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A typical babesiosis in an immunocompetent patient

Une babésiose atypique chez un patient immunocompétent

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Abstract. Babesiosis is a tick-borne infectious disease, caused by an intraerythrocytic parasite of the genus *Babesia*. It has clinical, biological and microbiological similarities with *Plasmodium* related infections. In rare cases, babesiosis may be complicated by hemophagocytic lymphohistiocytosis, which occurs preferentially in the immunodeficient patient. We report here the case of a non-immunocompromised patient living in Manhattan, New York hospitalized for a complicated babesiosis of a hemophagocytic lymphohistiocytosis. After 7 days of hospitalization and treatment by azithromycin 500 mg/day and atovaquone 750 mg twice a day, the patient was discharged with an improvement in clinical symptoms and biological parameters.

Key words: *babesiosis, Babesia, hemophagocytic lymphohistiocytosis, malaria*

Résumé. La babésiose est une maladie infectieuse transmise par les tiques, causée par un parasite intra-érythrocytaire du genre *Babesia*. Elle présente des similitudes cliniques, biologiques et microbiologiques avec les infections à *Plasmodium*. Dans de rares cas, préférentiellement chez le patient immunodéprimé, la babésiose peut se compliquer d'un syndrome d'activation macrophagique. Nous rapportons ici le cas d'un patient immunocompétent vivant à Manhattan, New York et hospitalisé pour une babésiose compliquée d'un syndrome d'activation macrophagique. Après 7 jours d'hospitalisation et un traitement par azithromycine 500 mg/jour et de l'atovaquone 750 mg 2 fois par jour, le patient est sorti d'hospitalisation avec une amélioration des signes clinico-biologiques.

Mots clés : *babésiose, Babesia, syndrome d'activation macrophagique, paludisme*

Case report

A 78-year-old French man, residing in the Manhattan district of New York City in the United States, and regularly travelling to Long Island in the Hamptons consulted the emergency room department 8 days after his arrival in Paris for fever, asthenia and anorexia evolving since 5 days. He has no significant medical history other than rhythmic heart disease that required the use of a pace maker.

On arrival at the emergency room, he did not have hemodynamic disorder, a fever at 38.2° and clinical jaundice. He said he was exhausted and complained of anorexia. He was eupneic in ambient air, cardiopulmonary auscultation was normal. The abdominal palpation found hepatomegaly at three finger breadths with an overflow to the left hypochondrium and no evident splenomegaly. The lymph node areas were free.

The biological results showed a bicytopenia with normocytic anemia at 8.6 g/dL associated with thrombocytopenia at 34,000/mm^3. The blood test also revealed an inflammatory syndrome with a C-reactive protein (CRP) at 270 mg/L, hyponatremia at 127 mmol/L, hepatic cytolysis with Serum-Glutamo-Oxaloacetate-Transferase (SGOT) at 94 IU/L and Serum-Glutamo-Pyruvate-Transferase (SGPT) at 53 IU/L, moderate cholestasis with conjugated bilirubin jaundice (total bilirubin 42 µmol/L, conjugated bilirubin 19 µmol/L).

A blood smear was observed under the microscope to check the blood count. Surprisingly, it revealed the presence of an

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intraerythrocytic parasite suggestive of *Plasmodium*. The search for malaria had not been requested by the clinical department. Thus, a loop mediated isothermal amplification specific for *Plasmodium* (Illumigene® Malaria LAMP) was performed twice but was negative both times.

There was no recent travel to malaria-affected areas, thus calling into question the diagnosis of malaria. The last trips were made in 2004 to Japan, Australia and India with no history of malaria.

In the presence of hemolytic anemia, the geographical origin of the patient and the microbiological analysis of the blood smear, the diagnosis of babesiosis was evoked and confirmed by microscoscopic examination on May-Grünwald Giemsa (MGG) stained thin blood smears. Parasitemia was elevated to 7%. Of particular note was the polyparasitic contamination of erythrocytes and merozoïtes arranged in a tetrad, which are characteristic of this infection and distinguish it from *Plasmodium* infection.

