Case Reports

Infectious Mononucleosis Hepatitis; An Unwelcome Present for Father Christmas

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Abstract

We describe a case of infectious mononucleosis (IM) hepatitis occurring in an elderly thespian, who had recently played the role of 'Father Christmas'. We discuss the importance of differing clinical manifestations in older and younger age groups, the changing epidemiology of Epstein Barr (EB) infection within the United Kingdom and the role of different virology tests in establishing a diagnosis. Raised awareness of this changing pattern of disease could prevent unnecessary investigation and consequent potential iatrogenic complications.

Keywords

Infectious Mononucleosis, Hepatitis.

Key Points

- The pattern of infection with IM varies between 'developed' and 'developing' countries. In 'developed' countries such as the United Kingdom older patients may remain disease susceptible.
- The pattern of disease in older patients with IM may differ from younger patients often with greater severity of illness and increased incidence of hepatitis, hepatomegaly and jaundice.
- Monospot screening tests are highly specific but the sensitivity is low and negative results may mislead especially where the clinical presentation is atypical.
- This case illustrates the importance of repeated and more specific virology testing in diagnosing acute EBV infection

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Case report

An eighty three year old man presented to the medical admissions unit having fallen at home. One week prior to admission he had developed rigors, fever and nausea and had received clarithromycin 500mg twice daily for a presumed chest infection. Two days later he began to fall when standing and the antibiotics were discontinued. He remained hot and shivery, developed loose stools, pleuritic type chest pain and had a further fall which precipitated his admission.

His past medical history included hypertension, cerebrovascular disease, ischaemic heart disease, asthma and asymptomatic gall stones. Before admission he was taking aspirin, propranolol, nifedipine, dipyridamole, simvastatin and co-codamol.

At presentation he was apyrexial but dehydrated with blood pressure (BP) 118/71 mmHg lying, 92/50 mmHg sitting. Chest and abdominal examinations were normal. Investigations showed hypokalaemia and abnormal liver biochemistry (Table 1). Chest X-ray was normal, ECG showed left ventricular hypertrophy. A working diagnosis of viral gastroenteritis was made and the antihypertensives and simvastatin were discontinued. The patient initially improved after receiving intravenous fluids.

Two days after admission he again deteriorated with rigors and collapse, pulse 120, BP 90/60 mmHg, a temperature of 38.2°C and described a new onset right hypochondrial pain. Liver biochemistry had worsened. A diagnosis of bacterial cholangitis was considered and the patient was treated with intravenous gentamicin 320 mg once daily, amoxicillin 500mg three times daily (tds) and metronidazole 500mg tds. Ultrasound of upper abdomen showed multiple stones within a thin walled gallbladder. Liver, pancreas and spleen appeared normal.

Despite aggressive fluid resuscitation and antibiotics his condition remained an increasing concern requiring admission to the high dependency unit. Virology was requested. The patient was negative for hepatitis B and C and screening monospot for IM was also negative. Too unwell for immediate endoscopic retrograde cholangiopancreatography (ERCP), he underwent magnetic resonance cholangiopancreatography (MRCP) which showed no stones in a non dilated common bile duct. Abdominal CT showed no other intra-abdominal pathology with only minor abdominal lymphadenopathy and a spleen that was upper limit of normal size. Fifteen

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Table 1. Blood results (days after admission).

	Day 1	Day 5	Day 10	Day 18	Day 20	Day 35
Albumin g/L	34	31	28	20	21	26
Alk P iu/L	312	609	1416	1439	1496	325
ALT iu/L	186	194	266	179	206	29
Bilirubin umol/L	22	44	116	121	126	23
Haemoglobin g/L	15.6	12.4	13.3	9.1	10.5	11.6
WCC (x10^9/L)	5.5	5.4	10.2	6.3	8.1	7.7
Neurtophils (x10^9/L)	4.48	3.14	3.6	2.21	3.45	5.1
Lymphocytes (x10^9/L)	0.67	1.93	5.95	3.59	4.25	1.99
Platelets (x10^9/L)	134	190	233	223	203	223
INR	1.1	1.1	1.0	1.3	1.2	1.0

days after admission and with continuing swinging temperatures and hypotension the patient underwent an ERCP and sphincterotomy. A small stone was removed from a non-dilated duct.

He at last began to improve but two days later he suddenly collapsed complaining of left pleuritic chest pain. CT pulmonary angiogram showed no evidence of thromboembolic disease but now showed an enlarged spleen. The patient's haemoglobin subsequently fell 3 grams and the presumptive diagnosis was upper GI haemorrhage secondary to the sphincterotomy.

At this point further virology and polymerase chain reaction (PCR) results revealed acute Epstein-Barr virus infection (EBV). PCR showed 15750 copies/ ml. EBV capsid IgM (VCA) was positive, EBV nuclear antigen IgG (EBNA) was negative. Cytomegalovirus testing was negative. A diagnosis of EBV hepatitis and cholestasis was made. The patient subsequently made a full recovery.

Our patient unluckily had an impressive white beard that had resulted in him playing the role of Father Christmas at the local primary school three weeks prior to his illness. In retrospect it is likely that this is how he contracted EBV

Discussion

Infectious mononucleosis is caused by a herpes virus that is spread by close contact between susceptible persons and EBV shedders. The pattern of infection with IM varies between developed and developing countries and between differing socioeconomic groups.[1] Worldwide approximately 90- 95% of adults eventually become EBV-seropositive. In developing countries and lower quartile socioeconomic groups seropositivity approaches 100% by age four. In the United Kingdom peak incidence of infection occurs in the fifteen to twenty four year old age group and data suggest that IM cases may be occurring later in life[2] and with increasing severity of illness.

