Clinical case

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A 50-year-old woman

- Referred to you for jaundice with fever (38°5 C), in a context of active Crohn's disease treated for 4 months with infliximab + azathioprine.
- After the last infliximab injection, 2 weeks ago, the patient began to complain of severe fatigue, abdominal pain, bilateral shoulder pain, diarrhea
- Fever and jaundice appeared 2 days ago.

A 50-year-old woman

- Blood test prescribed by GP :
  - ALT 990 IU/L, AST 554 IU/L, ALP 299 IU/L, GGT 155 IU/L, total bilirubin 100 µmol/L, direct bilirubin 70 µmol/L; prothrombin level: 75%,
  - Lymphocytes 6000, neutrophil polynuclear cells 4000; PCR 66 mg/L;
  - anti-HCV negative, anti-HAV IgM negative; anti-HBs antibodies > 1000 IU/mL.

- The abdominal ultrasound :
  - homogeneous liver without bile ducts dilatation;
  - perivesicular edema.
  - no splenomegaly, portal trunk and hepatic veins of normal size

- Clinical examination: sensitive abdomen without defense. The mobilization of the shoulders, arms and forearms is painful.

What is the most likely cause of this hepatitis?

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- Non-A, non-B, non-C viral hepatitis
  - biotherapy and immunosuppression are known to expose patients to the risk of opportunistic infections, particularly viral infections
  - flu-like syndrome
  - ALT/AST > 1 in favor of a periportal histological damage classically found in viral hepatitis
  - CBC : lymphocytosis compatible with a viral infection

What additional tests do you prescribe to confirm your hypothesis?

1. HSV, VZV, EBV, CMV serologies
2. DNA detection by PCR on blood for HSV, VZV, EBV, CMV
3. IgM anti-HEV
4. HEV RNA by RT-PCR on blood and/or stool
5. Anti-nuclear, smooth muscle, LKM1, SLA, LC1 autoantibodies

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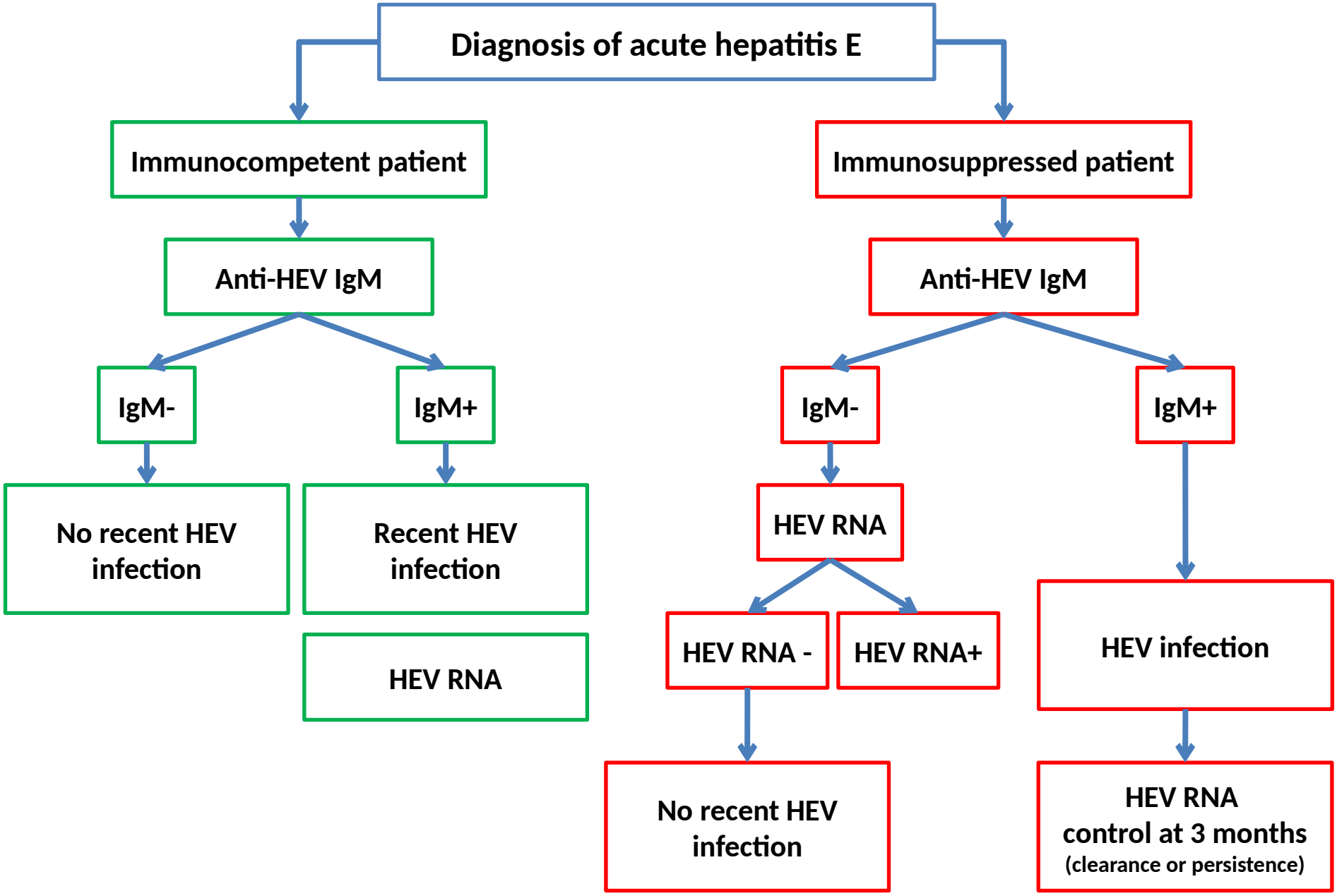
- Patient was hospitalized.
- Rectosigmoidoscopy: same appearance as the previous examination with rectal ulcerations and a visible rectal fistula opening
- ALT 1200 IU/L, AST 880 IU/L, ALP 321 IU/L, GGT 214 IU/L, total bilirubin 120 µmol/L, direct bilirubin 88 µmol/L; prothrombin level: 65%;
- No autoantibodies; IgG normal
- anti-VCA IgG+, anti-EBNA IgG+, EBV DNA not detectable;
- anti-CMV IgG+, CMV DNA not detectable;
- anti-VZV IgG+ antibodies, VZV DNA not detectable;
- anti-HSV1 HSV2 IgG and IGM negative antibodies, HSV DNA not detectable;
- HCV RNA not detectable;
- anti-HEV IgM positive antibodies, HEV RNA detectable in blood.


