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LETTER TO THE EDITOR

Low-virulent *Babesia venatorum* infection masquerading as hemophagocytic syndrome

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Dear Editor,

Babesiosis is a tick-borne zoonosis caused by intraerythrocytic protozoa. In Europe, it is probably underdiagnosed [1–4]. Symptoms can range from a mild flu-like disease to rapid death in immunocompromised patients.

We report here on a 52-year-old splenectomized male, with a medical history including T cell large granular lymphocytic leukemia (T-LGL), cyclic neutropenia, idiopathic trombocytopenic purpura, hypogammaglobulinemia, bouts of hemolytic anemia, and treatment with rituximab 2 years earlier. The patient was admitted to the Department of Hematology in March 2015 due to fever, muscle pain, and dark urine (not unusual as his hemolytic anemia often exacerbated during unspecific infections). His medication consisted of cyclosporine 150 mg/day, prednisolone 10 mg/day, human immunoglobulin 25 g i.v./4th week, fluconazole 100 mg/day, co-trimoxazole 1600 mg/320 mg twice weekly, and valaciclovir 100 mg/day. A bone marrow examination showed a few phagocytosing macrophages and monocytosis. A tentative diagnosis of hemophagocytic syndrome was entertained with supporting laboratory evidence including elevated triglycerides, ferritin, and soluble interleukin-2-receptor (Table 1). The patient was given cefotaxime i.v., became afebrile and was discharged. In April, he was readmitted with fever and became spontaneously afebrile within a few days without any specific treatment. In May, he was admitted again because of fever with rigors, this time to the Department of Infectious Diseases. Laboratory investigations revealed a similar picture as on the admission in March. A laboratory technician in the Department of Clinical Chemistry reviewed the white blood cell smear microscopically at 4th of May since the instrument gave an automatic alarm concerning the shape of some of the white cells. She noticed piriform inclusions in the erythrocytes (Fig. 1) and we found 4% *Babesia* parasites. Serology [2] was negative for *B. microti* IgG/IgM and *B. divergens* IgM and positive for *B. divergens* IgG (1:128). Molecular characterization [2, 5] with PCR and sequencing (18S rRNA) identified *B. venatorum*.

The patient was put on quinine and clindamycin for 1 week and quickly became afebrile. He was discharged with azithromycine and atovaquone for a further 5 weeks. He has been well since then.

Retrospectively, saved thin blood films and a bone marrow smear were re-evaluated. Although parasites were found on all blood slides, and in the bone marrow smears made 2 months earlier, he did not develop severe disease, perhaps due to the prophylactic administration of co-trimoxazole. This drug is not a first line agent but has been used anecdotally in severe *Babesia* infections [6]. The hemolysis and thrombocytopenia resolved at the first admission in March during treatment with cefotaxim. However, in April, there was a similar resolution without any new therapy. This fluctuation in parasitemia for several months may partly represent the natural course of a *Babesia* infection but could also be due to the injections with human immunoglobulin (for dates, see Table 1). As up to 50% of tick-infested individuals, the patient could not recall a recent tick-bite. We assume, however, that the infection originated from such a bite that went unnoted. More than 2 years had passed since his last blood transfusion, and in the meantime he recalled no history of recurrent fever.

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Table 1 Laboratory investigations in relation to admissions and treatments (reference values in parenthesis)

	1st adm[a,d]	2nd adm[b,d]					3rd adm[c,d]						
	7 Mar	13 Mar	17 Apr	19 Apr	23 Apr	27 Apr	2 May	3 May	4 May	5 May	7 May	10 May	18 May	24 June
Hb, g/L (134–170)	128	115	141	137	141	141	140	123	123	118	117	119	141	150
WBC, $\times 10^9$/L (3.5–8.8)	20.5	15.5	15.1	15.2	15.9	15.2	16.7	14.2	19.9	18.9	14.3	14.5	14.8	19.4
Platelets, $\times 10^9$/L (145–348)	74	250	511	75	139	204	100	77	59	62	71	252	271	251
LDH, μkat/L (1.8–3.4)	21	13	14					24	27	29	23	14	6.5	3.1
Haptoglobin, g/L (0.24–1.90)	<0.1	<0.1		<0.1				<0.1						
Ferritin, μg/L (27–365)	8728	5409	2711	2596	3843	2114				6618				1048
Parasitemia, %	POS[e,*]		1.0*	0.7*	0.1*	0.3*	2.0*		4.0	1.0	0.25	scanty	NEG	NEG
CRP, mg/L (< 3)	40	7.2	24	31	5.9	3.7	28	50	75	77	33	6.6		5
TG, mmol/L (0.4–2.6)	3,8	3.4								4.1				
Bilirubin, μmol/L (5–25)	21	7		13			26		25	17	9	7	7	
Soluble IL-2 R, kU/L (< 700)	4851			2353				3905						
Creatinine, μmol/L (60–105)	82	81	80	71			87		106	110			85	71

[a] Cefotaxim 7–13th of March

[b] No specific treatment

[c] Quinine + clindamycin 4–11th of May, atovaquone + azithromycin 12th of May–14th of June

[d] Intravenous immunoglobulin given 19th Feb, 19th March, 13th April, 11th May, and 11th June.

[e] Several percent *Babesia* parasites found in bone marrow smear

**Babesia* parasites found when old slides were investigated retrospectively at the time of diagnosis

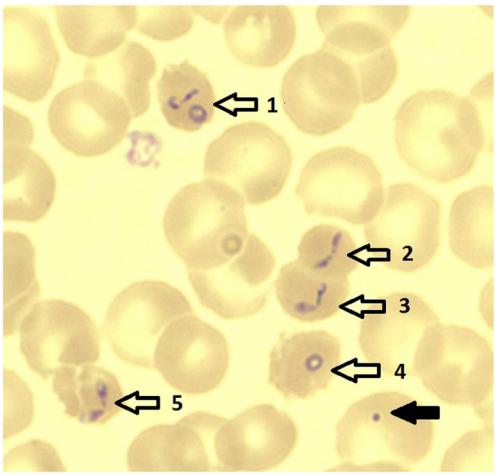

Fig. 1 A blood smear (×100 magnification under oil) from 4th of May showing red blood cells infected with *Babesia* parasites. Arrow (1) indicates a red blood cell containing both pear-shaped and round forms; (2), (3), and (5) show typical paired pear-shaped forms; (4) shows a round form of parasite. The solid, black arrow indicates a Howell Jolly body

A tentative diagnosis of hemophagocytic syndrome was first entertained as the patient fulfilled the criteria. *Babesia* infection with a reactive hemophagocytosis has been reported earlier but only in *B. microti* infection [7–9] and not in *B. venatorum* infection.

In Sweden, this is the first PCR-confirmed case of *B. venatorum*, although in ticks, all three *Babesia* spp. known to be pathogenic for humans (*B. divergens*, *B. venatorum*, *B. microti*) are present [10].

Compliance with ethical standards

Informed consent Informed consent was obtained from the patient described.

Conflict of interest The authors declare that they have no conflict of interest.

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