87

A 27-Year-Old Male Traveller Returning from the Peruvian Amazon With Persisting Polyarthralgias

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Clinical Presentation

History

A 27-year-old male Swiss tourist spent 3.5 weeks travelling in the rainforests of the Amazon Basin in northern Peru. During the second week of his stay he developed an acute febrile illness with chills, malaise, frontal headache, generalized myalgia and a transient, non-pruritic maculopapular rash.

The rash started on the forearms about 1 week after the onset of fever and spread to the trunk, neck and face before fading after 3 days. In addition, there were slowly progressive debilitating polyarthralgias affecting the peripheral joints accompanied by transient joint swelling. He also noticed painful cervical and inguinal lymphadenopathy, which was self-limiting, lasting for about 1 week.

The traveller presented at the local hospital, where physicians made a clinical diagnosis of dengue fever, and he received symptomatic treatment with paracetamol. Although the fever and the other symptoms subsided within 1 week, the polyarthralgias did not improve, showing a symmetrical pattern mainly affecting the small joints of the hands and feet as well as the wrists, ankles, and knees.

Upon return home to Switzerland a few weeks later, the patient consulted his general practitioner because of persisting, incapacitating polyarthralgias. The patient reported stiffness of the affected joints, mainly in the morning and after immobility. Physical examination of the affected joints did not reveal any clinical signs of inflammation (swelling, redness, effusion). Laboratory tests were performed including serological testing for dengue virus, chikungunya virus, parvovirus B19, Epstein-Barr virus, *Borrelia burgdorferi, Chlamydia trachomatis, Salmonella Typhi,* and S. Paratyphi but none revealed a cause for the symptoms. For two more months, the joint pains did not improve; thus the patient was referred to a rheumatologist and subsequently to a tropical medicine clinic for evaluation of a putative travel-related cause of his polyarthralgias.

Clinical Findings

The physical examination was completely unremarkable. The affected joints did not reveal any clinical signs of inflammation (no swelling, no redness, no effusion).

Laboratory results

Full blood count was normal. C-reactive protein was mildly elevated at 9 mg/L (<5), liver function tests were normal.

Questions

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

Discussion

A 27-year-old male Swiss tourist presents with persisting and incapacitating symmetrical polyarthralgias primarily affecting the small peripheral joints after returning from a trip to the Amazon Basin of northern Peru. The patient reports an acute self-limiting febrile illness accompanied by a rash before the onset of the polyarthralgias, which had clinically been diagnosed as dengue infection at a local hospital in Peru.

Answer to Question 1

What Are Your Differential Diagnoses?

Two main differential diagnoses should be considered in patients presenting with persisting or prolonged arthritis/arthralgias and a history of a preceding infection:

Reactive arthritis (Reiter's syndrome):

Reactive arthritis is a rheumatoid factor (RF)-seronegative, HLA-B27-linked arthritis often preceded by an infection. The most common triggers are gastrointestinal infections (caused by *Salmonella, Shigella* or *Campylobacter*) and sexually transmitted infections *(Chlamydia trachomatis)*. Reactive arthritis may manifest as monoarthritis (often affecting the knee or sacroiliac joint) or as oligoarthritis (usually of the lower extremities). The course may be additive (i.e. more joints becoming inflamed in addition to the primarily affected one) or migratory (new joints becoming inflamed after the initially inflamed joint has already improved). It usually develops within 2 to 4 weeks of the preceding infection. Reactive arthritis may also manifest with the classical triad of symptoms termed "Reiter's syndrome": (i) inflammatory arthritis of large joints, (ii) inflammation of the eyes manifesting as conjunctivitis or uveitis and (iii) urethritis in men or cervicitis in women. Other musculoskeletal manifestations include enthesitis (often involving the Achilles tendon) and dactylitis. In some cases, mucocutaneous lesions *(circinate balanitis)* or psoriasis-like skin lesions *(keratoderma blennorrhagicum)* may be present. Clinical manifestation may vary widely and patients may be oligosymptomatic. In the majority of cases the complaints are self-limiting and subside under symptomatic treatment with non-steroidal drugs over weeks to months.

Viral arthritis:

Although self-limiting polyarthralgias are present during the acute phase of many viral infections, prolonged polyarthritis/polyarthralgias are characteristic for certain viral infections. Worldwide, parvovirus B19, hepatitis B and C, HIV, rubella and the alphaviruses are the most common infections to consider in the differential diagnosis. Although rubella has become rare because of vaccination, the vector-borne, alphaviral infections are becoming increasingly relevant in endemic regions and in returning travellers (see Table 87.1). Unlike reactive arthritis, viral arthritis primarily presents as symmetrical polyarthritis of peripheral small joints.

