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Woman in her 40s with bloody vomit and muscle and joint pain

EDUCATIONAL CASE REPORT

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A woman in her forties developed a fever after a trip to East Africa. She was admitted to hospital after a week of muscle and joint pain and several episodes of bloody vomiting. Tests revealed significant thrombocytopaenia caused by a serious condition.

A woman in her forties was admitted to hospital in a reduced general condition, with headache, feverishness, myalgia, joint pain and abdominal pain lasting six days. She had been vomiting blood for the three days prior to admission. Her symptoms began on the day she returned from a stay of several weeks in her homeland in East Africa. She consulted her general practitioner (GP) on day three of her illness and visited the out-of-hours clinic on the following two days where she was treated with paracetamol and anti-inflammatory medication. However, her condition did not improve. The woman was then admitted to hospital as an emergency. She reported that several acquaintances contracted malaria during her trip, and that she had received numerous mosquito bites. She had not taken malaria prophylaxis. Upon admission, the patient was bedridden and in a reduced general condition. She was awake and alert, afebrile, with a blood pressure of 114/97 mmHg, regular pulse of 82, and a respiratory rate of 17 per minute. Clinical examination revealed a clot on her lower lip and blood spots on the oral mucosa. There were no signs of conjunctivitis, a rash or jaundice. Her abdomen was soft with normal bowel sounds but diffusely tender to palpation, most notably in the epigastric region. Initial blood tests showed haemoglobin 16.4 g/dL (reference range 11.7–15.3), leukocytes 3.99 × 10^9/L (3.5–10.0), of which neutrophils were 2.32 × 10^9/L (1.80–7.40), platelets 7 × 10^9/L (145–390), haematocrit 49 % (35–46), erythrocytes 5.7 × 10^{12}/L (3.9–5.2), D-dimer 3.06 mg/L FEU (< 0.5), INR 1.0 (< 1.2), sodium 133 mmol/L (137–145), haptoglobin 2.89 g/L (0.40–1.90), albumin 26 g/L (35–43), AST 97 U/L (< 35), ALT 39 U/L (< 45); erythrocyte sedimentation rate (ESR) 73 mm (< 20) and CRP 43 mg/L (< 5). Creatinine, urea, reticulocyte count, bilirubin and TSH were normal, as were the ECG and chest X-ray. PCR (nucleic acid amplification rapid tests) for influenza A and B and SARS-CoV-2 in nasopharyngeal secretions were negative, as was the rapid test for malaria in blood.

The most significant blood test findings were elevated haemoglobin levels, marked thrombocytopenia and moderate hyponatraemia. A low threshold should be maintained for ruling out malaria in patients presenting with fever after staying in an endemic region. Severe thrombocytopenia and bleeding can occur in severe malaria, but normal reticulocyte and bilirubin levels, along with elevated haptoglobin and haemoglobin, indicated that active haemolysis was unlikely. The malaria rapid test, which has high sensitivity in falciparum malaria with high-grade parasitaemia, was negative. However, fever after travel to tropical regions is often caused by common domestic infectious diseases.

Ruling out seasonal influenza and other respiratory viral infections, such as COVID-19, in the event of non-specific symptoms, should be part of the initial diagnostic work-up, along with blood and urine cultures, supplemented by serological tests where appropriate.

Due to the patient's generally reduced condition, haematemesis, pain and tenderness in the upper abdomen, a CT scan of the abdomen and pelvis was performed on the day of admission to rule out conditions such as perforated gastric ulcer or bleeding in the spleen or liver. The scan showed periportal oedema, free fluid in the gallbladder bed and pelvis. The fluid did not have the density of blood. There were no signs of cholecystitis or free air in the abdominal cavity. A small amount of pleural effusion was observed, along with liver changes consistent with hepatitis. Anti-inflammatory medication was discontinued, and intravenous pantoprazole 40 mg twice daily was initiated, along with saline infusion to correct hyponatraemia. The gastrointestinal surgeon concluded there was no suspicion of cholecystitis or cholangitis. The patient's thrombocytopenia was discussed with the duty haematologist, who suspected infection-induced immune thrombocytopenia (ITP). The patient was given 1 g/kg of intravenous immunoglobulin (IVIg), 40 mg of dexamethasone and one unit of platelets.

