Severe Viral Hepatitis in a Patient with Chronic Lymphocytic Leukemia (CLL) Complicated with Autoimmune Haemolytic Anemia (AIAH), Treated with Steroids

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Infection

SEVERE VIRAL HEPATITIS IN A PATIENT WITH CHRONIC LYMPHOCYTIC LEUKAEMIA (CLL) COMPLICATED WITH AUTOIMMUNE HAEMOLYTIC ANEMIA (AIAH), TREATED WITH STEROIDS

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Author Comments:

Maladies du sang

Angers, 03/2013, the 14th

Doctor Aline Tanguy-Schmidt

**Editor in chief
Infection**

Dear Editor,

You will find enclosed a manuscript entitled:

« Severe viral hepatitis in a patient with chronic lymphocytic leukemia (CLL) complicated with autoimmune haemolytic anemia (AIAH), treated with steroids »

by Corentin Orvain, Alexandra Ducancelle, Caroline Eymerit-Morin, Marie-Christine Rousselet, Frederic Oberti, Mathilde Hunault-Berger, and Aline Tanguy-Schmidt that we submit as an original article in Infection.

All authors concur with the submission of this manuscript, they have reviewed and approved for the final version of the manuscript. All authors will sign a statement attesting authorship, disclosing all potential conflict of interest, and releasing the copyright should the manuscript be available for publication.

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Looking forward to hearing from you,

Sincerely yours.

Aline Tanguy-Schmidt

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COMPLICATED WITH AUTOIMMUNE HAEMOLYTIC ANEMIA (AIAH), TREATED WITH STEROIDS

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Abstract:

Infectious complications are a major cause of morbidity and mortality in patients with chronic lymphocytic leukaemia (CLL) due to impaired immunity secondary to the disease itself and to the immunosuppressive therapies administered to these patients. We report a 78-year old woman with CLL who was treated with steroids for autoimmune hemolytic anemia (AIAH). A few weeks later, she was admitted for severe acute hepatitis with disseminated intravascular coagulation (DIC). Despite the symptomatic treatment of DIC, standard reanimation and probabilistic antibiotics, the patient died within 24 hours with severe hepatic failure. Autopsy was in favor of a disseminated viral infection with oesophageal, hepatic and pulmonary cytopathologic lesions with acidophilic intranuclear inclusions suggestive of herpes virus, even though HSV 1 and 2, CMV and HHV6 PCRs were negative. This case of severe viral hepatitis with oesophagitis occurring three weeks after the introduction of high-dose steroid treatment for AIHA in a CLL patient calls for anti-herpetic prophylaxis in such patients, immunodepressed by their diseases and the treatment they receive.

Keywords: autoimmune hemolytic anemia (AIAH) ; chronic lymphocytic leukemia (CLL) ; viral hepatitis

Introduction:

Infections complications are a major cause of morbidity and mortality in patients with chronic lymphocytic leukaemia (CLL) due to impaired immunity secondary to the disease itself (T-cell dysfunction, hypogammaglobulinemia), with bacterial infections and herpes virus reactivation being the most frequent [1][2]. The introduction of immunosuppressive therapy has led to the breakthrough of opportunistic infections, especially viral infections [1][2]. We report herein the case of a patient with CLL, who developed a severe viral hepatitis a few weeks after receiving steroid therapy for the treatment of autoimmune haemolytic anaemia (AIHA).

Case report:

A 78 year-old female patient with arterial hypertension and moderate hypertension-related chronic renal insufficiency was diagnosed with chronic lymphocytic leukaemia (CLL) in 2002. Diagnosis was made after exploration of lymphocytosis with lymphocyte immunophenotyping in favour of CLL with no indication for treatment, as the disease had no clinical repercussion. Disease re-evaluation was considered in 2006. At this time, there was still a lymphocyte B clone with a 4-point Matutes score: CD5 100%, CD23 100%, weak CD22 expression, FMC7 37% with a weak expression of a kappa surface immunoglobulin. There were no specific karyotypic features, with especially no 17p13 deletion. The patient had a positive direct Coombs test with no signs of hemolysis (G immunoglobulin autoantibody with no specific characteristics found after elution). Serum protein electrophoresis showed no hypogammaglobulinemia. During the follow-up, progressive anemia with no signs of hemolysis made CLL treatment necessary, and so, chlorambucil was introduced, starting September 2009.

