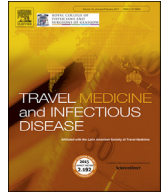




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Epstein-Barr virus and cytomegalovirus mononucleosis: Important causes of febrile illness in returned travellers

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ABSTRACT

Background: Diagnosing the cause of fever in the returned traveller is challenging. Efforts often focus on identifying 'exotic' pathogens. Primary Epstein-Barr virus (EBV) and cytomegalovirus (CMV) infections cause clinical features that overlap with many exotic pathogens. The age-matched seroprevalence of both EBV and CMV is greater in tropical than temperate areas. We describe the clinical and laboratory features of returned travellers diagnosed with primary CMV and EBV syndromes.

Methods: Patients with laboratory-confirmed primary EBV and CMV infections who had attended the Hospital for Tropical Diseases (HTD), London between 1st October 2011 and 1st October 2016 were identified. Clinical and laboratory data were obtained and analysed.

Results: Twenty-two patients with primary EBV infection and 31 with primary CMV infection were identified. The commonest presenting features of both infections were fever (81.1%), headache (50.9%) and arthralgia/myalgia (49.1%). Cervical lymphadenopathy was seen more frequently with EBV than with CMV (59.1% vs. 25.8%, $P = 0.02$). Transaminitis (79.2%) and lymphocytosis (52.8%) were the commonest laboratory abnormalities in both groups.

Conclusions: Primary EBV and CMV infections are important causes of febrile illness in returning travellers. Identification of these pathogens prevents unnecessary, expensive investigations for more 'exotic' pathogens and impacts clinical management for example facilitating prognostication and antimicrobial stewardship.

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1. Introduction

Many infections in returning travellers present with an 'undifferentiated fever' and early diagnosis is difficult when relying on clinical features and initial baseline blood test results. The challenge is in deciding which tests to perform subsequently, and empiric therapy. Undertaking a full repertoire of testing including the gamut of 'exotic' pathogens is expensive and may not be readily available.

Epstein-Barr virus (EBV) and human cytomegalovirus (CMV) are double-stranded DNA viruses belonging to the family Herpesviridae. Following primary EBV or CMV infection, these viruses establish lifelong, latent infection with frequent intermittent shedding of virus in bodily secretions. Transmission typically occurs through exposure to bodily fluids of an infected person including saliva, genital secretions, breast milk and urine (typically

from babies). Both viruses are extremely common worldwide with seroprevalence rates in adults of 45–100% for CMV and >90% for EBV [1,2]. Geographical variations exist in age of acquisition and overall seroprevalence of these infections. In temperate countries, EBV seroprevalence rates are declining, and the age of primary infection is increasing [3]. Higher CMV seroprevalence rates have been observed in areas of lower socioeconomic status [4]. The risk of EBV, CMV, HIV and *Toxoplasma gondii* acquisition by Europeans from travel to tropical areas has been previously described [5,6].

Primary EBV and CMV infections are usually diagnosed on the basis of serology and/or DNA detection by PCR. In primary EBV infection, IgM and IgG directed against the viral capsid antigen (VCA) usually appear at the time of onset of clinical symptoms [7]. EBV VCA IgM typically disappears within weeks but may persist for several months. EBV VCA IgG remains positive lifelong. In primary CMV infection IgM is usually detectable at symptom onset and usually declines over weeks to months, and CMV IgG persists for

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life [8]. Most primary EBV and CMV infections are associated with a self-limiting illness with features including fever, fatigue, malaise, pharyngitis, cervical lymphadenopathy, hepatosplenomegaly and a rash. Haematological and biochemical blood profiles may reveal a lymphocytosis, thrombocytopenia and/or a hepatitis [9]. Children are often asymptomatic or may suffer from a mild flu-like illness. A severe illness associated with primary infection occurs predominantly in the immunosuppressed. In the immunocompetent EBV may rarely be complicated by splenic rupture [10] and rare complications from both EBV and CMV infections includes upper airway obstruction, meningoencephalitis, Guillain-Barré syndrome, myocarditis and fulminant hepatic failure [10,11].

Primary EBV and CMV infections share common presenting features with many tropical infections including malaria, arboviral infections, rickettsial infections, leptospirosis and Q fever. It is often not possible to reliably distinguish between EBV, CMV and vast array of other viral and 'exotic' pathogens on the basis of clinical presentation. Investigating for the full range of exotic pathogens is often costly and time-consuming, whereas EBV and CMV testing is cheap and available in most hospitals. Identifying clinical and laboratory features suggestive of EBV and CMV infection should help direct rational testing for febrile returned travellers.

