CASE RECORDS of the MASSACHUSETTS GENERAL HOSPITAL

Case 17-2023: A 58-Year-Old Woman with Fatigue, Abdominal Bloating, and Eosinophilia

Natasha S. Hochberg, M.D., M.P.H., Vincent V. Dinculescu, M.D., and Thomas B. Nutman, M.D.

From the Department of Medicine, Boston University School of Medicine (N.S.H.), the Department of Radiology, Massachusetts General Hospital (V.V.D.), and the Department of Radiology, Harvard Medical School (V.V.D.) — all in Boston; and the Laboratory of Parasitic Diseases, National Institutes of Health, Bethesda, MD (T.B.N.).

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PRESENTATION OF CASE

Dr. Rachel M. Erdil (Medicine): A 58-year-old woman was evaluated in the infectious disease clinic of this hospital because of fatigue, abdominal bloating, and eosinophilia.

The patient had been in her usual state of health until 8 months before the current evaluation, when she fell and injured her right leg while hiking in a rainforest in the Democratic Republic of Congo (DRC). Before this injury, she had been traveling throughout the DRC for 1 month. She had hiked, walked barefoot, and gone swimming in freshwater lakes and rivers.

Approximately 55 hours after the fall, the patient was transported to the trauma center of a regional hospital. Imaging studies revealed fractures of the right tibia with associated hemorrhage. Packed red cells were transfused, and an external fixation device was placed. Once the patient's condition was stable, she was transferred to a hospital in the United States.

At the second hospital, the eosinophil count was 3530 per microliter (reference range, 0 to 400); the eosinophil count had been normal 18 months earlier. Other laboratory test results are shown in Table 1. One week after the fall, open reduction and internal fixation of the fracture was performed. The patient started physical therapy and was discharged home.

The patient had persistent weight gain and mild fatigue, which had developed 4 years before the current presentation. She had associated these symptoms with the onset of menopause. However, after the traumatic leg injury, she noticed that the symptoms increased in severity. One month before the current evaluation, the patient's weight had increased by 8.6 kg since the leg injury, and she took a 1-hour nap every afternoon because of fatigue. In addition, she had new abdominal bloating that did not abate with the use of probiotics. The patient sought evaluation at a clinic associated with the second hospital. On evaluation, the results of blood tests for thyroid, kidney, and liver function were normal, as were blood levels of electrolytes. A test for Lyme disease was negative. The results of testing for Epstein–

Table 1. Laboratory Data.

Variable	Reference Range, Other Hospital	8 Mo before Current Evaluation, Other Hospital	1 Mo before Current Evaluation, Other Hospital	Reference Range, This Hospital*	On Current Evaluation, This Hospital
Hemoglobin (g/dl)	11.1–15.9	11.7	14.8	13.5–17.5	14.4
Hematocrit (%)	34.0–46.6	—	44.6	41.0–53.0	43.1
White-cell count (per μl)	3400–10,800	10,700	7000	4500–11,000	7140
Differential count (per μl)					
Neutrophils	1400–7000	—	2660	1800–7700	2980
Lymphocytes	700–3100	—	1820	1000–4800	1900
Monocytes	100–900	—	490	200–1200	420
Eosinophils	0–400	3530	1960	0–900	1760
Basophils	0–200	—	70	0–300	70
Platelet count (per μl)	150,000–400,000	483,000	320,000	150,000–400,000	296,000
Epstein–Barr virus					
Anti–viral capsid antigen IgM	0.0–35.9	—	55.3	—	—
Anti–viral capsid antigen IgG	0.2–17.9	—	309.0	—	—
Anti–nuclear antigen IgG	0.2–17.9	—	18.3	—	—
Anti–early antigen IgG	0.0–8.9	—	>150.0	—	—

* 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.

Barr virus (EBV)–specific antibodies and other laboratory test results are shown in Table 1.

Two weeks before the current evaluation, the patient moved to New England and established care in the primary care clinic of this hospital. She continued to receive physical therapy for rehabilitation of the right leg. She reported that the weight gain, fatigue, and abdominal bloating had worsened at a rapid rate; her weight had increased by 13.6 kg since the leg injury. The patient was referred to the infectious disease clinic of this hospital.

The patient had a history of chronic migraines and hyperlipidemia. Review of systems was notable for mild cough and swelling of the right knee that began after the surgery. She had no fever, hot flashes, night sweats, headache, shortness of breath, chest pain, abdominal pain, diarrhea, nausea, vomiting, myalgias, arthralgias, or rash.

