Case 2-2019: A 36-Year-Old Man with Rash, Abdominal Pain, and Lymphadenopathy

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Presentation of Case

Dr. Katherine H. Schiavoni (Medicine): A 36-year-old man was admitted to this hospital because of abdominal pain, rash, and lymphadenopathy.

The patient had been well until 4 years before admission, when swelling developed in the right side of the neck. One year later, he was evaluated at this hospital and reported that the neck swelling had persisted but had not changed in size. He also reported that he had had no fevers, night sweats, or weight loss. On examination, there was an enlarged posterior cervical lymph node (2 cm in diameter) on the right side. The node was mildly tender and freely mobile, with a rubbery texture and slightly irregular shape. Results of liver-function tests were normal, as were blood levels of iron, ferritin, and total iron-binding capacity. A test for heterophile antibodies and a fourth-generation combination assay for human immunodeficiency virus type 1 (HIV-1) and type 2 (HIV-2) antibodies and HIV-1 p24 antigen were negative; other laboratory test results are shown in Table 1. Chest radiography revealed a normal cardiac silhouette and clear lungs. Biopsy of the lymph node was recommended, but the patient elected not to undergo the procedure.

Two years before admission, a diffuse, painless, erythematous, papular rash developed on the trunk and then spread to the arms, legs, scalp, and face. The papules appeared in separate crops, and over a period of 1 to 2 months, a small amount of purulent material drained from each papule, after which the lesions evolved into hyperpigmented nodules. The rash persisted, and 6 months later, the patient was evaluated at another hospital. A biopsy of the skin of the left arm was performed, and histopathological examination of the biopsy specimen revealed findings consistent with acute folliculitis. Treatment with doxycycline was initiated, but the rash persisted, with a waxing and waning pattern, during the next 8 months. Doxycycline was discontinued. Subsequent treatment with topical clobetasol resulted in only a mild decrease in the rash.

Six weeks before admission, a biopsy of the skin of the right thigh was performed. Histopathological examination of the biopsy specimen revealed acute...
neutrophilic folliculitis, with follicular rupture in the middle dermis and associated acute and chronic inflammation. Surface bacteria and yeast were present, but there were no bacterial or fungal organisms in the dermis. Treatment with oral clindamycin and rifampin was begun, and the patient was instructed to wash twice daily with chlorhexidine and apply mupirocin to open papules.

One day before admission, abdominal pain developed in the right upper quadrant. The pain was sharp, constant, worsened by movement and deep breathing, and unchanged with eating. There was no nausea, vomiting, or diarrhea. The pain progressively worsened during the next 24 hours, and the patient presented to the emergency department of this hospital for evaluation.

In the emergency department, the patient reported ongoing abdominal pain, as well as weight loss of 4.5 kg during the past year, which he attributed to increased regular exercise at a gym. Four weeks before admission, he had stopped exercising because of increased fatigue with exertion. The patient reported that he had not had fevers but had occasionally changed his pajamas at night because of sweating. He had microcytic anemia that had been attributed to β-thalassemia minor. The only medications were clindamycin and rifampin, and there were no known drug allergies.

The patient was born in Morocco and had moved to the United States 10 years before admission. He visited his family in a rural village in Morocco every few years, with the last visit occurring 5 months earlier. He had never smoked tobacco, and he did not drink alcohol or use illicit drugs. He did not consume unpasteurized dairy products. His father had died of complications of emphysema.

On examination, the temperature was 37.6°C, the pulse 66 beats per minute, the blood pressure 132/82 mm Hg, the respiratory rate 16 breaths per minute, and the oxygen saturation 97% while the patient was breathing ambient air. The weight was 76.2 kg; the last recorded weight, which had been obtained 4 years earlier, was 81.8 kg. The patient did not appear to be ill but was in mild distress because of abdominal pain.

