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Clinical Pearls

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Parvovirus B19-associated transient aplastic crisis following *P. falciparum* malaria and post-artesunate delayed haemolysis in a returning traveller

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A 38-year-old, previously healthy Italian man was hospitalized at the University Hospital of Antwerp, Belgium, for recurrence of fever, 7 days after treatment for thick smear-positive *Plasmodium falciparum* malaria in Yaoundé, Cameroon (Day 0, Figure 1). He had not taken any malaria chemoprophylaxis. In Yaoundé, he did not have anaemia, but bilirubin levels were increased (8 mg/dL; normal value < 1.2 mg/dL). Parasitaemia levels were not documented. He had been treated with artesunate 2.4 mg/kg intravenously at 0, 12 and 24 h, followed by quinine 500 mg base orally every 8 h for 3 days, and he returned to Europe symptom-free. At the time of admission in Antwerp, the blood smear was negative for malaria. The patient was empirically treated with four tablets of dihydroartemisinin-piperaquine 320/40 mg once daily for 3 days. Fever (38.3°C) persisted for 1 week. On Day 14, the haemoglobin level dropped to 10.5 g/dL, with increasing LDH and undetectable haptoglobin. No schistocytes were detected in a peripheral blood smear. A direct antiglobulin test was positive for IgG, and negative for complement. Causes of anaemia considered at this stage included post-artesunate delayed haemolysis (PADH) and autoimmune haemolytic anaemia, possibly induced by malaria, underlying infections or antimalarial drugs.

Paradoxically, at a haematocrit value of 0.31 (normal range 0.39–0.49), the patient's reticulocyte count was 2.0 (absolute reticulocyte count 73 000 cells/μL) (Supplementary Figure S1). The reticulocyte production index (RPI), a correction of the reticulocyte count for red blood cell depletion and for reticulocyte maturation time, was < 1, indicating that haemolysis was complicated by a hypoproliferative state.[1] From Day 17 through Day 20, mild neutropenia (1000–1500; normal 1800–7700 cells/μL) and presence of atypical lymphocytes were observed.

Serum tested negative for hepatitis B surface antigen, HCV, HIV and treponemal antibodies, and indicated past infections with CMV, EBV and dengue. On Day 15, IgM and IgG antibodies against parvovirus B19 (B19V) were detected. B19V-associated transient aplastic crisis (TAC) was suspected. B19V is a single-stranded DNA virus that spreads through respiratory secretions, blood-derived products or via materno–fetal transmission. Infection causes erythema infectiosum, hydrops fetalis, arthropathy and other pathologies, including TAC.[2] B19V targets erythroid progenitors and infection precipitates anaemia in haemolytic conditions (e.g. sickle cell disease). Infection confers lifelong protective immunity.[2]

When haemoglobin levels decreased to 6.1 g/dL on Day 19, two units of packed red blood cells were transfused. On Day 23, the RPI increased to 3.1, reflecting recovery from infection and increased compensatory erythropoiesis. After 3 months, anti-B19V IgG persisted and IgM antibodies were no longer detected.

Falciparum malaria and B19V co-infections have been identified as important contributors to anaemia in endemic countries,[3] but are rarely reported in travellers.[4] B19V prevalence in febrile returning travellers may be underreported, because B19V diagnostics are not part of the routine work-up. PADH in returned travellers rarely leads to transfusion-dependent anaemia.[5]