Current medications included levothyroxine and probiotics. There were no known allergies. The patient had previously traveled to the southwestern United States, North and East Africa, western Europe, and South and Southeast Asia. She currently lived in a suburban area of New England with her husband and cats in a house that had mold. She did not smoke tobacco, drink alcohol, or use illicit drugs.

On examination, the temperature was 36.1°C, the blood pressure 98/66 mm Hg, the heart rate 73 beats per minute, and the oxygen saturation 99% while the patient was breathing ambient air. The body-mass index (the weight in kilograms divided by the square of the height in meters) was 24.9. She appeared well. The lungs were clear on auscultation, and the abdomen was soft and nontender; there was no hepatomegaly or lymphadenopathy. The right knee and leg had healed surgical scars. The skin examination was normal.

The eosinophil count was 1760 per microliter. Tests for syphilis, human immunodeficiency virus infection, and strongyloidiasis were negative. The urinalysis was normal. Other laboratory test results are shown in Table 1.

Dr. Vincent V. Dinculescu: Computed tomography

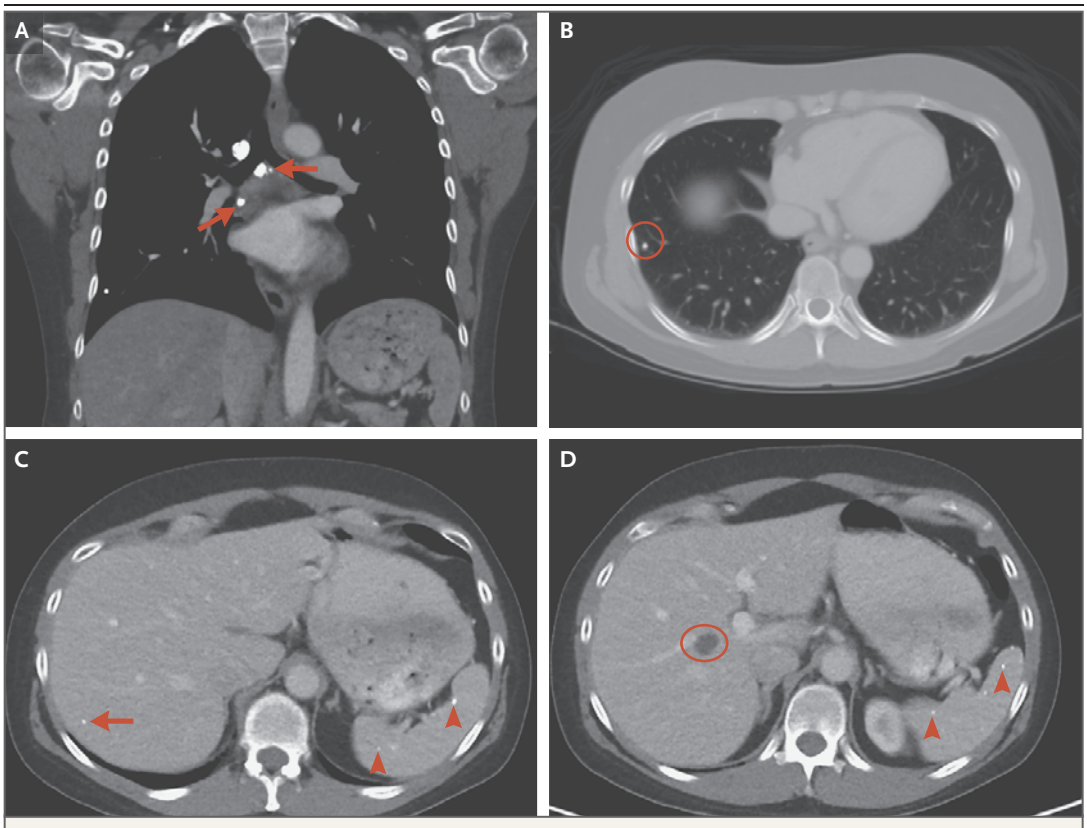

Figure 1. CT of the Chest and Abdomen.

