Correspondence

Importation of diseases following the relaxation of quarantine regulations

Sir,
In their editorial (Q J Med 1999; 92:683–7) Bellamy and Salmon mention the veterinary and zoonotic pathogens which may be imported from mainland Europe and rabies-free (‘designated’) areas, when the quarantine laws are relaxed. In fact, veterinarians in the UK will have to be prepared for infections and infestations from further afield.

British pets could visit any continent and return home apparently legally, provided that they leave and re-enter the UK via a designated country. Similarly, pets from Asia, Africa or the Americas will be able to enter the UK if they have been in a designated country where they could be vaccinated against rabies and have a blood test 6 months before arriving in Britain. It will not be possible to confirm that an animal has remained in Europe during that 6-month period.

The potential risks of importation of potential pathogens from all over the world should be thoroughly explored and assessed before the flood gates are opened.

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Seasonal variation in CHD

Sir,
That there is a seasonal variation in the manifestations of coronary artery disease as recently reported in the QJM1,2—a winter peak and summer trough in morbidity and mortality—is a universal phenomenon. The same findings have been reported from mainland China3 and Taiwan.4

The investigators from the Guangzhou Municipal Cardiovascular Co-operative Group5 analysed 943 patients with acute myocardial infarction admitted between 1976 and 1980 to 18 hospitals in Guangzhou, which is better known to the outside world as Canton.6 They found the peak incidence to be in the winter months—January, February, April and October—and the lowest incidence in August when typhoons were most frequent. Using regression analysis, they also found the incidence of acute myocardial infarction to increase under low humidity.

Therefore there is a definite meteorological influence on the incidence of acute myocardial infarction. But there is more to the meteorological parameters than just the ambient temperature. For example, Ruhenstroth-Bauer et al.7 from Germany found a significant positive correlation between the onset of acute myocardial infarction and 28 kHz atmospherics. Ku et al.8 from Kaohsiung, Taiwan, reported absence of a seasonal variation in myocardial infarction in a region without temperature extremes.

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5. Guangzhou Municipal Cardiovascular Cooperative Group. A preliminary analysis on the relationship of the incidence of...
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Serum transferrin receptor assay in iron deficiency anaemia and anaemia of chronic disease in the elderly

Sir,

More important than the differentiation between iron deficiency anaemia (IDA) and the anaemia of chronic disorders (ACD) is the distinction which often needs to be made between the coexistence of IDA and ACD vs. the sole diagnosis of ACD. Therefore, the issues raised by Chua et al.¹ need to be ‘fine tuned’ through the use of the ratio serum TfR/log ferritin, the so-called ‘TfR-F’ index.² In one study, the ratio achieved statistically significant separation between iron-deficient patients with coexisting ACD vs. patients with the sole diagnosis of ACD. In that study the ‘gold standard’ for the diagnosis of iron deficiency was the absence of stainable iron from a bone-marrow aspirate.² Although the study comprised 129 patients, including 64 with ACD and 17 with combined ACD and iron deficiency, no mention was made of the age range, and it is this omission which would justify embarking on a comparable study in the elderly age group.

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References


Recurrent and prolonged fever in asplenic patients with human granulocytic ehrlichiosis

Sir,

The ehrlichioses are emerging zoonotic infections transmitted by ticks and caused by obligate intracellular organisms of the genus Ehrlichia. Two forms of human infection have been distinguished: human monocytic ehrlichiosis (HME), caused by E. chaffeensis¹ and human granulocytic ehrlichiosis (HGE), caused by an organism shown to be phylogenetically similar to E. equi and E. phagocytophilia.² The first report of human ehrlichiosis in the US was published in 1987.³ These increasingly recognized infections present a difficult diagnostic challenge as a result of their protean clinical manifestations and the absence of a reliable laboratory marker, especially in the acute stage of the disease.

Although HGE is most commonly considered in cases of brief, acute febrile illness, it can take an unusual clinical course, especially in cases of coinfection with other parasites, such as Babesia or Borrelia. The disease can also take a different course in asplenic patients. We describe two cases of HGE in asplenic patients who presented with unusual features including prolonged and/or recurrent fever, atypical neurological manifestations and leukocytosis. To our knowledge, this is the first report of HGE in asplenic individuals.

Patient 1, a 71-year-old White male was admitted for evaluation of fever of unknown origin associated with acute mental status changes. For 6 weeks prior to admission, he had been suffering from recurrent episodes of fever, anorexia, diarrhea, and mild diffuse abdominal pain. More recently, the patient had developed progressive unsteadiness of gait and confusion. Prior to admission he had undergone an extensive diagnostic evaluation including CT scans of the brain, abdomen, and pelvis, ultrasound of the abdomen, serial chest radiographs, cultures of blood and stool, and C. difficile toxin screening, all with negative results. Several courses of empiric treatment with ciprofloxacin, ceftazidime, vancomycin and
metronidazole failed to improve his condition. His past medical history was significant for polycystic kidney disease, end-stage renal disease on hemodialysis, and splenectomy following splenic rupture 2 years prior to the current presentation. He was unaware of any recent exposure to ticks. The patient was diagnosed with HGE on the basis of an examination of peripheral blood smear revealing characteristic intraneutrophilic morulas and white blood cell count (WBC) of 14,400/mm³. His condition dramatically improved within 24 h after the initiation of treatment with i.v. doxycycline, and he was discharged 3 days later on oral doxycycline with the dose adjusted for his creatinine clearance (100 mg/day). At that time he was completely free of symptoms.

