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Case 27-2009: A 56-Year-Old Woman with Fever, Rash, and Lymphadenopathy

Jeremy S. Abramson, M.D., Subba Digumarthy, M.D., and Judith A. Ferry, M.D.

PRESENTATION OF CASE

From the Cancer Center (J.S.A.) and the Departments of Radiology (S.D.) and Pathology (J.A.F.), Massachusetts General Hospital; and the Departments of Medicine (J.S.A.), Radiology (S.D.), and Pathology (J.A.F.), Harvard Medical School.

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Dr. David T. Ting (Medical Oncology): A 56-year-old woman was admitted to this hospital because of fever, rash, and lymphadenopathy.

She had been well until 11 weeks earlier when, while residing in Florida, a pustule on the right hand developed shortly after a fire-ant sting. Four hours later, rigors and fever, with temperatures as high as 38.9°C, developed. The next day, an erythematous, pruritic rash appeared on the upper left arm, and she went to the emergency department of another hospital. Analysis of the urine reportedly suggested an infection, and levofloxacin was administered. During the next 3 days, the rash spread to the buttocks and legs. Levofloxacin was stopped and oral corticosteroid therapy, tapered over a period of 4 weeks, was prescribed. Within 5 days after beginning prednisone, all symptoms resolved. She saw an allergist, who performed serum protein electrophoresis, radioallergosorbent testing, and testing for systemic lupus erythematosus, rheumatoid arthritis, and serum levels of IgE and C-reactive protein. All test results were reportedly normal.

Approximately 6 weeks before admission, the patient noticed slightly enlarged, nontender lymph nodes in the neck and axillae. Two weeks before admission, examination by a physician in Florida revealed lymphadenopathy in the cervical, posterior auricular, and axillary regions and splenomegaly. A chest radiograph was normal, and ultrasonography of the abdomen revealed mild splenomegaly. Serologic testing for Lyme disease was reported to be positive, and doxycycline was begun, but gastrointestinal symptoms developed, and the medication was stopped after 7 days. Eleven days before admission, a rash and diffuse pruritus developed, with low-grade fever and mild nocturnal diaphoresis. Four days later, the temperature rose to 40.0°C, with rigors and drenching night sweats. The next day, she returned to her home in Massachusetts.

Four days before admission, the patient saw her primary care physician. The temperature was 39.4°C; other vital signs were normal. There was a diffuse erythematous rash, and palpable lymph nodes in the posterior auricular, anterior cervical, supraclavicular, axillary, and inguinal regions were mobile, nontender, and up to 1.5 cm in diameter. A short systolic ejection murmur was heard. The spleen was palpable 4 to 5 cm below the costal margin and was tender; the remainder of the

examination was normal. Laboratory-test results are shown in Table 1. Computed tomography (CT) of the neck, chest, abdomen, and pelvis after the administration of contrast material showed generalized lymph-node enlargement, up to 2.8 cm in diameter, and mild splenomegaly. An excisional biopsy of a left occipital lymph node (<1 cm in diameter) was performed. Pathological examination revealed changes thought to suggest dermatopathic lymphadenitis. Results of testing for Epstein-Barr virus (EBV) and parvovirus B19 antibodies were suggestive of past infection, and the level of angiotensin-converting enzyme was normal. Tests for malaria, toxoplasma, syphilis, and hepatitis viruses (A, B, and C) were negative; other test results are shown in Table 1. Specimens of blood were cultured and were sterile. Indomethacin was prescribed for fever. Two days later, she was admitted to this hospital.

The patient had hypertension, hyperlipidemia, gastroesophageal reflux disease, rosacea, and recurrent herpes simplex virus infection. She had worked in a professional occupation and was currently a homemaker; she lived with her husband, mother, and a pet dog. She moved seasonally between Massachusetts and Florida and had no recent international travel or exposure to ill persons. Before this illness, she had been physically active. She consumed two or three alcoholic beverages per week; she did not smoke or use illicit drugs and had no known allergies. Medications included diphenhydramine, indomethacin, omeprazole, and vitamin supplements. Her mother had had lung cancer, her maternal grandfather had died of pancreatic cancer, and her father had died of Parkinson's disease; her daughter and a half-brother were healthy.

On examination, the patient appeared uncomfortable, scratching her skin. The temperature was 38.1°C, the blood pressure 101/64 mm Hg, the pulse 123 beats per minute, the respiratory rate 18 breaths per minute, and the oxygen saturation 96% while she was breathing ambient air. There was a diffuse maculopapular rash and numerous nontender lymph nodes in the cervical, postauricular, and axillary regions. The abdomen was soft, and the spleen tip was palpable 2 cm below the left costal margin; the remainder of the examination was normal.

During the next 4 days, pain in the throat, cough, and diarrhea developed. The pharynx appeared slightly erythematous, but the examina-

tion was otherwise unchanged. Tests for human immunodeficiency virus, bartonella species infection, EBV DNA, and pharyngeal group A beta-hemolytic streptococcus were negative, as was a tuberculin skin test. Other laboratory-test results are shown in Table 1. Cultures of blood were sterile. Ultrasonography of the abdomen showed splenomegaly and enlarged peripancreatic and periportal lymph nodes. Transthoracic echocardiography revealed no valvular vegetations.

On the sixth day, bone marrow aspiration and biopsy were performed. Examination of the aspirate and biopsy specimen showed trilineage hematopoiesis, with myeloid hyperplasia and no malignant cells. Flow-cytometric analysis showed no monoclonal B-cell or abnormal T-cell populations; the karyotype was normal. Other laboratory-test results are shown in Table 1. The maximum temperature was 39.2°C. Cultures of the blood remained sterile. Acetaminophen, meperidine, and hydroxyzine were administered for fever, rigors, and pruritus.