Several biological abnormalities were suggestive of hemophagocytic lymphohistiocytosis: anemia at 6.8 g/dl, thrombocytopenia at 53,000/mm^3, hyperferritinemia at 3,227 μg/L, moderate hypertriglyceridemia at 1.99 mmol/L, and fibrinogen lowering to 2.4 g/L. The H-score (probability score for hemophagocytic lymphohistiocytosis) was 92% [1]. In addition, serology for hepatitis A, B C and E were negative, as were serology HIV 1 and 2; previous contact with CMV and EBV; Serology toxoplasmosis negative; syphilis negative; serology of rickettsioses negative. Lyme serology was positive with immunoblot confirmation. Plasma protein electrophoresis was normal and there was no Howell-Jolly body on the blood smear. Hemoglobinuria was also observed. Treatment with azithromycin 500 mg/day and atovaquone 750 mg twice a day has been initiated with rapid clinical and biological improvement. Strict apyrexia was obtained 24 hours after the start of treatment as well as the negativation of the blood smear in 48 hours.

The biological assessment 48 hours after the start of treatment showed a clear regression of the inflammatory syndrome (CRP 90 mg/L) while the anemia was more marked with a hemoglobin at 6.8 g/dL and hemolysis stigmas were still present. In order to postpone plasma exchanges, it was decided to carry out a blood transfusion with close monitoring of hemoglobin levels.

The transfusion yield was quite satisfactory since the hemoglobin level, 72 hours after initiation of treatment was 9.6 g/dL. At the same time, there was a gradual reactivation of the platelet rate until normalization.

After 7 days of hospitalization, the patient was discharged from the department. He was apyretic, no longer had clinical jaundice nor asthenia. The inflammatory syndrome was still regressing with a CRP of 22 mg/L, stable hemoglobin at 9.8 g/dL and normalized platelets at 222,000/mm^3.

The patient was contacted again one week after discharge, he reported no physical complaints, had not had a fever and had resumed normal activity.

Biologist's comment

Human babesiosis is an emerging zoonosis of worldwide distribution due to a protozoan parasite of the genus *Babesia* whose transmission is mediated by ticks of the genus *Ixodes* or less commonly through blood transfusion or transplacentally [2]. Several species of *Babesia* are responsible for the disease in humans, the main ones being *Babesia microti* in North America, *B. divergens* and *B. venatorum* in Europe. The infection has been mainly described in North America but also in other regions of the world, notably Europe, China, Australia, or South America [3-5]. In the United States, *Babesia microti* is particularly present in the North East, namely the New England region, as well as the states of New York, New Jersey, Wisconsin and Minnesota, areas in which this pathogen is endemic including in immunocompetent patients [6]. In Europe, prevalence is lower with about 50 cases reported since 1960, with a very high prevalence of severe cases due to divergent *B. divergens* mainly in splenectomized patients unlike in North America where many cases of immunocompetent patients have been described. A few cases of importation of *B. microti* have been reported, particularly in patients who have travelled in North America.

The diagnosis of babesiosis is based on clinical and epidemiological criteria, medical history, physical examination, and laboratory tests.

Biological tests usually show hemolytic anemia, thrombocytopenia and normal or slightly reduced blood count for leukocytes. Liver enzymes (alkaline phosphatase, aspartate and alanine aminotransferases) and bilirubin are elevated in severe disease. The diagnosis of babesiosis is confirmed by microscopic identification of the intra-erythrocytic parasite on MGG stained thin blood smears (*Figure 1*). Trophozoites of *Babesia* spp. are round, oval or pear-shaped and have a blue cytoplasm with a red chromatin. They are distinguished from *Plasmodium* by the absence of hemozoin, and the presence of merozoïtes arranged in a tetrad (Maltese cross) [7]. This "Maltese cross" are pathognomonic for *Babesia* infection but are rarely noted. Vacuoled extraerythrocytic, round and oval merozoites are strongly suggestive of *Babesia* and can also be observed. Polymerase Chain Reaction (PCR), more sensitive, is used to confirm the diagnosis and identify the species involved. To finish, serology allows a retrospective diagnosis and could be relevant in pre-transfusion blood screening which is not performed neither in Europe nor in the US.