The typical features of IM including fatigue, fever, pharyngitis and lymphadenopathy may not occur in the very young or older patients. Children may be asymptomatic while older patients tend to experience myalgia and longer lasting temperatures. Lymphadenopathy and pharyngitis are less common in older patients while hepatomegaly and jaundice are more common.[3,4] Rarely hepatitis can be fatal[5] and EBV is one of the recognised infective causes of haemophagocytic lymphohistisocytosis which also carries a high mortality rate[1].

The commonest laboratory finding in IM is a lymphocytosis and some patients, including ours, have a relative neutropenia and/ or thrombocytopenia. Lymphocytosis, however, did not develop in this patient until 10 days after admission. Elevated aminotransferases are also common and generally self limiting.[5,6] Our patient had progressive and severely abnormal liver biochemistry. Although other diagnoses (Table 2) including EBV and drug induced jaundice were considered our initial working diagnosis was cholelithiasis. This diagnosis was based on symptoms compatible with cholangitis and the presence of gall bladder stones.

Because of failure to improve clinically our patient eventually underwent ERCP and sphincterotomy and although a small common bile duct stone was found, we believe in retrospect that this was irrelevant to his illness.

Our patient had had an MRCP prior to this, an investigation with a reported sensitivity for the diagnosis of CBD stones of over 89%, with a higher specificity rates of 98-100%, with a positive predictive values of 84-100% and a negative predictive value of 99%. The decision to proceed to ERCP in the absence of an alternative diagnosis and a deteriorating clinical status was probably justified. However if the serological diagnosis of EBV had been confirmed, ERCP would not have been performed we would have avoided the subsequent complications that our patient experienced.

We diagnosed EBV infection relatively late during our patient's admission because of the absence of a typical presentation and a negative screening heterophile antibody test.

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Table 2. Differential diagnosis of painless cholestatic liver biochemistry in the elderly with non dilated biliary tree.

Extra Hepatic cholestasis
- CBD stones (either early biliary obstruction or stone passed)
- Cholangiocarcinoma
- Primary sclerosing cholangitis

Intrahepatic cholestasis
- Primary liver disease
  - Primary biliary cirrhosis
  - Ig G4 cholangiopathy
- Drug induced liver injury
  - Augmentin
  - Erthromycin
  - Tricyclic antidepressant therapy
  - ACE inhibitors
  - H2 Antagonists
- Viral Hepatitis
  - Cytomegalovirus
  - EBV
  - HIV
- Hepatic venous outflow obstruction
  - Right heart failure
  - Hepatic vein thrombosis
  - Small vessel veno-occlusive disease
- Space occupying liver lesions
  - Liver abscess
  - Metastatic disease
- Infiltrative diseases
  - Lymphoma
  - Leukaemia
  - Granulomatous liver disease (TB/Amyloid/Sarcoid)
- Systemic causes
  - Total parenteral nutrition
  - Hyperthyoidism

The "monospot" screening test is a latex agglutination test that utilises the reaction of heterophile antibodies to antigens on horse erythrocytes. A positive result is highly specific but the sensitivity is low, particularly in the early stages of illness, with 25% negative results within the first week of symptoms falling to 5% at three weeks.[7] With high clinical suspicion it is important to either repeat early negative screening tests or to send more specific antibody tests.

IgM and IgG antibodies directed against the EBV capsid antigen (VCA) have high sensitivity (97%) and specificity (94%).[8] IgM VCA are generally present at the onset of clinical symptoms and disappear within three months. They are useful therefore as indicators of acute illness. IgG VCA may persist for life.

IgG antibodies directed against EB viral nuclear antigen (EBNA) appear later at around six to twelve weeks of symptomatic illness and persist for life. Their presence early during illness excludes acute infection.

PCR assay of blood is positive in over 75% acute infections becoming negative post primary infection.[9]

Our patient was initially monospot negative. However a positive IgM VCA and negative IgG EBNA together with PCR positive assay later confirmed an acute infection. In retrospect we were misled by the age of our patient, his known biliary stone disease and the negative IM monospot screening test. Increasingly older members of the UK adult population remain EBV susceptible and close contact with EBV infected children who may well be asymptomatic may result in atypical and severe illness.

We also considered drug induced liver injury (DILI) as a possible cause of our patient's illness. The prevalence of DILI may be as high as 20% in the elderly population[10] and DILI is the most common cause of extremely high levels of alkaline phosphatase (> 1000 IU/L) in hospitalized patients.[11] Our patient had received clarithromycin which can cause cholestasis. However the abnormal LFTs were present within four days of receiving only 48 hours of clarithromycin in the community and this together with the ongoing pyrexia, and systemic symptoms which would be uncommon in DILI.

Our 'Father Christmas', while giving out presents to children, received a 'present' he could well have done without! Medical staff should be aware of the changing pattern of EBV illness within the UK, the limitations of monospot testing and the importance of repeated and more specific virology testing in diagnosing acute EBV infection. Such awareness could prevent unnecessary investigation and intervention and as in our patient could prevent potential iatrogenic complications.

Conflict of Interest

All authors have no conflict of interest to declare. No extraneous funding was obtained.

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