On the eighth day, excisional biopsy of a right cervical lymph node (2.2 cm in diameter) was performed. Pathological examination revealed follicular hyperplasia and focal paracortical expansion, with vascular proliferation and a polymorphous population of small lymphocytes, immunoblasts, plasma cells, and eosinophils. Immunophenotyping studies showed T cells and polyclonal B cells, with no evidence of EBV infection. The differential diagnosis included an atypical reactive process and a T-cell lymphoma. Results of analysis of the T-cell receptor and immunoglobulin genes by molecular genetic techniques and results of cytogenetic analysis were pending.

Prednisone (60 mg daily) was begun. The rash, fevers, and rigors resolved within 48 hours. The patient was discharged on the 13th day. During the next 3 weeks, fevers and rigors returned, with temperatures up to 39.4°C. An ¹⁸F-fluorodeoxyglucose positron-emission tomographic (FDG PET) scan showed extensive FDG-avid lymphadenopathy in the cervical, axillary, mediastinal, hilar, retroperitoneal, and inguinal chains bilaterally. The spleen was markedly enlarged and FDG-avid. Testing for Lyme disease, cytomegalovirus (CMV), histoplasma, and cryptococcus were negative; other results are shown in Table 1.

Twenty-three days after discharge from the hospital, a diagnostic procedure was performed.

Table 1. Laboratory Data.*

Variable	Reference Range, Adults†	2 to 4 Days before Admission	On Admission
Hematocrit (%)	36.0–46.0 (women)	41.7	33.5
Hemoglobin (g/dl)	12.0–16.0 (women)	14.0	12.7
White-cell count (per mm ³)	4,500–11,000	9,700	11,600
Differential count (%)			
Neutrophils	40–70	86	78
Lymphocytes	22–44	2	4
Monocytes	4–11	7	8
Eosinophils	0–8	2	1
Band forms	0–10	2	5
Atypical lymphocytes	0	1	3
Myelocytes	0	0	1
Platelet count (per mm ³)	150,000–400,000	123,000	170,000
Erythrocyte sedimentation rate (mm/hr)	1–20‡	52	
Reticulocytes (%)	0.5–2.5		2.6
Protein (g/dl)			
Total	6.0–8.3	7.2	6.7
Albumin	3.3–5.0	3.9	3.2
Globulin	2.6–4.1		3.5
C-reactive protein (mg/liter)	<8.0		82.6
β ₂ -microglobulin (mg/liter)	0.6–2.5‡	2.9	
Sodium (mmol/liter)	135–145	138	135
Potassium (mmol/liter)	3.4–4.8	3.5	3.0
Chloride (mmol/liter)	100–108	98	98
Carbon dioxide (mmol/liter)	23.0–31.9	29	25.9
Urea nitrogen (mg/dl)	8–25	7	15
Creatinine (mg/dl)	0.6–1.5	0.8	1.18
Glomerular filtration rate (ml/min/1.73 m ² of body-surface area)	<60	79§	50
Glucose (mg/dl)	70–110	131	127
Bilirubin (mg/dl)			
Total	0.0–1.0	0.9	1.1
Direct	0.0–0.4		0.6
Phosphorus (mg/dl)	2.6–4.5		1.6
Magnesium (mmol/liter)	0.7–1.0		0.8
Calcium (mg/dl)	8.5–10.5	8.8	8.2
Alkaline phosphatase (U/liter)	30–100	93	190
Aspartate aminotransferase (U/liter)	9–32	28	68
Alanine aminotransferase (U/liter)	7–30	21	117
Lactate dehydrogenase (U/liter)	110–210	312	477
Ferritin (ng/ml)	10–200	383.2	461

Table 1. (Continued.)*

Variable	Reference Range, Adults†	2 to 4 Days before Admission	On Admission
Iron (μg/dl)	30–100		62
Iron-binding capacity (μg/dl)	9–32		183
Immunoglobulins (mg/dl)	7–30		
IgA	69–309		245
IgG	614–1295		1,243
IgM	53–334		509
Serum protein electrophoresis		Normal pattern	Normal pattern
Antinuclear antibody	Negative at 1:60 and 1:120	Positive at 1:640, diffuse pattern	Positive at 1:640, speckled pattern
Rheumatoid factor (IU/ml)	Negative, <30	<20	<30
Anti-Smith antibody	Negative		Negative
Anti–double-stranded DNA antibody	Negative		Negative
Anti-U1RNP antibody	Negative		Negative
Antimitochondrial antibody	Negative at 1:20		Negative
Anti–smooth-muscle antibody	Negative at 1:20		Positive at 1:40

* To convert the values for β_2 -microglobulin to nanomoles per liter, multiply by 84.75. 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 bilirubin to micromoles per liter, multiply by 17.1. To convert the values for phosphorus to millimoles per liter, multiply by 0.3229. To convert the values for magnesium to milligrams per deciliter, divide by 0.4114. To convert the values for calcium to millimoles per liter, multiply by 0.250.

† 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 reference range is for the other hospital.

§ At the other hospital, the mean glomerular filtration rate for a population 50 to 59 years of age was 93 ml per minute per 1.73 m².

DIFFERENTIAL DIAGNOSIS

Dr. Jeremy S. Abramson: This patient presented with a nearly 3-month history of a systemic illness characterized by fevers and malaise, generalized lymphadenopathy, a diffuse pruritic rash, and splenomegaly. I cared for this patient and am aware of the diagnosis. May we review the radiographic studies?

