Robert Listernick, MD, and colleagues discuss hard-to-diagnose cases.

A 6-Year-Old Male with Daily Fever Accompanied by Nausea and Abdominal Pain

Robert Listernick, MD

A 6-year-old boy was well until 7 weeks prior to admission at the Ann & Robert H. Lurie Children’s Hospital of Chicago, when he developed daily fever accompanied by nausea, abdominal pain, phono- and photophobia. He was admitted to an outside hospital where an abdominal X-ray was notable for heavy stool burden. He underwent an intestinal “clean out,” which resulted in improved abdominal pain, and he was discharged home. Because of persistent headaches, nausea, and fever, he was treated with valproic acid with only mild initial improvement.

There was no history of rash, arthritis, conjunctivitis, diarrhea, or other symptoms. Family history was negative. The patient’s family lives in rural central Illinois. There is one dog at home. There is no significant travel history, although they do have a neighbor who travels occasionally to Macedonia. Two months previously, the patient visited a friend’s farm where he fed horses and was in contact with cows and chickens.

The patient’s medical history is interesting in that he had an episode of Epstein-Barr virus (EBV)-associated infectious mononucleosis 9 months earlier that was characterized by fever, fatigue, enlarged cervical lymphadenopathy, and splenic enlargement.

His evaluation prior to transfer included hemoglobin of 11.5 g/dL, white blood cell count of 9,800/mm³ with 59% neutrophils and 34% lymphocytes, and platelet count of 439,000/mm³. C-reactive protein and erythrocyte sedimentation rate were normal. Serum chemistries, hepatic transaminases, and pancreatic enzyme levels were normal. Respiratory viral panel and two blood cultures were negative. Antinuclear antibodies were present at level of 1:320. EBV viral capsid antigen (VCA)-immunoglobulin (Ig) M, and EBV VCA-IgG, and EBV nuclear antigen (EBNA) antibodies were all positive.

Growth parameters and physical examination were entirely normal.

Robert Listernick, MD, moderator: Let’s start out interpreting the EBV serology.

Anne Rowley, MD, pediatric infectious disease physician: Most of the time, simply ordering EBV-IgM and EBV-IgG VCA is sufficient for diagnosis. Both may be positive at the start of symptoms; IgM usually wanes after 3 months. EBNA antibodies usually don’t become positive for 6 to 12 weeks following onset of symptoms; their presence generally signifies past infection. EBNA antibodies remain present for life.

Julie Stamos, MD, pediatric infectious disease physician: I agree, although I’ve seen the EBV-IgM remain positive for as long as 6 months. Overall, I believe that these results are most consistent with his history of past infection.

Dr. Listernick: He has a true fever of unknown origin (FUO). How should we proceed?

Robert Tanz, MD, academic general pediatrician: Most importantly, he needs a thorough history and physical examination. Specific questions to be asked include a history of various exposures, such as tuberculosis (foreign travelers, inmates, homeless shelters, family members with chronic cough, etc), foreign travel (both the patient’s travel history as well as exposure to foreign travelers), animals, and raw/unpasteurized milk or meat.

Dr. Listernick: What would be your initial evaluation?

Dr. Tanz: If the history or physical examination pointed to a specific diagnosis, I would home in on that specific test. If not, a more gen-
general first pass would be to perform complete blood count with differential, urinalysis, serum transaminases, chest X-ray, and tuberculin skin testing. I would also culture blood, urine, and stool if the child had diarrhea. In this child, despite the lack of meningismus, I would be concerned about meningitis because of the headache and prolonged fever. Following neuroimaging to rule out the possibility of mass lesion, I would perform a lumbar puncture.

**Dr. Listernick:** The chest X-ray and tuberculin test were negative. Eventually, the patient was referred to an optometrist due to headaches and was found to have papilledema, which led to a second hospitalization at the outside hospital. Magnetic resonance imaging (MRI) of the brain was normal and he underwent lumbar puncture that revealed 244 white blood cells/mm³ (84% lymphocytes, 15% monocytes, 1% neutrophils) and 0 red blood cells, glucose of 26 mg/dL (low) and protein of 79 mg/dL (high). Gram stain, bacterial culture, and polymerase chain reaction testing for enterovirus, herpes simplex virus (HSV)-1, and HSV-2 were all negative. Interpretation?

