A 52-year-old previously healthy man was admitted to an inpatient internal medicine resident hospital service with a 2-week history of profound generalized fatigue, nocturnal fevers (temperature as high as 39.4 °C [103 °F]), cold sweats, anorexia, and bilateral hand swelling and numbness. The swelling progressed to symmetrically involve his elbows, shoulders, knees, and ankles. He also reported arthralgias and profound weakness that had caused him to be confined to a wheelchair. He experienced joint stiffness of less than 30 minutes' duration in the morning that improved with activity. He denied recent tick bites, exposures to sick contacts, or travel outside of Minnesota and reported no recent weight loss, sore throat, or infection. A full review of systems was otherwise unremarkable. Family history was remarkable for an aunt and cousin with lupus.

On physical examination, swelling and tenderness were observed at multiple sites, most prominently at the dorsum of hands, elbows, wrists, knees, and ankles, suggesting tenosynovitis. He also had significant effusions in his knees bilaterally and moderate nonpitting edema, particularly in his hands and feet. A macular, nontender, purple rash was noted on the dorsum of his left hand. No lymphadenopathy was present. Bibasilar crackles were heard in his lungs. Findings on neurologic examination, including strength testing, were normal. No hepatosplenomegaly was observed. The remainder of the examination was unremarkable.

Laboratory studies yielded the following results (reference ranges provided parenthetically): hemoglobin, 15.8 g/dL (13.5-17.5 g/dL); leukocyte count, 19.7 × 10⁹/L (3.5-10.5 × 10⁹/L), with a neutrophil count of 17.5 × 10⁹/L (1.7-7.0 × 10⁹/L); platelet count, 270 × 10⁹/L (150-450 × 10⁹/L); creatinine level, 0.8 mg/dL (0.8-1.2 mg/dL); blood urea nitrogen, 14 mg/dL (8-24 mg/dL); bicarbonate, 28 mEq/L (22-29 mEq/L); glucose, 129 mg/dL (70-100 mg/dL); alanine aminotransferase, 98 U/L (8-48 U/L), aspartate aminotransferase, 46 U/L (8-48 U/L); alkaline phosphatase, 173 U/L (45-115 U/L); total bilirubin, 0.8 mg/dL (0.1-1.0 mg/dL); albumin, 3.7 g/dL (3.5-5.0 g/dL); and international normalized ratio, 1.0. Urinalysis showed a predicted 24-hour protein of 1011 mg, with 4 to 10 red blood cells per high-power field, less than 25% of which were dysmorphic, and 1-3 white blood cells per high-power field. No casts were seen. Chest radiography revealed infiltrates or atelectasis in the right middle lobe and lingula.

1. On the basis of the patient's initial history, physical examination, and laboratory testing, which one of the following diagnoses seems least likely?
   a. Wegener granulomatosis
   b. Adult Still disease (ASD)
   c. Rheumatoid arthritis
   d. Lyme disease
   e. Meningococcemia

   Wegener granulomatosis typically presents with persistent rhinorrhea, oral and nasal ulcers, polyarthritides, and myalgias. Chest radiography often reveals hilar adenopathy, pulmonary nodules, and opacities. Patients may also have active urinary sediment and renal insufficiency. Our patient presented with abnormal findings on chest radiography, active urinary sediment, polyarthritides, and myalgias, all of which may be consistent with Wegener granulomatosis.

   Adult Still disease is an inflammatory disease that is characterized by high fevers that recur daily, polyarthritides, rash, and neutrophilic leukocytosis. It may be accompanied by lymphadenopathy, hepatosplenomegaly, and mildly elevated results on liver function tests; it typically also presents with normocytic normochromic anemia and reactive thrombocytosis. There may also be pulmonary infiltrates and renal involvement. Our patient’s symptoms could be consistent with this disease.