Dr. Subba Digumarthy: CT images obtained 3 days before admission after the administration of intravenous contrast material show diffuse lymphadenopathy. In the neck, there are lymph nodes in all the compartments, affecting jugular, posterior cervical, parotid, submandibular, submental, and supraclavicular regions (Fig. 1A). In the thorax, there are enlarged bilateral axillary and lower left paratracheal lymph nodes (Fig. 1B). In

the abdomen and pelvis, there are multiple enlarged celiac, periportal, periaortic, and bilateral inguinal lymph nodes and diffuse, homogeneous splenomegaly (Fig. 1C and 1D). The lymph nodes show avid enhancement after the administration of intravenous contrast material, suggestive of hypervascularity.

Dr. Abramson: The causes of generalized lymphadenopathy can be broadly broken down into infectious, inflammatory, and neoplastic causes. Critical factors in this patient's history include her age, duration of lymphadenopathy, associated symptoms, and the presence of splenomegaly and a rash. She had mild normocytic anemia, mild thrombocytopenia, and a normal white-cell count, with increased band forms and some atypical lymphocytes. Her symptoms responded to corticosteroids.

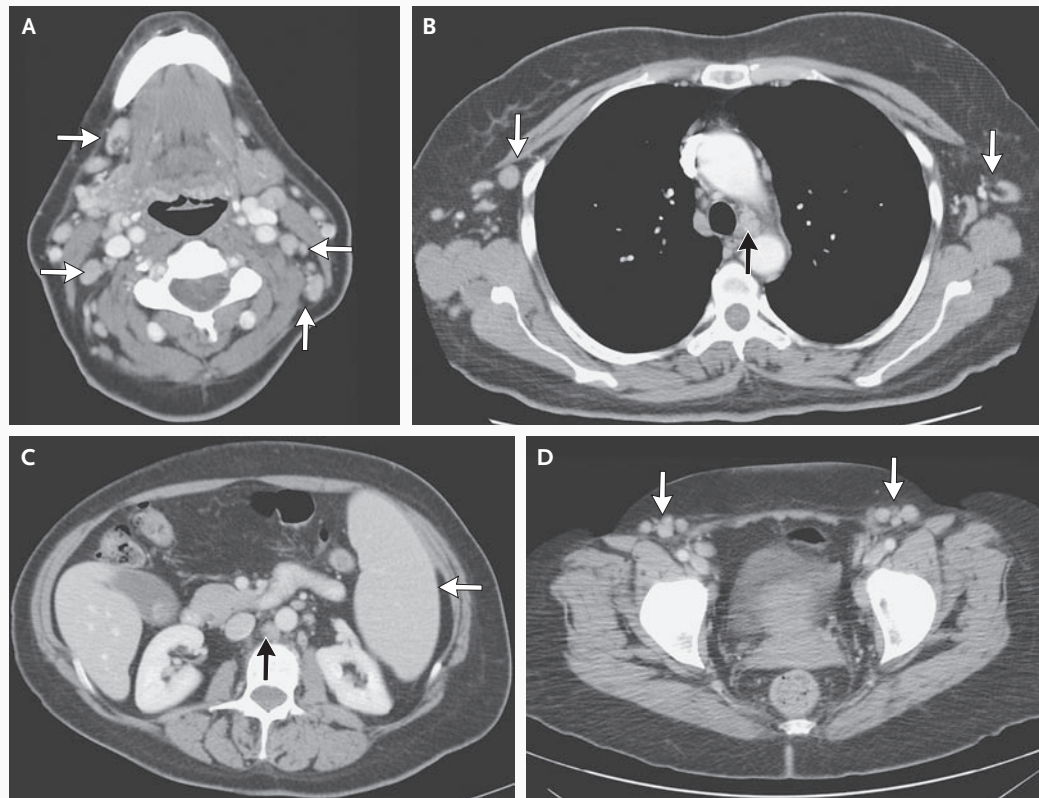


Figure 1. CT Images of the Neck and Chest Obtained 3 Days before Admission.

The lymph nodes show enhancement after the administration of intravenous contrast material. A CT scan of the neck (Panel A) shows diffuse lymphadenopathy (arrows) involving all the compartments of the neck. A CT scan of the chest (Panel B) shows enlarged bilateral axillary lymph nodes (white arrows) and a left lower paratracheal lymph node (black arrow). A CT scan of the abdomen (Panel C) shows splenomegaly (white arrow) and an enlarged retroperitoneal node (black arrow). An image of the pelvis (Panel D) shows enlarged bilateral inguinal lymph nodes (arrows).

HYPERSENSITIVITY REACTIONS

This patient's story begins with a self-reported fire-ant bite, raising the possibility of a response to envenomation. An acute systemic response to hymenoptera envenomation is an anaphylactic response in patients with preformed antibodies, but the patient's history is not consistent with such a reaction.¹ Local reactions include erythema, swelling, and pain, but these resolve within hours. The sterile pustule reported at the envenomation site is characteristic of the sting of a fire ant, which is endemic in the southeastern United States, where the exposure occurred,¹ and generalized cutaneous and systemic reactions to fire-ant stings have been described.^{2,3} Serum-sickness-like reactions characterized by fever, generalized lymphadenopathy, arthralgias, and rash occasionally but rarely occur after hymenoptera stings,⁴⁻⁶ but such reactions would be expected to occur

more than several hours after exposure and would have resolved over time. This patient's evolving systemic illness is thus unlikely to be the result of the fire-ant sting.