**Sameer Patel, MD, pediatric infectious disease physician:** He has meningitis. But the chronicity of symptoms coupled with the lymphocytic predominance and his well appearance virtually eliminates the possibility of “run of the mill” bacterial meningitis. Delving a little deeper into the results, the most striking abnormality is hypoglycorrhachia, the profoundly low level of glucose in his cerebrospinal fluid (CSF).

**Dr. Listernick:** Why is hypoglycorrhachia so concerning?

**Dr. Patel:** It’s rarely low in viral meningitis save for mumps meningoencephalitis or meningitis due to lymphocytic choriomeningitis, neither of which he has given his chronic course. Hypoglycorrhachia suggests a far less common etiology such as fungal meningitis, or rheumatologic disease such as sarcoidosis. Hypoglycorrhachia is common in tuberculous meningitis that classically has a subacute course; however, he appears far too well for someone with 7 weeks of tuberculous meningitis.

If all else fails and a diagnosis continues to be elusive, leptomeningeal biopsy could be considered.

**Dr. Listernick:** One week after the previous hospitalization and lumbar puncture, he was re-hospitalized here. Repeat lumbar puncture revealed 165 white blood cells/mm³ (79% lymphocytes, 15% monocytes, 3% neutrophils), glucose of 22 mg/dL, and protein of 122 mg/dL. Gram stain, India ink stain, and cultures were all negative. Repeat MRI scan of the brain showed signal changes along the basal cisterns and subtle leptomeningeal enhancement. These were interpreted as highly non-specific findings that could be related to a variety of infectious, inflammatory, and neoplastic processes. The report ended with the radiologists’ mantra: “clinical correlation required.” He is now 8 weeks into his illness and has remained intermittently febrile. In the mornings, he has more severe headaches and nausea that improves by late afternoon. What is the thinking now?

**Dr. Stamos:** Even though infectious meningitis due to tuberculosis or fungus was still a strong possibility, we felt we needed to broaden our differential diagnosis to consider neoplastic and inflammatory conditions. We asked the oncologists to see him.

**Jason Fangusaro, MD, pediatric neuro-oncologist:** Meningeal disease without a neuroradiologically visible...
primary tumor would be exceedingly rare. The two main tumors that could possibly present in this fashion would be a primary leptomeningeal primitive neuroectodermal tumor (PNET) or primary leptomeningeal central nervous system (CNS) melanoma. Leptomeningeal disease could also conceivably represent metastatic spread of a non-CNS solid tumor to the brain. Finally, primary CNS leukemia might present in this fashion, though we rarely look at neuroimaging when making a diagnosis of leukemia. However, I think all of these possibilities are highly unlikely because I would expect a patient with meningeal cancer to clearly become progressively sicker over an 8-week period. This child sounds remarkably well. Also, his neuroradiologic findings are quite subtle compared with what we generally see in a child who has leptomeningeal cancer.

Dr. Listernick: How did you rule out cancer in this child?

Dr. Fangusaro: Cytologic examination of the CSF was negative for malignant cells. This exam can miss the presence of melanoma cells, so I asked the lab to perform a paraffin block and stain for melanin; this result was normal as well. If all else fails and a diagnosis continues to be elusive, leptomeningeal biopsy could be considered.

Dr. Listernick: Moving on, no rheumatologist was available today but I’d like to point out that many of the childhood rheumatologic diseases can be causes of chronic aseptic meningitis, such as this child had. These would include systemic lupus erythematosus, Behcet’s disease, and sarcoidosis. However, Dr. Fangusaro recommended performing a computed tomography scan of the chest, abdomen, and pelvis looking for primary solid tumor.

Dr. Fangusaro: I thought the likelihood of finding a solid mass that had metastasized to the brain was exceedingly small but it certainly was less invasive than a leptomeningeal biopsy.

Dr. Listernick: This proved to be quite prescient. The patient was found to have right hilar adenopathy and multiple nodules in the right lung, all unseen on previous chest X-ray.

Dr. Rowley: By all rights, he should have histoplasmosis, putting together the hilar adenopathy, lung nodules, and chronic low-grade meningitis. In addition, he lives in downstate Illinois, an endemic area for histoplasmosis.

Dr. Listernick: How does one establish the diagnosis of histoplasmosis?

