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A 42-Year-Old Traveller Returning from Thailand With Fever and Thrombocytopenia

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Clinical Presentation

History

A 42-year-old German man presents to a hospital in Germany. For the past 6 days he has had a fever of up to 40°C (104°F), arthralgias and retro-orbital pain.

The day before presentation, he returned from a 10-week trip to Thailand, where he had spent 2 months on Little Koh Chang, an island in the Andaman Sea. After that, he spent 5 days in Hua Hin at the Gulf of Thailand and another 5 days in Bangkok. He has not taken any antimalarial chemoprophylaxis, which is in line with the national recommendations in his home country for this trip.

His past medical is unremarkable.

Clinical Findings

On examination, GCS is 15/15, Temperature 39.1°C (102.4°F), BP 156/80 mmHg, pulse 106 beats per minute, respiratory rate 16 breath cycles per minute, SpO_2 95% on ambient air. There is no skin rash and no lymphadenopathy. Upon auscultation, his chest is clear. Abdominal examination does not show any intercostal tenderness, no tenderness on palpation and no organomegaly.

Laboratory results

FBC shows thrombocytopenia of 81 × 10^9/L (reference: 150–300) and is otherwise normal, CRP 55 mg/L (reference: <5), AST 62 U/L (reference: 10–50 U/L), ALT 106 U/L (reference: 10–50).

Dengue NS1 antigen test is negative, the rapid diagnostic test for malaria (which detects *Plasmodium falciparum*-specific histidine-rich protein II and the panmalarial aldolase) is negative.

Questions

1. What is your differential diagnosis?
2. How do you proceed?

Discussion

A 42-year old German man presents with a fever for 6 days, retro-orbital pain and arthralgias after extensive travel in southern Thailand. He is febrile, but otherwise physical examination is unremarkable. Full blood count reveals thrombocytopenia, CRP and liver function tests are slightly elevated. Rapid diagnostic tests for dengue and malaria are negative.

Answer to Question 1

What Is Your Differential Diagnosis?

Given the clinical syndrome of fever, retro-orbital pain, arthralgias and thrombocytopenia after a visit to Thailand, the most likely differential diagnosis to suspect is dengue fever. Dengue is the most common febrile tropical disease seen in returning travellers from South and South-east Asia. The duration of fever, however, is borderline long for dengue. The dengue NS1 antigen test reflecting dengue viraemia may already be negative at day 6 and does not reliably rule out the infection. Chikungunya and Zika are additional important arboviral infections to suspect.

Influenza is another important differential diagnosis to have in this patient. Fever and associated symptoms are usually of shorter duration but may last as long as 8 days. Acute HIV infection may present with persistent fever and thrombocytopenia, and possible exposures should definitely be inquired. Enteric fever presents with persistent febrile temperatures and otherwise non-specific symptoms. Because food hygiene in Thailand is overall very good, typhoid and paratyphoid fever are nowadays rarely seen imported from

this country. Malaria has to be ruled out in any febrile traveller returning from a possibly endemic area, thrombocytopenia also being a hallmark feature. Malaria is nowadays rarely seen in travellers returning from Thailand; however, overlooking it could be lethal. A negative rapid diagnostic test (RDT) does not rule out malaria because RDTs are of unsatisfactory sensitivity for diagnosis of non-falciparum malaria. Also, in falciparum malaria high parasitaemia may cause a prozone phenomenon with a false negative RDT.

Answer to Question 2

How Do You Proceed?

To reliably rule out dengue and indeed any of the arboviral infections, serology at this point is the diagnostic test of choice, because viraemia is short and IgM should be positive by day 6 of fever. Convalescent samples taken 10 to 14 days later should show a further rise in titres.