INFECTIONS

The most common infectious cause of fever and lymphadenopathy is infectious mononucleosis due to EBV. Cervical lymph nodes are commonly affected, but generalized lymphadenopathy is frequent, as is splenomegaly.⁷ A rash is present in about 10% of cases and often occurs after exposure to antibiotics. Symptoms usually resolve within 2 to 4 weeks after onset, in contrast to this patient's course. The test for antibodies against Epstein-Barr viral antigens indicated past exposure rather than acute infection. Infectious mononucleosis syndromes may be caused by other herpesviruses, including CMV.⁸ In the immuno-

competent host, CMV mononucleosis is similar to EBV-related disease, though pharyngitis and cervical lymphadenopathy may be less prominent. This syndrome generally resolves spontaneously in immunocompetent hosts; in this patient, testing for active CMV infection was negative.

Patients with acute infection with the human immunodeficiency virus (HIV) may present with fever, malaise, lymphadenopathy, and rash 3 to 6 weeks after exposure.⁹ This patient had negative enzyme-linked immunosorbent assays for HIV-1 and HIV-2 antibodies; although the antibody test may be negative during the early acute phase of the disease, testing was performed nearly 3 months after the onset of illness, by which time antibodies should have appeared.

Bacterial infections may produce generalized lymphadenopathy, fever, and rash, but numerous sets of blood cultures were negative, and an echocardiogram showed no evidence of endocarditis. Serologic testing ruled out common pathogens such as *Bartonella* species, toxoplasma, histoplasma, and syphilis. An initial test for Lyme borreliosis was positive, prompting antibiotic therapy, and although Lyme disease may present with fever and rash, lymphadenopathy and splenomegaly are not characteristic.¹⁰ False positive results may occur, and they do not distinguish well between acute infection and previous exposure. Furthermore, this patient's rash did not have the classic annular appearance of Lyme disease.

AUTOIMMUNE CONDITIONS

Autoimmune conditions, including systemic lupus erythematosus (SLE), rheumatoid arthritis, Sjögren's syndrome, and sarcoidosis, may present with fever, lymphadenopathy, rash, and splenomegaly. When lymphadenopathy occurs in these diseases, the histologic findings on lymph-node biopsy may include reactive follicular and paracortical hyperplasia, which are nonspecific findings consistent with those reported in this case.¹¹

The majority of patients with SLE have constitutional symptoms such as fever and malaise. Rash is common, particularly a malar rash, but maculopapular eruptions may occur. Lymphadenopathy occurs frequently,¹¹ but splenomegaly does not. A positive antinuclear-antibody test is highly sensitive for SLE, although it is not specific. Tests for antibodies to anti-double-stranded DNA and anti-Smith were negative in this case.

Rheumatoid arthritis most commonly presents

with slowly progressive fatigue and malaise, followed by the development of polyarthritis. A small percentage of patients, however, will present acutely with a systemic inflammatory syndrome of fever, lymphadenopathy, splenomegaly, and polyarthritis. This patient did not have arthritis, but lymphadenopathy may precede joint pain.¹² Furthermore, maculopapular eruptions are not associated with rheumatoid arthritis. These findings, along with the absence of detectable rheumatoid factor, make rheumatoid arthritis unlikely.

Adult-onset Still's disease may present as fever of unknown origin.¹³ It occurs predominantly in young adults and is characterized by fevers, arthralgias, and an evanescent salmon-colored rash. This patient's age and clinical features make adult-onset Still's disease unlikely.

Sarcoidosis may present acutely with fever and malaise. Lymphadenopathy is usually present and may occur anywhere in the body, but it is customarily most prominent in the pulmonary hila. Splenomegaly may occur. Rash occurs in a minority of patients, most commonly erythema nodosum, although maculopapular eruptions may occur. Pulmonary parenchymal disease is present in the majority of patients. The absence of pulmonary findings and the absence of granulomas on the lymph-node-biopsy specimen effectively rule out this diagnosis.

MULTICENTRIC CASTLEMAN'S DISEASE

Multicentric Castleman's disease, a lymphoproliferative disease that is due to human herpesvirus 8 (HHV-8) infection and occurs most commonly in persons with advanced acquired immunodeficiency syndrome,¹⁴ presents with fever and malaise, diffuse lymphadenopathy, hepatosplenomegaly, and anemia.¹⁴ This patient's rash is not characteristic of multicentric Castleman's disease, however, and the absence of HIV infection makes the disease unlikely in this patient.

KIKUCHI'S LYMPHADENITIS

Kikuchi's lymphadenitis, also known as histiocytic necrotizing lymphadenitis, is a benign syndrome of unknown cause that occurs predominantly in young adults, who present with lymphadenopathy and fever, as this patient did. The lymphadenopathy is typically limited to the cervical nodes, but in rare instances, patients have generalized lymphadenopathy.¹⁵⁻¹⁷ Cutaneous manifestations

have been described in up to 40% of cases.¹⁸ Examination of lymph-node–biopsy specimens reveals a characteristic pattern of necrotizing lymphadenitis, which should have been recognized if it had been present in this case. Resolution of Kikuchi’s lymphadenitis occurs spontaneously, usually within weeks after onset, in contrast to the case of our patient, and splenomegaly is not typical.