A coronal contrast-enhanced image of the chest (Panel A) shows partially calcified, nonenlarged subcarinal lymph nodes (arrows). An axial image (Panel B) shows a fully calcified nodule in the lower lobe of the right lung (circle). Axial contrast-enhanced images of the abdomen obtained during the portal venous phase (Panels C and D) show a calcified lesion in the right lobe of the liver (arrow) and a low-attenuation hepatic lesion measuring 1.6 cm in diameter (circle), which is incompletely characterized but is probably a cyst. Multiple small calcified splenic lesions (arrowheads) are also present.

(CT) of the chest and abdomen (Fig. 1), performed after the administration of intravenous contrast material, revealed calcified, nonenlarged subcarinal lymph nodes, along with calcified lesions in the right lung, liver, and spleen, findings suggestive of granulomatous disease. There was also a low-attenuation hepatic lesion measuring 1.6 cm in diameter, which was probably a cyst.

Dr. Erdil: A diagnostic test was performed.

DIFFERENTIAL DIAGNOSIS

Dr. Natasha S. Hochberg: This patient was referred to the infectious disease clinic of this hospital because of moderate eosinophilia associated with travel, most recently to the DRC, where she had sustained a traumatic fracture of the right leg. Other exposures included walking barefoot, swimming in freshwater, spending time by rivers, and receiving a blood transfusion. Her current symptoms are notable for progressive fatigue, abdominal bloating, weight gain, and mild cough.

Eosinophilia affects 8 to 9% of returning travelers[1,2] and is a common reason for patients to be referred to an infectious disease clinic. I will focus my differential diagnosis on the finding of eosinophilia, considering both noninfectious and infectious causes (Table 2), and then concentrate specifically on helminthic infections.

NONINFECTIOUS CAUSES OF EOSINOPHILIA

Medications such as nonsteroidal antiinflammatory drugs and various antibiotic drugs can be

associated with eosinophilia. This patient was taking levothyroxine, which is not typically associated with eosinophilia. Hematologic diseases, cancers, allergies, asthma, and rheumatologic diseases can also cause eosinophilia. However, these conditions are unlikely in the absence of findings such as lymphadenopathy, hepatosplenomegaly, anemia, an abnormal white-cell or platelet count, and allergic symptoms. Adrenal insufficiency can cause eosinophilia, as well as fatigue and low-normal blood pressure, but this condition is unlikely in a patient with weight gain; weight loss and anorexia would be expected.

The six hypereosinophilic syndromes are characterized by an eosinophil count of greater than 1500 per microliter, but these syndromes involve organ dysfunction, which was not present in this patient.[3] Episodic angioedema with eosinophilia, also known as Gleich's syndrome, is characterized by waxing and waning angioedema, urticaria, fever, and weight gain[4]; only eosinophilia and weight gain were present in this patient.

Table 2. Noninfectious and Infectious Causes of Eosinophilia.

Noninfectious
Dietary supplements or medications: e.g., nonsteroidal antiinflammatory drugs, β-lactam antibiotic drugs, or nitrofurantoin
Hematologic or neoplastic disease: lymphoma, eosinophilic leukemia, mastocytosis, or solid tumors such as adenocarcinoma of the bowel or lung
Asthma or allergic disease: e.g., atopic dermatitis, allergic rhinitis, or eosinophilic esophagitis
Rheumatologic or connective-tissue disease: eosinophilic granulomatosis with polyangiitis, sarcoidosis, or inflammatory bowel disease
Immunologic disease or immunodeficiency: Omenn's syndrome, Job's syndrome, or graft-versus-host disease
Hypereosinophilic syndrome: myeloid, lymphocytic, overlap, associated, familial, or idiopathic
Other causes: adrenal insufficiency, radiation exposure, or cholesterol emboli
Infectious
Fungal infection: coccidioidomycosis, allergic bronchopulmonary aspergillosis, paracoccidioidomycosis (less common), or histoplasmosis
Bacterial or mycobacterial infection: bartonellosis, syphilis, scarlet fever, or tuberculosis
Viral infection: human immunodeficiency virus infection or infection with human T-lymphotropic virus type 1
Parasitic infection: protozoan infection (cystoisospora infection, sarcocystis, or *Dientamoeba fragilis* infection), ectoparasitic infection (scabies or myiasis [rare]), or helminthic infection

INFECTIOUS CAUSES OF EOSINOPHILIA

Nonhelminthic Infections

This patient was tested for EBV infection as part of the evaluation of worsening fatigue. The pattern of EBV-specific antibodies seen in this patient is consistent with either recent EBV infection or reactivated EBV infection due to another illness. There is a hypereosinophilic syndrome associated with an EBV-infected T-cell clone, but this condition is extremely rare.[5] EBV-associated lymphoma is unlikely in the absence of lesions identified on CT. Chronic active EBV infection would typically cause fever and lymphadenopathy.[6] Although recent EBV infection is possible, it would not explain several key features of this patient's presentation, including the persistent eosinophilia, which is more likely to be due to another infectious disease, and the weight gain.

