77

A 51-Year-Old Female Traveller Returning from Central America With Conjunctivitis, Rash and Peripheral Oedema

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Clinical Presentation

History

A 51-year-old female Swiss traveller presented to the outpatient department 6 days after returning from a 2-week holiday to Guatemala and El Salvador. Four days after her return, the patient noticed a generalized slightly pruritic maculopapular rash on the face, trunk, and extremities. There was no fever and no other accompanying symptoms. On the next day the rash worsened and a non-purulent bilateral conjunctivitis developed. The patient did not report any chronic underlying disease nor the intake of any medication.

Clinical Findings

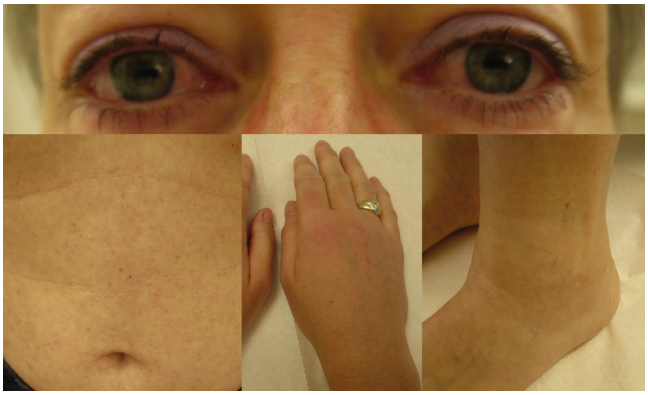
The patient was afebrile. Upon inspection there was conjunctivitis and a generalised maculopapular rash, also involving the face. Additionally, the patient showed tender oedema of the hands, elbows, knees and feet (Fig. 77.1). There was also generalized lymphadenopathy (cervical, axillary, and inguinal).

Laboratory results

The full blood count was normal. CRP was 8 mg/L (<5) and creatinine was very mildly elevated (87 µmol/L, range 35–80 µmol/L). Liver function tests were normal.

Questions

1. What are your differential diagnoses?
2. What diagnostic tests would you perform?



• **Fig. 77.1** Conjunctivitis, maculopapular skin rash, and peripheral oedema of the patient.

Discussion

Six days after returning from a 2-week holiday to Guatemala and El Salvador, a 51-year-old female Swiss traveller presents with a slightly pruritic disseminated maculopapular rash, conjunctivitis, peripheral painful oedema (hands, elbows, knees and feet) and a generalized lymphadenopathy.

Answer to Question 1

What Are Your Differential Diagnoses?

The clinical presentation is highly suggestive of an arboviral infection, which is also in line with the putative incubation period. The three most important arboviral infections in Central and South America are dengue, chikungunya and zika. Dengue is endemic throughout much

TABLE 77.1 Comparative Clinical Symptom Patterns Observed in Dengue, Chikungunya and Zika Infections.

	Dengue	Chikungunya	Zika
Incubation period (days)	4–10	3–7	3–12
Asymptomatic infection (%)	50–80	3–28	~80
Fever	+++	+++	+
Headache	+++	++	+
Conjunctivitis	-	-	++
Arthralgias	++	+++	+
Myalgias	++	+	+
Skin rash	++	++	+++
Peripheral oedema	-	-	++
Haemorrhagic manifestations	++	(+)	-
Circulatory collapse/ shock	+	-	-
Thrombocytopenia	++	++	-
Lymphadenopathy	++	++	+

of Central and South America, and it is the most frequent arboviral infection in travellers returning from the tropics. Chikungunya was absent in Central and South America until the virus was introduced in 2013. After its introduction, the virus spread to most tropical regions of the American continent. Zika was absent in Central and South America until 2015, when the virus was introduced to Brazil and caused a pandemic affecting most tropical regions of the American continent in the subsequent years.

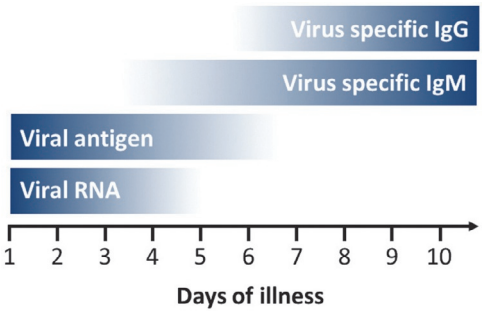
Acute dengue, chikungunya, and zika infections have similar presentations and may be clinically indistinguishable. However, the presence of a skin rash, conjunctivitis and peripheral oedema in an afebrile patient is highly suggestive of a Zika virus infection (Table 77.1).

