

## CLINICAL CARE CONUNDRUM

## Mapping Out the Diagnosis

The approach to clinical conundrums by an expert clinician is revealed through the presentation of an actual patient's case in an approach typical of a morning report. Similarly to patient care, sequential pieces of information are provided to the clinician, who is unfamiliar with the case. The focus is on the thought processes of both the clinical team caring for the patient and the discussant.

Yoshiro Hadano, MD<sup>1</sup>  
Gurpreet Dhaliwal, MD<sup>2</sup>  
Sanjay Saint, MD, MPH<sup>3</sup>  
Lawrence M. Tierney, Jr, MD<sup>2</sup>  
Hideta Sakemi, MD<sup>1</sup>

<sup>1</sup> Department of General Internal Medicine, Rakuwakai Otowa Hospital, Kyoto, Japan.

<sup>2</sup> Department of Medicine, San Francisco VA Medical Center and University of California San Francisco School of Medicine, San Francisco, California.

<sup>3</sup> Department of Veterans Affairs Health Services Research and Development Center of Excellence, and Department of Internal Medicine, University of Michigan, Ann Arbor, Michigan.

**A 19-year-old Japanese man** was admitted to a hospital near Kyoto, Japan, because of fever and rash. Two weeks prior to admission, he developed mild headache and low-grade fever; a rapid test for influenza was negative. His symptoms transiently improved with acetaminophen, but 8 days prior to admission, he developed fever to 38.5°C and a pruritic maculopapular rash over his back that spread to his limbs. Six days prior to admission, a chest radiograph was clear; clarithromycin was prescribed for presumed upper respiratory infection. He visited the emergency department the day before admission because of continued fever of greater than 39°C, fatigue, and headache. Because there was no jolt accentuation of the headache (ie, worsening with rapid horizontal rotation), or neck pain with extreme neck flexion, he was discharged on acetaminophen. He returned the next day with worsening fatigue and was admitted. He denied chills, rigor, weight loss, photosensitivity, sore throat, neck pain, cough, dyspnea, chest pain, nausea, vomiting, diarrhea, abdominal pain, back pain, and arthralgia.

Fever and diffuse rash are often due to infection, although drugs, autoimmune processes, and cancer must be considered. The presence of headache does not focus the differential diagnosis substantially, because many of the candidate diagnoses can be accompanied by meningitis or encephalitis, or even more frequently, nonspecific headaches. In one small study, jolt-induced aggravation of headache was shown to be a sensitive indicator of cerebrospinal fluid pleocytosis. The absence of neck stiffness and the 2-week duration makes bacterial meningitis unlikely, but a more indolent form of aseptic meningitis may need to be evaluated with a lumbar puncture.

The 2-week illness without rapid deterioration makes some serious causes of fever and rash, such as toxic shock syndrome, disseminated meningococcal infection, or toxic epidermal necrolysis unlikely. A viral exanthema is possible, although the 2-week duration is longer than usual. Given his youth, however, his immunization history should be queried, and acute infection with human immunodeficiency virus (HIV) should be considered. A more indolent infection, such as subacute bacterial endocarditis, disseminated gonococcal infection, or syphilis is plausible. Among autoimmune etiologies, systemic lupus erythematosus (SLE) and

Behcet's disease (which is prevalent in Japan) can involve the central nervous system and cause fever. A careful inquiry directed at prescribed, complementary, and illicit drugs is required.

**The patient's past medical history** was notable only for mumps at the age of 10. His medications included acetaminophen, clarithromycin, and an herbal medicine, which he had been taking for the prior several days. He reported no tobacco or illicit drug use and rarely drank alcohol. He had never been sexually active. He worked in a factory and reported occasional contact with silver. He lived with his parents; there was no family history of tuberculosis or connective tissue diseases. His father was from Kyushu (the southernmost major island in Japan) and had chronic hepatitis C. The patient denied recent animal exposure or recent travel. His childhood vaccinations were said to be up to date.

Mumps at age 10 might signal general lack of immunization, in which case childhood viral exanthema-like measles (characterized by fever, headache, and diffuse rash) would warrant consideration. The listed medications had been started after the onset of illness and therefore are unlikely to be causal. Silver causes at least 2 skin conditions—contact dermatitis and argyria—but not the systemic illness seen here. Human T lymphotropic virus-1 (HTLV-1) is endemic in southern Japan, but only a minority of infected humans are afflicted with associated adult T cell leukemia/lymphoma or myelopathy. Leukemia and lymphoma are the most likely cancers to cause fever, rash, and central nervous system involvement (with T cell disorders demonstrating a particular tropism for the skin). Overall, however, the differential has not changed substantially.