LYMPHOMAS

Having ruled out most non-neoplastic causes of lymphadenopathy, lymphoma has to be of primary concern with this patient. Most lymphomas present subacutely over a period of weeks to months, in contrast to the abrupt onset seen in this patient. The majority of non-Hodgkin’s lymphomas are of B-cell origin, and the diagnosis is typically straightforward on examination of an excisional biopsy specimen of an involved lymph node. Fever, lymphadenopathy, and splenomegaly may be seen in many lymphomas, but a diffuse rash is not a common feature; thus, if this patient has lymphoma, the acute presentation, the presence of a rash, and the absence of diagnostic features on lymph-node–biopsy specimens provide clues to the specific subtype.

What lymphomas evade identification on routine biopsy? Hodgkin’s lymphoma may present with diffuse lymphadenopathy and constitutional symptoms and is characterized pathologically by rare malignant Reed–Sternberg cells. T-cell/histiocyte-rich large-B-cell lymphoma is an uncommon variant of diffuse large-B-cell lymphoma that usually presents at an advanced stage with fever and constitutional symptoms¹⁹ and is also characterized histologically by a minority of malignant cells in a background rich in nonmalignant and inflammatory cells. These histologic features make the diagnosis of both diseases difficult with the use of fine-needle aspiration biopsy and core biopsy. In this case, however, two excisional biopsies were performed, neither of which showed features of these entities. This finding, along with the abrupt clinical presentation and rash, makes these and other B-cell lymphomas unlikely.

PERIPHERAL T-CELL LYMPHOMAS

Peripheral T-cell lymphomas represent only 12% of all non-Hodgkin’s lymphomas²⁰ and present unique diagnostic challenges. Unlike B-cell lymphomas, in which the presence of monotypic

immunoglobulin light chains and other characteristic immunophenotypic features can readily identify a clonal or abnormal population, distinguishing between reactive and neoplastic T cells is often not possible with the use of morphologic and immunophenotypic techniques alone. The diagnosis often requires analysis of T-cell receptor genes for clonal rearrangements. Peripheral T-cell lymphoma, not otherwise specified, is the most common T-cell lymphoma in adults, accounting for 26% of all mature T-cell lymphomas, with geographic variability in frequency.²¹ It occurs at a median age of 60 years and is almost always diagnosed at an advanced stage. Peripheral T-cell lymphoma, not otherwise specified, is usually characterized by subacute development of lymphadenopathy and systemic symptoms, rather than by acute development of a profound systemic illness and rash, making it unlikely in this patient.

ANGIOIMMUNOBLASTIC T-CELL LYMPHOMA

Angioimmunoblastic T-cell lymphoma (AITL) is the second most common peripheral T-cell lymphoma, accounting for approximately 15% of T-cell lymphomas in the United States and nearly 30% in Europe.²¹ Unlike other non-Hodgkin’s lymphomas, this disease characteristically presents acutely with diffuse lymphadenopathy and fever, mimicking an infectious disease, and the presence of a diffuse, pruritic, maculopapular rash.^{22–25} Lymphadenopathy is usually not bulky (1 to 3 cm in diameter), and the swollen lymph nodes are in the size range seen in inflammatory or infectious processes, as in this case. The rash and lymphadenopathy may wax and wane, as they did in this case, providing the misleading impression of a response to antibiotics or a resolving inflammatory process. Splenomegaly is present in just over half of patients with AITL, and cytopenias, including anemia and thrombocytopenia, may occur. Up to 80% of patients have polyclonal hypergammaglobulinemia, which contributed to this entity’s original description as “angioimmunoblastic lymphadenopathy with dysproteinemia.” This patient had only a slightly elevated level of IgM. Immune dysregulation may result in the presence of autoantibodies (including antinuclear antibodies), rheumatoid factor, anti-smooth-muscle antibodies, antiphospholipid antibodies, and false positive serologic tests for Lyme borreliosis, several of which this patient had.²² In up to half of patients, a diagnosis of AITL is not made on examination of the initial

biopsy specimens, and the median time from presenting symptoms to diagnosis is 3.6 months.^{22,26} For this reason, in the context of clinical suspicion, serial biopsies may be necessary to show the evolution of a recognizably malignant process.

This patient's clinical presentation makes AITL the most likely diagnosis. The diagnostic procedure was another excisional lymph-node biopsy.

DR. JEREMY S. ABRAMSON'S
DIAGNOSIS

Angioimmunoblastic T-cell lymphoma.

PATHOLOGICAL DISCUSSION

Dr. Judith A. Ferry: The left occipital lymph node, from which a biopsy specimen was obtained at another hospital and submitted to us for review, is a small lymph node with preserved architecture (Fig. 2A). The paracortex is slightly expanded by a polymorphous mixture of small lymphocytes, histiocytes, eosinophils, high endothelial venules, and occasional immunoblasts, including a few with irregular nuclei that appeared atypical (Fig. 2B). This appearance is not specific for any diagnosis and may occur in a variety of reactive conditions, including viral infections and autoimmune diseases.

A biopsy specimen of a larger, right cervical lymph node obtained on the sixth hospital day showed more pronounced paracortical expansion and some reactive follicles (Fig. 2C). The interfollicular area contained small numbers of medium-size or smaller atypical lymphoid cells with slightly irregular nuclei and clear cytoplasm (Fig. 2D). Immunostaining revealed CD20+ B cells mainly in the follicles, with a preponderance of CD3+ T cells in the expanded paracortex, which is a normal pattern. Nodular meshworks of CD21+ follicular dendritic cells were associated with the follicles; in addition, however, wisps of CD21+ dendritic-cell staining extended beyond follicles into the interfollicular area, which is an abnormal finding that can be seen in early nodal involvement by AITL. Many CD10+ cells were scattered outside the follicles (Fig. 2D, inset). CD10+ expression in normal lymph nodes is typically restricted to germinal-center B cells, whereas in cases of AITL, CD10+ T cells may be found in the paracortex; therefore, this finding was suggestive of AITL.

