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A patient with fever, abdominal pain and bicytopenia: Trouble once again with these IgM antibodies!

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ABSTRACT

We here report the case of a 30-year old man with a history of ulcerative colitis, who presented clinical and biological features compatible with a viral hepatitis. Initial serological results revealed the presence of IgM antibodies against many viruses, and the most likely diagnosis was viral hepatitis A. However, further investigations were performed and concluded to cytomegalovirus primary infection.

1. Case presentation

A 30 year-old French male patient attended the emergency department for fever, nausea, vomiting and abdominal pain. He presented a 7-day history of flu-like syndrome (fever, chills, headache, asthenia, anorexia and myalgia). The patient had been treated with azathioprine and mesalamine for 5 years for an ulcerative colitis. He had no recent travel history but reported consumption of dates from Algeria, one month before onset of symptoms. On admission, the temperature was 39 °C and the physical examination found a mild left sided abdominal pain. There was no hepatomegaly, splenomegaly or lymphadenopathy. The abdominal CT scan was normal, without any evidence of colitis.

Initial laboratory findings included leucopenia (2040/mm^3) with lymphopenia (400/mm^3) and thrombocytopenia (62,000/mm^3). There were no atypical lymphocytes.

A moderate increase of alanine aminotransferase (116 U/L), aspartate aminotransferase (154 U/L), and gamma -glutamyl transpeptidase (221 U/L) levels was observed. Prothrombin time was normal. C reactive protein was at 60 mg/L and procalcitonin was not increased. Serum protein electrophoresis found only hyper-α1-globulinemia. The patient was admitted to the hepatology and gastroenterology unit. Five sets of blood cultures, urine and stool cultures remained negative, and the antibiotherapy with ciprofloxacin and metronidazole started on admission, was stopped after 4 days. During hospitalization, liver function worsened with maximum alanine aminotransferase and aspartate aminotransferase levels of 355 U/L and 472 U/L, respectively. The total bilirubin level was increased at 152 μmol/L with a predominance of direct bilirubin at 128 μmol/L. Azathioprine treatment was stopped because of the additional risk of hepatic toxicity.

Etiological investigation of acute hepatitis was initiated. Autoantibodies including antineutrophil cytoplasmic antibody (ANCA), anti-smooth muscle antibody (ASMA), anti-liver-kidney microsomal-1 (anti-LKM$^-$1) antibody, anti–liver cytosol 1 (anti-LC1) antibody, antimitochondrial antibody (AMA), and gastric parietal cell antibody were all negative. Results of initial virological assays are summarized in Table 1. Significant IgM and IgG antibody levels were found for hepatitis A virus (HAV), herpes simplex virus (HSV) and Epstein Bar virus (EBV). IgM antibodies without IgG were also detected for cytomegalovirus (CMV).

What is the most likely etiology of the patient's condition?

In routine, are further investigation needed to confirm this diagnosis?

Based on available data, what final diagnosis can be retained?

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Table 1
Initial virological investigations.

Test	Result	Assay/manufacturer
Hepatitis A virus		CMIA, Architect, Abbott Diagnostics)
IgG antibody	Positive (Index: 5.2, threshold: 1)	
IgM antibody	Positive (Index: 11.4, threshold: 1.2)	
Hepatitis B virus		CMIA, Architect, Abbott Diagnostics
HBs antigen	Negative	
HBc antibody	Negative	
HBc IgM antibody	Negative	
HBs antibody	Negative	
Hepatitis C virus		CMIA, Architect, Abbott Diagnostics
HCV antibody	Negative	
Hepatitis E virus		ELISA, Wantai Hepatitis E Virus Diagnostics, Eurobio
IgG antibody	Negative	
IgM antibody	Negative	
Human Immunodeficiency Virus		ELISA, Enzygnost, Siemens
HIV testing	Negative	
Cytomegalovirus		CLIA, Liaison, Diasorin
IgG antibody	Negative	
IgM antibody	Positive (titer: 67U/mL, threshold: 22)	
Herpes Simplex Virus		CLIA, Liaison, Diasorin
IgG antibody	Positive (Index: 1.6, threshold: 1.1)	
IgM antibody	Positive (Index: >3.5, threshold: 1.1)	
Varicella Zoster Virus		CLIA, Liaison, Diasorin
IgG antibody	Positive	
IgM antibody	Negative	
Epstein Barr Virus		CLIA, Liaison, Diasorin
VCA IgG antibody	Positive (titer: 61U/mL, threshold: 20)	
VCA IgM antibody	Positive(titer: 105U/mL, threshold: 40)	
EBNA IgG antibody	Positive (titer: 199U/mL, threshold: 20)	
Human Herpes Virus-6		IFA/HHV-6, Biotrin
IgG antibody	Positive	
IgM antibody	Negative	

2. Evidence-based opinion

2.1. What is the most likely etiology of the patient's condition?

The patient's symptoms, even if non-specific, are highly suggestive of viral infection. An exacerbation of ulcerative colitis with concomitant infection is possible but the abdominal CT scan was normal. A bacterial infection was ruled out. However, initial virological results (shown in Table 1) do not allow definite etiological diagnosis. Significant levels of IgM antibodies were found against four different viruses. The profile of EBV antibodies could suggest reactivation of latent infection since the patient was under immunosuppressive therapy. HSV serology is compatible with ongoing infection (primary infection or reactivation), but no clinical evidence for this was found. Isolated CMV IgM antibodies might suggest an early stage of primary infection. The serological profile observed for HAV (high levels of IgM and moderate levels of IgG) is compatible with an ongoing infection. Taken together, the most likely scenario is a viral infection associated with polyclonal stimulation of the immune system. IgM cross-reactivity is common between herpes viruses, and a significant rate of false IgM results in herpes viruses has also been reported during infection with other viruses such as Parvovirus B19 [1] or HAV [2]. This cross-reactivity in herpes viruses' IgM antibodies during typical cases of HAV infection is especially frequent in our experience. In addition, experimental evidence supports that both specific and non-specific IgM antibodies are detectable during acute HAV infection. Indeed it has been shown that pre-existing plasma cells are released into the circulation during HAV primary infection and contribute to the production of Antigen-non-specific IgM antibodies [3]. Therefore, the clinical picture, though not typical, may be due to HAV. If lymphopenia is not the rule, initial thrombocytopenia could be a valuable finding during acute hepatitis A [4]; but these findings could also be related to azathioprine treatment. In developed countries, most cases of HAV infection are travel-related (travel to highly endemic countries); however, an increasing number of food-borne HAV cases among non-travelers has been reported [5].

At this stage, the most likely diagnosis is HAV infection with serological cross-reactivity with herpes viruses.

2.2. In routine, are further investigations needed to confirm this diagnosis?

Based on available results, if the patient was immunocompetent with a typical context, further investigations would not be mandatory to conclude for acute hepatitis A with serological cross-reactivity with the other viruses. However, in the present case, the patient is potentially immunosuppressed, with non-specific symptoms. Indeed, these symptoms could be related to each of the viruses found positive for IgM antibodies. The levels of aminotransferases were high but lower than expected in acute hepatitis A. Additional tests, and especially molecular assays were thus requested. Surprisingly, CMV real-time PCR was positive in the blood at 12,473 copies/mL. EBV DNA and HHV6 DNA were also detectable but below the quantification threshold (<500 copies/mL). HSV DNA and hepatitis E virus (HEV) RNA were found negative in the blood. Thereafter, HAV RT-PCR was performed on serum and stool samples, and was negative. The HAV IgG avidity index (AI) was high (78%).