**A hemophagocytosis syndrome attributed to phenobarbital**

Un syndrome d’activation macrophagique attribué au phénobarbital

**Introduction**

Hemophagocytosis syndrome (HS) is a rare life-threatening condition resulting in a hyperinflammatory state. It is due to inappropriate stimulation and proliferation of cytotoxic lymphocytes and macrophages inducing phagocytosis of blood cells and causing multiorgan damage. This syndrome can be primary in children, or secondary to several etiologies in adults, such as infections, neoplasias mainly hemopathies or autoimmune diseases. It has been rarely reported as a side effect of drugs. We report herein a HS attributed to phenobarbital intake.

**Case report**

R.S. is a 24-year-old woman without any medical or atopic history. She was treated with phenobarbital (Gardénal®) on the 15th February 2014 for epilepsy. She was taking 1 tablet a day. Her biological tests (liver tests, blood count, ferritin and triglyceride) on the 5th February 2014, before phenobarbital introduction, were in normal range.

Around three weeks later, on the 7th March, she developed fever (38.5 ºC) and vomiting. She was prescribed acetaminophen, amoxicillin with clavulanic acid, salicylic acid and omeprazol during four days. On the 9th March 2014, she presented a maculopapular eruption on the whole body despite the face with persistent fever. She has not developed any lymphadenopathy. She was hospitalized on the 13th March 2014. The biological tests revealed a cytolysis (transaminases were up to 12 times the normal values [12N]), total/direct bilirubin levels were 58.9/40.8 µmol/L (NV < 22/6.8 µmol/L), the alkaline phosphatase level (ALP) was 3.6N. Prothrombin time (PT) was 77%. The triglyceride level was 2.91 mmol/L (NV: 0–2.00 mmol/L). The blood count was normal and the eosinophiles were 100/mm³.

On the 20th March, the phenobarbital was stopped. The fever and the eruption persisted. The triglyceride level reached 3.24 mmol/L. Four days later, the transaminases climbed to 22.7N for alanine aminotransferase (ALT) and 18N for aspartate aminotransferase (AST), the total/direct bilirubin was 258/221 µmol/L, the glutamyl transferase (GGT) was 11.2N, lactate dehydrogenase (LDH) was 562 U/L (NV: < 460 U/L) and the PT declined to 42.3%; a bicytopenia was found two days later including leucocytopenia (WBC = 2200/mm³; neutrophils = 748/mm³) and anemia (hemoglobin level = 9.9 g/dL). On the 28th March, the liver tests began to improve (ALT = 13.6N; AST = 6.2N) and the PT reached 53.3% but the blood cell count worsened with WBC at 1070/mm³, neutrophils at 80/mm³ and hemoglobin level at 9.2 g/dL. Ferritin level was higher than 2000 ng/ml, it reached 6886 ng/ml three days later, and the fibrinogen level was in normal range. The eruption became hyperpigmented around the 30th March 2014. On the 1st April, hemoglobin level continued declining until reaching 6.6 g/dL while liver test continued to improve.

The patient received antibiotic therapy (pipercillin/tazobactam, colistin, amphotericin B) in front of febrile neutropenia. On the 13th April 2014, she started steroids. A chest X-ray showed a mild pleural effusion but without pneumopathy. An abdominal ultrasound showed a hepatomegaly and a splenomegaly, free biliary ducts and a moderate ascites. A CT-scan confirmed the presence of hepatomegaly with absence of splenomegaly and lymphadenopathies. A bone marrow puncture revealed an excess of macrophage with mature lymphoid cells and the presence of some other cells with HS containing erythrocytes, the granulocyte lineage was few represented. A liver biopsy showed no tumoral proliferation. Viral serologies such as EBV, hepatitis A, B, C and human immunodeficiency virus (HIV), serologies of ricketsia, syphilis and toxoplasmosa were negatives. Serologies of CMV and rubella showed an old immunization. The MNI test was negative. The immunological tests such as antinuclear antibodies (ANA), anti-LKM1, anti-mitochondria and anti-smooth muscle antibodies were negatives. An immunophenotyping with flow cytometry of hemopathies showed normal profile of T-cells population. Immunoglobulin monitoring revealed IgA at 0.36 g/L (NV: 0.71-3.6), IgG and IgM were in the normal range.

Apyrexia was obtained around the 14th April 2014, about three weeks after phenobarbital cessation. The blood cell count and the PT became normal on the same date. The liver tests and the hemoglobin level continued to improve until returning to normal values in late May with partial regression of hyperpigmentation. The regression of steroids was initiated on the 15th May 2014 until its cessation on the 9th June 2014. The follow up in March 2015 showed a complete disappearance of the hyperpigmentation, normal blood cell count and liver tests.

