Aerospace Medicine Clinic

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You're the newly assigned flight surgeon attached to a 5th-generation fighter squadron trying to establish yourself as an approachable and competent member of the team. A healthy and experienced 41-yr-old male pilot walks into your office one day in October and tells you he's been experiencing fever, body aches, headache, and fatigue for 3 wk. He has been religiously self-medicating with 800 mg of ibuprofen 2–3 times daily, which has kept his symptoms at bay. However, after 7–8 h his symptoms reliably return.

At the onset, he noted a couple days of intermittent loose stools which have long resolved. He denies muscle tenderness, joint pain or swelling, or any lymphadenopathy or edema. His measured temperature at home has ranged from 99°F to 100.7°F, above his normal of about 98°F. He endorses intermittent, mild cough, but denies nasal congestion, postnasal drip, sinus pressure, sore throat, or Eustachian tube dysfunction. He denies eye redness or irritation, abdominal discomfort, pulmonary or cardiac symptoms, new back or neck pain, and skin changes or lesions. He has had some sweating with his fevers, but no drenching sweats or weight loss. He has purposely increased his fluid intake since symptoms began and has experienced 2–3 episodes of nocturia per night, but denies dysuria, flank pain, nausea, and vomiting. He has no known sick contacts and his wife and two preschool-aged children feel well. His only travel out of the country over the past year was several weeks in East Asia roughly 6 mo prior. He denies eating undercooked food or knowingly being bitten by any insects. He has never experienced these symptoms before. His symptoms have not interfered with his squadron duties and he has maintained his flying schedule of two sorties per week, which he states have been unaffected by his symptoms. Additionally, he plays soccer on weekends and has continued competing without difficulty.

A thorough physical examination reveals normal vital signs including a current oral temperature of 97.8°F. The remainder of his exam is unremarkable as well, without notable head, eyes, ears, nose, or throat, cardiopulmonary, abdominal, or neurological findings. There are no swollen joints, skin rashes, or lymphadenopathy.

1. What category of illness can give rise to this presentation?

   A. Malignancies
   B. Infections
   C. Systemic rheumatic disease
   D. All of the above

ANSWER/DISCUSSION

1. D. Without further information, it is helpful to think of this as a case of fever of unknown origin (FUO). The original definition of FUO comes from a 1961 case series involving 100 patients:[14]

1. Fever higher than 38.3°C;
2. Duration of at least 3 wk; and
3. Uncertain diagnosis after 1 wk of study in the hospital.

Of course, this pilot does not strictly meet even the modern definition of FUO, which eliminates inpatient evaluation.[15] In addition, 38.3°C translates to 100.94°F, a higher fever cutoff than the commonly used 100.4°F, which is also used in the definition of neutropenic fever.[4] Therefore, he only strictly meets one of FUO's criteria. However, given the clinical context, a healthy adult male with a fever syndrome lasting 3 wk and nonspecific history and exam findings, it is helpful to keep in mind the breadth of potential diagnoses as you decide how best to evaluate your aviator's presentation.

Infections represent the largest proportion of all fevers and the list of potential offenders is lengthy. Influenza, primary HIV infection, Epstein-Barr virus, cytomegalovirus, coxsackievirus, parvovirus, and adenovirus are all potential viral causes of fever and capable of producing nonspecific systemic symptoms. Bacteria are capable of infecting the central nervous system, sinuses, respiratory and GI tracts, skin, and other organs and can cause fever; in patients with established FUO, tuberculosis is the most common infectious etiology.[5] Occult abscesses are

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commonly found in the abdomen and pelvis. Osteomyelitis does not always have localizing symptoms and bacterial endocarditis will have negative blood cultures 2–5% of the time.[4] Fungi and parasites (such as malaria, protozoa, and amebae) are all less common but potential causes of fever that can last longer than a typical febrile illness. History and physical, as always, guide the evaluation.

Malignancies are a less common, although worrisome, etiology of protracted fever. Lymphoma, leukemia, renal cell carcinoma, and hepatocellular or other cancers that metastasize to the liver are the most common neoplasms associated with FUO and fever in general. Blood smear and/or imaging should be performed if there is high suspicion.

Finally, as the ability to detect certain infections has increased over the last century, systemic rheumatic diseases have emerged as the most common noninfectious etiology of FUO when a diagnosis is ultimately found.[5] Adult-onset Still's Disease is most common in young and middle-aged adults and is characterized by daily fevers, systemic arthritis, and an evanescent rash.[7] Giant cell arteritis should be considered in any adult above the age of 50, often presenting as headache, abrupt loss of vision, symptoms of polymyalgia rheumatica (which can occur without signs of vasculitis), unexplained fever or anemia, and a high erythrocyte sedimentation rate. It is estimated that about 15% of elderly adults with FUO are ultimately diagnosed with giant cell arteritis.[17] Polyarteritis nodosa, Takayasu's arteritis, granulomatosis with polyangiitis (Wegener's), and mixed cryoglobulinemia are other less common causes of FUO.[2] A diagnosis is never found in approximately half of patients with FUO.[13] Most of these patients have a good prognosis without sequelae.[9,19]

2. What should be the next step in this pilot's management?

   A. Continue flying status and follow up in 1 wk.
   B. Continue flying status and pursue further workup.
   C. Restrict him from flying status and follow up in 1 wk.
   D. Restrict him from flying status and pursue further workup.