In situ hybridization for EBV was negative.

Flow-cytometric analysis showed no abnormal B-cell or T-cell population. With polymerase chain reaction, no clonal T-cell population was identified, although a clonal B-cell population was found with the use of primers for the immunoglobulin heavy-chain gene. No clonal B-cell or T-cell population was identified by Southern blot hybridization on frozen tissue. The pathologic features were thought to be highly suggestive of AITL, but in the absence of a clonal T-cell receptor gene rearrangement, we were reluctant to make a definite diagnosis.

The diagnostic procedure was excision of an enlarged left axillary lymph node (Fig. 3A). The architecture was nearly entirely effaced by a diffuse cellular infiltrate that extended beyond the lymph-node capsule but did not obliterate the subcapsular sinus. Loose clusters of small to medium-size atypical cells with slightly irregular nuclei and abundant clear cytoplasm (Fig. 3B) were associated with increased numbers of high endothelial venules but were still interspersed with small lymphocytes, plasma cells, eosinophils, histiocytes, and scattered immunoblasts. Flow-cytometric analysis showed a mixture of polytypic B cells and T cells with a normal CD4:CD8 ratio. Immunohistochemical staining on paraffin sections showed that the atypical cells were T cells that were CD3+, CD4+ and coexpressed CD10 and CXCL13, which are characteristic of follicular helper T cells. Many CD20+ B immunoblasts were present, which were negative for EBV by in situ hybridization. There were large, irregularly expanded meshworks of CD21+ follicular dendritic cells associated with the atypical T cells and proliferating venules. Cytogenetic analysis showed a normal female karyotype (46,XX). However, the results of cytogenetic analysis on the right cervical lymph node had become available and showed a highly abnormal karyotype (Fig. 4).

The architectural effacement, together with the abnormal cytogenetic findings on the previous specimen, supported a diagnosis of lymphoma. The predominance of medium-size CD4+ T cells with clear cytoplasm coexpressing CD10 and CXCL13 — indicating a follicular helper T-cell phenotype²⁶⁻³⁰ in a mixed reactive background — and the highly abnormal pattern of staining with CD21 established a diagnosis of AITL.²⁸

The diagnosis of AITL can be challenging, as illustrated by this case. In early stages, the archi-

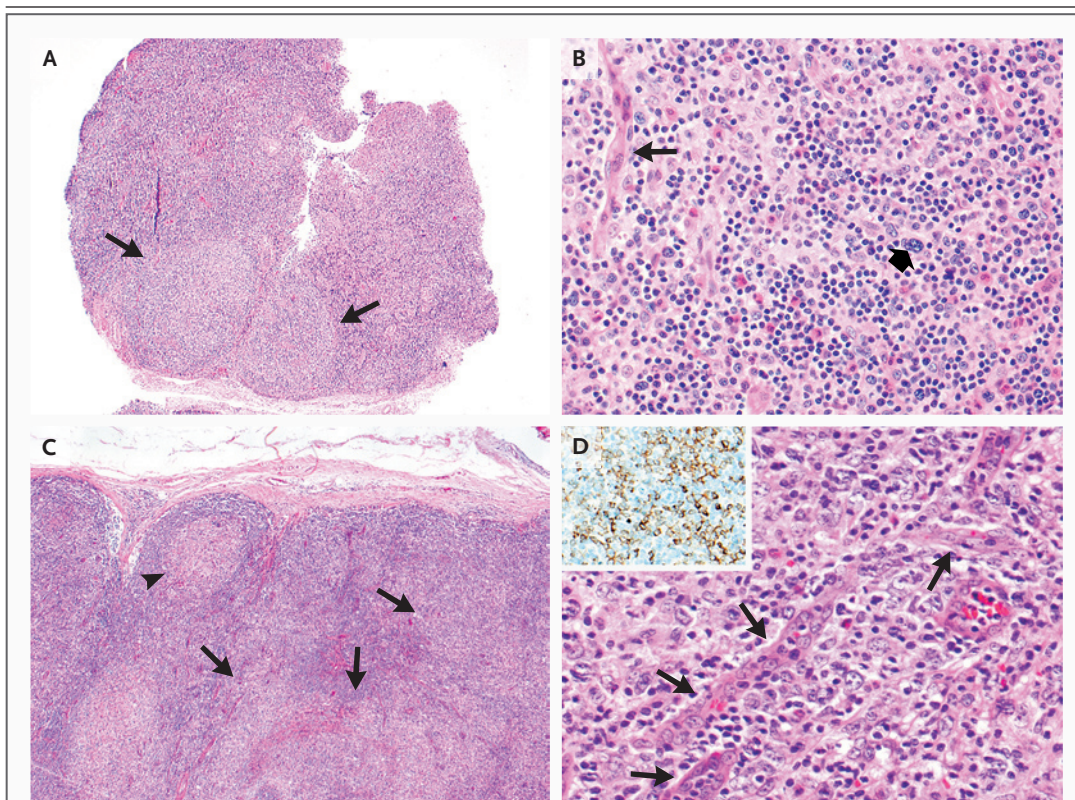


Figure 2. Cervical Lymph-Node–Biopsy Specimens.