**On physical examination, the patient** was mildly overweight and appeared acutely ill. His blood pressure was 136/78 mm Hg, pulse rate was 76 and regular, temperature was 39.2°C and respiratory rate was 20 with an oxygen saturation of 98% on room air. A diffuse but nonconfluent erythematous maculopapular rash was present over his chest wall, back, medial aspects of both thighs, and around the knees. There was no jolt-induced headache. His eyes, nose, oral cavity, and throat were all clear. The neck was supple. There were palpable lymph nodes, each about 1 cm in size, which were firm and moderately

tender, in his left neck and left axilla. Lungs and heart were normal. The abdomen was soft, nontender, with normal bowel sounds and no hepatosplenomegaly. His genitalia were normal. Rectal examination revealed no masses or tenderness and a scant amount of brown stool that was negative for occult blood. Neurologic examination was unremarkable.

The multifocal lymphadenopathy does not help distinguish among the categories of disease under consideration. The diffuse maculopapular rash is similarly nonspecific, occurring more frequently with infection and drug reaction than malignancy and autoimmunity. Acute HIV, Epstein-Barr virus (EBV), syphilis, SLE, drug exposure, or a hematologic malignancy would all be suitable explanations for fever, headache, diffuse rash, and disseminated lymphadenopathy in a previously healthy young man.

**Laboratory data obtained on admission** was notable for a white blood cell (WBC) count of 2100/ $\mu$ L with 72% neutrophils, 19% lymphocytes, and 9% monocytes. Hemoglobin was 13.5 mg/dL with a mean corpuscular volume of 85 fL. Platelet count was 136,000/ $\mu$ L. Erythrocyte sedimentation rate was 26 mm/hour. Serum chemistries revealed a sodium level of 135 mEq/L, potassium level of 3.6 mEq/L, chloride level of 100 mEq/L, blood urea nitrogen of 9.8 mg/dL, creatinine level of 1.0 mg/dL, glucose level of 101 mg/dL, calcium level of 8.8 mg/dL, albumin of 4.6 mg/dL, total protein of 8.4 mg/dL, aspartate aminotransferase of 42 IU/L (normal < 35 IU/L), alanine aminotransferase of 27 IU/L, total bilirubin of 0.5 mg/dL, and lactate dehydrogenase (LDH) level of 463 IU/L (normal < 260 IU/L). Chest radiography and electrocardiogram were normal.

A mild elevation in LDH is nonspecific, but without hemolysis or infarction of the kidney, lung, or muscle, it suggests a lymphoproliferative process. Leukopenia with thrombocytopenia can be seen in a number of disorders, most commonly infections including viruses (e.g., EBV, HIV, dengue), malaria, Rocky Mountain spotted fever, or ehrlichiosis/anaplasmosis. Confirmation of his lack of travel could help prioritize those considerations. An invasive bone marrow disorder cannot be excluded, although the near-normal hemoglobin argues against it. Autoimmune cytopenias are seen in SLE. Given his age, lymphadenopathy, LDH elevation, and absence of infectious exposures, lymphoma rises to the top of the list.

Noninvasive measures should include examination of the peripheral smear, HIV testing (including HIV RNA for acute infection), EBV serologies, and tests for syphilis and SLE. Lumbar puncture (for evaluation of aseptic meningitis) and lymph node biopsy would be informative. Skin biopsy may be helpful to evaluate for aggressive T cell lymphoproliferative disorder, but this can await the results of initial testing.

**The patient was given intravenous fluids** and acetaminophen as needed. Blood cultures, urine culture, cytomegalovirus and EBV serologies, hepatitis B surface antigen, hepatitis C virus antibody, HIV antibody, antinuclear antibody, complement and ferritin levels, and

quantiferon-TB were ordered. The urine was normal and a urinary antigen test for *Legionella* was negative. Contrast-enhanced computed tomography scan of the chest and abdomen was normal except for mild splenomegaly and an enlarged left axillary lymph node.

The ferritin may have been ordered to help evaluate for Still's disease, which is characterized by sustained fever, lymphadenopathy, and transient rash; however, the characteristic leukocytosis and arthralgias are absent. The computed tomography findings are most notable for the absence of generalized lymphadenopathy or significant hepatosplenomegaly that is seen in lymphoma, leukemia, and lymphotropic processes such as acute EBV infection. The localization of disease to the skin (where the predominant lymphocytes are of T cell origin) with relatively modest lymphadenopathy suggests a T cell lymphoma, perhaps of an indolent variety. Vertical transmission of HTLV-1 decades ago would make adult T cell leukemia or lymphoma a major consideration.