The patient was admitted in December 2009 for rapid aggravation of anemia which was poorly tolerated. Hemoglobin levels were at 5.5 g/dL, and anemia was normocytic (92.7fL) and aregenerative (reticulocyte count was 39 G/L), with newly hemolytic features with unconjugated bilirubin at 37 µmol/L and lactate dehydrogenase at 484 UI/L with an upper reference limit at 360

1 UI/L (those values were normal six months earlier). There was a normal haptoglobin at 0.9 and
2 elevated ferritin at 2157 µg/L in this context of hemolysis, with normal aminotransferase levels and
3 without inflammation. There was no other cytopenia and there was no schizocytosis. The same
4 positive direct Coombs test was found with a G immunoglobulin autoantibody, with no specific
5 characteristics found after elution. To maintain an acceptable hemoglobin level, the transfusion of 5
6 units of packed red blood cells in three days was necessary.

7 With the hypothesis of iatrogenic medullar aplasia, chlorambucil treatment was interrupted. Also,
8 the occurrence of an autoimmune hemolytic anemia calls for introduction of steroid therapy
9 (prednisone 1 mg/kg/day). No aggressive immunochemotherapy could be administered to treat a
10 hypothetical CLL medullar involvement due to the patient's age and concomitant medical conditions.
11 Nevertheless, the rapid response of anemia to steroids allowed for discharge of the patient.

12 Three weeks later, the patient was admitted to the emergency department for acute abdominal pain
13 and diffuse ecchymosis. She had neither fever nor hemodynamic failure. No additional clinical
14 features were found. She had newly marked aminotransferase increase, with aspartate
15 aminotransferase (ASAT) up to 336 UI/L (N<37) and ALAT up to 247 UI/L (N<43) associated with
16 coagulation disorders (platelet count 18 G/L, prothrombin time (PT) 20%, fibrinogen <0,30 g/L with
17 soluble complexes and D-dimer index between 16 and 32) with serum albumin at 46 g/L and normal
18 serum bilirubin in favor of overt disseminated intravascular coagulation (DIC). There was no renal
19 function aggravation. Lactate dehydrogenase was at seven times the upper reference limit (2904
20 UI/L) and serum ferritin was at 481 µg/L. Normocytic aregenerative (reticulocytes: 60 G/L) and
21 hemolytic (haptoglobin: <0.2) anemia was present.

22 The hepatic echosonography was normal; inferior vena cava, sus-hepatic and portal veins were
23 permeable. Renal veins were also permeable. Abdominal scanning did not reveal any abnormalities
24 either, including no sign of mesenteric ischemia or tumor. Hepatic parenchyma and intra and extra-
25 biliary ducts were normal. The bone marrow exploration was poor, with important cellular lysis.

1 There were rare mast cells, no blasts and no signs in favor of haemophagocytic syndrome. By
2 contrast, there were many small chain cocci bacteria in the bone marrow.
3

4 Despite symptomatic treatment of the disseminated intravascular coagulation, standard reanimation
5 and probabilistic antibiotics, the patient died within 24 hours with severe hepatic failure (PT 5%).
6

7 Autopsy was performed and showed a steatotic liver without ascites or peritonitis and many
8 punctiform oesophageal ulcerations. The other abdominal or thoracic organs did not show any
9 abnormalities. Hepatic parenchyma architecture was normal with portal spaces filled with a mild
10 mononuclear inflammatory infiltrate. Macro-vesicular steatosis was confirmed, associated with
11 patchy acidophilic hepatocellular necrosis, without cellular inflammation. Next to these necrotic foci,
12 altered hepatocytes displayed abnormal nuclei with a thick nuclear membrane, margination of
13 chromatin and a large vitreous acidophilic inclusion (figure 1). Some of these altered hepatocytes
14 were giant and multi-nucleated, with multiple acidophilic inclusions (figure 2). Similar nuclear
15 inclusions were found in the epidermoid cells next to the oesophageal mucosae ulcerations and in
16 rare pneumocytes. Splenic and bone marrow tissues were infiltrated by small lymphocytes showing
17 residual CLL. The final pathologic diagnosis was a disseminated viral infection with cytopathologic
18 lesions suggestive of herpes virus.
19