A low-power view of a left suboccipital lymph node (Panel A, hematoxylin and eosin) shows a small lymph node with intact architecture. Two reactive follicles (arrows) contain germinal centers without mantle zones and appear somewhat poorly delineated. A view of the paracortex at higher magnification (Panel B, hematoxylin and eosin) shows a mixed population of small lymphocytes, histiocytes, eosinophils, and immunoblasts, some of which appear atypical (short arrow); also shown is a venule with plump endothelial cells (high endothelial venule), a characteristic finding in the lymph-node paracortex (arrow). A low-power view of a right cervical lymph node (Panel C, hematoxylin and eosin) shows a reactive follicle (arrowhead), with focal expansion of the paracortex (arrows) and preservation of the architecture, an open subcapsular sinus, and no extension of the infiltrate beyond the capsule. A higher-power view of the paracortex of the same lymph node (Panel D, hematoxylin and eosin) shows a mixture of small lymphocytes, immunoblasts, eosinophils, and small numbers of slightly enlarged lymphoid cells with clear cytoplasm, which were not seen on an earlier biopsy, as well as more high endothelial venules (arrows). Many scattered and clustered CD10+ cells are present in the paracortex (inset [immunoperoxidase stain on paraffin section]).

texture may be preserved, with reactive follicular hyperplasia, and the abnormal infiltrate confined to the paracortex. The cytologic atypia of the neoplastic cells may be subtle, and they may be outnumbered by the reactive population, so that morphologic features of malignant conditions might not be apparent and evidence of clonality might not be seen on molecular genetic analysis. The differential diagnosis includes reactive lymphadenopathy due to viral infection, drug hypersensitivity, or infectious mononucleosis.^{22,31} In fact, when AITL was first described,^{32,33} it was thought to be an abnormal immune reaction and

was called immunoblastic or angioimmunoblastic lymphadenopathy.^{32,33} Identification of clonal T-cell populations by molecular genetic studies and clonal cytogenetic abnormalities^{34–36} later led to its classification as a T-cell lymphoma. The cell of origin is believed to be a follicular helper T cell.²⁸

Clonal rearrangement of the immunoglobulin heavy-chain gene, as seen in our case, is also found in 25 to 45% of cases.^{22,28} In approximately 10% of cases, the B-cell clones progress to diffuse large-B-cell lymphoma, which is often EBV-positive.^{37,38}

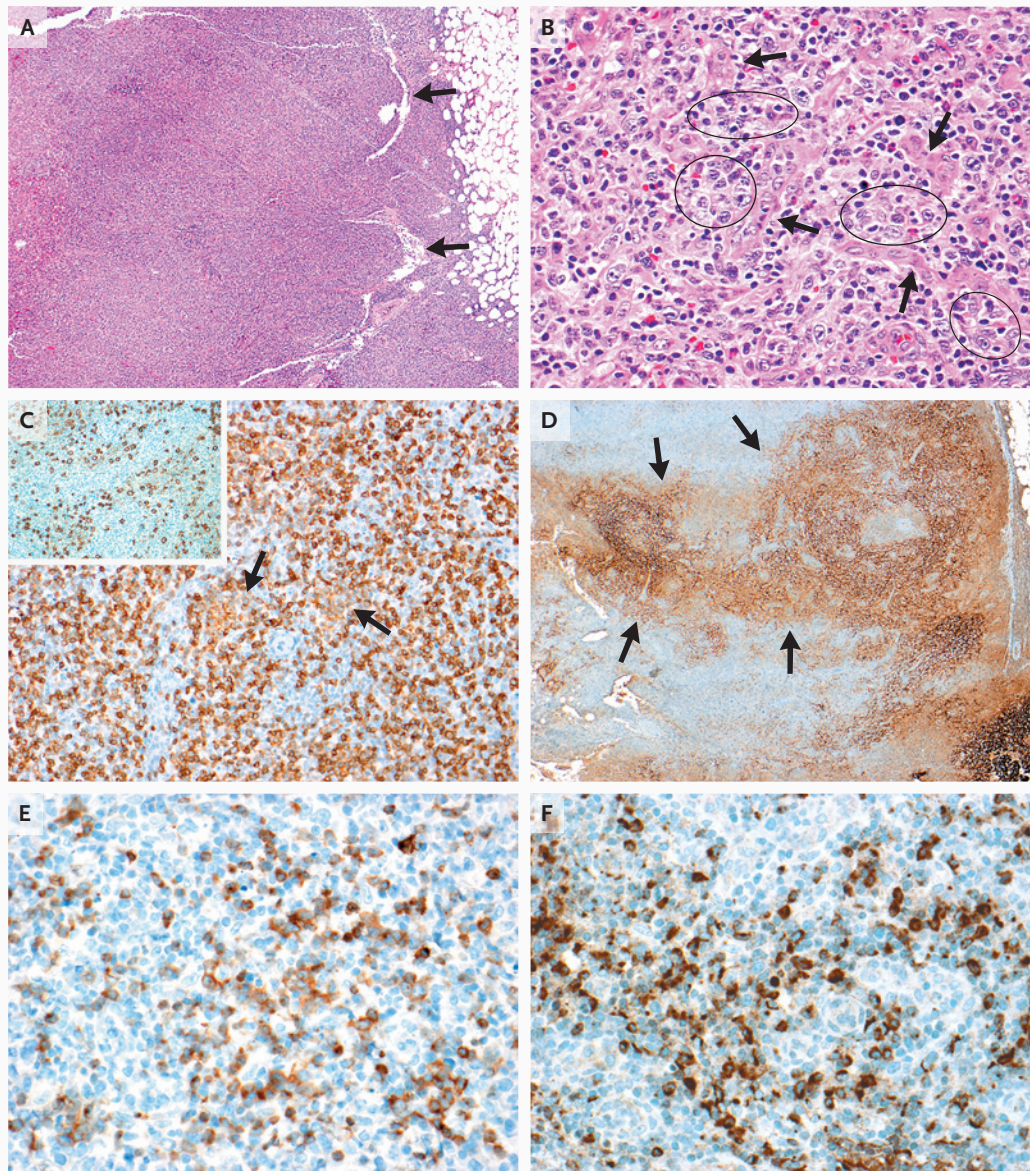


Figure 3. Left Axillary Lymph-Node–Biopsy Specimen.