Among the nonhelminthic infections that can cause eosinophilia, coccidioidomycosis is a possibility in this patient, given that she had traveled to the southwestern United States. The presence of calcified lymph nodes on CT would be consistent with previous histoplasmosis or tuberculosis, but she did not have findings or risk factors that would suggest reactivation of these infections.

Helminthic Infections

Given this patient's extensive travel in urban and remote regions of Africa and Asia, helminthic infection is the most likely cause of her eosinophilia. Helminthic infections account for 14 to 64% of cases of eosinophilia in returning travelers.[7-9] Assessment of the degree and timing of eosinophilia, the symptoms, the history of exposures, and the location of travel may provide clues to help narrow the differential diagnosis.

The extent and duration of eosinophilia can help determine the cause of illness.[1,9,10] During this patient's evaluation at the second hospital, 8 months before the current presentation, she had an eosinophil count of 3530 per microliter, which is considered to be moderate eosinophilia (defined as an eosinophil count of 3000 to 5000 per microliter, although the definition varies). At the time of the current presentation, her eosinophil count was still elevated but had decreased somewhat. Because eosinophilia can be caused by parasite migration through tissue, the elevated eosinophil count for 8 months suggests the continued migration of organisms, which can

Table 3. Helminthic Infections Associated with Symptoms and Signs Observed in Patients with Eosinophilia.

Symptom or Sign	Associated Helminthic Infection
Systemic	
Fever	Katayama fever, visceral larva migrans, or tropical pulmonary eosinophilia
Neurologic or ophthalmologic	
Photophobia and nuchal rigidity	Eosinophilic meningitis (due to *Angiostrongylus cantonensis*, gnathostoma species, or coccidioides species)
Headache or possible seizure	Neurocysticercosis, echinococcosis, schistosomiasis, paragonimiasis, fascioliasis, trichinellosis, toxocariasis, or sparganosis
Peripheral neuropathy	Loiasis or gnathostomiasis
Transverse myelitis	Schistosomiasis
Ophthalmologic symptoms	Visceral larva migrans, onchocerciasis, or loiasis
Respiratory	
Wheezing, dyspnea, and cough	Löffler's syndrome (due to *Ascaris lumbricoides*, hookworm, or *Strongyloides stercoralis*), tropical pulmonary eosinophilia, or acute schistosomiasis
Hemoptysis	Paragonimiasis
Gastrointestinal or hepatobiliary	
Nausea, vomiting, diarrhea, and abdominal pain	Many helminthic infections
Pain or tenderness in the right upper quadrant	Echinococcosis, fascioliasis, opisthorchiasis, or clonorchiasis
Dermatologic	
Nodule	Onchocerciasis, dirofilariasis, paragonimiasis, fascioliasis, trichinellosis, echinococcosis, cysticercosis, coenurosis, or sparganosis
Papule	Onchocerciasis or dracunculiasis
Migratory swelling or angioedema	Loiasis, gnathostomiasis, or mansonellosis
Serpiginous lesion	Cutaneous larva migrans or *S. stercoralis* infection
Transient pruritus	Schistosomiasis, hookworm infection, or *S. stercoralis* infection
Urticaria	Many helminthic infections
Facial edema	Trichinellosis

occur with liver and lung fluke disease, filarial infection, visceral larva migrans, hookworm infection, trichinellosis, and selected other helminthic infections.[11] By contrast, when organisms have migrated to the gastrointestinal tract or have become encysted, the eosinophil count may be only slightly elevated or normal.

Symptoms may not occur until the helminth reaches its anatomical destination, so knowledge of incubation periods can be useful. Ascariasis and hookworm infection have incubation periods of 2 to 3 weeks, and fluke infections such as schistosomiasis and fascioliasis have incubation periods of a few months; these diagnoses are unlikely in this patient. She had mild, nonspecific symptoms after 8 months. Therefore, helminthic infections that have a long incubation period, such as some filarial infections, are more likely.