**On the third hospital day, WBC count was** 1800/ $\mu$ L with 67% neutrophils, 22% lymphocytes, and 1% atypical lymphocytes; LDH rose to 623 IU/L. He had continued fatigue and high fever while the rash gradually faded with oral antihistamines and steroid ointment. On hospital day 4, bone marrow biopsy and skin biopsy of his left thigh were performed.

The further decline in WBC and rise in LDH are modest and therefore do not significantly modify the differential diagnosis. Likewise, 1% atypical lymphocytosis is too low to pinpoint an etiology. Because unremitting fevers start to extend into their third week without a clear source of infection, the probability of malignancy and autoimmunity rise. Improvement with oral antihistamines and topical steroids frequently suggests an underlying allergic process, but the remainder of the clinical picture is not in keeping with atopy or allergy. Cutaneous lymphomas (eg, mycosis fungoides) can have waxing and waning skin manifestations, and can be temporarily or definitively treated by topical steroids. The persistence of his fatigue is of concern given the absence of anemia, cardiopulmonary involvement, or motor weakness.

**Bone marrow biopsy showed normocellular** marrow with no abnormal cells and some activated macrophages with hemophagocytic activity. Skin biopsy failed to show specific pathology.

**His left cervical lymph nodes gradually enlarged.** Ultrasound of the neck showed multiple enlarged lymph nodes (left side dominant) with dimension of 17 mm  $\times$  9 mm  $\times$  31 mm. Blood and urine cultures returned negative, as did HIV antibody. cytomegalovirus and EBV serologies were consistent with previous infection and the ferritin level was 578 ng/mL (normal, 39-340 ng/mL). *Toxoplasma* serology and HTLV-1 antibody were ordered.

The absence of malignant cells on bone marrow biopsy does not exclude lymphoma, but makes a myelophthisic

cause of the cytopenias less likely. The macrophage hemophagocytosis reflects immune activation, which in turn is usually caused by the same viral infections, autoimmune conditions, and lymphoproliferative disorders which constitute the current differential diagnosis.

Bone marrow and skin biopsies are both subject to sampling error, and detection of cutaneous T cell lymphoma is notoriously difficult. However, taken together, the absence of cancer on 2 specimens reduces that possibility.

Sustained unilateral cervical lymphadenopathy with fever in a young Japanese man without any histologic evidence of lymphoma points to Kikuchi's disease, ie, lymphadenitis of unknown etiology associated with varying degrees of systemic manifestations. Fever is a frequent feature, we believe, but diffuse sustained rash, cytopenias, and headache are less common or are seen in severe forms of the disease. The diagnosis of Kikuchi's requires the diligent exclusion of SLE and lymphoma. Examination of the peripheral smear and a lymph node biopsy are required.

Of note, there is also a localized form of Castleman's disease, a nonmalignant lymphoproliferative disorder, that similarly is characterized by focal lymphadenopathy. In distinction to Kikuchi's, however, localized Castleman's is largely asymptomatic and responds marvelously to excision.

**On hospital day 9, an excisional biopsy of his** left anterior cervical lymph nodes was performed, which revealed paracortical foci with necrosis and a histiocytic cellular infiltrate consistent with subacute necrotizing lymphadenitis (Kikuchi-Fujimoto disease). Antinuclear antibody, *Toxoplasma*, and HTLV-1 antibodies returned negative.

There is no treatment for Kikuchi's. It is usually self-limited, but steroids are sometimes given for symptomatic control.

**His condition began to improve after** hospital day 9 without specific treatment, including his WBC count and LDH level. He was discharged home on hospital day 15. In the outpatient clinic 1 and 3 months later, he was well and active without recurrences of any symptoms or laboratory abnormalities. His WBC count was 6600/ $\mu$ L and LDH was 268 IU/L.

