CASE REPORT

Fever in returning travellers due to a noninfectious disease: Two case reports

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Abstract

Each year, increasing numbers of people from developed countries travel to developing countries. It is not rare for these travellers to experience illness during or following their trips. It has been estimated that fever is present in 25% of those who seek medical attention following travel. In the majority of cases, the focus of the investigations centre around an infectious etiology, which can lead to a delay in establishing the noninfectious cause of fever. Two cases of fever, which were due to a noninfectious disease, are reported in returning travellers.

Key Words: Fever; Noninfectious; Returning traveller

CASE PRESENTATIONS

Case 1
A 63-year-old Vietnamese man presented with fever, chills and nonbloody diarrhea three days after returning from a three-month trip to Vietnam. He developed fever, chills and rigors three days before presentation. The diarrhea had started 10 days prior, and it was accompanied by nausea and nonbloody emesis. He had spent time in both rural and urban settings, and reported no significant exposures, unusual activities, drugs or sexual activities. His immunizations were up to date; he was taking no medications and had not used antimalarial chemoprophylaxis. His past medical history was significant for untreated hepatitis C, genotype 1b, which was acquired from a blood transfusion.

On physical examination, the patient had a temperature of 39°C, but had no other abnormalities. Investigations revealed a hemoglobin level of 122 g/L, with a mean corpuscular volume of 108 fL; and a white blood cell count of 3.8 x 109/L, with a granulocyte level of 0.9 x 109/L and a platelet level of 108 x 109/L. The international normalized ratio was 1.2, and partial thromboplastin time was 32 s. The patient’s electrolyte levels; renal function; liver enzyme, bilirubin, glucose, albumin and pancreatic enzyme levels; thyroid function tests; and vitamin B12 and folate levels were normal. The patient’s urinalysis was bland; four sets of blood films were negative for malaria, and his tuberculosis skin test was nonreactive. Stool cultures and three sets of blood cultures were also normal. The patient’s urinalysis was bland; four sets of blood films were negative for malaria, and his tuberculosis skin test was nonreactive. Stool cultures and three sets of blood cultures were nonreactive.

The patient was started on intravenous ciprofloxacin and cefotaxime. Over the next two days, he defervesced, but required oxygen to maintain his saturations. A repeat chest x-ray showed a left-sided pleural effusion and left lower lobe atelectasis. Antibiotics were switched to intravenous levofloxacin and vancomycin. He subsequently became tachycardic and hypotensive, and went into respiratory distress requiring intubation, mechanical ventilation and vasopressor support. A high-resolution computed tomography scan of the chest, abdomen and pelvis revealed bilateral pleural effusions with atelectasis, multifocal patchy airspace disease and a small amount of free fluid in the abdomen.

Repeat bloodwork revealed a hemoglobin level of 95 g/L; a white blood cell count of 16.7 x 109/L, with a granulocyte level of 0.9 x 109/L and a platelet level of 108 x 109/L. The international normalized ratio was 1.2, and partial thromboplastin time was 32 s. The patient’s electrolyte levels; renal function; liver enzyme, bilirubin, glucose, albumin and pancreatic enzyme levels; thyroid function tests; and vitamin B12 and folate levels were normal. The patient’s urinalysis was bland; four sets of blood films were negative for malaria, and his tuberculosis skin test was nonreactive. Stool cultures and three sets of blood cultures were nonreactive.

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After three months of treatment, her hemoglobin level was 91 g/L. The patient reported that her fevers had subsided, but she continued to experience night sweats and fatigue. She had lost an additional 16 kg. Bone marrow biopsy showed changes consistent with myelofibrosis.

**DISCUSSION**

Illness after travel is a significant problem. Reviews (1-3) have suggested that 15% to 37% of travellers have health impairments after their return, with approximately 10% of all travellers ultimately seeking physician consultation. Fever is a common symptom in returned travellers, and it can be an important indicator of potentially serious disease. One large series (4) suggested that 28% of travellers reported fever as their primary reason for seeking care. The evaluation of the febrile returned traveller is often difficult because the infections that travellers acquire are often unusual or unfamiliar to most physicians, and the incubation period of many tropical and nontropical infectious diseases is variable.

The present report describes two cases of febrile returned travellers in which the final diagnosis was elusive and ultimately unrelated to the history of travel. In the first case presentation, a 63-year-old man presented to the emergency department with fever shortly after he had returned from a three-month trip to Vietnam. An aggressive search for an infectious etiology was prompted when initial blood work showed pancytopenia. However, his bone marrow biopsy revealed changes consistent with acute myelogenous leukemia and blast crisis. In the second case presentation, a 49-year-old woman presented with fever, fatigue and myalgias following a seven-day vacation to the Caribbean. Extensive investigation was undertaken, but the diagnosis was delayed by almost one year until the bone marrow biopsy revealed myelofibrosis. Interestingly, both patients defervesced before the final diagnosis was made. Although cultures were negative, this raises the possibility that an infectious agent may have responded to antibiotics in the first case and resolved on its own in the second. Earlier consideration of processes unrelated to travel may have spared the patients unnecessary investigations and possibly altered outcome.