In ITP, thrombocytopenia is primarily caused by immune-mediated platelet destruction, either as a primary condition or secondary to other diseases such as systemic lupus erythematosus, HIV, chronic lymphocytic leukaemia or lymphoma. The condition can affect both children and adults. The diagnosis is largely based on the exclusion of other causes of thrombocytopenia, such as pseudothrombocytopenia, infections, antiphospholipid syndrome, rheumatic inflammatory diseases, malignant bone marrow disorders, liver disease and certain medications. Microangiopathic processes such as thrombotic thrombocytopenic purpura, haemolytic-uraemic syndrome and disseminated intravascular coagulation were also relevant differential diagnoses. The absence of haemolysis and kidney failure indicated that these conditions were unlikely. Treatment of ITP depends on the platelet count and whether there is active bleeding. First-line treatment consists of steroids and intravenous immunoglobulin (IVIg) (1).

The following day, the patient was hypotensive, with a blood pressure of 97/80 mmHg. She was clinically stable and afebrile, but tender to palpation in the epigastric region and under the right costal margin. Her platelet count had increased to 21, and no further episodes of haematemesis were reported. Intravenous treatment with piperacillin/tazobactam was initiated out of concern for overlooking a possible biliary tract infection. Blood cultures taken upon admission were sterile, and no bacterial growth was detected in the urine sample. PCR testing of nasopharyngeal secretions for a panel of common respiratory pathogens was negative. Microscopy of a thick blood smear showed no evidence of malaria parasites. Serological tests were ordered for hepatitis A (HAV), B (HBV) and C (HCV), dengue virus, mononucleosis viruses (Epstein-Barr virus (EBV) and cytomegalovirus (CMV)), HIV, parvovirus B19, as well as toxoplasmosis and syphilis.

In cases of bleeding disorders occurring as part of a febrile illness after travel to tropical regions, several differential diagnoses must be considered. In addition to severe malaria, leptospirosis and extremely rare tropical diseases such as yellow fever and other viral haemorrhagic fevers should be considered based on travel history, exposure and information about ongoing infectious outbreaks at the travel destination. The clinical presentation, laboratory data and epidemiological context in this case did not warrant special isolation measures.

A blood smear was prepared due to abnormal results from the automated analysis. Digital microscopy of the peripheral blood smear revealed no schistocytes but showed 6.3 % plasma cell-like cells and atypical lymphocytes (Figure 1), along with a very large number of damaged cells (nuclear shadows), which accounted for 58 % of the leukocytes. The laboratory doctor considered the findings consistent with a viral illness, such as dengue fever. A new blood smear prepared using a gentle centrifugation method showed that the damaged cells largely consisted of plasma cell-like cells, now comprising 33 % of the leukocytes. The microbiology department reported a positive dengue virus test (IgG, IgM and NS1 antigen) the day after admission. On repeat examination of the patient, petechiae were observed on the extremities, along with larger ecchymoses caused by pressure from the blood pressure cuff and blood sampling (Figure 2). Serum albumin had fallen to 16 g/L. Intravenous and oral rehydration therapy was continued.