Diagnosis of acute hepatitis E
Immunocompetent patient
Immunosuppressed patient
Anti-HEV IgM
Anti-HEV IgM
IgM-
IgM+
IgM-
IgM+
No recent HEV infection
Recent HEV infection
HEV RNA
HEV RNA
HEV RNA -
HEV RNA+
HEV infection
No recent HEV infection
HEV RNA control at 3 months (clearance or persistence)

What is your attitude towards acute hepatitis E?

1. Enteric isolation
2. Close biological follow-up
3. Azathioprine discontinuation
4. Infliximab discontinuation
5. Ribavirin treatment

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VIRAL HEPATITIS

Treatment of autochthonous acute hepatitis E with short-term ribavirin: a multicenter retrospective study

Jean Marie Péron[1], Florence Abravanel[2], Maeva Guillaume[1,3], René Gérolami[4], Jean Nana[1], Rodolphe Anty[5], Alexandre Pariente[6], Christophe Renou[7], Christophe Bureau[1], Marie-Angèle Robic[1], Laurent Alric[8], Jean pierre Vinel[1], Jacques Izopet[2] and Nassim Kamar[9]

- French collaborative study: 21 cases of acute hepatitis E treated with ribavirin
- 9 : severe hepatitis (PT≤ 60%, 3 with alcoholic cirrhosis), 6 : age >70 years, 4 : immunosuppressive treatment, 2 : chemotherapy
- 6 patients had underlying alcoholic cirrhosis, 2 of whom had ascites and encephalopathy
- In 19 patients, ribavirin was discontinued upon negativation of HEV RNA in serum. The median duration of treatment was 26 days.

➢ 2 patients developed severe anemia.

➢ 2 patients with encephalopathy died.

➢ One patient relapsed transiently.

➢ All patients cleared HEV and had normal liver function tests.

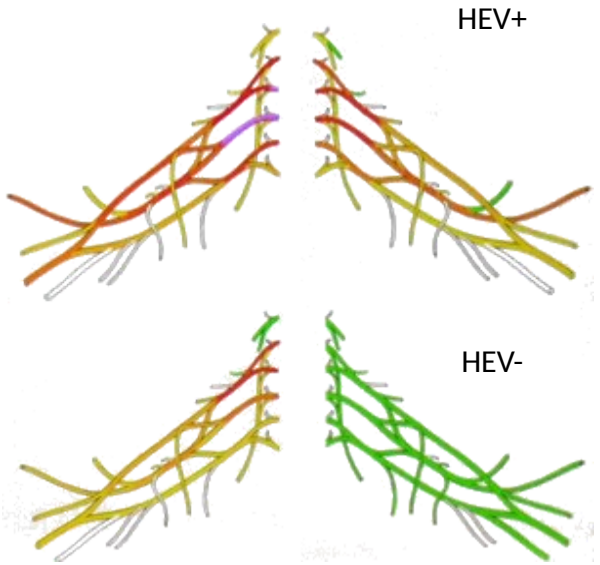
➢ All immunosuppressive therapies and chemotherapies that were temporarily discontinued could be resumed.