An evaluation for systemic, neurologic, ophthalmologic, respiratory, gastrointestinal, and dermatologic symptoms and signs of helminthic infections (Table 3) would be indicated in this patient, with the understanding that some manifestations may not have developed yet. The patient had cough, which could reflect parasite

migration through the lungs. However, transient Löffler's syndrome (due to *Ascaris lumbricoides*, hookworm, or *Strongyloides stercoralis*) and tropical pulmonary eosinophilia (due to a response to microfilariae in the lungs) are unlikely in this patient; the lung examination was normal, and CT of the chest did not reveal opacities, consolidation, nodules, or septal thickening. Alternatively, her cough could reflect acute schistosomiasis. However, symptoms such as wheezing and dyspnea usually appear approximately 3 to 4 weeks after exposure, and findings on chest imaging such as ground-glass opacities can be seen.[12] At least half of patients with acute schistosomiasis have fever, and some have acute cercarial dermatitis and weight loss; the absence of these features makes this diagnosis unlikely in this patient. Furthermore, schistosomiasis is not necessarily associated with prolonged eosinophilia.

The patient's exposures included walking barefoot, which suggests the possibility of hookworm infection, *S. stercoralis* infection, or visceral larva migrans due to *Toxocara canis* or possibly *T. cati*. However, prolonged eosinophilia would not be expected with these conditions, and compatible symptoms were absent. Exposure to freshwater is associated with schistosomiasis, but we have established that this diagnosis is unlikely in this patient. Mosquito and other insect bites, which are very likely to occur in the remote regions where this patient had traveled, make filarial infections possible. Travel near rivers in the DRC introduces the possibility of black fly bites and *Onchocerca volvulus* exposure. Blood transfusion has been associated with microfilarial transmission in rare cases.[13] To evaluate for other possible exposures, I would ask the patient whether she had consumed tap water, had used ice in her drinks, or had eaten undercooked or raw foods, including meat, fish, shellfish, snails, and vegetables, while traveling.

Geography is of paramount importance when considering possible causes of eosinophilia. Among returning travelers with eosinophilia, those who traveled to non-African countries most commonly have *S. stercoralis* infection or a gut-lumen helminthic infection.[9] By contrast, those who traveled to African countries that are not in West Africa most commonly have schistosomiasis, and *S. stercoralis* infection is the second most likely possibility. Those who traveled to West African countries have an increased risk of filarial infections. Although the DRC is not in West Africa, it is nearby, so these infections are still possible and important to consider.

FILARIAL INFECTIONS

Lymphatic filariasis (due to *Wuchereria bancrofti*, *Brugia malayi*, or *B. timori*) and infections with other filariae, such as *Loa loa*, *O. volvulus*, and mansonella species, are possible diagnoses in this patient. Among travelers, infection with *W. bancrofti* or another lymphatic-dwelling filarial parasite usually occurs during a longer trip than this patient had taken.[14,15] Even during long-term travel, the risk of infection is limited because pathogen transmission is inefficient,[16] although transmission varies according to the vector.[17] Lymphatic filariasis in travelers can be associated with lymphadenitis, lymphedema, lymphangitis, scrotal inflammation (in men), urticaria, and respiratory symptoms.[10,14] Although this patient had mild cough, she did not have the other symptoms, and her CT findings were not consistent with tropical pulmonary eosinophilia. Therefore, lymphatic filariasis is unlikely.

L. loa can be found in the DRC, predominantly in the northeastern region of the country.[18] *L. loa* infection in travelers tends to occur during a longer trip than this patient had taken.[14,15] Typical features of the infection in travelers include allergic symptoms, urticaria, and transient localized angioedema, also known as Calabar swellings.[10,14,19] In one case series, only 16% of returning travelers and migrants with *L. loa* infection were asymptomatic.[14] This patient had nonspecific symptoms that were not consistent with *L. loa* infection, so this diagnosis is unlikely.