A low-power view of a left axillary lymph node (Panel A, hematoxylin and eosin) shows a diffuse cellular proliferation resulting in near-complete loss of the normal architecture. The infiltrate invades perinodal fat, but the subcapsular sinus is patent and in areas appears distended (arrows), a characteristic feature of angioimmunoblastic T-cell lymphoma (AITL). At higher magnification (Panel B, hematoxylin and eosin), there is a mixed population of lymphocytes and eosinophils, similar to that seen in the cervical lymph-node–biopsy specimen, but there are also clusters of large lymphoid cells with clear cytoplasm (circled areas), which are adjacent to proliferating high endothelial venules (arrows). The majority of lymphoid cells are CD3+ T cells (Panel C, immunoperoxidase technique on paraffin sections); some are small, strongly positive cells, whereas the larger cells show fainter staining (arrows). Scattered small and large CD20+ B cells (inset) are present. Numerous large, irregular extrafollicular aggregates of CD21+ follicular dendritic cells are present (Panel D, arrows, immunoperoxidase technique on paraffin sections), an abnormal finding that is a hallmark of AITL. Some of the large T cells are CD10+ (Panel E, immunoperoxidase technique on paraffin sections) and CXCL13+ (Panel F, immunoperoxidase technique on paraffin sections, courtesy of Dr. D. Dorfman, Brigham and Women's Hospital, Boston); this immunophenotype is characteristic of follicular helper T cells and is characteristic of AITL.

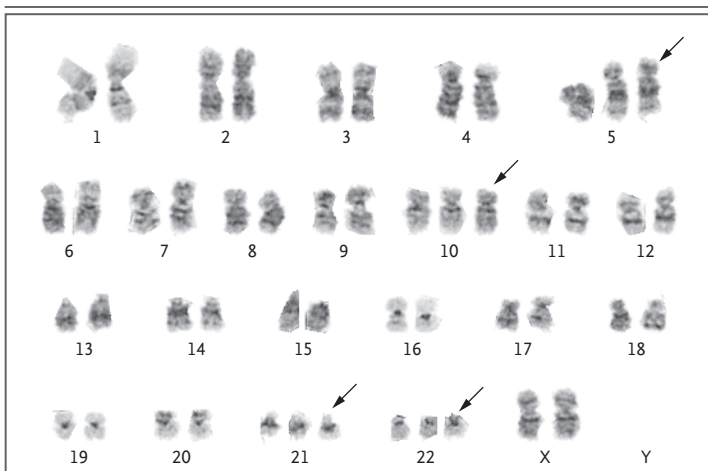


Figure 4. Karyotype of Right Cervical Lymph Node.

An abnormal, hyperdiploid metaphase shows additional copies of chromosomes 5, 10, 21, and 22 (arrows); the karyotype was 50,XX,+5,+10,+21,+22[12]/33,X,-X,-1,-2,-3,-5,-7,-7,-11,-16,-17,-19,+mar1,+mar2[1]/46,XX[2]. Trisomies of chromosomes 3, 5, and X are common in AITL. (Image provided by the Cytogenetics Laboratory at Brigham and Women's Hospital, Boston.)

MANAGEMENT

Dr. Abramson: It is challenging to treat a patient with AITL, such as this one; like many other peripheral T-cell lymphomas, the disease has a poor prognosis, with a median overall survival of less than 3 years.²¹⁻²⁵ Combination chemotherapy achieves a complete response in 50 to 70% of patients, but less than 30% remain disease-free.^{22-24,39-41} High-dose chemotherapy with autologous stem-cell support has been reported to

result in long-term survival in more than half of patients.^{42,43} Favorable results have also been reported with allogeneic stem-cell transplantation, but this procedure is associated with a high risk of graft-versus-host disease and death.^{44,45} New therapies under investigation in AITL and other peripheral T-cell lymphomas include the anti-CD52 monoclonal antibody alemtuzumab,^{46,47} denileukin diftitox (interleukin-2 bound to diphtheria toxin),⁴⁸ the proteasome inhibitor bortezomib, histone deacetylase inhibitors, new antifolate molecules, monoclonal antibodies against T cells with specificity for certain antigens, and in AITL, antiangiogenic therapy.^{49,50}

This patient was treated with a combination of cyclophosphamide, doxorubicin, vincristine, and prednisone administered at 14-day intervals for six cycles, to which she achieved a complete response. She was preparing for consolidation with high-dose chemotherapy and autologous stem-cell transplantation, but autoimmune cytopenias developed, followed by recurrent disease. She underwent reduced-intensity allogeneic stem-cell transplantation from a matched, unrelated donor and is in remission 6 months after the transplantation, with mild cutaneous graft-versus-host disease.

ANATOMICAL DIAGNOSIS

Angioimmunoblastic T-cell lymphoma.

Dr. Ferry reports equity ownership in Dupont. No other potential conflict of interest relevant to this article was reported.

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