   Rheumatoid arthritis, a systemic disease with symmetric involvement of joints, may have systemic symptoms, including myalgias, fatigue, low-grade fevers, and weight loss. Extra-articular manifestations of the disease can include synovial inflammation and parenchymal lung disease. It may also present as glomerulonephritis and rheumatoid vasculitis, both of which are characterized by active urinary sediment. Our patient had joint swelling, arthralgias, fevers, fatigue, myalgias, and active urinary sediment, all of which could be consistent with rheumatoid arthritis.

   Lyme disease may present with constitutional symptoms, such as fevers, fatigue, anorexia, myalgias, arthral-
gias, and anorexia. Another classic feature is erythema migrans, which typically presents around the beltline, axilla, or inguinal regions and is characterized by painless areas of erythema with central clearing. Up to 20% of people with Lyme disease, however, do not develop erythema migrans. Although our patient did not have erythema migrans or any known exposures to ticks, Lyme disease is still in the differential diagnosis.

Our patient had a fever, but its presentation over the course of a few weeks rather than a few hours made a meningococcal infection unlikely. His rash was very different than the classic hemorrhagic or petechial rash seen in meningococcemia. Meningococcemia may present with arthritis, but it is typically monoarticular, unlike that in our patient.

Our differential diagnosis included Wegener granulomatosis, ASD, Reiter syndrome, viral arthritis, Lyme disease, syphilis, vasculitis, poststreptococcal arthritis, and rheumatoid arthritis. Additional blood tests were ordered to narrow the differential diagnosis.

2. Which one of the following laboratory tests is least likely to help narrow the differential diagnosis in this patient?

a. Antinuclear cytoplasmic antibody (ANCA) assay
b. Anticyclic citrullinated peptide antibody (anti-CCP) assay
c. Antinuclear antibody (ANA) assay
d. Peripheral blood smear
e. Parvovirus B19 IgM assay

Typically, an ANCA assay can be used to aid in diagnosis of Wegener granulomatosis and would be a helpful test for narrowing the differential diagnosis in this patient. Of patients with Wegener granulomatosis, 80% to 90% test positive for PR-3 ANCA. An anti-CCP assay could provide useful information because these antibodies are found in most patients with rheumatoid arthritis. An ANA assay may be positive in 30% to 40% patients with rheumatoid arthritis and may be indicative of other inflammatory disorders, such as systemic lupus erythematosus. It is a non-specific test and is particularly helpful when findings are negative. A peripheral blood smear is unlikely to be helpful in narrowing the differential diagnosis in this case because no specific hematologic changes would be expected for any of the diseases being considered. Parvovirus B19 often presents as seronegative arthritis in adults. Up to 15% of newly diagnosed cases of arthritis are secondary to parvovirus. As a result, it would be reasonable to check for IgM antibodies to suggest recent infection.

In this patient, laboratory studies revealed an erythrocyte sedimentation rate of 33 mm/h (0-22 mm/h) and a C-reactive protein level of 301.9 mg/L (≤8.0 mg/L). Results for ANCA, ANA, rheumatoid factor, anti-CCP, parvovirus B19 IgM, and cryoglobulin assays and for serum protein electrophoresis were all within normal limits, as were C3 and C4 complement levels. Follow-up urinalysis showed normal microscopy. A 24-hour urine test showed excretion of 223 mg/d of protein. Findings on blood cultures, urine cultures, urine polymerase chain reaction for Chlamydia trachomatis, and stool cultures for Salmonella, Shigella, and Yersenia species were all negative. Serologic findings were also negative for antistreptolysin O DNA, human immunodeficiency virus, cytomegalovirus, Epstein-Barr virus, and hepatitis viruses, as well as on the Venereal Disease Research Laboratory test (a serologic test for syphilis). After a week without a diagnosis, the patient was prescribed empiric amoxicillin-clavulanate and discharged home.

At his outpatient follow-up a week later, his condition had not noticeably improved. He had a new erythematous, macular, migratory rash on his chest, arms, and volar aspects of his wrists bilaterally, which seemed most pronounced during the evening.