### Table 1. Laboratory Data.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Reference Range, Adults*</th>
<th>3 Yr before Admission</th>
<th>On Admission</th>
</tr>
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<tbody>
<tr>
<td>Hematocrit (%)</td>
<td>41–53</td>
<td>39.9</td>
<td>30.2</td>
</tr>
<tr>
<td>Hemoglobin (g/dl)</td>
<td>13.5–17.5</td>
<td>13.0</td>
<td>9.3</td>
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<td>White-cell count (per mm³)</td>
<td>4500–11,000</td>
<td>7370</td>
<td>9460</td>
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<tr>
<td>Differential count (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutrophils (%)</td>
<td>40–70</td>
<td>63.1</td>
<td>75.8</td>
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<tr>
<td>Lymphocytes (%)</td>
<td>22–44</td>
<td>24.4</td>
<td>11.2</td>
</tr>
<tr>
<td>Monocytes (%)</td>
<td>4–11</td>
<td>11.5</td>
<td>11.7</td>
</tr>
<tr>
<td>Eosinophils (%)</td>
<td>0–8</td>
<td>0.8</td>
<td>0.5</td>
</tr>
<tr>
<td>Basophils (%)</td>
<td>0–3</td>
<td>0.1</td>
<td>0.2</td>
</tr>
<tr>
<td>Platelet count (per mm³)</td>
<td>150,000–400,000</td>
<td>167,000</td>
<td>301,000</td>
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<tr>
<td>Red-cell count (per mm³)</td>
<td>4,500,000–5,900,000</td>
<td>6,760,000</td>
<td>5,510,000</td>
</tr>
<tr>
<td>Mean corpuscular volume (fl)</td>
<td>80.0–100.0</td>
<td>59.0</td>
<td>54.8</td>
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<tr>
<td>Mean corpuscular hemoglobin (pg)</td>
<td>26.0–34.0</td>
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<td>16.9</td>
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<tr>
<td>Mean corpuscular hemoglobin concentration (g/dl)</td>
<td>31.0–37.0</td>
<td>32.6</td>
<td>30.8</td>
</tr>
<tr>
<td>Total protein (g/dl)</td>
<td>6.0–8.3</td>
<td>8.2</td>
<td>8.6</td>
</tr>
<tr>
<td>Albumin (g/dl)</td>
<td>3.3–5.0</td>
<td>4.9</td>
<td>3.3</td>
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<tr>
<td>d-dimer (ng/ml)</td>
<td>&lt;500</td>
<td></td>
<td>734</td>
</tr>
</tbody>
</table>

* 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.
Erythematous, follicular papules and hyperpigmented nodules, some with central erosion and ulceration, were distributed on the trunk, arms, legs, face, and scalp (Fig. 1). Examination of the heart and lungs was normal. Bowel sounds were present, and the abdomen was soft, with tenderness on palpation of the right upper quadrant, but was not distended. There was right axillary lymphadenopathy but no submandibular, cervical, supraclavicular, or inguinal lymphadenopathy.

Blood levels of electrolytes, glucose, and lactate dehydrogenase were normal, as were results of renal-function and liver-function tests; other laboratory test results are shown in Table 1. Tests for antibodies to hepatitis B virus (HBV) surface antigen and antibodies to HBV core antigen were positive. Tests for HBV surface antigen, hepatitis C virus antibodies, and Treponema pallidum antibodies were negative, as was a fourth-generation combination assay for HIV-1 and HIV-2 antibodies and HIV-1 p24 antigen. Urinalysis revealed normal findings, and blood cultures were negative. Imaging studies were obtained.

Dr. Alexis M. Cahalane: Abdominal ultrasonography revealed an ill-defined mass (9.0 cm by 5.6 cm) in the right lobe of the liver, with no evidence of dilatation of intrahepatic bile ducts. Computed tomography (CT) of the chest, performed after the administration of intravenous contrast material (Fig. 2A and 2B), revealed multiple prominent cardiophrenic lymph nodes (≤3.4 cm in maximal short-axis diameter) on the right side, including some with central necrosis. CT of the abdomen and pelvis (Fig. 2C) revealed multiple ill-defined hypodensities throughout the right lobe and in the fourth segment of the liver, with the largest measuring 2.7 cm by 2.0 cm. Trace perihepatic ascites and mild splenomegaly were present, with the spleen measuring 13.5 cm in craniocaudal dimension.

Magnetic resonance imaging (MRI) of the liver, performed after the administration of intravenous contrast material (Fig. 2D, 2E, and 2F), revealed multiple areas of abnormality in the right lobe that corresponded to the lesions seen on CT, with the largest measuring 3.1 cm by 6.3 cm by 3.5 cm. The lesions had mild peripheral hyperintensity on T₁-weighted images and restricted diffusion on diffusion-weighted images. On images obtained during the portal venous phase, the lesions had peripheral enhancement with central hypoenhancement. On images obtained 4 minutes after the administration of contrast material, the lesions had a “cluster of grapes” appearance. Mild splenomegaly was also detected.

Dr. Schiavoni: The patient was admitted to the hospital, and fine-needle aspiration and core biopsy of a right axillary lymph node were performed.

Dr. Ruth K. Foreman: Examination of the aspirate and biopsy specimen (Fig. 3) revealed benign-appearing lymph-node tissue with normal architecture and associated necroinflammatory debris. There was no histologic evidence of cancer. Acid-fast, Gomori methenamine–silver, periodic acid–
Schiff, Brown–Hopps, and Steiner stains for microorganisms were negative, as was an immunohistochemical stain for spirochetes. Tissue from the biopsy was sent to the microbiology laboratory for culture.