20 Immunohistochemical labelling was negative for type 1 Herpes Simplex Virus (HSV), adenovirus, and
21 cytomegalovirus (CMV) on liver and oesophageal sections. Polymerase Chain Reactions (PCR) carried
22 out on the oesophageal formalin-fixed tissue were negative for HSV 1 and 2, CMV and human herpes
23 virus (HHV-6). Serology showed prior immunisation against HSV, CMV, Epstein-Barr virus (EBV) and
24 varicella-zoster virus (VZV) and no viral hepatitis (hepatitis A: negative anti-HAV IgM, hepatitis B:
25 vaccinee profile ; hepatitis C: negative anti-HCV) on the hospitalization day. No serological herpes
26 virus reactivation could be investigated due to insufficient quantity of serum.
27

28 Even though intranuclear inclusions are the most distinctive feature for herpes virus infections,
29 additional specific explorations could not prove the responsibility of herpes group virus. Still, for this
30 patient, immunodepressed by her CLL, the treatment she received (chlorambucil, steroids), and the
31

1 presence of severe hepatitis with DIC and herpes group like provoked lesions, enables at least the
2 diagnosis of disseminated viral infection.
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6 **Discussion:**

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9 Herpes simplex virus (HSV) hepatitis is rare and accounts for only 1% of all acute liver failures. The
10 importance of recognizing HSV-induced acute liver failure is based on its extremely severe clinical
11 course with a near 75% lethality rate [3]. HSV hepatitis is just one of several clinical manifestations of
12 HSV sepsis leading more frequently to encephalitis, pneumonia and esophagitis.
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16 This hepatitis is often severe, sometimes fulminant, caused by immunosuppression, most commonly
17 associated with defects in cell-mediated immunity, or immunosuppressing therapy, even
18 administered for a short time [3]. Herpetic hepatitis has non-specific clinical features: fever occurs in
19 82% of the patients but can lack in case of immunosuppression, leucopenia and thrombopenia are
20 frequent, and cytolysis is almost always present in typically anicteric patients [3]. Cutaneous lesions
21 are very evocative of the diagnosis and should be investigated, but are not always present [4].
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26 Diagnosis of herpetic hepatitis is based on the liver biopsy showing hemorrhagic necrosis of liver
27 parenchyma, a reduced inflammatory infiltration and characteristic intranuclear viral inclusions. The
28 herpes virus can be isolated by PCR in the blood stream or in cutaneous lesions if they exist. In
29 immunocompetent patients, primo-infection is the most common whereas it is mostly viral
30 reactivation in immunocompromised patients [4].
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35 Infections in CLL patients, particularly bacterial, are one of the most pejorative factors, even in
36 untreated patients. The incidence of moderate to severe infections ranges from 0.25 to 0.5 per
37 patient-year [5]. These complications are due to alterations in immune functions including both
38 qualitative and quantitative defects: T-cell dysfunction and hypogammaglobulinemia. Other defects
39 involve NK cells, neutrophils, monocytes/macrophages and complement. Untreated patients
40 especially encounter lower respiratory tract bacterial infections and herpes virus reactivation (Herpes
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1 Zoster Virus reactivation being the most frequent). Fungal and opportunistic infections are rare in
2 untreated patients [2].
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4 CLL patients are also exposed to infections due to immunosuppression from cytotoxic therapy and
5 corticosteroids. As seen in our patient, the incidence of opportunistic infections is frequent in
6 patients receiving steroids for the treatment of CLL-related AIHA, which worsens the state of
7 immunodeficiency [6]. The recent introduction of immunosuppressive treatments including purine
8 analogues such as fludarabine, and monoclonal antibodies such as rituximab and alemtuzumab adds
9 the risk of opportunistic infections, especially viral infections [2]. Viral infections occur less often in
10 patients receiving alkylating-based therapy than with the newer agents [7], or they occur in heavily
11 pre-treated patients with advanced disease [8] [9]. In fludarabine-based regimens, besides the usual
12 bacterial infections, the occurrence of numerous opportunistic diseases is due to the prolonged T-
13 lymphocyte depletion (for up to two years after receiving treatment). These opportunistic diseases
14 include Candida, mycobacterial and herpes virus infections [2]. Finally, patients receiving
15 alemtuzumab are at high risk of cytomegalovirus (CMV) reactivation [10].
16

