An Unrecognised Cause of Fever

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A 47-year-old woman presented to the emergency department (ED) with a 24-hour history of fever, rigors, and bilateral knee pain. Her past medical history was significant for rheumatoid arthritis, diagnosed nine years ago. This subsequently evolved into mixed connective tissue disease with scleroderma and inflammatory myositis. She also had pulmonary fibrosis caused by previous methotrexate use, osteoporosis, hypertension, and a total abdominal hysterectomy for fibroids. Current medications were azathioprine, 100 mg daily, prednisone, 25 mg daily, enteric coated acetominophen, omeprazole, etidronate, prazosin, and pentoxifylline.

She had also experienced some night sweats and myalgias. She denied any cough, shortness of breath, chest pain, vomiting, diarrhea, abdominal pain, dysuria, headache, neck stiffness, or neurologic symptoms. Her knees were the only painful joints. She had no recent history of sick contacts or travel. Screening investigations for latent tuberculosis were negative prior to starting immunosuppressive therapy (Table 1 and 2).

On chest X-ray, there was a diffuse reticular pattern that had not changed from her previous films. Bilateral knee X-rays did not reveal any evidence of fracture but suggested effusions. Urinalysis was negative. An arthrocentesis was performed on her left knee. The gram stain was negative and no crystals were seen. Cultures of urine, synovial fluid, and blood were sent. The patient received intravenous (IV) fluids and ASA in the ED) and, after several hours, defervesced and felt better and was discharged home.

Table 1
Initial Bloodwork

Hb	118
MCV	88
WBC	7.1
Platelets	211
Na	139
K	3.4
Cl	102
HCO_3^-	26
Creatinine	59
BUN	5.1
INR	1.01
PTT	30.2

HB = hemoglobin, MCV = mean cell volume, WBC = white blood cell count, Na = sodium, K = potassium, Cl = chloride, $HC0_3^-$ = bicarbonate, BUN = blood urea nitrogen, INR = international normalised rate, PTT = partial thromboplastin time

Table 2
Physical Examination

- She appeared Cushingoid but looked well.
- Heart Rate was 117 beats per minute and Blood Pressure was 110/65 mmHg.
- Respiratory rate was 18 breaths/minute.
- Oxygen saturation was 98% on room air.
- Temperature 39.8 C.
- Neck was supple, oropharynx was clear and there was no lymphadenopathy.
- Respiratory exam revealed bilateral "Velcro" crackles (unchanged from previous exam).
- Cardiovascular, abdominal, and neurologic examinations were all normal.
- Musculoskeletal examination showed no signs of acute joint inflammation aside from small bilateral knee effusions. There were no rashes or skin ulcers.

What's your diagnosis?

First case followup

Forty-eight hours later, her blood culture result was reported to the ER physician. It was positive for Listeria monocytogenes. The patient was phoned to return to the hospital. She no longer had knee pain, but her intermittent fevers and rigors persisted. Her physical exam was unchanged; she was afebrile with a temperature of 36.9 C and she was admitted.

Answer: Listeria

Why was this patient infected?

This patient has several reasons to be immunosuppressed. First, she has rheumatoid arthritis. Patients with autoimmune disease have a risk for infection that is independent of the immunosuppressive therapy they are taking. Many afflicted patients are on at least one, and usually more, medications that have the specific role of suppressing the immune system. Corticosteroids alter immune responses on multiple levels. They decrease the numbers of lymphocytes in circulation. Despite increasing the number of neutrophils in circulation by increasing demargination, they actually prevent migration of neutrophils to areas of infection because adhesion is affected. They also inhibit cytokine release and impair the bactericidal abilities of neutrophils. At higher doses they also interfere with antibody formation. The risk for atypical infection in people taking steroids is dose dependent. When looking at the risks by dose, a study of systemic lupus erythematosus patients found that those taking less than 10 mg daily had a 1.5 relative risk for serious infections while those taking more than 40 mg a day had a relative risk of 8.[1] In addition to causing immunosuppression, steroids can inhibit many of the inflammatory responses to infections. They may mask a fever or other clinical signs of infection, making a diagnosis difficult.

In addition to prednisone, this patient was also on azathioprine. Azathioprine and its metabolites may have several deleterious effects on host defenses, most importantly bone marrow suppression and subsequent neutropenia. The combination of prednisone and azathioprine may cause more infections and a higher mortality from infections than either agent alone.[2]

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Table 3

Who is at risk for Listeria infection?