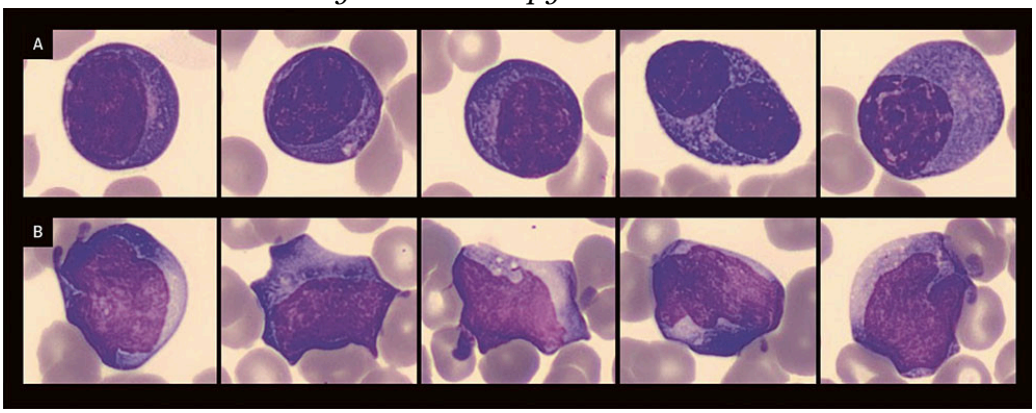

Figure 1 Examples of plasma cells (a) and reactive lymphocytes (b) in the patient's peripheral blood smear.

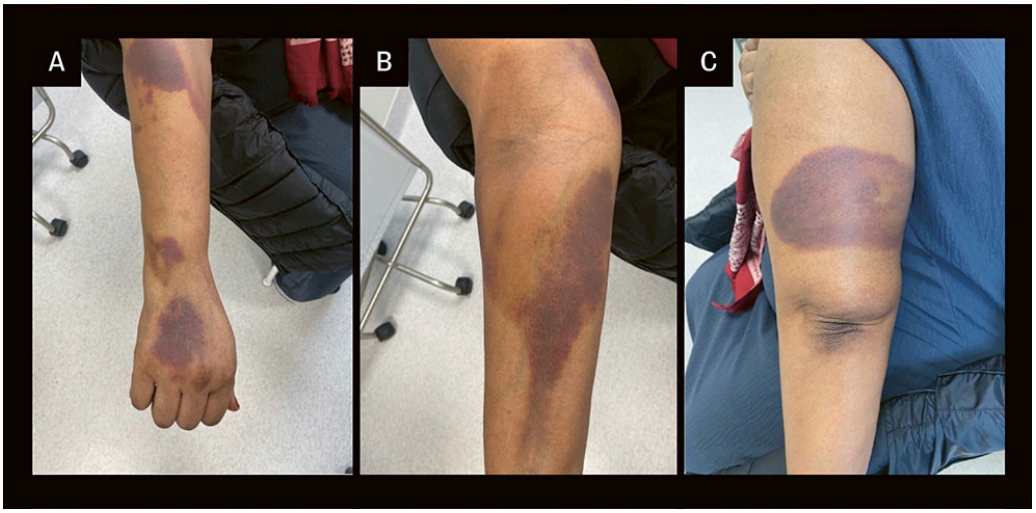

Figure 2 Cutaneous bleeding

It was now confirmed that the patient had a severe dengue virus infection: dengue haemorrhagic fever. Elevated haemoglobin and haematocrit levels, along with hypoalbuminemia at admission, as well as ascites and pleural effusion, reflected significant capillary leakage, which is characteristic of this condition (2). The patient also experienced cutaneous bleeding following blood pressure measurements, and repeated episodes of gastrointestinal bleeding. However, the condition did not progress to circulatory collapse.

Treatment with dexamethasone and antibiotics was discontinued, and no further platelet transfusions or IVIg were administered. Due to diminishing abdominal pain and cessation of haematemesis, the planned gastroscopy was not performed. A CT scan of the head conducted on day two due to severe dizziness showed no signs of intracranial bleeding. Serological confirmation tests confirmed the diagnosis, with positive results for viral antigen, IgM and IgG, as well as a positive PCR test for dengue virus RNA. PCR analyses for Zika and chikungunya viruses were performed simultaneously, which all proved to be negative. Serostatus for hepatitis B virus, hepatitis C virus and HIV was negative, while IgG antibodies against hepatitis A virus, toxoplasma, parvovirus, Epstein-Barr virus and cytomegalovirus were detected, which is consistent with past infection. A positive anti-syphilis screening test was observed, but confirmatory tests at the reference laboratory were negative. At discharge on day five after admission, the patient was showing signs of a clinical improvement, with a rising platelet count exceeding 100 × 10^9/L and normalised haemoglobin levels. The patient was informed about the potential risk of a new dengue virus infection in future trips to her homeland, which could lead to severe illness. She was also advised on the importance of preventive measures against mosquito bites. However, the Norwegian health authorities' advice on vaccination was not considered straightforward in this situation, and the discharging doctor did not give a recommendation for vaccination (3).