The two most likely filarial infections in this case are onchocerciasis and mansonellosis. *O. volvulus* infection is endemic in many areas of the DRC.[20] The parasite is transmitted by simulium black flies, which breed along fast-flowing rivers and streams, and the infection can lead to blindness (which is why onchocerciasis is also referred to as river blindness). Onchocerciasis is relatively rare among travelers because it usually occurs after a long period of exposure. The infection typically occurs with a trip duration of 6 to 12 months and often as long as 2 years.[14,21] However, those traveling in areas where the dis-

ease is highly endemic can become infected after a short, intense exposure.[21] The median time to symptom onset is approximately 1 to 2 years in travelers, and up to 20% of patients are asymptomatic. Symptomatic travelers often have pruritus with acute papular onchodermatitis from microfilarial migration.[10,21] Ocular involvement occurs almost exclusively in migrants. Overall, the timing of exposure and the absence of specific symptoms could be compatible with this patient's presentation.

Among the three species of mansonella that cause infection in humans, *Mansonella perstans* is the species that is most likely to be acquired in the DRC.[22,23] The parasite is transmitted by biting midges. In one case series involving travelers with *M. perstans* infection, the minimum trip duration was 4 weeks, although the average stay was almost 5 years.[14] Most patients with *M. perstans* infection are asymptomatic or have nonspecific symptoms, including fatigue. When specific symptoms occur, they are predominantly related to migration of adult worms and include transient subcutaneous swellings that are similar to Calabar swellings, as well as serositis and ocular symptoms.[10]

In summary, I suspect that this patient had a filarial infection with possible concomitant reactivated EBV infection. Onchocerciasis is a possibility, given that travelers can become infected after a short, intense exposure; the infection could still be in the incubation period. However, the relatively brief exposure, the presence of fatigue, and the absence of specific symptoms in this patient are most consistent with *M. perstans* infection. To establish this diagnosis, I would request examination of a blood smear prepared with concentration or filtration of the specimen and Giemsa staining. To assess for filarial infections more generally, I would request filarial serologic testing.

DR. NATASHA S. HOCHBERG'S DIAGNOSIS

Mansonella perstans infection.

DIAGNOSTIC TESTING

Dr. Thomas B. Nutman: The diagnostic test in this case was the detection of *M. perstans* microfilariae in a Giemsa-stained thick blood smear with the specimen concentrated with the use of Knott's concentration method (Fig. 2A).

The definitive diagnosis of *M. perstans* infection is made through the detection of the parasite microscopically.[24,25] Most often, this is accomplished through the identification of microfilariae in a blood smear. In rare cases, adult worms can be identified in tissue specimens.

The sensitivity of microfilarial detection can be increased with the use of Knott's concentration method or with the use of a 3-μm polycarbonate filtration device. Each of these concentration techniques allows for microfilarial quantification because 1 ml of whole blood is used. In this case, the use of a 3-μm polycarbonate filtration device to filter 1 ml of whole blood allowed for the quantification of 52 microfilariae per milliliter (Fig. 2B through 2D).

In stained blood smears, microfilariae of *M. perstans* measure 180 to 200 μm in length, are unsheathed, and have a characteristic blunted tail with terminal nuclei.[24] *M. perstans* microfilariae can be found in the blood throughout the 24-hour daily cycle. As such, *M. perstans* can be mistaken for *L. loa* when detected during the day, or for *W. bancrofti* when detected at night, in areas where the parasite distribution overlaps, as it does in much of Africa.

In this case, a quantitative polymerase-chain-reaction (PCR) assay specific for *M. perstans*, which was performed to corroborate the findings on blood-smear examination, was positive. A quantitative PCR assay specific for *L. loa*, a pathogen that is often detected concurrently with *M. perstans*, was negative. Several quantitative PCR assays specific for *M. perstans* have been developed and used successfully in the context of clinical trials[26,27] and field-based studies.[28-30] The use of these assays for the diagnosis of individual patients or for molecular identification in tissue samples remains an approach that is limited to research settings. Antifilarial IgG and IgG4 serologic assays that are based on crude filarial antigens can be positive in patients with *M. perstans* infection, but these assays cannot be used to distinguish between active and previous infection. Moreover, there is extensive cross-reactivity among the various filarial species, so a definitive species-specific diagnosis cannot be made with serologic testing alone.

