He had smoked two packs of cigarettes daily and marijuana once weekly for the past 30 years. He did not drink alcohol or use illicit drugs. He worked as a manual laborer and driver. He had not traveled outside of New England. He was single and had had multiple female sexual contacts but had always used barrier protection; the young grandchild of his current sexual partner had recently had a self-limited febrile illness with a diffuse maculopapular, erythematous rash.

On examination, the patient appeared fatigued. The temperature was 37.1°C, the heart rate 89 beats per minute, the blood pressure 132/57 mm Hg, and the oxygen saturation 98% while he was breathing ambient air. The weight was 79 kg, and the body-mass index (the weight in kilograms divided by the square of the height in meters) 28.1. He had mild periorbital edema and mild exfoliative scale on the temple and forehead. A blanching, maculopapular rash was present on the trunk. On the arms, legs, and dorsal feet, there were thin, faintly violaceous plaques with mild exfoliative scale. Small flaccid bullae, including some that were hemorrhagic, were noted on several fingers and the palms, and a few had ruptured (Fig. 1). He did not have a rash on mucosal surfaces or nail changes. There were mildly tender, mobile lymph nodes in the bilateral cervical, submandibular, axillary, and inguinal distributions, including a 1-cm axillary node and a 2-cm inguinal node. There was mild abdominal tenderness in the upper quadrants, with hepatosplenomegaly. The stool was guaiac-negative. The remainder of the examination was normal.

Blood levels of thyrotropin, creatine kinase, troponin T, amylase, lipase, and vitamin D were normal, as were the serum osmolality, basophil count, prothrombin time, and activated partial-thromboplastin time. Other laboratory test results are shown in Table 1.

The patient was admitted to the general medicine unit. Two sets of blood cultures were obtained. Examination of a peripheral-blood smear revealed atypical-appearing mononuclear cells.

Dr. Shaunagh McDermott: On the second hospital day, CT of the chest, abdomen, and pelvis was performed after the intravenous administration of contrast material. There were areas of centrilobular emphysema and bronchial-wall thickening, scattered pulmonary nodules (2 to 3 mm in diameter) in the upper lobes, and multiple enlarged lymph nodes (Fig. 2A and 2B). There was also splenomegaly (spleen length, 15.2 cm; normal length, ≤12.0 cm), with a splenic cyst (Fig. 2B).

Dr. Tsiaras: On the third hospital day, the temperature rose to 38.4°C and the heart rate was 110 beats per minute. Laboratory test results are shown in Table 1. Cultures of the urine and blood were obtained. Serum protein electrophoresis revealed mild, diffuse hypergammaglobulinemia,