Answer to Question 2

What Diagnostic Tests Would You Perform?

When testing for arboviral infections, the kinetics of the different test parameters have to be taken into account. During the early phase of infection, viral RNA and viral antigen (e.g. dengue specific NS1) are circulating in the blood and can be detected by RT-PCR and specific antigen assays, respectively. After some days, viraemia is fading, terminated by the host's immune response, and viral RNA and antigen become undetectable in the blood samples, while now specific IgM and IgG rise and become detectable (Fig. 77.2).

The diagnosis is made by the detection of viral RNA, viral antigen or specific IgM, or by the documentation of a ≥ fourfold rise of specific IgG antibody titres in paired (acute and



• **Fig. 77.2** Kinetics of the different arboviral test parameters.

convalescent) serum samples. In resource-poor countries, as well as in daily clinical practice in travel medicine, rapid diagnostic tests (RDTs) for dengue (testing for NS1-Ag, IgM, and IgG) and chikungunya (testing for IgM) are widely available and often the primarily performed diagnostic tests. RDTs to diagnose Zika virus infections are under development.

In our case, RDTs for dengue and chikungunya were negative.

The Case continued...

Because the performed RDTs for dengue and chikungunya both showed a negative result, the patient's blood samples were sent to a reference laboratory for arboviruses and our clinical suspicion of a Zika virus infection was confirmed by PCR as well as seroconversion (Table 77.2). A rise in

TABLE 77.2 Blood Test Results

	First serum sample†	Second serum sample‡	Interpretation
Dengue IgM IIFT	negative	negative	negative
Dengue IgG IIFT	1:20	1:5120	*cross-reactivity*
Dengue NS1-Ag	negative	negative	negative
Chikungunya IgM ELISA	negative	ND	negative
Chikungunya IgM IIFT	ND	negative	negative
Chikungunya IgG IIFT	ND	negative	negative
Zika IgM IIFT	negative	1:640	positive
Zika IgG IIFT	1:20	1:5120	positive
Zika RT-PCR	positive	ND	positive

†obtained 6 days after onset of symptoms
‡obtained 7 days after the first serum sample
IIFT: Indirect Immunofluorescence Test; RT-PCR: real-time reverse transcription polymerase chain reaction; ELISA: Enzyme-linked Immunosorbent Assay; ND: not done.

anti-Dengue IgG was interpreted as cross-reactivity which is common among viruses of the same family.

SUMMARY BOX

Acute Arboviral Infection

Acute dengue, chikungunya, and Zika infections have similar presentations and are often clinically indistinguishable. Although the pattern of clinical symptoms can point towards the correct diagnosis, specific molecular or immunological tests are necessary to make a final diagnosis.

Interpretation of serological test results demands some caution, because cross-reactivity of antibodies directed against viruses belonging to the same family of viruses may be misleading.

Although dengue virus NS1 antigen tests are mostly specific for dengue virus infection, serological assays may show cross-reactivity with Zika virus (ZIKV) specific antibodies (as in our case). The diagnostic value of RT-PCR for detection of Zika virus RNA in the blood is limited because viraemia is usually low and limited to the first few days after disease onset. However, Zika virus RNA detection in urine provides a feasible alternative: ZIKV is detectable with higher RNA loads and for a longer period (10–20 days after onset of symptoms) in urine samples than in serum samples.

Arboviral infections are self-limiting and, in the absence of specific treatment options, clinical management is exclusively supportive. Special features of Zika virus include its sexual transmissibility, the potential to trigger post-infectious Guillan-Barré-Syndrome, and, in the case of intrauterine infection, its ability to cause severe foetopathy (primarily microcephaly).

Further Reading

1. Young PR, Ng LFP, Hall RA, et al. Arbovirus Infections. In: Farrar J, editor. Manson's Tropical Diseases. 23rd ed. London: Elsevier; 2013 [chapter 14].
2. Baud D, Gubler DJ, Schaub B, et al. An update on Zika virus infection. *Lancet* 2017;390(10107):2099–109.
3. Peters R, Stevenson M. Zika virus diagnosis: challenges and solutions. *Clin Microbiol Infect* 2019;25(2):142–6.