ANSWER/DISCUSSION

2. D. Overall, prognosis for this pilot is good because of his proven ability to maintain full function and his syndrome remaining stable without progression. However, the most prudent decision at this juncture would be to restrict him from flying status while pursuing at least a brief workup. Diagnosis of FUO assumes that a decent effort has been made to figure out the etiology of his fever syndrome. Many of the conditions on the differential diagnosis are treatable and not all are self-limiting. A considerable amount of useful information can be gleaned from tests that provide results in a timely manner. Specific clinical scenarios will dictate how far you proceed with your initial evaluation. However, reasonable steps to consider include a complete blood count (CBC) with differential, blood cultures, chemistries, liver functions and transaminases, urinalysis (UA) with culture and microscopy, and a chest X-ray. Without the knowledge that certain etiologies are excluded, such as hematologic malignancies and severe infections, it would be unwise to allow him to continue flying a high-performance, single-seat fighter aircraft.

You tell him that you need to order some tests to determine what's going on. Your initial evaluation includes CBC, comprehensive metabolic profile, UA with culture, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), infectious mononucleosis screen (heterophile antibodies), cytomegalovirus and parvovirus serologies, malaria antigen test, and a blood smear evaluating for parasites (including malaria). By the end of the day, basic labs return and reveal ALT 373, AST 217, ESR 17, CRP 0.86, and a mild lymphocytosis (54.7%) with 14% atypical lymphocytes. The remainder of the CBC, comprehensive metabolic panel, UA, heterophile antibodies, and malaria antigen test are normal. You suspect an infectious etiology for this pilot's syndrome.

3. What category of infection most likely causes this laboratory profile?

   A. Parasitic
   B. Bacterial
   C. Viral
   D. Fungal

ANSWER/DISCUSSION

3. C. The laboratory profile, as well as history and physical, are most consistent with a viral etiology.[18] Viruses drive the TH1 response, aimed at intracellular pathogens, driving lymphocytosis and activation (observed as atypical lymphocytes). Parasitic diseases are not always this apparent, but may be expected to cause eosinophilia if driving febrile inflammation. Most bacterial pathogens tend to drive neutrophilia, if not frank leukocytosis, and are likely to drive higher inflammatory markers over several weeks. Although your pilot may have been exposed to endemic fungi during his training and travel, they are much less common and would require additional testing to evaluate.

A few days later the remainder of the results return, notable only for a positive cytomegalovirus (CMV) IgM.

4. What is the most likely cause of his febrile syndrome?

   A. Acute CMV infection.
   B. Acute viral hepatitis (A, B, C) infection.
   C. Alcoholic hepatitis.
   D. Nonalcoholic fatty liver disease.

ANSWER/DISCUSSION

4. A. Modestly elevated transaminases are frequent in CMV infection due to the tropism of most herpesviruses for hepatocytes.[20] Less commonly, alkaline phosphatase and total bilirubin elevations are present as well. Portal vein thrombosis is a rare complication of acute CMV-associated hepatitis.

The other conditions may produce a similar pattern, but history does not support alcohol use nor hepatitis B or C exposure potential. Hepatitis A can be acquired from local contaminated food consumption, but he has been vaccinated. Nonalcoholic liver disease tends to be insidious, marked by chronic transaminase elevation and stigmata of chronic liver disease rather than an acute-onset febrile syndrome.

Prevalence rates for CMV vary worldwide, with most estimates ranging from 45–100%.[3] Prevalence increases with low socioeconomic development, such as Africa and Asia.[12] It also increases with age, with a U.S. study finding a seropositivity rate of 36% in 6- to 11-yr-olds, increasing to 91% in those greater than 80 yr of age.[6] CMV infection can produce a wide variety of presentations.[8,16] Most newly acquired cases in immunocompetent individuals are asymptomatic, especially in children. However, organ-specific life-threatening complications can also present, particularly in immunocompromised hosts. CMV is the most common congenital viral infection.[10] Asymptomatic or symptomatic CMV infection during pregnancy increases the risk for hearing loss and long-term developmental delay in children.

When symptomatic, the most common syndrome is CMV mononucleosis (sometimes called monospot-negative mono). CMV mononucleosis differs from Epstein-Barr virus mononucleosis in that systemic symptoms typically predominate, while lymphadenopathy and tonsillitis are not as common.[9] Heterophile antibody tests are negative with CMV mononucleosis so CMV must be tested for by serology. Cardinal laboratory abnormalities present in both forms include an absolute lymphocytosis and greater than 10% atypical lymphocytes.[11] Treatment is supportive and antiviral therapy is rarely necessary. Symptoms usually resolve within days to weeks.

AEROMEDICAL DISPOSITION

This pilot's symptoms began to resolve in the days following his initial outpatient visit. By the time acute CMV infection was confirmed, his symptoms had completely resolved and he was no longer taking medication. He was advised to refrain from contact with pregnant women for the next couple of weeks as a precaution. Your pilot recovered uneventfully and without recurrence.

CMV infection or mononucleosis is not specifically disqualifying per medical standards of the Federal Aviation Administration nor the U.S. Army, Navy, or Air Force. However, all services provide for appropriate aeromedical decision-making in the event of a condition that affects an aviator's ability to safely operate an aircraft. For instance, Title 14 CFR § 61.53 prohibits operations in any flight crewmember capacity while suffering a medical condition or taking medication "that would make that person unable to meet the requirements for the medical certificate necessary for the pilot operation."[1] Your pilot uneventfully resumes his high level of performance without complications, sequelae, or requirement for a waiver.

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