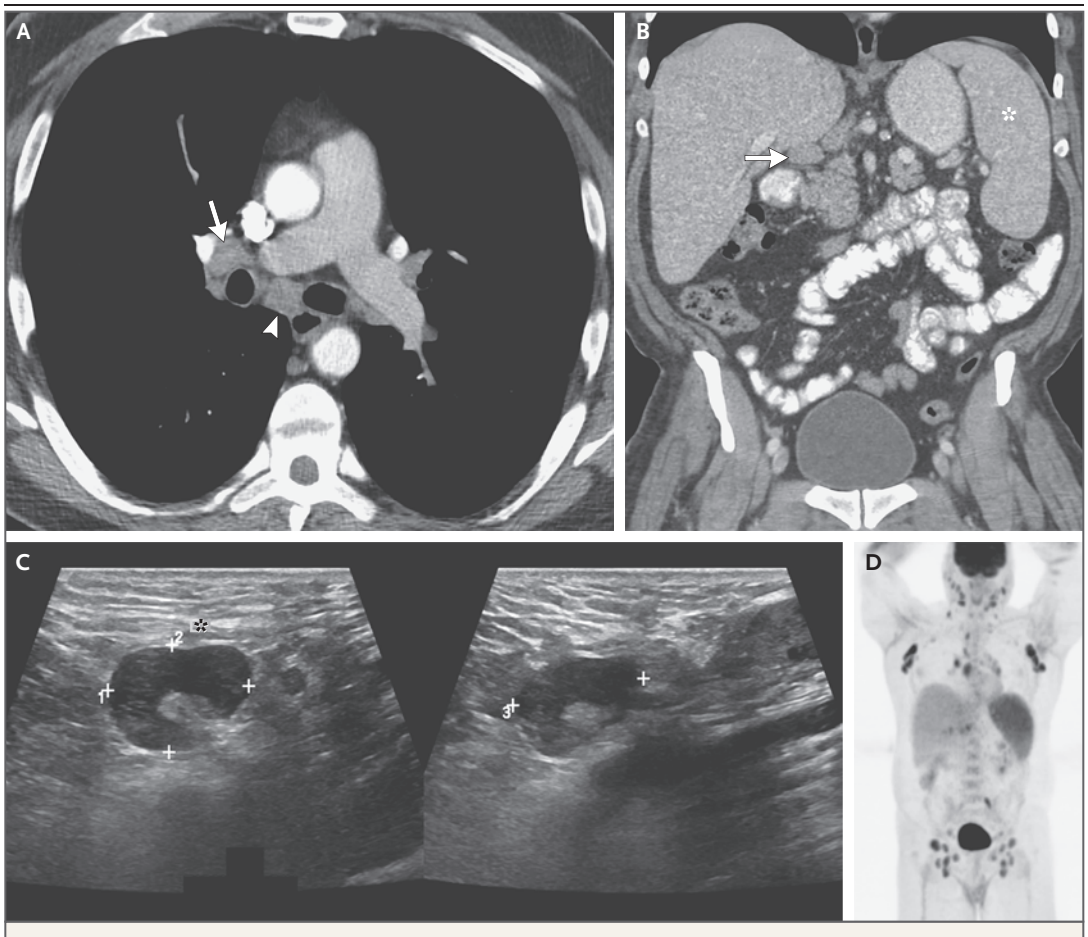

Figure 2. Imaging Studies.

CT was performed after the intravenous administration of contrast material. An axial image of the chest (Panel A) shows enlarged right hilar (arrow) and subcarinal (arrowhead) lymph nodes. A coronal image of the abdomen (Panel B) shows enlarged periportal lymph nodes (arrow) and splenomegaly (asterisk). Ultrasound images of the leg (Panel C) show an enlarged right inguinal lymph node (asterisk), with preservation of a normal fatty hilum. A positron-emission tomographic scan (Panel D) shows lymphadenopathy with intense ^{18}F-fluorodeoxyglucose (FDG) avidity in the neck, chest, abdomen, and pelvis and diffuse increase in FDG uptake in the spleen.

with a level of IgG lambda M component in the gamma region of 0.07 g per deciliter. Levels of serum free kappa and lambda light chains were normal. Additional imaging studies were obtained.

Dr. McDermott: Ultrasonography of the legs and arms was negative for venous thrombosis; however, enlarged lymph nodes were noted incidentally (Fig. 2C). CT with positron-emission tomography (PET) was performed on the sixth hospital day. There were multiple lymph nodes with ^{18}F-fluorodeoxyglucose (FDG) avidity in the axillary, cervical, supraclavicular, paratracheal, hilar, subcarinal, portal, iliac, and inguinal distributions, and there was diffuse increase in FDG uptake in the spleen (Fig. 2D).

Dr. George Eng: Flow cytometry of a peripheral-blood specimen was negative for a monotypic B-cell population and for T cells with immunophenotypic abnormalities. Biopsy of an enlarged right inguinal lymph node was performed on the seventh hospital day; histopathological examination of the biopsy specimen revealed florid paracortical hyperplasia, without evidence of cancer (Fig. 3). Flow cytometry of the biopsy specimen was negative for cancer.

Dr. Tsiaras: Diagnostic test results were received.