**Dr. Schiavoni:** Additional diagnostic tests were performed, and a diagnosis was made.

### Differential Diagnosis

**Dr. Steven T. Chen:** This 36-year-old man had an indolent disease course that was characterized by generalized lymphadenopathy and a diffuse rash, ultimately followed by acute pain in the right upper quadrant. Imaging studies were notable for liver lesions that were suggestive of small pyogenic abscesses.

Lymphadenopathy was first detected in the neck 4 years before admission; by the time of admission, it was detected in the peridiaphragmatic, anterior mediastinal, and axillary regions, with some nodes measuring more than 4 cm in diameter and having central necrosis. The rash, which developed 2 years before admission and involved the face, arms, legs, and torso, had been diagnosed as folliculitis and treated with multiple courses of antibiotics, without resolution. On examination of the clinical photographs (Fig. 1), the lesions do not appear to be accentuated in hair-bearing areas. This calls the diagnosis of folliculitis into question. However, these photographs were not taken with high enough resolution to allow definitive assessment of whether the eruption is follicular, a finding that would help to narrow the differential diagnosis. The presence of lesions on the central back argues against a self-induced, prurigo-like process. The eruption is described as consisting of erythematous and hyperpigmented nodules and papules,
with ulceration, and the photographs show that
the lesions have a brown and brawny appearance
that is most consistent with a granulomatous
process. Results of diascopy are not reported,
but the finding of “apple jelly” nodules on this
test would have provided additional support for
characterization of the lesions as a manifestation
of granulomatous disease.

Assuming that the generalized lymphadenopa-
thy, liver abscesses, and granulomatous skin
eruption can all be explained by a unifying di-
agnosis, I will focus my differential diagnosis on
three categories of causes. Listed in order of in-
creasing likelihood, these categories are autoim-
mune diseases (specifically sarcoidosis), lympho-
proliferative disorders, and infections.

SARCIOIDOSIS
Although several autoimmune diseases may have
indolent progression similar to the disease course
seen in this patient, the granulomatous skin
eruption and liver lesions that were present in
this patient specifically prompt consideration of
sarcoidosis and would be atypical of other autoim-
mune diseases. Sarcoidosis could also explain the
presence of peripheral lymphadenopathy and
necrosis, a finding that was evident in some
enlarged axillary lymph nodes on imaging. How-
ever, sarcoidosis is typically associated with
perihilar mediastinal lymphadenopathy, whereas
this patient had anterior mediastinal lymphade-
nopathy. Furthermore, 95% of cases of sarcoidosis
involve the lungs, and the absence of pulmonary
symptoms such as cough, dyspnea, and chest
pain and of reticular opacities on CT makes the
diagnosis of sarcoidosis unlikely. Finally, to es-

tablish the diagnosis of sarcoidosis, it is neces-
sary to rule out other diseases with similar pre-
sentations, such as lymphoproliferative disorders
and infections.

LYMPHOPROLIFERATIVE DISORDERS
In this patient, the indolent disease course makes
some lymphoproliferative diseases — such as
Hodgkin’s lymphoma, follicular lymphoma, multi-
centric Castleman’s disease, and immunopro-
liferative small intestinal disease — much more
likely than the lymphoproliferative diseases that
typically follow a more aggressive trajectory (e.g.,
diffuse large B-cell lymphoma, Burkitt’s lympho-

a, and angioimmunoblastic T-cell lymphoma).

Hodgkin’s lymphoma deserves careful consider-
ation in this case, given that the average age at
diagnosis in the United States is 39 years and
this patient was 36 years of age, that the lymph-
adenopathy began in the neck and later involved
other sites, and that a variety of cutaneous eru-
ptions have been associated with Hodgkin’s lym-
phoma, including paraneoplastic dermatoses and
skin infiltration.

Follicular lymphoma may also begin with
peripheral lymphadenopathy and progress to
involve mediastinal lymph nodes, and the dis-

ease course may span several years; however, it
typically occurs in older patients and rarely oc-
curs in persons in this patient’s age group. Multi-
centric Castleman’s disease is another lymphopro-
liferative disorder that can begin with generalized
lymphadenopathy and can have an indolent
course; however, cutaneous involvement is rare,
and fever, which was not reported by this pa-
tient, is typical.