In reviewing the English language literature, there were no published case reports emphasizing the role noninfectious diseases can play in mimicking infectious causes after travel. The data from those case series that provided useful information are summarized in Table 1 (5-12). The prevalence of noninfectious diseases as the cause of fever ranged from 0% to 4.8%.

**TABLE 1**

<table>
<thead>
<tr>
<th>Reference</th>
<th>Patients (n)</th>
<th>Adult (A), pediatric (P)</th>
<th>Country</th>
<th>Inpatient (I), outpatient (O)</th>
<th>Travel destination</th>
<th>Percentage with noninfectious etiology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parola et al (5)</td>
<td>613</td>
<td>A</td>
<td>France</td>
<td>I</td>
<td>Tropical</td>
<td>0.8</td>
</tr>
<tr>
<td>Antinori et al (6)</td>
<td>147</td>
<td>A</td>
<td>Italy</td>
<td>I</td>
<td>Tropical</td>
<td>4.8</td>
</tr>
<tr>
<td>Klein and Millman (7)</td>
<td>31</td>
<td>P</td>
<td>England</td>
<td>I</td>
<td>Tropical</td>
<td>3.2</td>
</tr>
<tr>
<td>West and Riordan (8)</td>
<td>162</td>
<td>P</td>
<td>England</td>
<td>I</td>
<td>Tropical/subtropical</td>
<td>0.6</td>
</tr>
<tr>
<td>O'Brien et al (9)</td>
<td>232</td>
<td>A</td>
<td>Australia</td>
<td>I</td>
<td>All areas</td>
<td>2.6</td>
</tr>
<tr>
<td>Ansart et al (10)</td>
<td>257</td>
<td>A</td>
<td>France</td>
<td>O</td>
<td>Tropical</td>
<td>0.0</td>
</tr>
<tr>
<td>Bottreau et al (11)</td>
<td>1743</td>
<td>A, P</td>
<td>Belgium</td>
<td>I, O</td>
<td>Tropical</td>
<td>2.2</td>
</tr>
<tr>
<td>Doherty et al (12)</td>
<td>195</td>
<td>A, P</td>
<td>England</td>
<td>I</td>
<td>Tropical</td>
<td>0.5</td>
</tr>
</tbody>
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The patient continued to have ongoing fatigue and muscle weakness over the next four months. While she initially indicated that she had no other accompanying symptoms, on further review, she admitted to night sweats and decreased energy and generalized weakness since her return. She reported no significant exposures, no unusual activity, no drugs and had a monogamous relationship with her husband of 25 years. Her immunizations were up to date, and she had not received travel advice or used any prophylaxis.

On physical examination, she was afebrile with Medical Research Council grade 4/5 weakness of the hip flexors, dorsiflexors and plantar flexors. The remainder of her neurological examination was unremarkable. Her bloodwork revealed a hemoglobin level of 93 g/L and a platelet count of 512,000/μL. Her electrolyte levels, renal function, coagulation parameters, thyroid function and creatine kinase levels were normal. The patient's albumin level was 29 g/L, aspartate aminotransferase level was 127 U/L. Her electrolyte levels, renal function, coagulation parameters, thyroid function and creatine kinase levels were normal. The patient's liver enzymes had normalized, except for an alkaline phosphatase of 186 U/L; albumin level was 28 g/L and C-reactive protein level was 135 mg/L. Twenty-four hour urine analysis revealed 290 mg of protein. The colonoscopy and endoscopy did not show any pathology. The patient was started on oral iron supplements.

Dysplasia of all cell lines consistent with acute myelogenous leukemia and confirmed by flow cytometry. The patient died of multiorgan failure three days later.

**Case 2**

A 49-year-old previously healthy woman presented with fever, fatigue and myalgias two weeks after a seven-day vacation to the Caribbean. She reported intermittent febrile episodes, fleeting myalgias in her arms and legs, decreased energy and generalized weakness since her return. She reported no significant exposures, no unusual activity, no drugs and had a monogamous relationship with her husband of 25 years. Her immunizations were up to date, and she had not received travel advice or used any prophylaxis.

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The noninfectious causes identified included four cases of connective tissue disease (9) and one case report each of Reiter's syndrome (5), acute myeloid leukemia (7), Kawasaki's disease (8), erythema nodosum (9) and thyrotoxicosis (9). Malignancy should be considered in the differential diagnosis of fever of unknown origin in the traveller.

A number of large studies (9,13) have generally highlighted malaria, gastroenteritis, dengue fever, typhoid, respiratory tract infections and hepatitis as the most frequent causes of illness. These studies emphasize the importance of the timing of the fever and the destination in guiding diagnosis, as well as empirical therapy. Thus, the approach to the patient traditionally involves taking a careful travel history with geographical and activity-based assessment.

The cause of fever after travel remains undiagnosed in approximately 25% of cases (4,11). Fortunately, those patients who have fevers of an unknown cause generally recover uneventfully (11). We highlight that overemphasizing the travel history can sometimes lead the clinician away from establishing the correct diagnosis. Noninfectious causes of fever after travel are not common, but they should be considered once life-threatening, treatable or transmissible infections have been excluded.

**REFERENCES**