- Individuals who are at the extremes of age.
- Individuals who have a predisposing condition, such as corticosteroid treatment (most important risk factor), AIDS, hematologic or solid tumor malignancies, collagen vascular diseases, organ transplantation, end-stage renal disease, diabetes, and iron overload states.
- Most common cause for meningitis in patients with lymphoma, organ transplant, or who are receiving corticosteroids.
- One third of all Listeria infections occur during pregnancy. (Incidence is highest in the third trimester and more often in twin or triplet pregnancies than single pregnancies).

never causes meningitis in this group (Table 3). In fact, the diagnosis may be missed if blood cultures are not drawn. It is the fetus that experiences the significant effects of maternal infection since, for some unknown reason, Listeria seems to have a predilection for placental tissue and crosses the placenta to infect the fetus. This can lead to premature labour and delivery, stillbirth, or a severe in utero infection, granulomatosis infantiseptica, in which the fetus has skin lesions and disseminated abscesses and/or granulomas. Most are born stillborn or die shortly later. If the mother is an asymptomatic carrier of Listeria, the fetus may be exposed to Listeria at the time of delivery. This may cause neonatal sepsis or meningitis within the first week of life.

What are the manifestations of Listeria?

In healthy adults, Listeria usually causes afebrile gastroenteritis that lasts two to three days with full recovery in virtually all patients. Many will not actually be diagnosed as having Listeria. One per cent to 5% of the general population is colonised with Listeria and may asymptomatically excrete it in their stool.[3]

In pregnancy, Listeria commonly causes a flu-like illness with fever, chills, and back pain, and it virtually

Table 4

What infections is this patient at risk for?

- Bacterial infections [Staph aureus, Listeria monocytogenes, gram negatives (especially E. coli and Pseudomonas aeruginosa)]
- Viral infections (herpes zoster, cytomegalovirus)
- Fungal infections (candida albicans)
- Opportunistic infections (pneumocystis cariini pneumonia)

Table 5

How are patients infected?

- Listeria monocytogenes infects humans by contaminating vegetables or foods of animal origin that are then ingested (most common are unpasteurised or contaminated milk, soft cheeses, and under-cooked meat).
- Colonisation of the genital tract and rectum of pregnant women may lead to infection of their fetuses and neonates; human to human spread has not been described.

Second case followup

The patient was treated with ampicillin 2 g IV every six hours and gentamicin 50 mg IV every eight hours. Her immunosuppressant regimen was not changed. She continued to do well in the hospital and, after five days, the gentamicin was discontinued and she was discharged home with a peripherally inserted central catheter line for home care administration of IV ampicillin. She received a total of three weeks of ampicillin and at followup was well.

In children or adults with the predisposing conditions discussed in Table 3, the most common presentations are either Listeria bacteremia or meningitis/meningoencephalitis. There are also some less common presentations that include: cerebritis, rhombencephalitis, brain abscesses and focal infections (Table 4).

With Listeria bacteremia, the presentation is sepsis of unknown origin. Diagnosis is made only after positive blood culture results. With meningitis, there is a range of clinical presentations from mild disease to coma. Unlike other bacterial meningitis, Listeria may present more sub-acutely, have fewer signs of meningeal irritation, and be associated with more movement disorders and seizures. The cerebrospinal fluid (CSF) analysis may have a significant lymphocytosis (greater than 25%). The protein is mildly to moderately elevated and the glucose is normal in at least half the cases. Gram stain on the CSF has extremely poor sensitivity (less than 40%) and, when organisms are seen, Listeria may be mistaken for other pathogens, such as pneumococci, diptheroids, or haemophilus. For this reason, in an immunocompromised patient or elderly patient, if the gram stain is negative with a lymphocytic meningitis, one should include Listeria coverage empirically. The culture results often provide a higher yield.

How do you manage Listeria?

There are no randomised, controlled trials for the optimal drug or the duration of therapy for Listeria.

Ampicillin is usually the antibiotic of choice in treating Listeria infections. It should be administered in daily doses of 200 mg/kg and divided in to four to six IV doses. For serious infections, central nervous system (CNS) involvement, or immunosuppressed patients, an aminoglycoside should be added for synergistic bactericidal activity. Gentamicin is usually

added at daily doses of 5 mg/kg divided into three IV doses. Because of the risks of renal and ototoxicity, gentamicin can be discontinued at one week or with clinical improvement. If a patient is allergic to penicillin, then trimethoprim-sulfamethoxazole is the preferred alternative, at daily doses of 20 mg/kg of the trimethoprin divided into four IV doses. Other antibiotics do not have the same efficacy against Listeria, and therefore, should not be substituted. There is no defined duration of treatment that is optimal for all patients. Generally, patients who are immunocompetent and have bacteremia alone can be treated for two weeks. Patients who are immunocompromised should be treated from three to six weeks. All patients with CNS involvement should be treated for at least three weeks and in some cases up to six to eight weeks.

For patients on immunosuppressant medications, a decision must be made what to do with these medications while they are infected with Listeria. If possible, decreasing the dose or stopping medications may be helpful yet this must be balanced against the risk of their underlying reason for immunosuppression. For most patients, continuing immunosuppression does not a have deleterious effect on their recovery, however, if clinical improvement does not occur quickly with antibiotic therapy or there is any worsening of condition, then immunosuppressant medications should be decreased or withheld. ℞

References

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Suggested Readings

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