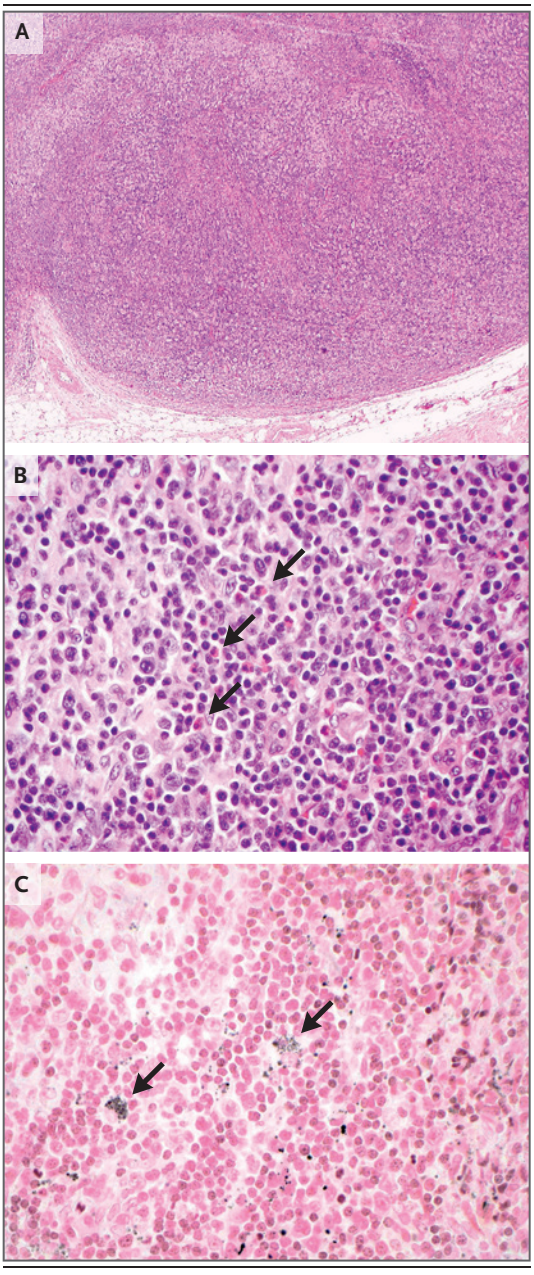

Figure 3. Lymph Node–Biopsy Specimen.

A right inguinal lymph node was enlarged (3.5 cm by 2.0 cm by 0.5 cm), with a tannish-white, fleshy gross appearance. Hematoxylin and eosin staining (Panel A) shows areas of marked paracortical expansion containing abundant interdigitating Langerhans' cells and showing preservation of sinus patency. At higher magnification, there is an abundance of small, mature-appearing lymphocytes and a notable scattering of eosinophils. In the areas of paracortical expansion, there are histiocytes containing pigmented material (Panel B); on Fontana–Masson staining, the material is confirmed as melanin (Panel C). Results of immunohistochemical staining for B-cell and T-cell markers were normal. The overall interpretation of these findings is florid paracortical hyperplasia with dermatopathic features.

DIFFERENTIAL DIAGNOSIS

Dr. Sarah E. Turbett: When reviewing a case with many clinical, laboratory, imaging, and pathological features, the goal is to identify a few key elements that will help to guide the differential diagnosis. In this case, I will first focus on the eosinophilia.

EOSINOPHILIA

Eosinophils serve many functions in the body, including mediation of allergic responses, eradication of parasitic infections, and down-regulation of the inflammatory response.[1] Eosinophils reside mainly in tissues, and a normal absolute eosinophil count in the peripheral blood is 0 to 500 per cubic millimeter.[2] Eosinophilia is defined as the presence of an absolute eosinophil count of more than 500 per cubic millimeter and is often categorized as mild (500 to <1500 eosinophils per cubic millimeter), moderate (1500 to 5000), or severe (>5000).[2] It can also be categorized according to whether it is polyclonal (reactive) in nature or whether it is caused by clonal expansion due to a neoplastic process.[3]

On admission to the hospital, this patient had a total white-cell count of 11,000 per cubic millimeter, and 23% of those cells were eosinophils (absolute eosinophil count, 2530 per cubic millimeter). This degree of eosinophilia is considered to be moderate. In developing a differential diagnosis for this patient, I will focus on the common causes of eosinophilia, including cancer, Addison's disease, parasitic infections, and allergy. Various connective-tissue diseases and rheumatologic conditions can also cause eosinophilia, but I do not think these diseases are likely to explain this patient's presenting symptoms.