3. Which one of the following is the most likely explanation for the presence of the new rash in this patient?

a. The rash is an allergic drug reaction to amoxicillin-clavulanate
b. The rash represents a manifestation of ASD
c. The rash is consistent with leukemia cutis
d. The rash represents worsening Wegener granulomatosis
e. The rash is a manifestation of Sweet syndrome

Given that the rash appeared a few days after the initiation of amoxicillin treatment, it may be an allergic drug rash. However, amoxicillin typically causes a widespread erythematous morbilliform rash or, in severe cases, a pruritic rash with desquamation, often accompanied by fever, nausea, and vomiting. Therefore, the patient's rash was inconsistent with a drug rash.

Adult Still disease typically presents with a nonpruritic, nontender, evanescent, salmon-colored, macular or maculopapular rash, which is usually located on the trunk or extremities and accompanied by a fever. Our patient's rash is likely a manifestation of ASD, as it was most prominent in the evenings, coinciding with his nocturnal fevers.

The patient's laboratory results showed no evidence of leukemia, and leukemia cutis would not present as a migratory, waxing-and-waning rash. Wegener granulomatosis is typically not associated with a rash. The rash of Sweet syndrome presents as tender, erythematous, well-demarcated papules and plaques, which show dense neutrophilic infiltrates microscopically. In comparison, our patient had an evanescent, erythematous, nonpainful rash on his chest and extremities, without any vesicular, pustular, or ulcerative
appearance, none of which is consistent with the rash of Sweet syndrome.

Given our patient’s high-grade fevers, neutrophilic leukocytosis, polyarthritis, rash, and elevated erythrocyte sedimentation rate, a diagnosis of ASD was established.

4. After learning of his new diagnosis, the patient asked about his prognosis. Which one of the following would be the most appropriate reply to the patient’s question?
   a. Your disease is typically self-limiting and should resolve in 2 to 3 weeks
   b. Your disease is typically progressive, with high mortality. You are likely to be wheelchair bound for the rest of your life
   c. There are no known treatment options, and we can only treat your symptoms
   d. Your disease is associated with a high incidence of malignancies. Most patients will die of a malignancy within 3 to 4 years of the diagnosis
   e. Your disease typically has an unpredictable and variable course. However, most patients have a favorable prognosis, with good functional status

A monophasic, self-limiting course of disease is present in only a third of patients and can take up to a year to resolve even with treatment. Our patient’s disease is unlikely to resolve in the next 2 to 3 weeks. Most patients with ASD have a good functional status, and the disease does not have a high mortality rate. Only a third of patients have persistently active disease with associated destructive arthritis. Several treatment options are available for patients with ASD. No association between ASD and the incidence of malignancies is known. Although the prognosis of individual patients with ASD is unknown, population studies have shown that ASD may have 1 of 3 clinical patterns: monophasic, intermittent, or chronic. At this point, the disease pattern in our patient is unknown, and his prognosis cannot be predicted.

Our patient was advised that his disease had an unpredictable and variable course and that he would likely have good functional status. He then asked about his treatment options.

5. Which one of the following is the most appropriate treatment for this patient?
   a. Nonsteroidal anti-inflammatory drugs as needed for pain control
   b. Corticosteroids
   c. Tumor necrosis factor inhibitor therapy
   d. Anakinra (recombinant human interleukin-1 receptor antagonist)
   e. Doxycycline for 4 weeks

Nonsteroidal anti-inflammatory drugs may be used in the treatment of patients with relatively mild ASD. Corticosteroids are required to suppress the inflammation in most patients, especially those who, like our patient, have a high fever, debilitating joint symptoms, or internal organ involvement. Tumor necrosis factor inhibitors, including infliximab and etanercept, have been studied as treatment for ASD, but they are not considered the first line of treatment, and studies of them have thus far been limited to small case series. Many case reports have described the use of anakinra to control disease activity in patients whose disease is refractory to other treatment options, but it would not be the first line of treatment in this patient. Doxycycline and other antibiotics have no role in the treatment of ASD.