Discussion

Dengue virus infection is endemic in tropical and subtropical regions worldwide (Figure 3) (4), and epidemics have caused major socioeconomic problems over several decades. It is estimated that dengue virus causes up to 400 million cases of illness annually, placing a particular burden on the health services in low-income countries (5, 6). The Norwegian Surveillance System for Communicable Diseases (MSIS) reported 133 cases in Norway in 2024, and over the past ten years, the annual incidence has varied between approximately 30 and 100 cases (3). The rapid spread of dengue virus is linked to climatic and demographic changes and weakened vector control over the past 30–40 years.

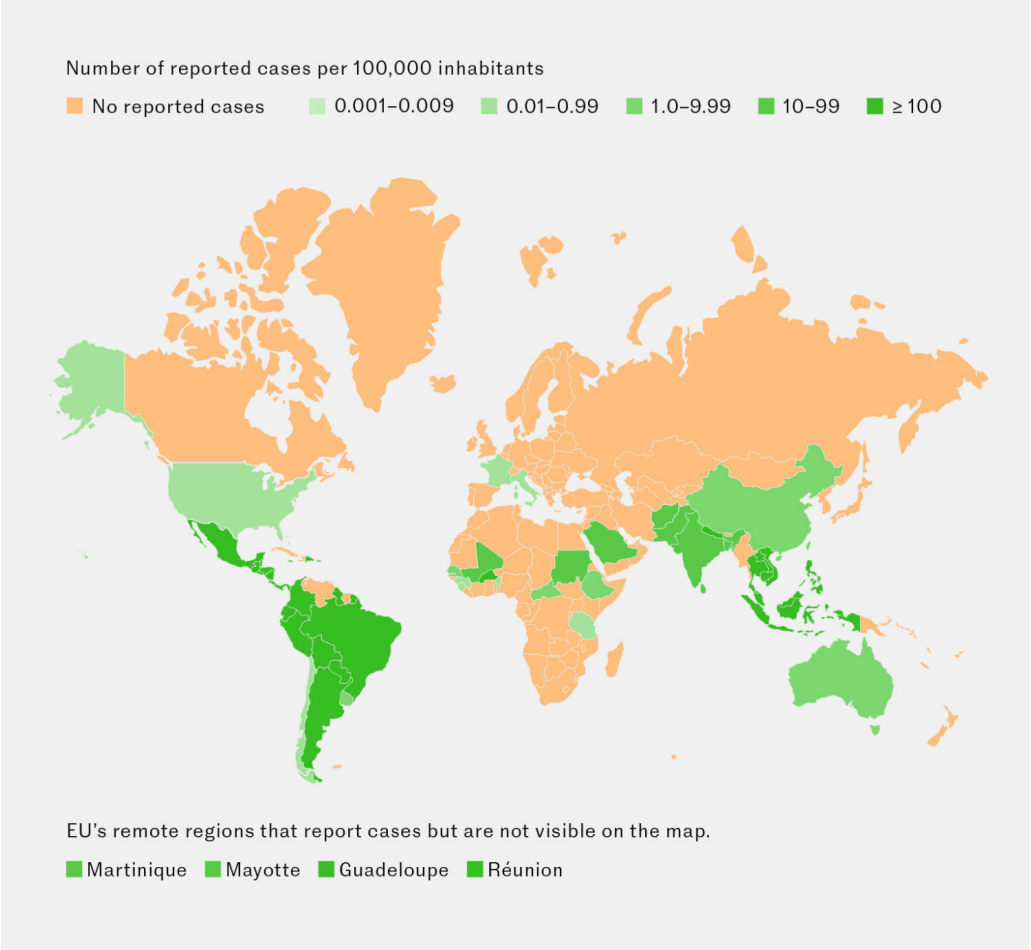

Figure 3 Incidence map of dengue fever cases in the fourth quarter 2024 (4).