2. Objectives

To describe the clinical and laboratory profiles of returned travellers diagnosed at a regional tropical medicine centre presenting with primary EBV and CMV infections and to use these data to identify clinical and laboratory features suggestive of primary EBV and CMV.

3. Methods

3.1. Study setting

The Hospital for Tropical Diseases (HTD) is a tertiary referral centre for infectious and tropical diseases based at University College London Hospitals (UCLH), UK. The HTD provides inpatient care, a national clinical advice service and an emergency walk-in clinic for acutely unwell returned travellers.

3.2. Study design

Laboratory-confirmed cases of primary EBV and CMV infections seen at the HTD between 1st October 2011 and 1st October 2016 were identified retrospectively. Demographic, clinical and laboratory data were acquired from electronic patient records and pathology systems. Primary EBV infection was diagnosed with positive serum EBV VCA IgM positive by enzyme immunoassay (EIA) with or without EBV DNA detected in blood using a real-time multiplex (CMV/EBV/adenovirus) polymerase chain reaction (PCR) quantitative assay. Primary CMV infection was diagnosed with positive serum CMV IgM by EIA with or without CMV DNA detected in blood using a real-time multiplex (CMV/EBV/adenovirus) PCR quantitative assay. Samples were also tested for IgG antibodies (EBV VCA IgG, Epstein-Barr nuclear antigen IgG and CMV IgG). Where further diagnostic confirmation was required, CMV IgG avidity testing was performed.

3.3. Exclusion criteria

Cases were excluded if:

1. there was no documented travel abroad within the preceding 6 months.

2. both EBV VCA IgM and CMV IgM were positive but virus-specific PCR, IgG avidity or IgG seroconversion were not used/able to establish the diagnosis. Primary EBV infection can lead to the production of IgM antibodies that may also bind to antigens used in CMV IgM diagnostics assays (and vice-versa) thereby producing cross-reactivity [12].

3.4. Statistical analysis

The demographics, clinical and laboratory features of patients with CMV and EBV infection were compared using SPSS (Statistics for Windows version 24.0 (IBM, Armonk, NY)). The Mann-Whitney *U* test was used for the analysis of continuous variables and the Pearson's chi-squared test for categorical variables with a two-tailed *P*-value < 0.05 considered statistically significant.

4. Results

Twenty-two cases of primary EBV infection and 31 cases of primary CMV infection were identified during the 5-year study period. Primary EBV and CMV infections therefore comprised 3.5% (53/1507) of all our unwell returned traveller episodes during the study period. Demographics and travel history of patients with primary EBV and CMV infections are summarised in Table 1, and clinical features in Table 2. Patients were aged from 18 to 62 years. None of the 53 patients in this study were known to be immunocompromised.

Patients with primary EBV and CMV had most commonly visited Asia (50.0% and 45.2%) and Africa (22.7% and 29.0%). Patients with primary CMV infection were older than those with primary EBV infection (*P* = 0.001). The two groups did not otherwise differ significantly with respect to demographic or travel details.

Nine (40.6%) patients with EBV and 18 (58.1%) of patients with CMV had seen another healthcare professional for this episode of illness prior to attending the HTD, and several had undergone extensive investigation including abdominal ultrasound and CT scans, neuro-imaging, lumbar puncture, and a referral for a cervical lymph node biopsy. These investigations commonly identified splenomegaly, but no other pathology.

The most common presenting features for both EBV and CMV infection (Table 2) were fever (77.3%, 83.9%), headache (54.5%, 48.4%) and arthralgia/myalgia (40.9%, 54.8%). Lymphadenopathy was significantly more commonly reported in patients with EBV than those with CMV (59.1% vs. 25.9%, *P* = 0.015). There were no statistically significant differences between the two groups with regards to any other clinical features.

The most common laboratory abnormality at presentation in both EBV and CMV infection was an elevated alanine transaminase (ALT) (81.8%, 77.4%) and the median/maximum ALT in primary EBV and CMV infections were 130/1096IU/L and 99/1215IU/L, respectively. A lymphocytosis (54.5%, 51.6%) was the second commonest laboratory abnormality at presentation with primary EBV and CMV infection. There were no statistically significant differences between the two groups with regards to laboratory parameters.

In addition to serological tests, PCR was performed in some patients, either at clinician request or to confirm an initially ambiguous serological result. EBV DNA was detected in all 8 patients for whom this was requested and CMV DNA was detected in 11 of 15 patients. EBV DNA levels ranged from positive below the lower limit of quantification (100 copies/ml) to 52,000 copies/ml. The viral load appeared related to symptom duration, with the highest viral load being from a patient with an 8-day illness, and the lowest from a patient with an illness duration of >2 months. CMV DNA levels ranged from positive below the lower limit of quantification (<100 copies/ml) to 5500 copies/ml.

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