Our patient was prescribed 1 mg/kg per day of prednisone. During the next few weeks, he improved greatly, with near resolution of his symptoms. At follow-up, his physical examination was unremarkable, and his cell counts and erythrocyte sedimentation rate had normalized.

**DISCUSSION**

Adult Still disease is an inflammatory disorder characterized by fever, arthritis, and evanescent rash. The etiology of ASD is not well understood, but various bacterial and viral pathogens have been suspected to play a role. It also has no clear association with human leukocyte antigen typing. The annual incidence is approximately 0.16 cases per 100,000 person-years and is slightly higher in women. The mean age of presentation is 38 years, but more than 67% of those who present with ASD are older than 35 years.

Multiple diagnostic criteria have been proposed. The most commonly used and those with the highest sensitivity (94%) for the diagnosis of ASD are the Yamaguchi diagnostic criteria. A diagnosis of ASD requires the presence of 5 features, with at least 2 being major diagnostic criteria (Table).

The fevers of ASD typically occur daily or twice daily and often in the evening hours, with wide fluctuations of body temperature in a short time period. In about 20% of cases, the fever may persist between spikes and does not completely resolve. The rash of ASD is typically a non-pruritic, evanescent, salmon-colored maculopapular rash that tends to occur with fever spikes. It predominantly involves the trunk and extremities and may be elicited by scratching or heat. If performed, skin biopsy usually demonstrates mild perivascular inflammation and dermal edema.

Arthralgias, arthritis, and myalgias are present in almost all patients with ASD. The most commonly involved joints, in descending order, are the knees, wrists, ankles, elbows, proximal interphalangeal joints, and shoulders. The synovial fluid is typically inflammatory, with a mean leukocyte count of 13.0 × 10^9/L. Myalgias may be profound and debilitating and may be accompanied by a mild increase in aldolase and
creatinine kinase levels. Findings on electromyography and muscle biopsy studies are typically normal.

Mild lymphadenopathy is seen in approximately 65% of patients. Splenomegaly may also be present. Lymph node biopsy typically shows paracortical proliferation, which may cause confusion with lymphoma. However, unlike lymphoma, immunohistochemistry reveals benign polyclonal B-cell hyperplasia. In 70% of patients, levels of aspartate aminotransferase, alanine aminotransferase, and lactate dehydrogenase that are not attributable to drug toxicity or allergy. Negative findings on antinuclear antibody and rheumatoid factor tests

Exclusion
Infections, especially sepsis and infectious mononucleosis
Malignancies, especially lymphomas
Rheumatic diseases, especially polyarthritis nodosa and rheumatoid vasculitis

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<th>TABLE. Yamaguchi Diagnostic Criteria for Adult Still Disease</th>
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<tr>
<td>Major</td>
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<tr>
<td>Arthritis or arthralgia lasting ≥2 wk, with swelling or limitation of motion</td>
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<td>Temperature ≥39°C, persistent or intermittent, for ≥1 wk</td>
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<td>Typical rash: a nonpruritic macular or maculopapular rash that is salmon-colored and is usually found over the trunk or extremities during febrile illness. Persistent eruption is not characteristic of the disease</td>
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<td>Leukocytosis: (leukocyte count, 10.0 × 10^9/L) with at least 80% granulocytes</td>
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<td>Minor</td>
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<td>Sore throat</td>
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<td>Lymphadenopathy and/or splenomegaly</td>
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<td>Abnormal findings on liver function studies (particularly elevated levels of aspartate aminotransferase, alanine aminotransferase, and lactate dehydrogenase) that are not attributable to drug toxicity or allergy</td>
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<td>Negative findings on antinuclear antibody and rheumatoid factor tests</td>
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REFERENCES

Correct answers: 1. e, 2. d, 3. b, 4. e, 5. b