CANCER

Could this patient have had a cancer that was driving the production of eosinophils? Certain myeloid, lymphoid, and solid-tumor neoplasms result in eosinophilia. Myeloid neoplasms are the result of clonal expansion due to mutations in hematopoietic stem cells, whereas lymphoid and solid-tumor neoplasms are often reactive pro-

cesses.[3] This patient's systemic symptoms, lymphadenopathy, and hepatosplenomegaly are consistent with myeloid and lymphoid neoplasms. However, the absence of circulating leukocyte precursors in the peripheral blood, the negative results on flow cytometry, and the benign lymph node–biopsy specimen make these diagnoses unlikely. In addition, the PET scan did not show an FDG-avid mass, which would be present if the symptoms were due to a cancer.

ADDISON'S DISEASE

Addison's disease is characterized by the onset of fatigue, weight loss, and abdominal pain. Hypotension and fever can also develop in the context of adrenal crisis. When eosinophilia is present, it is often mild, with the absolute eosinophil count rarely rising above 1000 per cubic millimeter.[4,5] This patient had some symptoms that were compatible with a diagnosis of Addison's disease, including fever and fatigue. However, his overall clinical presentation did not fit well with this diagnosis, and his degree of eosinophilia was higher than would be expected.

PARASITIC INFECTION

Most parasitic infections cause eosinophilia because of migration of organisms through tissues. Parasites are typically present in specific geographic areas, and parasitic infections frequently occur after a patient has resided in or traveled to an area in which the parasite is endemic.[6] This patient had been born in New England and had a minimal travel history, and thus, his potential exposure was limited to two parasites that are associated with eosinophilia: trichinella species and toxocara species.

Trichinellosis is caused by *Trichinella spiralis*, and the infection occurs through ingestion of infected undercooked pork or wild game meat. Clinical features include fever, myalgias, facial edema, and rash, and common laboratory abnormalities include eosinophilia and an elevated creatine kinase level.[7,8] This patient had several findings that were consistent with a diagnosis of trichinellosis, including fever, periorbital edema, rash, and eosinophilia; however, myalgias were not a prominent feature of his presentation and the creatine kinase level was normal. Nearly all patients with trichinellosis have myalgias, and an elevated creatine kinase level is seen in the majority of cases.[8] The absence of these findings, combined with the absence of exposure to trichinella species, rules out this diagnosis.

Toxocariasis results from the ingestion of dirt that has been contaminated with dog or cat feces containing the cysts of *Toxocara canis* or *T. cati*, respectively.[8] Clinical and laboratory features include fever, abdominal pain, hepatomegaly, urticarial rash, pulmonary and ocular symptoms, and eosinophilia.[8] Although this patient presented with some of these features, his constellation of symptoms and findings cannot be explained solely by toxocariasis, and the absence of a history of exposure makes this diagnosis unlikely.