17 There are currently no standard guidelines for antimicrobial prophylaxis concerning CLL patients.
18 Antiviral prophylaxis is mostly recommended during fludarabine-based therapies in elderly CLL
19 patients with a low CD4 count [11]. Antimicrobial prophylaxis seems more controversial in younger
20 untreated patients [12]. This remains a low-point in knowledge concerning infections in CLL patients
21 as there are no control trials exploring antimicrobial prophylaxis in these patients. Also, in order to
22 reduce infection rates, the use of low-dose intravenous immunoglobulin has been explored in
23 patients with hypogammaglobulinemia, with a reduction in infection rates but no cost effectiveness
24 [13].
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26 In conclusion, this case of life-threatening viral infection, possibly from the herpes virus group,
27 occurring in a CLL affected patient, brings up the question of efficient prophylaxis and, particularly,
28 systematic anti-herpetic prophylaxis.
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References:

- [1] Dearden C. Disease-specific complications of chronic lymphocytic leukemia. Hematology Am Soc Hematol Educ Program 2008; 450-6.
- [2] Morrison VA. Infectious complications of chronic lymphocytic leukaemia: pathogenesis, spectrum of infection, preventive approaches. Best Pract Res Clin Haematol 2010; 23: 145-53.
- [3] Kaufman B, Gandhi SA, Louie E, Rizzi R and Illei P. Herpes Simplex Virus hepatitis: case report and review. Clin Infect Dis 1997; 24 : 334-8.
- [4] Bourliere M. Les hépatites virales non alphabétiques. FMC-HGE 2004.
- [5] Molica S. Infections in chronic lymphocytic leukemia: risk factors, and impact on survival, and treatment. Leuk Lymphoma 1994; 13: 203-14.
- [6] Mauro FR, Foa R, Cerretti R, et al. Autoimmune hemolytic anemia in chronic lymphocytic leukemia: clinical, therapeutic, and prognostic features. Blood 2000; 95: 2786-92.
- [7] Morrison VA, Rai KR, Peterson BL, et al. Impact of therapy with chlorambucil, fludarabine, or fludarabine plus chlorambucil on infections in patients with chronic lymphocytic leukemia: Intergroup Study Cancer and Leukemia Group B 9011. J Clin Oncol 2001; 19: 3611-21.
- [8] Hensel M, Kornacker M, Yammeni S, Egerer G, Ho AD. Disease activity and pretreatment, rather than hypogammaglobulinaemia, are major risk factors for infectious complications in patients with chronic lymphocytic leukaemia. Br J Haematol 2003; 122: 600-6.
- [9] Molteni A, Nosari A, Montillo M, Cafro A, Klersy C, Morra E. Multiple lines of chemotherapy are the main risk factor for severe infections in patients with chronic lymphocytic leukemia with febrile episodes. Haematologica 2005; 90: 1145-7.
- [10] Hillmen P, Skotnicki AB, Robak T et al. Alemtuzumab compared with chlorambucil as first-line treatment for chronic lymphocytic leukemia. J Clin Oncol 2007; 25: 5616-23.
- [11] Shvidel L, Shtalrid M, Bairey O, et al. Conventional dose fludarabine-based regimens are effective but have excessive toxicity in elderly patients with refractory chronic lymphocytic leukemia. Leuk Lymphoma 2003; 44: 1947-50.
- [12] Eichhorst BF, Busch R, Schweighofer C, Wendtner CM, Emmerich B and Hallek M. Due to low infection rates no routine anti-infective prophylaxis is required in younger patients with chronic lymphocytic leukemia during fludarabine-based first line therapy. Br J Haematol 2006; 136: 63-72.
- [13] Molica S, Musto P, Chiurazzi F, et al. Prophylaxis against infections with low-dose intravenous immunoglobulins (IVIg) in chronic lymphocytic leukemia. Results of a crossover study. Haematologica 1996; 81: 121-126.

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