Immunoproliferative small intestinal disease
is rare in the United States but is more common
among young men in the Middle East and North
Africa, so it merits consideration in this patient,
who was born and raised in Morocco. Immuno-
proliferative small intestinal disease is thought
to occur in the context of a chronic infection
that leads to B-cell activation and clonal prolif-
eration, and affected patients usually present with
abdominal pain, chronic diarrhea with malab-
sorption, or an abdominal mass. This patient
reported abdominal pain at the time of admis-
sion, but the pain was acute. Furthermore, there
was no diarrhea, the weight loss was less severe
than would be expected with this disorder, and
imaging studies did not reveal bowel-wall thick-
ening or an abdominal mass. These findings
make immunoproliferative small intestinal dis-
ease unlikely.

Although it is reasonable to consider lympho-
proliferative disorders in the differential diagno-
sis for this patient, the findings on imaging
studies of the liver are more consistent with an
infectious process. Other findings — including
the normal blood lactate dehydrogenase level
and the absence of relevant findings on histo-
 pathological examination of the biopsy speci-
mens — may not rule out lymphoproliferative
disorders, but they make these diagnoses un-
likely.
INFECTIONS

Which infections could cause generalized lymphadenopathy, a granulomatous skin eruption, and liver abscesses in an otherwise healthy young man who has lived in Morocco and New England? Among bacterial infections, brucellosis is a consideration, but the absence of fever and of a history of exposure makes this diagnosis unlikely.9

Syphilis is ruled out by the negative screening test for T. pallidum antibodies. Cryptococcosis and endemic mycoses such as histoplasmosis can result in clinical and imaging findings similar to those seen in this patient but would not usually lead to such a protracted illness in a presumably immunocompetent person. Although leishmaniasis is endemic in Morocco, it is unlikely in this patient because the appearance of the skin lesions is not consistent with the cutaneous form of this disease10 and because visceral leishmaniasis would be expected to cause a more severe illness, with fever, pancytopenia, and more marked weight loss and splenomegaly. In addition, the findings on imaging studies of the liver are not typical of leishmaniasis.11

Mycobacterial infections deserve close consideration in this case. Although we often think of Mycobacterium leprae when considering mycobacterial skin disease, the incidence of leprosy in Morocco is low and the appearance of the skin lesions in this patient is not consistent with this diagnosis. An infection with atypical mycobacteria such as M. fortuitum can cause skin lesions but would not usually involve the reticuloendothelial system in an immunocompetent person. M. bovis infection could account for this patient’s presentation; however, without exposure to unpasteurized milk, this diagnosis is also unlikely.12 Because the patient had taken trips to Morocco, where tuberculosis is endemic,13 I would focus on M. tuberculosis infection as the most likely cause of this patient’s presentation.

TUBERCULOSIS

Cutaneous involvement is relatively uncommon in M. tuberculosis infection. Patients with cutaneous tuberculosis can present with a variety of clinical findings, which can be classified according to the method by which mycobacteria are disseminated to the skin.14

Direct inoculation of mycobacteria from an exogenous source into a host can be manifested by tuberculous chancr or tuberculosis verrucosa cutis. These cutaneous manifestations are localized to the site of inoculation,14 whereas this patient’s rash was diffuse. The spread of mycobacteria from an endogenous source may result in scrofuloderma, a supplicative nodular process that often develops on the skin overlying affected lymph nodes and then drains, leading to sinus formation and resultant cordlike scars. Although this patient had lymph-node involvement, his cutaneous findings were more widely distributed than would be expected with scrofuloderma.

Hematogenous spread of mycobacteria, known as miliary tuberculosis, may have cutaneous manifestations, such as a generalized, monomorphic papular, pustular, or nodular process. However, this patient’s systemic symptoms were less severe than would be expected with miliary tuberculosis, which is typically associated with fever and more marked night sweats and weight loss. In addition, miliary tuberculosis has a characteristic pattern on CT of the lungs, but there were no abnormal findings on CT of the lungs in this patient.

Lupus vulgaris is a chronic, scarring, and deforming process that may occur either as a direct result of an underlying focus of M. tuberculosis infection or after hematogenous or lymphatic spread of infection. The eruption associated with lupus vulgaris classically affects the central portion of the face and can progress slowly over a long period of time.

The other category of cutaneous tuberculosis is tuberculids, skin eruptions that are thought to occur in reaction to an underlying, often occult, focus of M. tuberculosis infection.14 There are three main types of tuberculids: erythema induratum, lichen scrofulosorum, and papulonecrotic tuberculid. Erythema induratum appears as red-to-violaceous nodules or plaques on the posterior calf and is localized, in contrast to the diffuse rash that was seen in this patient. Lichen scrofulosorum appears as many discrete, often monomorphic, 2-to-4-mm, flat-topped papules, usually on the trunk. Papulonecrotic tuberculid is usually a symmetric, recurring eruption of 2-to-8-mm, firm, inflammatory papules that can turn into pustules and become necrotic over time, scarring over a period of weeks. If papulonecrotic tuberculid goes untreated, it may persist for years. This patient’s indolent disease course and the
description and appearance of his rash are highly consistent with the papulonecrotic tuberculid form of cutaneous tuberculosis, and therefore, this is the most likely diagnosis in this case.