ALLERGY

In areas that do not have a substantial burden of parasites, allergic reactions to drugs are the most common cause of eosinophilia.[2] Manifestations of drug-induced eosinophilia can range from an asymptomatic process to a process with clinically significant end-organ involvement, such as the DRESS (drug reaction with eosinophilia and systemic symptoms) syndrome. Symptoms of the DRESS syndrome often develop 2 to 8 weeks after the initiation of a new drug, and many drugs have been implicated in the DRESS syndrome, including proton-pump inhibitors and statins, two classes of medications that this patient had been taking for many years.[9]

The European Registry of Severe Cutaneous Adverse Reactions (RegiSCAR) provides a scoring system to estimate the likelihood that a patient has the DRESS syndrome. According to this scoring system, this patient meets the criteria for definite DRESS syndrome (Table 2).[10] Although this diagnosis fits well with the clinical features in this case, the trigger for the DRESS syndrome is unclear, since omeprazole and rosuvastatin were not new medications for this patient. He noted that he had started to take new pain medications approximately 5 weeks before admission, but details about these medications are unknown, making it difficult to associate them with his illness. A reevaluation of the case details would be necessary to determine whether there were any potential triggers for the DRESS syndrome.

REEVALUATION OF THE CLINICAL PRESENTATION

Other salient features of this patient's clinical presentation include fever, rash, lymphadenopathy, hepatosplenomegaly, and atypical lympho-

Table 2. RegiSCAR Scoring System for the DRESS Syndrome.*

Criterion	This Patient	Score
Temperature ≥38.5°C	No (maximum temperature, 38.4°C)	–1
Enlarged lymph nodes (≥1 cm in diameter at ≥2 sites)	Yes	1
Atypical lymphocytes	Yes	1
Eosinophilia	Yes	2
Absolute eosinophil count of 700–1499	Yes	
Absolute eosinophil count of ≥1500	Yes	
Rash covering >50% of body surface area	Yes	1
Rash suggestive of DRESS syndrome (≥2 of the following: facial edema, purpura, infiltration, and desquamation)	Yes	1
Skin-biopsy specimen with evidence of DRESS syndrome	No	0
Organ involvement	Yes	1
1 Organ	Yes (liver)	
≥2 Organs	No	
Disease duration of ≥15 days	Yes	0
Evaluation for other causes (≥3 tests performed and negative)	Yes	1
Antinuclear antibody	Negative	
Blood cultures	Negative	
Hepatitis A, B, or C virus	Negative	
Chlamydia	Not performed	
Mycoplasma	Not performed	
Total score		7

* On the European Registry of Severe Cutaneous Adverse Reactions (RegiSCAR) scoring system, a score of less than 2 indicates no DRESS (drug reaction with eosinophilia and systemic symptoms) syndrome, 2 or 3 possible DRESS syndrome, 4 or 5 probable DRESS syndrome, and 6 or more definite DRESS syndrome.

cytosis. Although pharyngitis was not reported, the constellation of findings is consistent with a mononucleosis-like syndrome.[11] The differential diagnosis for a mononucleosis-like syndrome includes acute infection with Epstein–Barr virus (EBV), cytomegalovirus (CMV), human herpesvirus 6 (HHV-6), HIV, toxoplasma, or adenovirus.[11]

Acute HIV infection, toxoplasmosis, and adenovirus infection may cause a mononucleosis-like syndrome; however, there are aspects of the case that make each of these diagnoses unlikely. This patient had negative screening tests for HIV infection and an undetectable plasma HIV RNA level, findings that rule out the diagnosis of acute HIV infection. Acute toxoplasmosis is characterized by fever and lymphadenopathy; however, this patient did not report any exposure to cats or ingestion of undercooked meat that could have resulted in infection. Adenovirus infection is also unlikely, because this patient did not have respiratory or ocular symptoms, which are common features of this illness.

Acute EBV and CMV infections are consistent with this patient's presentation, and the contact with a sick young child provides an appropriate risk of exposure to infection. The weakly positive heterophile antibody test is also supportive of one of these diagnoses, since EBV and CMV can each cause a positive heterophile reaction.[12,13] Features of this case that are not consistent with these infections include the results of EBV-specific serologic tests, which suggested a past infection rather than a current infection, and the negative CMV antigenemia assay, which indicated the absence of viremia, a classic feature of acute CMV infection.[12] In view of these findings, these infections are unlikely to be the trigger of the patient's symptoms.