Dr. Rowley: It depends upon the clinical scenario. Generally, we use a combination of tests, including serology, urine antigen detection, and cultures or biopsies of presumably infected tissue.

Dr. Listernick: His titers for Histoplasma yeast antibody were < 1:8 and for Histoplasma mycelial antibody were ≥ 1:64. Urine histoplasma and blastomyces antigens were both low-level positive. His CSF histoplasma titers were very high.

Dr. Rowley: These indicate that he has evidence of recent, active histoplasmosis. Classically, yeast antibody titers rise and fall first, followed by a rise in mycelial antibody. The high titer suggests more recent infection.

Dr. Listernick: And the urine results?

Dr. Rowley: The specificity of urine antigen testing for either of these fungal diseases is probably around 95%, although the sensitivity is somewhat lower. There is some cross-reactivity between the antigen tests for histoplasmosis and blastomycosis; this clinical scenario is much more indicative of histoplasmosis.

The following day, the CSF histoplasma antigen was found to be positive as well, dispelling any doubt about the diagnosis.

Dr. Listernick: I’ve never seen fungal meningitis except in really sick neonates or oncology patients.

Dr. Rowley: It’s not common but it does occur. It can be extremely indolent. In fact, one national expert told me that symptoms often may last for as long as a year before the diagnosis is made. In addition, as far as he can tell, half of the patients with CNS histoplasmosis are immunocompromised and half are normal.

Dr. Stamos: The fungal meningitis we think of as being more common in immunocompetent patients is due to Cryptococcus, which also can smolder for a long time before being diagnosed. His CSF cryptococcal antigen testing was negative. In California, coccidiomycosis might be the first diagnosis considered when confronted with a patient who has presumed fungal meningitis.

Dr. Listernick: Treatment?

Dr. Rowley: We recommended an initial course of intravenous amphotericin B, duration to be determined, followed by 1 year of oral itraconazole. There appears to be a significant relapse rate if patients are treated solely with amphotericin B for only 12 weeks, as has been recommended previously in the literature.

Dr. Listernick: So here’s the $64 question — is he immunocompetent?

Ramsay Fuleihan, MD, pediatric immunologist: As we learn increasingly more about the immune system, we continue to find specific immunologic defects that put patients at risk for specific infections. I have to wonder whether he has a defect in the innate immune system. One example would be a gain-of-function mutation
in *STAT1*, which leads to an overactive interferon-gamma signaling pathway that inhibits Th17 cells. These individuals have been found to be susceptible to a number of infections, including histoplasmosis.

**Dr. Listernick:** The following tests were normal: immunoglobulin levels, HIV testing, natural killer cell T-cell percentage, testing for both autoimmune lymphoproliferative syndrome and X-linked lymphoproliferative syndrome, and flow cytometry for chronic granulomatous disease. Routine white blood cell flow cytometry revealed that a marked elevation in the percentage of the patient’s lymphocytes express the gamma/delta T-cell receptor phenotype. What does this mean?

**Dr. Fuleihan:** Most T cells have alpha/beta receptors; the gamma/delta receptors are alternative T-cell receptors. This is a curious result because the remainder of the flow cytometry is normal. I’m not sure of its significance, but we sent testing to see if there are any functional T-cell problems. In other words, do the T cells work normally?

**Dr. Rowley:** There are data that suggest that the percentage of gamma/delta T cells may be elevated in fungal infections. So this may be a result, rather than a cause, of the histoplasmosis.

**Dr. Listernick:** Time will tell. I’ll let our audience know in the future if any functional immunologic abnormality is found. Thank you, everyone.

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**Key Learning Points**

1. In general, the diagnosis of Epstein-Barr virus (EBV) infection can be established by ordering immunoglobulin M and immunoglobulin G antibodies directed against EBV-viral capsid antigen.

2. The diagnosis of fever of unknown origin is best made by performing a thorough history and physical examination. Specific questions to be asked include a history of various exposures—tuberculosis (e.g., foreign travelers, inmates, homeless shelters, family members with chronic cough), foreign travel (both the patient’s travel history as well as exposure to foreign travelers), animals, and raw/unpasteurized milk or meat.

3. The differential diagnosis of chronic aseptic (bacterial culture negative) meningitis includes infection due to tuberculosis or fungi, as well as a number of rheumatologic and neoplastic diseases.