The virus is a member of the flavivirus family and includes four distinct human-pathogenic serotypes that are transmitted by daytime-biting mosquitoes in the Aedes family. Most infections are asymptomatic, but about one in four develop dengue fever. The condition is usually mild and self-limiting, lasting 2–7 days, and occurs 3–10 days after being bitten by an infected mosquito (7). The early phase of dengue fever can resemble other arboviral infections, as well as illnesses such as influenza and malaria. Characteristics are fever, headache, severe muscle and joint pain, retro-orbital pain, and about half of patients experience a maculopapular rash, nausea and abdominal pain. The febrile phase can be biphasic, and minor bleeding symptoms can occur.

Typical laboratory abnormalities include neutropenia, thrombocytopenia, elevated liver transaminases and hyponatremia. The disease was traditionally classified according to severity: dengue fever, dengue haemorrhagic fever and dengue shock syndrome. More recent clinical categorisation distinguishes between dengue fever and severe dengue. The course of illness can be chronologically divided into a febrile phase (lasting 2–7 days), a critical phase (24–48 hours) and a recovery phase (2–4 days). Warning signs during the critical phase, such as persistent vomiting, severe abdominal pain, facial oedema, mucosal bleeding, severe fatigue, hepatomegaly, intense thirst, pale and cold skin, and rising haematocrit, predict an increased risk of developing severe dengue virus infection (8, 9). Complications can include hepatitis, myocarditis, pancreatitis and central nervous system involvement. A case of

encephalitis has previously been reported in the Journal of the Norwegian Medical Association (10). Recovery usually occurs without lasting effects, but post-infectious fatigue and depression are not uncommon. The fatality rate for dengue is below 1 %, rising to 2–5 % in severe cases and up to 20 % if left untreated (5, 8).

Infection with a specific serotype provides lifelong immunity against that serotype. Our patient's positive IgG result on the rapid qualitative test performed less than one week into the illness supported the suspicion that she had previously been infected with dengue virus, probably with a different serotype. Severe dengue rarely occurs during primary infection. The risk increases with reinfection by a different serotype. Immune complexes consisting of virus and non-neutralising antibodies against the serotype that previously infected the patient are taken up by phagocytes. This results in increased viral replication, known as antibody-dependent enhancement (7–9), and contributes to increased production of inflammatory mediators, endothelial dysfunction, coagulopathy and capillary leakage. Age, time since the previous infection, antibody concentration and serotype are also important factors in the development of severe dengue virus infection (2, 7–9). The bleeding tendency can result from factors such as thrombocytopenia due to bone marrow suppression, increased platelet destruction, apoptosis, extravasation, platelet function defects, coagulopathy and endothelial damage (11, 12).

Diagnosis of the viral infection is typically based on a combined immunochromatographic antigen and antibody test that includes IgM and IgG. The detected antigen component is a non-structural viral protein (NS1), which can be identified during the first week of illness and indicates a current or recent dengue virus infection (Figure 4). The test is easy to perform but has limitations in terms of sensitivity and specificity. Confirmatory analyses are therefore often performed using other methods. Increasing IgM and/or IgG titres in paired samples can also support diagnosis when there is clinical suspicion of disease despite negative antigen and IgM results in the initial test. The National Medical Microbiological Reference Function for diagnosing viral imported infections at Oslo University Hospital also offers supplementary serotype-specific antibody testing. PCR analysis can detect viral RNA during the febrile phase in the first week of illness. The IgM response appears 3–5 days after primary infection and later in secondary infection, while IgG typically rises within 1–3 weeks, but occurs much earlier and often more intensely in reinfections (Figure 5) (7, 13).