HHV-6 Infection

Could this patient have had acute primary or reactivated HHV-6 infection? As an infection that commonly occurs during childhood, primary HHV-6 infection rarely occurs in adults and is

often manifested by a mononucleosis-like syndrome.[14] The patient's contact with his partner's sick grandchild provides an appropriate risk of exposure to infection, and HHV-6 infection could theoretically explain the weakly positive heterophile antibody test, since EBV and HHV-6 are closely related viruses. No laboratory tests are available to rule out this diagnosis.

It is unclear whether HHV-6 infection can act as a trigger for the DRESS syndrome in the context of a possible drug exposure. Both primary and reactivated HHV-6 infection have been associated with the DRESS syndrome, with the hypothesis that viral replication leads to preferential activation and expansion of drug-specific CD4+ helper T cells and cytotoxic CD8+ T cells.[9,15,16] Although this hypothesis is relatively controversial, it offers a theoretical connection between HHV-6 infection and the DRESS syndrome and thus provides a potential unifying explanation of this patient's clinical presentation.

I think the most likely diagnosis in this case is the DRESS syndrome triggered by an unknown drug exposure in the context of HHV-6 infection. It is unclear whether this patient acquired acute HHV-6 infection from contact with a sick young child or whether he had reactivation of infection. I would recommend obtaining an HHV-6 DNA level and HHV-6 IgM and IgG antibody titers from the peripheral blood.

Dr. David M. Dudzinski (Medicine): Dr. Tsiaras, what was your clinical impression when you evaluated this patient?

Dr. Tsiaras: This patient's clinical presentation was consistent with a diagnosis of the DRESS syndrome. The specific causative drug in this case is not clear. The patient reported that treatment with a new analgesic medication had been initiated approximately 2 weeks before the onset of symptoms. This latency period between drug exposure and the onset of symptoms is compatible with the DRESS syndrome due to new analgesic medications. The DRESS syndrome is associated with reactivation of human herpesviruses, especially HHV-6, in the majority of cases.[17] For this reason, it was recommended that the patient be evaluated for HHV-6 infection.

CLINICAL DIAGNOSIS

The drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome.

DR. SARAH E. TURBETT'S DIAGNOSIS

The DRESS syndrome, most likely triggered by a drug reaction, associated with human herpesvirus 6 infection.

DIAGNOSTIC TESTING

Dr. Eng: The diagnostic test, a quantitative real-time polymerase-chain-reaction assay of the peripheral blood for HHV-6, was performed 2 days after admission, approximately 3 weeks after the initial onset of symptoms. The test was positive, at a viral load of 112,836 copies per milliliter (reference range, <500). Two weeks after the initial testing, the viral load decreased to less than 500 copies per milliliter. Both the absolute viral load and the relatively rapid decrease in viral load helped to rule out the possibility of chromosomally integrated HHV-6 as the cause of the elevated viral load. Of note, HHV-6 has the capacity to integrate into the human genome; this occurs in approximately 1% of the general population.[18-20] After the virus integrates into the genome, very high viral loads (often >1 million copies per milliliter) can be detected in the blood but do not necessarily indicate active infection.

Serum HHV-6 IgM and IgG antibody titers were also obtained. The IgM antibody titer was elevated, at higher than 1:320 (reference range, <1:20), and the IgG antibody titer was also elevated, at higher than 1:10,240 (reference range, <1:10). These findings further support the diagnosis of HHV-6 infection. Elevated IgM and IgG antibody titers can be identified in the context of acute HHV-6 seroconversion or reactivation,[21] and results from a previous HHV-6 serologic panel would be required to definitively distinguish between these two scenarios. Overall, these test results support the diagnosis of an HHV-6 mononucleosis-like illness associated with the DRESS syndrome.