### Commentary

Kikuchi-Fujimoto disease (KFD), also called Kikuchi's disease, is a benign histiocytic necrotizing lymphadenitis described by both Kikuchi and Fujimoto in 1972.<sup>1,2</sup> It is rare in the United States, but seems more common in Asia, especially Japan, where at least 143 cases have been reported since 1972. The etiology has not been determined, but a viral cause—including EBV, and human herpesvirus 6 and 8—has been suggested.<sup>3</sup> An autoimmune etiology is also implicated because of infrequent association with SLE. In gen-

eral, young women are most likely to be affected. In a review of 244 cases by Kucukardali and colleagues, 77% of patients were female and the mean age was 25; 70% were younger than 30 years of age.<sup>4</sup>

The common presentation is low-grade fever with unilateral cervical lymphadenopathy.<sup>4</sup> Although generalized lymphadenopathy can occur, it is rare. Other common clinical manifestations include malaise, joint pain, rash, arthritis, and hepatosplenomegaly. No specific laboratory tests for diagnosis are available, but leukopenia (seen in 43% of patients), increased erythrocyte sedimentation rate (40%), and anemia (23%) may be observed.<sup>4</sup> In this case, atypical lymphocytes were seen, and are reported in one-third of patients.<sup>5</sup> KFD is generally diagnosed by lymph node biopsy, which typically shows irregular paracortical areas of coagulation necrosis that can distort the nodal architecture, while different types of histiocytes are observed at the margin of necrotic areas.

Other diseases in the differential diagnosis—several of which were considered by the discussant—include lymphoma, tuberculosis, SLE, and even metastatic adenocarcinoma. KFD is self-limited; symptoms typically resolve within 1 to 4 months. Patients with severe manifestations have been treated with anti-inflammatory drugs and glucocorticosteroids. A recurrence rate of 3% to 4% has been reported.<sup>6</sup>

The clinicians taking care of this patient initially focused on ruling out those infections occasionally resulting in prolonged fever in a previously healthy young man, such as viruses from the herpes family, HIV, viral hepatitis, tuberculosis, syphilis, infective endocarditis, and intra-abdominal abscess. Physical examination, specifically lymphadenopathy and mild splenomegaly, made *Herpesviridae* infections, tuberculosis, syphilis, and lymphoma difficult to exclude. Once the initial evaluation ruled out common infections, attention focused on malignancy and histiocytic necrotizing lymphadenitis, given his ethnicity and geographic location.

The discussant was similarly concerned about infection, malignancy, and noninfectious inflammatory diseases, such as SLE, as possible causes. As evidence of these treatable diseases failed to accumulate, the discussant, an American physician with teaching and clinical experience in Japan, considered endemic diseases such as Behcet's, HTLV-1, and KFD because they fit the unfolding pattern. Given our global society, clinicians will increasingly benefit from becoming familiar with the less common diseases that afflict the various populations around the world.

### Teaching Points

1. The combination of fever, lymphadenopathy, and leukopenia in young adults suggests SLE, lymphoma, and HIV. Clinicians should also consider KFD in patients from Japan and neighboring countries.

2. Lymph node biopsy is usually diagnostic of KFD, although interpretation of histopathology can be difficult and sometimes leads to confusion with SLE and lymphoma.
3. KFD typically resolves without specific treatment.

---

**Address for correspondence and reprint requests:**

Hideta Sakemi, MD, Department of General Internal Medicine, Rakuwakai Otowa Hospital, Otowachinji-cho, Yamashina-ku, Kyoto, Kyoto City 607-8062, Japan; Telephone: +81-75-593-4111; Fax: +81-75-593-6935; E-mail: rakuwadr073@rakuwadr.com Received 3 May 2010; revision received 30 September 2010; accepted 13 October 2010.

## References

1. Kikuchi M. Lymphadenitis showing focal reticulum cell hyperplasia with nuclear debris and phagocytes: a clinicopathological study. *Acta Hematol Jpn.* 1972;35:379–380.
2. Fujimoto Y, Kozima Y, Yamaguchi K. Cervical subacute necrotizing lymphadenitis: a new clinicopathological agent. *Naika.* 1972;20:920–927.
3. Bosch X, Guilabert A, Miquel R, Campo E. Enigmatic Kikuchi-Fujimoto disease: a comprehensive review. *Am J Clin Pathol.* 2004;122:141–152.
4. Kucukardali Y, Solmazgul E, Kunter E, Oncul O, Yildirim S, Kaplan M. Kikuchi-Fujimoto Disease: analysis of 244 cases. *Clin Rheumatol.* 2007;26:50–54.
5. Lin HC, Su CY, Huang CC, Hwang CF, Chein CY. Kikuchi's disease: A review and analysis of 61 cases. *Otolaryngol Head Neck Surg.* 2003;128:650–653.
6. Dorfman RF. Histiocytic necrotizing lymphadenitis of Kikuchi and Fujimoto. *Arch Pathol Lab Med.* 1987;11:1026–1029.