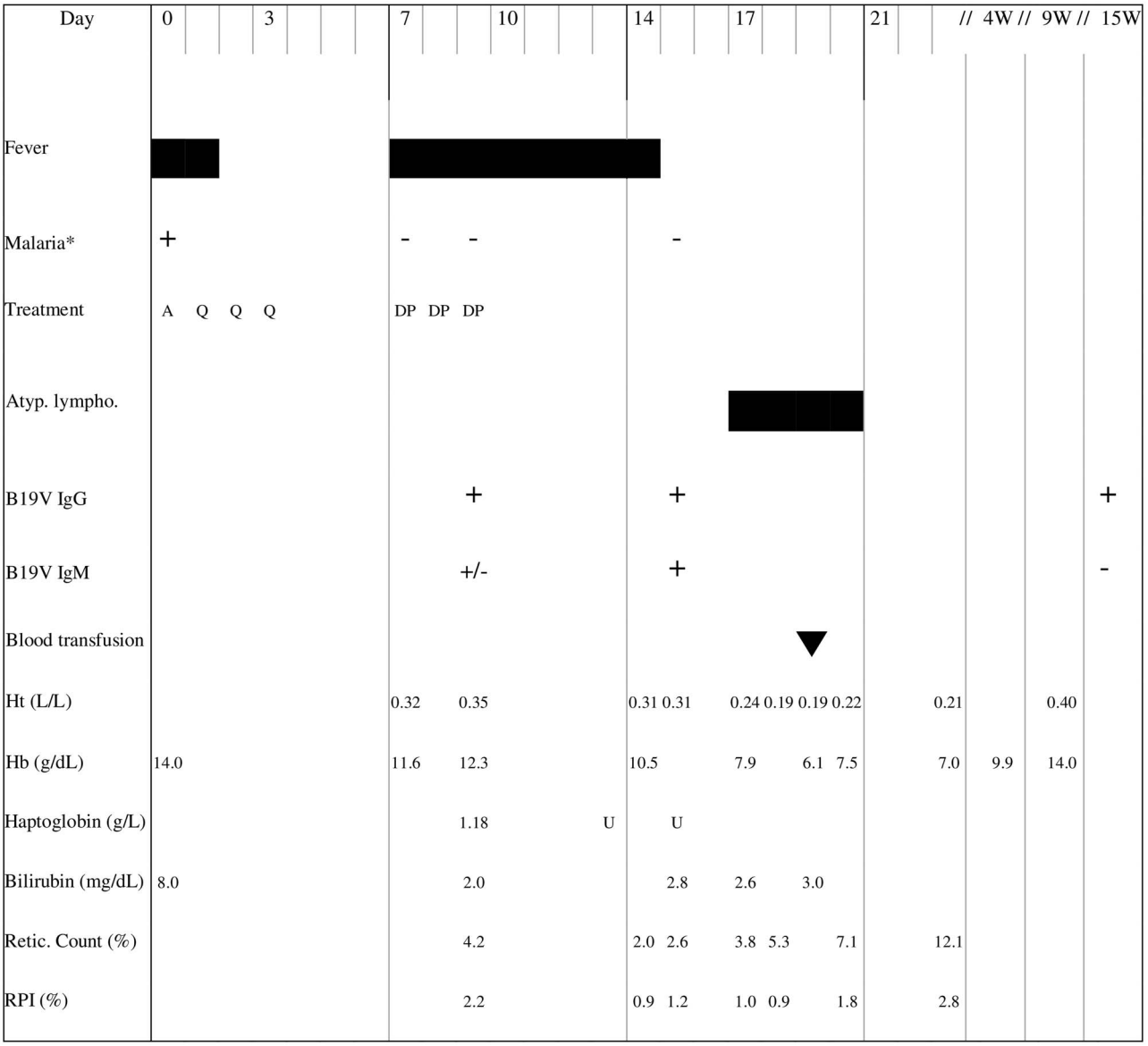

Figure 1. Clinical and laboratory data of a traveller with B19V-associated TAC following *P. falciparum* malaria and post-artesunate delayed haemolysis. Fig. 1. (Legend) Day 0 is the time of malaria diagnosis (Cameroon, 29 June 29 2021). W denotes weeks. Malaria* denotes 'thick blood smear'; Treatment (for malaria): A, artesunate; Q, quinine; DP, dihydroartemisinin-piperaquine; Atyp. lympho, atypical lymphocytes detected; B19V, parvovirus B19; IgG, immunoglobulin G; IgM, immunoglobulin M; Ht, haematocrit; Hb, haemoglobin; ▼ Blood transfusion of two units of red blood cells; retic. Count: reticulocytes, expressed as a percentage of red blood cells; + positive; − negative; +/− equivocal result; U, undetectable; RPI, reticulocyte production index. The formula used to calculate the RPI is: RPI = (reticulocyte count * Ht/0.45)/maturation correction, where 0.45 is the normal Ht-value; the maturation correction reflects the longer life span of premature reticulocytes and is corrected for Ht-values ≥0.40 (L/L) by factor 1.0, for Ht-values 0.30–0.39 by 1.5, for Ht-values 0.20–0.29 by 2.0 and for Ht-values < 0.20 by 2.5. Interpretation: an RPI > 3% shows a normal marrow response to anaemia. An RPI < 2% is an inadequate response to correct anaemia[1]

However, a B19V-associated TAC that impairs erythropoiesis for 7 to 10 days after malaria-related haemolysis or PADH is potentially life-threatening. TAC can be adequately managed by timely blood transfusions.[2] Reticulocytopenia and an RPI < 2% following *P. falciparum* malaria should alert clinicians to concomitant B19V infection.

Supplementary data

Supplementary data are available at *JTM* online.

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Author roles

R.H. conceptualized and developed the initial draft manuscript. All authors reviewed and approved the final manuscript.

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