How do you interpret the shoulder pain ?

1. Neuralgic amyotrophy due to HEV infection
2. Due to the flu-like syndrome

Clinical phenotype of HEV associated neurological amyotrophy

- Retrospective multi-centre study: 11 centres in 7 countries
- Purpose: to show that the phenotype of HEV+ neurological amyotrophy (NA) is different from HEV- NA.
- 57 HEV+ cases, 6 with normal liver tests and 61 HEV-
- HEV+ cases:
  - Bilateral brachial plexus involvement more frequent (80% vs. 8.6%, $p < 0.001$) and more extensive (80% vs. 8.6%, $p < 0.001$)
  - Nerve damage outside the brachial plexus more frequent ($p < 0.001$)
  - ↓ Tendon reflex in the affected member
  - More sensory symptoms ($p = 0.04$)
  - More myalgia ($p = 0.02$)
  - Some muscles more affected
  - More muscles affected
  - Slower muscle recovery
  - Ribavirin profit not assessable
  - Best therapeutic strategy should be determined



Van Eijk JJ. Neurology 2017

A 50-year-old woman

- Neurological amyotrophy confirmed by neurologist: antalgic treatment
- Discharged from hospital after few days.
- During the follow up: persistence of 2N cytolysis but VHE RNA undetectable in blood
- Azathioprine and infliximab resumed 2 months after hospitalization because of Crohn's disease reactivation.
- You see the patient 2 months after treatment reintroduction.
- On the last biological check-up: 3N cytolysis; HEV RNA + in the blood.

What is your hypothesis regarding this HEV RNA + ?

1. Probable chronic HEV infection in immunosupressed patient
2. Probable HEV reinfection
3. False positive

What is your therapeutic attitude?

1. Ribavirin 800 mg/d for 3 months
2. Ribavirin 1000 mg/d for 6 months
3. Ribavirin 1000 mg/day for 9 months
4. Azathioprine discontinuation
5. Infliximab discontinuation

Treatment of chronic HEV infection

Study	Population	Treatment regimen	Outcome
Kamar N et al[108]	Renal transplant recipients, France	Dose: median 800 mg per day Duration: 3 months	SVR 67%
Kamar N et al[127]	Solid organ (all) transplant recipients with genotype 3 infection, France	Dose: median 600 mg per day Duration: median 3 months	SVR in 78%
Debing Y et al[128]	Solid organ (all) transplant recipients with genotype 3 infection, Germany	Dose: initial daily dose 600-1000 mg Duration: not specified	Treatment successful in 87%
Mallet V et al[129]	Kidney-pancreas transplant and idiopathic immunodeficiency	Dose: 400-600 mg per day Duration: 3 months	RNA negative at 2 and 3 months post-treatment cessation
Pischke S et al[130]	Solid organ (all) transplant recipients	Dose: initial daily dose 600-1000 mg Duration:5 months	SVR in 81%
Tavitian S et al[131]	Haematological malignancy	Dose: median 800 mg per day Duration: median 3 months	RNA undetectable after 30 days in all treated patients
Galante A et al[132]	Orthotopic liver transplant recipients	Dose:initial daily dose 400-800 mg Duration: 3 months	SVR in 75%

Donelli MC. APT 2016

A 50-year-old woman

- Ribavirin 400mg x 2/day for 3 months.
- Azathioprine is stopped and infliximab is maintained.
- Blood test at one month : hemoglobin 11.5g/dL, ALT and AST normal and HEV RNA undetectable.
- Confirmed at 2 and 3 month.
- One month after ribavirin discontinuation: ALAT 2N and HEV RNA detectable.

What is your therapeutic approach?

1. Treatment with sofosbuvir
2. New treatment with ribavirin : longer and higher dose

Treatment of relapse

- Relapse observed in 13 to 33% of cases after a first treatment with ribavirin

A 50-year-old woman

- Patient retreated with ribavirin 1000 mg/day for 6 months.
- Poor tolerance with nausea, diarrhea, fatigue and dyspnea.
- At 1 month: ALT and AST normal, HEV RNA undetectable, and hemoglobin is 10 g/dL.
- Confirmed until the end of treatment and up to 6 months after stopping treatment.
- Considered to be cured of HEV infection