**Discussion**

In literature, drug-induced HS was mainly described in association with DRESS syndrome. Therefore, it was attributed to the systemic inflammatory response induced by DRESS syndrome with activation of macrophages and production of cytokines [1]. Lambotte et al. reported 2 cases of hemophagocytosis following DRESS syndrome related to glycopeptides in the first case and to trimethoprim-sulfamethoxazole in the second one [1]. In the 2 cases, despite the withdrawal of the suspected drugs, the symptomatology of DRESS persisted then the characteristics of hemophagocytosis (cytopenia, cytolsis, hypofibrinogenemia, hemophagocytosis pictures) appeared; the evolution was favorable within a month. Another case was reported by Miyazaki
et al., hemophagocytosis occurred after a little improvement of DRESS syndrome related to salazopyrine [2].

In our case, we did not identify a DRESS syndrome associated with HS. Our patient presented, at first, classic symptomatology of DRESS syndrome: fever, cutaneous eruption, and a liver dysfunction. The lack of hypereosinophilia and lymphadenopathies were against this diagnosis. The regiSCAR score of DRESS according to the Regiscar group is 2 or “possible case” [3]. The cytopenia and the increase of ferritin and triglyceride levels are not usual features of drug hypersensitivity syndrome. These characteristics suggest more a HS. Indeed, the association hypertriglycericemia–hyperferritineemia is strongly evocative of this diagnosis. The myelogram brought an additional proof showing hemophagocytosis pictures.

In our case, the diagnosis of HS was retained in front of the presence of 5 criteria over 8 of the HS diagnostic criteria (at least 5 must be fulfilled to make the diagnosis) [4,5]; fever \(\geq 38.5^\circ C\), bicytopenia (hemoglobin < 9 g/dL, neutrophils < 1000/mm\(^3\)), hypertriglycericemia > 3 mmol/L, hyperferritineemia > 500/mm\(^3\) and hemophagocytosis in the bone marrow puncture. Other features were also noticed in this case as elevated transaminases, bilirubin and LDH levels.

Generally, the cytopenia in HS concerns the erythrocytes and platelets with severe thrombopenia. In our case, the platelet count was always normal with a severe leukocytopenia and an anemia.

The role of phenobarbital was retained in front of the compatible delay (three weeks), the favorable evolution after the drug withdrawal and the lack of another etiology. In literature, the evolution is variable from few days to several weeks depending on the etiology and the treatment undertaken. In our case, phenobarbital was withdrawn and the patient was put on steroid therapy. The evolution was slowly favorable after three weeks after cessation of phenobarbital.

The role of the other drugs (acetaminophen, amoxicillin/clavulanic acid, salicylic acid, omeprazol, tazobactam/piperacillin, colistin) was rejected since we considered all the symptoms in the same clinical picture. Those drugs were given after the onset of the fever and vomiting, besides, the evolution was not suggestive of their role.

The mechanism of HS seems to be related to an immunomodulating effect of phenobarbital. In fact, antiepileptic drugs (AEDs) can directly affect both hemorrhal and cellular immunity, modifying the expression and the synthesis of some molecules, mainly cytokines. Carbamazepine may increase some cytokines levels (IL-1, IL-2, IL-6) [6]. Furthermore, phenobarbital seems to reduce lymphocyte T cytotoxicity [7]. In fact, the primum movens of HS is a “cytokin shock” and a functional defect of NK cells and T lymphocytes CD8.

In literature, we found two other cases of DRESS syndrome which evolved to a HS. Phenobarbital was the suspected drug in the first case, and allopurinol in the second one [8,9]. In Miyazaki et al.’s case as in these two cases, infection with HHV6 was detected (positive HHV6 DNA in the 1st case and positive serology in the 2 last cases) [2,8,9]. In our patient, HHV6 serology was not performed. Other viral serologies were negative in our patient especially EBV serology. According to Janka and Lehmborg, EBV is the most frequent trigger virus for the HS [4].

Other etiologies of HS were unlikely in our patient. Hemopathies were ruled out in front of the lack of tumoral proliferation in myelogram, liver biopsy and CT-scan, the absence of lymphadenopathies and the normal profile of T-cells in immunophenotyping with flow cytometry.

Autoimmune diseases were unlikely since the negativity of ANA. Adult-onset Still’s disease diagnosis needs the presence of at least 5 over 8 diagnosis criteria (including 2 major) [10]. In our patient, there were only 3 criteria (rash, liver test abnormalities, and negativity of ANA).

IgA deficiency was evoked in front of a low IgA level, and the eventual drug allergy. But the patient is not known to have repeated infections nor atopic history. On another hand, hypogammaglobulinemia was associated with DRESS syndrome in literature [11,12]. AEDs were also shown to induce hypogammaglobulinemia [13].

As in our case, Yang et al. reported a HS associated with anticonvulsivant drugs, in particular lamotrigine. In that case, the patient did not present a DRESS syndrome [14]. Thus, even if there are only few reports of drug-induced HS, clinicians must recognize this syndrome since its possible fatal outcome. This depends mainly on the treatment of its cause and, in this instance, the withdrawal of the culprit drug.

**Disclosure of interest:** the authors declare that they have no competing interest.

**References**


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