Confirming the diagnosis of papulonecrotic tuberculid is challenging. Although an interferon-γ release assay would be part of the laboratory evaluation in this patient, a positive assay would not help to discriminate between latent and active tuberculosis. Tuberculids are commonly considered to be hypersensitivity eruptions, and in patients with these disorders, acid-fast stains of smears or histopathological sections of skin-biopsy specimens would not normally be expected to identify mycobacteria, although it is possible. Similarly, mycobacterial cultures of skin-biopsy specimens are unlikely to be positive, although the tuberculid reaction can be seeded by the hematogenous spread of mycobacteria and organisms can be isolated from these lesions in some cases. In this patient, acid-fast stains and cultures would be more likely to be diagnostic if specimens were obtained from an underlying focus of *M. tuberculosis* infection, such as an affected lymph node or a liver abscess. Although *M. tuberculosis* may take several weeks to grow in culture, its isolation would allow for the performance of antimicrobial susceptibility testing, the results of which would inform the selection of a therapeutic antibiotic regimen.

**DR. STEVEN T. CHEN’S DIAGNOSIS**

Papulonecrotic tuberculid (cutaneous tuberculosis).

**PATHOLOGICAL DISCUSSION**

*Dr. Foreman:* A punch biopsy of the skin of the right forearm was obtained (Fig. 4). Histopathological examination of the specimen revealed a superficial and deep necrotizing granulomatous inflammatory infiltrate. The necrosis surrounded naked hair shafts; this finding is suggestive of a possible folliculocentric process. Acid-fast, Fite, Gomori methenamine–silver, periodic acid–Schiff with diastase, and Brown–Hopps stains for microorganisms were negative, as was an immunohistochemical stain for spirochetes. A section of the specimen was submitted to the microbiology laboratory for mycobacterial culture.

**DISCUSSION OF MANAGEMENT AND FOLLOW-UP**

*Dr. Meridale V. Baggett (Medicine):* Dr. Ryan, would you tell us what happened next?

*Dr. Edward T. Ryan:* An enzyme-linked immunospot interferon-γ release assay for a cell-mediated immune response to *M. tuberculosis* was strongly positive. At this point, we thought that the complete clinical picture — including the epidemiologic history, chronicity of the disease process, dermal manifestations, apparently necrotic axillary lymph nodes, hepatic lesions, markedly positive interferon-γ release assay, weight loss, night sweats, and presence of necrotizing granulomas on examination of the skin-biopsy specimen —
strongly supported the diagnosis of papulonecrotic tuberculid with accompanying tuberculous lymphadenitis and hepatic involvement. The patient had recently begun to take oral clindamycin and rifampin, and we thought that the rifampin could have partially treated his tuberculosis.

While the results of mycobacterial culture of biopsy specimens of the axillary lymph node and skin were pending, we obtained three induced-sputum samples and a urine specimen for mycobacterial culture, to increase the likelihood of establishing a microbiologic diagnosis and obtaining information on susceptibility that could guide future therapy. Once these samples had been collected, antituberculous therapy consisting of daily rifampin, isoniazid, pyrazinamide, and ethambutol (RIPE) was administered, along with vitamin B6.

After the empirical initiation of antituberculous treatment, the patient did well and no new skin lesions developed. Approximately 4 weeks later, the culture of the axillary lymph node-biopsy specimen grew M. tuberculosis complex. Subsequent susceptibility testing revealed that the isolate was susceptible to first-line antituberculous agents in vitro. After 8 weeks of RIPE therapy, pyrazinamide and ethambutol were discontinued, and treatment with isoniazid and rifampin was continued. Approximately 3 months after the initiation of therapy, the patient’s energy level had returned to normal, clinical examination revealed that the axillary lymph nodes had decreased in size, and follow-up abdominal imaging revealed that the hepatic lesions had diminished. A 6-to-12-month course of antituberculous therapy is planned.

**FINAL DIAGNOSIS**

Papulonecrotic tuberculid (cutaneous tuberculosis).

This case was presented at the Medical Case Conference. No potential conflict of interest relevant to this article was reported.

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

We thank Dr. Sherry H. Yu for contributing the clinical photographs.