DISCUSSION OF MANAGEMENT

Dr. Tsiaras: Once the diagnosis of the DRESS syndrome is established, prompt identification and discontinuation of the causative drug are mandatory. The most frequently encountered culprit medications include antibiotics (e.g., sulfonamides) and anticonvulsant, antiviral, antipyretic, and analgesic agents.[17] In most cases, clinical judgment is sufficient to determine the most

likely causative drug. For more challenging cases, in which the patient has been exposed to multiple new drugs, clinical tests have been developed to aid in identification of the causative agent. These include patch tests and lymphocyte transformation tests. Correct identification and immediate withdrawal of the causative drug are associated with improved outcomes and prevention of future episodes of the DRESS syndrome.[22]

After the suspected causative drug is withdrawn, supportive therapy is provided to patients with the DRESS syndrome. If erythroderma is present or the body surface is extensively affected by exfoliative dermatitis, then treatment in a specialized intensive care unit or burn unit may be required. Diagnostic studies are performed and repeated often to monitor for visceral organ involvement. If considerable visceral organ injury or organ failure is identified, then immediate organ-specific medical therapy is provided and the appropriate specialists are involved. Despite prompt discontinuation of the causative drug, symptoms of the DRESS syndrome typically last for more than 15 days and may persist for several months. Continued close follow-up of patients with the DRESS syndrome is recommended until complete resolution of symptoms.[22]

Guidelines for the treatment of the DRESS syndrome are limited, and evidence for systemic treatment is derived from case series and expert opinion. Systemic glucocorticoids are considered to be first-line therapy. A dose of prednisone of 1.0 mg per kilogram of body weight per day or the equivalent, with gradual tapering over a period of 3 to 6 months, is often recommended. In milder cases of the DRESS syndrome, high-potency topical glucocorticoids may be sufficient for relief of symptoms.[22] Glucocorticoid-sparing agents — including intravenous immune globulin, cyclosporine, cyclophosphamide, mycophenolate mofetil, and rituximab — have been used in a small number of cases of the DRESS syndrome, with varying efficacy.[17] The use of antiviral drugs that are effective against HHV-6 has been proposed for the treatment of patients who have the DRESS syndrome and confirmed HHV-6 reactivation; however, evidence is insufficient to support the use of such treatment.[22]

This patient's cutaneous eruption diminished over the course of his hospitalization; only hydrated petrolatum was used to manage the symptomatic dry desquamation. Systemic glucocorticoid therapy was not initiated because a workup for lymphadenopathy was ongoing during his hospitalization. At the time of discharge, his eosinophil count had normalized and results of liver-function tests were improving. The patient was seen by hematology for follow-up 1 week after discharge. Persistent periorbital edema was noted, but the lymphadenopathy and cutaneous eruption had continued to diminish. He was advised to take 20 mg of prednisone daily for 4 days for the treatment of persistent facial edema. Six weeks after discharge, the patient noted dry skin but no rash. The lymphadenopathy had further diminished, the facial edema had resolved, and laboratory test results were normal. The patient was taking no medications, and he had returned to work.

Dr. Dudzinski: It is very important to learn the identity of the medication that was likely to have caused the DRESS syndrome in this patient. Were you able to narrow down the list?

Dr. Tsiaras: I agree that it is important to identify the culprit medication in this case. Unfortunately, despite multiple attempts by the primary inpatient team, the precise medication remains unknown. In preparation for this discussion, we reviewed all available medical records from the other hospital; the physicians who cared for this patient had also noted that they had been unable to determine which new drug had been prescribed. To complicate the matter, the patient had taken several over-the-counter medications that he had been unable to recall. We thought it was unlikely that the statin or omeprazole was the culprit, given that he had used them for several months. In addition, the patient had possibly taken an over-the-counter nonsteroidal antiinflammatory drug (NSAID) for analgesia, but he had been taking aspirin for a long time, so the effect would probably be related to the specific NSAID rather than the broad class of drugs. If this patient had received the recommended outpatient follow-up, patch testing could have been considered to help identify the culprit agent. I realize that this is not the ideal outcome, but unfortunately, in the care of patients, we sometimes have to acknowledge that we have incomplete information.

FINAL DIAGNOSIS

The drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome, associated with human herpesvirus 6 infection or reactivation.

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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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