However, he was readmitted to our hospital in 12 days after his initial discharge, with recurrence of mental status changes and new onset of a right parietal syndrome (acute confusion, left hemi-inattention, left-sided weakness, and left hemianopia). CT of the brain, cerebrospinal fluid analysis, carotid ultrasound, echocardiography, and transcranial doppler were performed, and were unremarkable. At that time the examination of peripheral blood smear was negative for intraneutrophilic morulas. Once again, the patient improved with complete resolution of all of his neurological deficits within 24 h of the administration of a full dose (200 mg/day) of i.v. doxycycline and was uneventfully discharged from the hospital 2 days later. Shortly thereafter, the patient was readmitted with severe gastrointestinal bleeding from an open duodenal ulcer. Despite the low-flow state during hypovolaemic shock, the patient never experienced focal neurological signs again.

Patient 2, a 30-year-old man, presented to our hospital with a 2-week history of fever, headaches, and body aches. Prior to admission, the patient was treated with oral clarithromycin for 7 days. He initially improved, but severe daily headaches associated with high fevers, rigors, and night sweats relapsed when the antibiotic was discontinued. He denied any known recent tick bites. The patient is a hunter, and 1 week prior to the onset of symptoms he had killed and skinned a deer. His past medical history was significant for splenectomy at age 16 following a motor vehicle accident and psoriasis. The physical examination revealed maculo-papular rash involving the neck and upper torso and bilateral conjunctival injection. Laboratory evaluation revealed hyponatremia (129 mmol/l) and WBC of 16,300/mm³. An examination of peripheral blood smear revealed characteristic intraneutrophilic morulae. The patient was started on oral doxycycline 100 mg twice a day with rapid improvement in his symptoms. He was discharged home 24 h later to complete 10 days of therapy with oral doxycycline.

Peripheral blood smears and buffy coats of both patients were made and later stained with Wright stain preparation (Sigma) in the Section of Haematology at Danbury Hospital’s Department of Pathology and Laboratory Medicine. Serum samples of both patients were tested at Danbury Hospital’s Department of Pathology and Laboratory Medicine, Section of Immunology, using a solid-phase enzyme immunoassay to detect serum antibodies to Borrelia burgdorferi. Testing for the antibodies to HGE agent (which appears to be identical to E. equi) was performed using an antibody immunofluorescence assay at the State of Connecticut, Department of Public Health, Division of Laboratory Services. Babesia microti antibody titre detection was performed at Boston Biomedica Clinical Laboratories using an antibody immunofluorescence assay.

Upon admission, examination of the peripheral blood smears of both patients revealed presence of characteristic intraneutrophilic morulae. For patient 1, the serological markers in acute serum were positive for HGE (IgG > 1:5120) and babesiosis (IgG = 1:512, IgM = 1:512), and negative for Lyme disease. The examination of the peripheral blood smear of patient 2 revealed toxic granulations and intracellular morula formation in neutrophils (Figure 1). His monospot and babesia serology (< 1:64 IgG and IgM titres) came back negative, the HGE test (IgG > 1:2048) was positive.

Ehrlichiosis is rarely considered in the differential diagnosis of prolonged or recurrent fever; however, Roland et al. described four cases of prolonged fever in patients with ehrlichiosis. Another report of a single patient infected with Ehrlichia who developed relapsing (saddleback) fever was recently published. Organisms of the genus Ehrlichia also cause prolonged fever in animals.

Both of our patients were asplenic. This is particularly interesting since a growing body of evidence from the veterinarian and basic research literature suggests that the spleen plays a significant role in protection against ehrlichiosis. Hodzic et al. found the organism in the spleen of all mice inoculated with Ehrlichia isolated from a patient with HGE. At necropsy, splenomegaly was consistently present in all infected mice examined 10 days after inoculation, but spleens recovered their normal size at later intervals. We hypothesize that individuals deprived of protective function of the spleen may develop some atypical features in the course of HGE.

Our asplenic patients had unusually prolonged fever that quickly resolved with doxycycline treatment. They also had remarkably elevated WBC count, contrary to the neutropenia ordinarily observed in acute HGE.
In the case of patient 1, babesiosis could play a significant role in the clinical presentation of prolonged fever. Babesiosis is known to follow a more severe course in asplenic patients. At the same time, characteristic intraerythrocytic ring forms were not observed on our patients peripheral blood smears and he did not develop the haemolytic anaemia commonly observed in babesiosis. After institution of treatment with doxycycline, our patient promptly recovered, suggesting either that the infection with Babesia was entirely subclinical or unusually responsive to tetracyclines.

CNS manifestations occur in up to 25% of patients infected with E. chaffeensis. Confusion, meningitis, ataxia, and, rarely, vertigo and seizures have been reported. Morulae in cerebrospinal fluid granulocytes or monocytes have been described, indicating the ability of Ehrlichia species to penetrate into the cerebrospinal fluid. A remarkable case of meningismus, altered mental status, unilateral arm weakness, and partial Bell’s palsy secondary to E. chaffeensis infection was reported in 1997, in which a brain biopsy revealed perivascular and intramural mononuclear cell infiltrate in the leptomeninges, and Virchow-Robin spaces filled with mildly atypical lymphoid cells.

The development of focal signs could arguably represent a transient ischemic attack (TIA) in our patient 1. Nevertheless, we attributed the right parietal syndrome to CNS involvement by Ehrlichia, taking into consideration the remarkable improvement of the neurological deficit with appropriate antibiotic therapy. A negative diagnostic investigation and lack of recurrent neurological symptoms when the patient subsequently developed severe hypovolemia secondary to gastrointestinal blood loss also argued against a diagnosis of TIA.

In summary, we believe our case reports provide a good example of how variably HGE can manifest itself and bring to attention the possibility of particularly unusual presentations and protracted courses in the setting of asplenic patients. We propose that HGE should be added to the list of potential causes of overwhelming postsplenectomy infections.

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