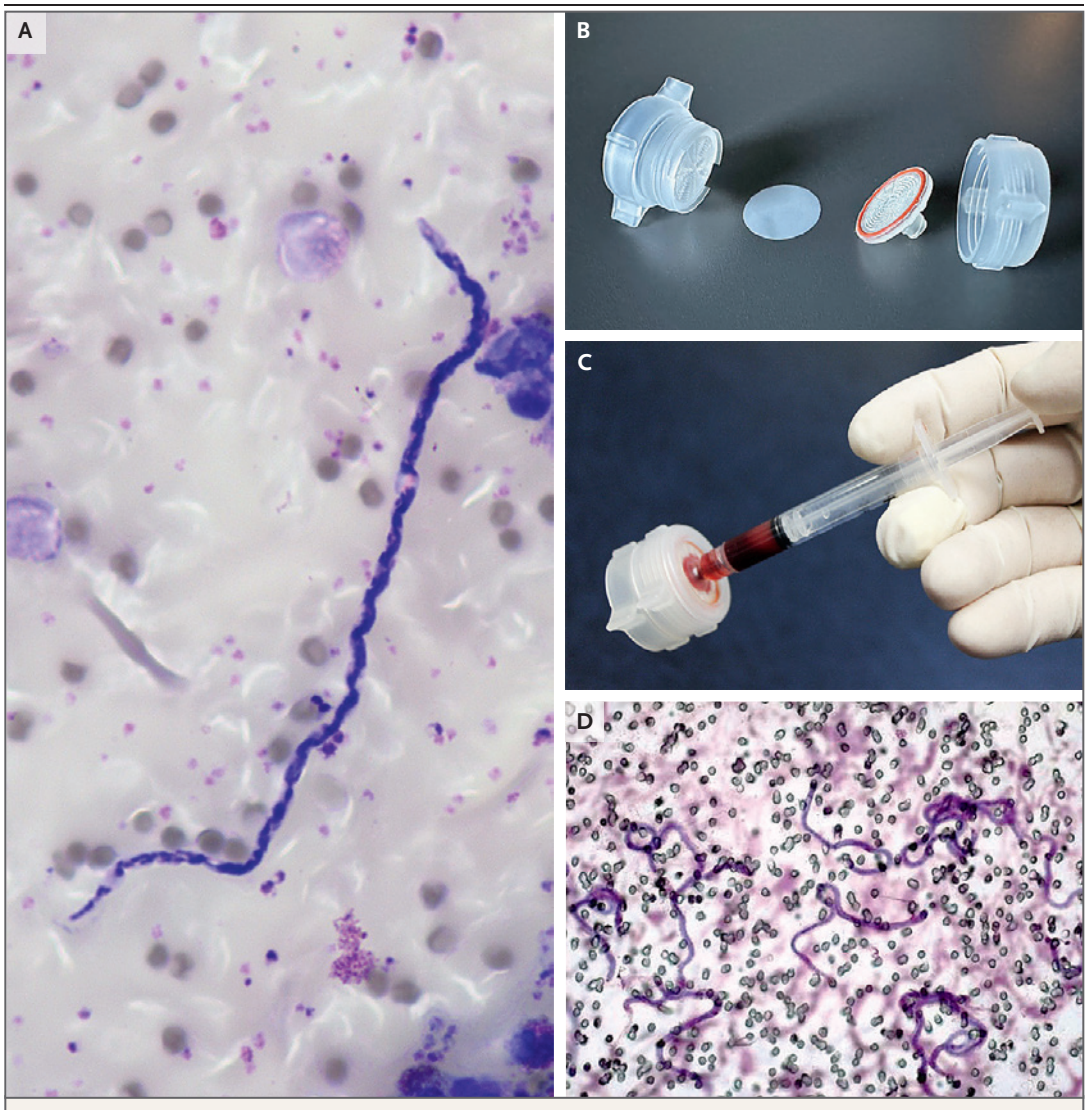

Figure 2. Blood Specimens.

A Giemsa-stained thick blood smear with the specimen concentrated with the use of Knott's concentration method (Panel A) shows a single microfilaria that measures 180 to 200 μm in length, is unsheathed, and has a blunted tail with terminal nuclei. (Panel A is courtesy of the Clinical Parasitology Laboratory at Mayo Clinic.) The use of a 3-μm polycarbonate filtration device (Panel B) to filter 1 ml of whole blood (Panel C) allowed for the quantification of 52 microfilariae per milliliter on a Giemsa-stained dried polycarbonate filter (Panel D).