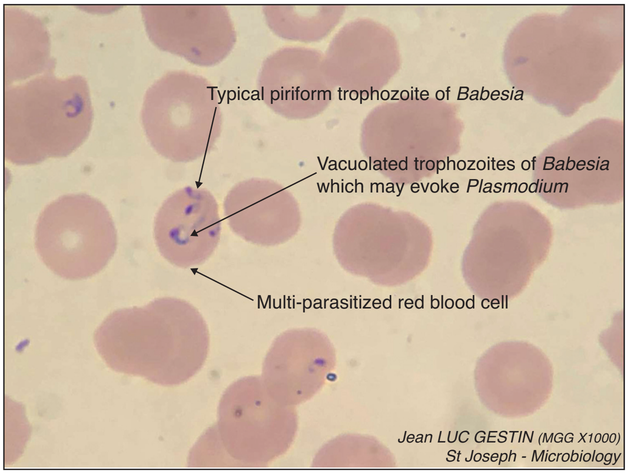

Figure 1. Typical presentation of babesiosis in a blood smear (X 1,000).
Multiparasitic infection of erythrocytes can be observed. Picture obtained at X1000 showing intra-erythrocytic parasites on MGG stained thin blood smears. Trophozoites of Babesia spp. are round, oval or pear-shaped (piriform) and have a blue cytoplasm with a red chromatin.
MGG: May-Grünwald Giemsa

Clinician's comment

Babesiosis is a differential diagnosis of malaria that should be considered in any patient with unexplained febrile illness, who resides or has recently traveled to an area endemic for *Babesia* or who has received a blood transfusion in the past 6 months. The clinical presentation of the disease varies from asymptomatic or limited infection to a severe and life-threatening picture of infection in immunocompromised patients. Anamnesis is essential for distinguish this infections, in particular, the place of life, recent travels, the notion of tick bites or the risk of exposure to ticks. In this report, the diagnosis of malaria, initially suspected in the presence of intraerythrocytic parasites, could quickly be ruled out through interrogation, although some cases of "airport malaria" have already been described [8]. However, the absence of travel to endemic areas and the presence of several parasites in erythrocytes, with a characteristic "Maltese cross", made it possible to correct the diagnosis, which was later confirmed by PCR. Hemophagocytic lymphohistiocytosis is a rare but potentially fatal disease. It is defined by clinical (fever and splenomegaly), biological (cytopenias, hypofibrinogenemia, hyperferritinemia and hypertriglyceridemia) and cyto-histological (medullary, splenic or lymph node hemophagocytosis) criteria. Many etiologies of hemophagocytic lymphohistiocytosis have been described, including malignant blood diseases, solid cancers, connectivity and infections, whether bacterial, viral, fungal or parasitic. The vast majority of hemophagocytic lymphohistiocytosis cases described during babesiosis have been reported in immunocompromised or splenectomized patients. We report here a case of hemophagocytic lymphohistiocytosis in a non-immunocompromised patient with a functional spleen. The main risk factor in this case is related to his age. Although it presented several risk factors for hemophagocytosis-related mortality (age, anemia < 10 g/dL, thrombocytopenia $< 100{,}000$, ferritinemia > 500 µg/L, jaundice and increased alkaline phosphatases) [9], the rapidly favourable clinical course allowed to avoid a specific hemophagocytosis treatment.

Conclusion

Babesiosis is a differential diagnosis of malaria that should be considered in patients returning from endemic areas, particularly in the Northeastern United States. From a microbiological point of view, the presence of red cells poly-parasitized by piriform trophozoites arranged in the "Maltese cross" is strongly suggestive of babesiosis and distinguishes it from *Plasmodium* infection. These 2 infections can be easily confounded apart from possible tick bite stigmas. The diagnosis will have to be confirmed by PCR on the species level. *Babesia* infection can be potentially severe and can be complicated by a hemophagocytic lymphohistiocytosis that should be sought in the event of suggestive clinical-biological abnormalities.

Consent

The patient gave his free, informed, and signed consent for the publication of his case.

Conflicts of interest: None of the authors has any conflict of interest to disclose.

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