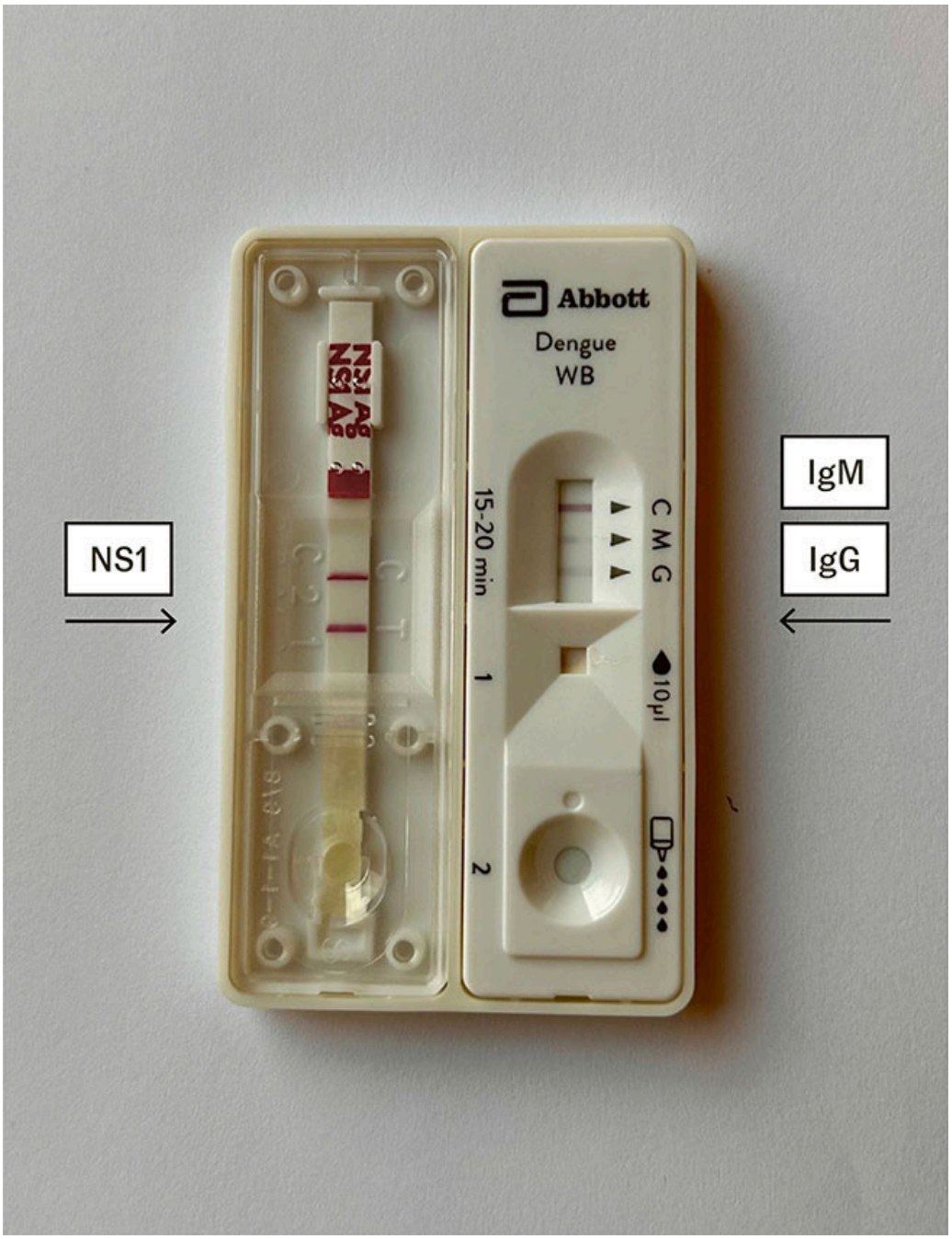

Figure 4 Positive immunochromatographic rapid test for viral antigen (NS1), IgM and IgG in the patient.