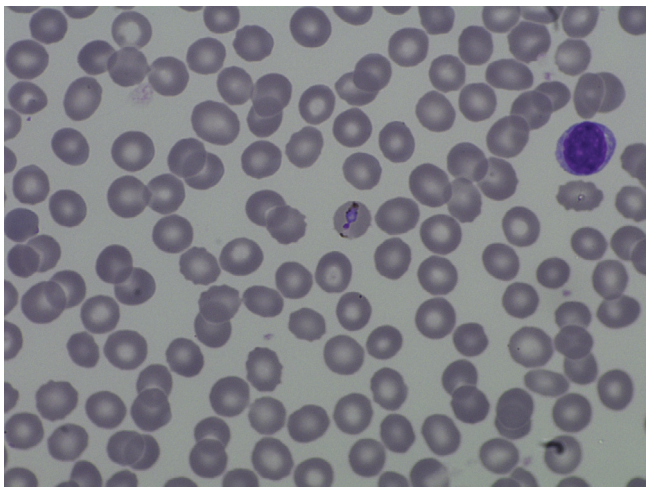
For diagnosis of influenza a deep nasopharyngeal swab should be obtained, and care must be taken to apply the correct technique. For acute HIV infection fourth-generation diagnostic tests which include p24 antigen, should be able to diagnose acute infection. Western Blot may still be negative at this stage, but in case of doubt, HIV PCR would help establish the diagnosis. Blood cultures would be the appropriate test to rule out enteric fever.

For malaria, microscopy (thick and thin films) remains the diagnostic gold standard. Three negative films taken on consecutive days are considered to safely rule out malaria.

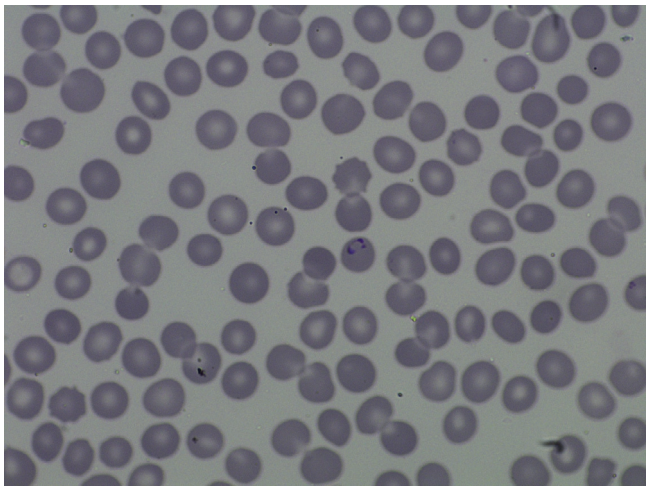
If malaria parasites are detected but the species remains unclear even at a referral laboratory, species-specific polymerase chain reaction (PCR) may be useful.

The Case Continued…

A thick blood film showed *Plasmodium* species trophozoites at a density of 920/μL. On thin film however, the microscopist on duty was unable to determine the *Plasmodium* species. Based on the negative result of the rapid diagnostic test, non-falciparum malaria was suspected. The patient was admitted to the infectious diseases ward. Treatment was started with atovaquone/proguanil 250/100mg, 4 tablets once daily for 3 days. The patient rapidly recovered and was discharged on the fourth day. For further parasite differentiation, malaria microscopy was repeated by the head parasitologist. After intense reading of the Giemsa-stained thin blood film, 2 parasite-infected erythrocytes were identified with morphological characteristics compatible with *Plasmodium malariae* or *P. knowlesi* infection (Figs. 92.1 and 92.2). Subsequently, species-specific PCR confirmed the presence of a mono-infection with *P. knowlesi.*



• **Fig. 92.1** Young trophozoite (ring form) of *P. knowlesi* (Giemsa-stained thin film).



• **Fig. 92.2** Late trophozoite (band form) of *P. knowlesi* (Giemsa-stained thin film).

SUMMARY BOX

Knowlesi Malaria

P. knowlesi is primarily a zoonotic parasite reported increasingly in humans across South-east Asia. Its reservoir is in various species of macaques.

Knowlesi malaria is now recognized as the most common form of malaria in Malaysia and parts of western Indonesia and it is increasingly reported from other parts of South-east Asia.

Its prevalence may have long been underestimated because of the inability to reliably distinguish *P. knowlesi* from other *Plasmodium species,* in particular *P. malariae.* PCR-based methods have been a major breakthrough in recognizing the importance of *P. knowlesi.* Rapid diagnostic tests lack sensitivity and specificity

for this parasite, and physicians practising in the region or seeing returned travellers from South-east Asia need to be aware of these pitfalls.

P. knowlesi has a 24-hour erythrocytic cycle and therefore causes a quotidian (daily) fever pattern with relatively high parasitaemias seen in some patients. It may cause severe disease, similar to falciparum malaria. Treatment is the same as for acute falciparum malaria.

Further Reading

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