M. perstans — formerly known as *Acanthocheilonema perstans*, *Dipetalonema perstans*, *Tetrapetalonema perstans*, and the causative agent of perstans filariasis — is one of eight filarial parasites that infect humans.[31] The pathogen is transmitted through a bite from one of several species of culicoides midges. Infective third-stage larvae (L3s) migrate from the bite site in the skin and mature over a period of several months, becoming adult worms that are typically found in the peritoneal, pleural, and pericardial cavities. The adult worms can live for at least 10 years.[32] After mating, the female worms produce microfilariae that are found in the bloodstream. Although the prevalence of *M. perstans* infection is unknown, the latest estimates exceed 115 million across the regions of sub-Saharan Africa and Central and South America where the infection is endemic.[22]

Like the majority of patients with other bloodborne filarial infections, most patients with *M. perstans* infection are clinically asymptomatic.[33] When clinical manifestations occur, the most common findings include evanescent migratory subcutaneous swellings that are similar to Calabar swellings, as well as serositis with pleural and pericardial inflammation. Corneal granulomatous nodules, neuropsychiatric manifestations such as meningoencephalitis, and hepatitis have been associated with *M. perstans* infection but are less common.[22,34,35] Nonspecific symptoms — such as pruritus (with or without accompanying rash), urticaria, arthralgias, and myalgias, as well as marked fatigue and abdominal symptoms, which were present in this patient — occur frequently with *M. perstans* infection.[33,36] Eosinophilia is also common; the serum IgE level may be elevated.[14,33]

LABORATORY DIAGNOSIS

Mansonella perstans infection.

DISCUSSION OF MANAGEMENT

Dr. Nutman: Many anthelmintic drugs have been used, either alone or in combination, to treat *M. perstans* infection. These include diethylcarbamazine, ivermectin, albendazole, mebendazole, thiabendazole, praziquantel, and levamisole. However, none of these treatments have been associated with a high level of efficacy, even when used for an extended period (e.g., 45 days) or when used in combination (e.g., diethylcarbamazine plus albendazole or mebendazole).[37]

It was discovered that the intracellular endosymbiont wolbachia is present in many filariae that cause infection in humans, including *O. volvulus*, *W. bancrofti*, *B. malayi*, and *B. timori*, with *L. loa* being the most notable exception.[38] Whether wolbachia is present in *M. perstans* became a controversial matter.[28,39] Wolbachia has been definitively shown to be present in *M. perstans* parasites from Mali, Cameroon, Ghana, and Gabon, although it appears to be absent in *M. perstans* parasites from Uganda.[26,27,40] These findings paved the way for the use of doxycycline in patients with *M. perstans* infection.

Randomized trials have shown that doxycycline has activity against wolbachia in *M. perstans* infection and is nearly 100% effective in clearing *M. perstans* microfilariae from the blood for at least 24 months.[26,27] In addition, several case reports have shown that doxycycline can drive sustained clearance of *M. perstans* microfilariae.[41,42] Because wolbachia is present at much greater numbers in adult worms (macrofilariae) than in microfilariae, the effect of doxycycline is thought to be primarily macrofilaricidal. Therefore, on the basis of limited data regarding *M. perstans* infection,[26] the administration of a dose of a microfilaricidal agent (e.g., ivermectin) before and soon after a 6-week course of doxycycline has been advocated for accelerating and sustaining microfilarial clearance.

If symptoms are present, they typically resolve after doxycycline therapy, although in many cases, it can be difficult to ascribe nonspecific symptoms to *M. perstans* infection per se. The blood eosinophil count decreases after therapy, but it can take up to a year for the eosinophil count to normalize. Similarly, the levels of microfilariae begin to decline within 3 months after therapy, but it can take up to a year for full microfilarial clearance to occur in most patients. This is most likely because *M. perstans* microfilariae, once released into the bloodstream, can have a life span of more than 2 years.[43]

FOLLOW-UP

Dr. Erdil: This patient took doxycycline daily for 6 weeks. She also took a dose of ivermectin the day before the doxycycline course was started and the day after the course was completed. The fatigue gradually abated. Abdominal bloating has persisted, but the patient is doing well otherwise and continues to travel extensively. One year after the initial evaluation in the infectious disease clinic, the eosinophil count was 530 per microliter. Examination of a blood smear for filariae will be pursued when the patient returns from travel.

FINAL DIAGNOSIS

Mansonella perstans infection.

This case was presented at the 2022 Harvard Medical School postgraduate course "Infectious Diseases in Adults," directed by Drs. Rajesh T. Gandhi, Sandra B. Nelson, and Nesli Basgoz.

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

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