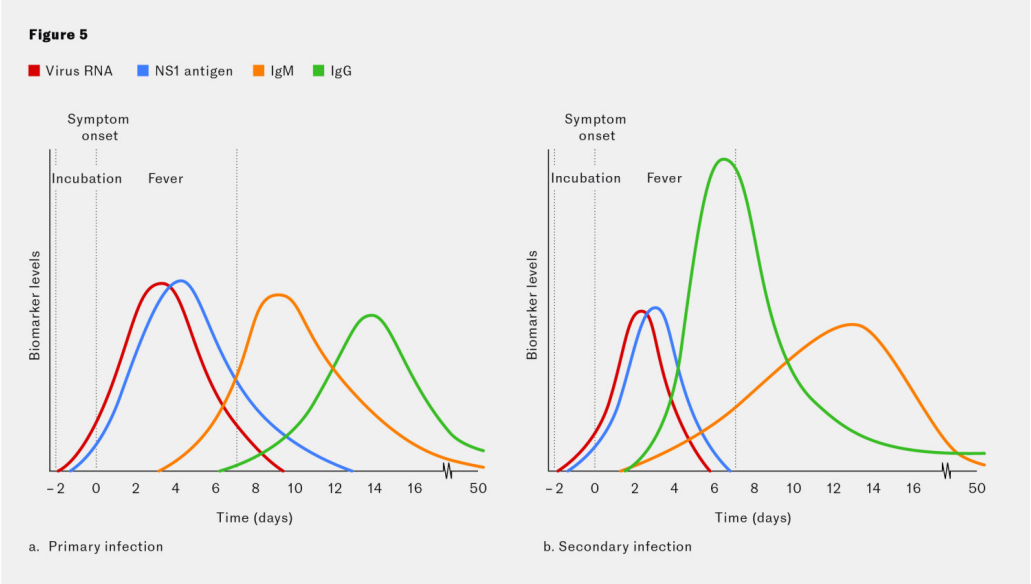

Figure 5 Time window for various diagnostic tests in primary and secondary dengue virus infection.

Atypical lymphocytes are reactive lymphocytes that can be seen in viral diseases such as mononucleosis. The cells are large, with abundant blue cytoplasm (indicating active DNA synthesis), and resemble a hybrid between lymphocytes and monocytes (Figure 1b). A marked increase in the number of plasma cells is, however, less common. Plasmacytosis is a common finding in blood smears from patients with dengue fever (14). In a prospective study, polyclonal plasma cells were found in 73 % of patients with dengue fever during the first week of illness (15). In some cases, the plasmacytosis can be so pronounced that plasma cell leukaemia must be considered as a differential diagnosis (16). Dengue fever is treated symptomatically, as no specific antiviral treatment is currently available. The World Health Organization (WHO) recommends hospital admission when warning signs appear (5, 6). Rehydration therapy is a core part of treatment, but platelet transfusion should only be considered in cases of bleeding and severe thrombocytopenia ($< 20 \times 10^9$/L). Steroid treatment is not recommended for dengue shock syndrome, and there is no evidence that IVIg therapy improves the prognosis for severe dengue.

Vaccine development has been challenging, partly due to the antigenic variation between the different serotypes and the risk that cross-reactivity could trigger a more severe infection in patients without prior exposure to the virus. The vaccine available in Norway, Qdenga, is tetravalent and based on live attenuated dengue virus type 2, which is genetically modified with a capsid antigen from the other three serotypes. Experience with vaccinating tourists is limited. The Norwegian Institute of Public Health recommends that the vaccine only be offered to individuals who have had a primary infection and who are traveling to endemic areas (3). Swedish authorities allow vaccination of dengue-naive individuals for long-term travel to endemic regions, while the WHO recommends the vaccination of children in highly endemic areas (5). The immune response triggered by secondary dengue virus infection provides broad immunological protection. The risk of severe illness during a third or fourth infection is low (5), which supports the decision not to vaccinate our patient.

Summary

Dengue fever is a global public health issue and a relatively common cause of fever in individuals returning from endemic areas. Dengue haemorrhagic fever is less common and is mainly seen in secondary infections with a different serotype of the virus. The combination of thrombocytopenia and reactive plasmacytosis in a blood smear can serve as a diagnostic clue in patients who have recently returned from dengue-endemic areas. Although there is no specific treatment, these patients must be monitored and treated in hospital with active rehydration therapy.

The patient has consented to publication of the article.

The article has been peer-reviewed.

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