TABLE 87.1 Characteristics of Human Pathogenic Alphaviruses

Virus	Epidemiology and Endemic Regions	Occurrence and Number of Reported Cases	Frequency of Main Symptoms (%)
Chikungunya	Tropical and subtropical regions of Asia, Africa and Latin America	Large sporadic epidemics	Fever: 90 Rash: 40–50 Myalgia: 90 Arthralgia/arthritis: >95
Sindbis Virus Group	Eurasia, Africa, Australia, Oceania; primarily reported from West Russia ("Karelian fever"), Finland ("Pogosta disease"), and Sweden ("Ockelbo disease")	Geographically most widely distributed alphavirus (lack of data on human cases) Karelian fever: rare (no data) Pogosta disease: ~140 cases (range 1–1282)/year Ockelbo disease: ~30 cases/year	Fever: 15–40 Rash: 90 Myalgia: 50 Arthralgia/arthritis: 95
Ross River	Australia, Papua New Guinea, West Papua	~5000 cases per year in Australia; in 1979–1980 an epidemic with >60000 cases hit some pacific islands (New Caledonia, Fiji, Samoa, Cook Islands)	Fever: 20–60 Rash: 40–60 Myalgia: 40–80 Arthralgia/arthritis: 80–100
Barmah Forest	Australia	~2000 cases/year	Fever: 50 Rash: 40–60 Myalgia: 50–80 Arthralgia or arthritis: 70–95
O'Nyong Nyong	East Africa	Rare epidemics; >2 million cases in 1959–1961	Fever: 80–100 Rash: 70–90 Myalgia: 70 Arthralgia/arthritis: 60–100
Mayaro	South America, primarily the Amazonian rainforest, Caribbean	Sporadic single cases and small outbreaks (involving ~10–100 cases)	Fever: 100 Rash: 30–50 Myalgia: 75 Arthralgia/arthritis: 50–90

Adapted from Suhrbier, A., Jaffar-Bandjee, M.C., Gasque, P., 2012. Arthritogenic alphaviruses - an overview. Nat Rev Rheumatol, 8(7):420–9.

TABLE 87.2 Results of the Serological Testing for Alphavirus Infections Performed in Our Case

	Blood Sample Taken on 29 August			Blood Sample Taken on 12 September			
Virus	IgM-IFA	IgG-IFA	PRNT	IgM-IFA	IgG-IFA	PRNT	Interpretation of test result
Mayaro	1280	2560	40	40	2560	160	positive
Sindbis	<20	160	<20	<20	160	<20	negative
Chikungunya	<20	160	n.d.	<20	160	n.d.	negative
Ross River	<20	160	n.d.	<20	160	n.d.	negative
Barmah Forest	<20	20	n.d.	<20	20	n.d.	negative

IFA: indirect immunofluorescence assay (screening assay)
PRNT: plaque reduction neutralization test (confirmatory assay)
n.d.: not done (screening assay negative [and epidemiologically not supported])

Answer to Question 2

What Diagnostic Test Would You Perform?

The diagnostic principles for most alphaviruses are the same: During the first days of the acute infection, detection of viral RNA in the blood by PCR may confirm the diagnosis. Beyond the acute phase, the diagnosis is based upon serological detection of specific IgM and IgG antibodies against the respective virus. Cross-reactivity within the same virus family is common. Reference laboratories therefore usually perform parallel testing for potentially cross-reacting viruses (see Table 87.2) and apply a two-step approach, using highly sensitive screening assays followed by highly specific confirmatory assays.

The Case Continued…

Given the patient's travel history, the course of the illness and the clinical signs and symptoms experienced during the journey, Mayaro virus (MAYV) infection was strongly suspected. (Chikungunya was not yet endemic in the Americas at the time this patient was seen).

The serological results (Tab. 87.2) confirmed the suspected diagnosis of Mayaro infection. The patient received symptomatic treatment with ibuprofen, and the polyarthralgias subsided slowly over the following weeks and months before finally disappearing completely.

SUMMARY BOX

Mayaro-Fever

Mayaro-virus is an alphavirus. Alphaviruses are arthropod-borne viruses (arboviruses) that circulate among a wide variety of wild animals in relative mosquito vector-specific and host-specific enzootic cycles; infection of humans (dead-end hosts) is exclusively incidental. The Mayaro virus (MAYV) circulates in an enzootic, sylvatic cycle (similar to that for yellow fever) involving forest-dwelling *Haemagogus* species mosquitoes as vectors and non-human primates as natural hosts. Infections in humans mostly occur sporadically, are strongly associated with occupational or recreational exposure in rainforest environments and represent spillover from the enzootic cycle. MAYV has so far been only reported from South America and the Caribbean.

Mayaro infection presents as a dengue-like, febrile illness lasting 3 to 7 days. It typically manifests with chills, headache, retro-orbital and epigastric pain, myalgia, arthralgia, nausea, vomiting, diarrhoea and a maculopapular rash (sometimes followed by desquamation). Haemorrhagic manifestations have been described but are rare. Like other alphaviruses, Mayaro may cause debilitating and long-lasting polyarthralgias, which are suspected to arise from the inflammatory immune response stimulated by the prolonged virus persistence in joint tissues. Treatment is exclusively symptomatic with non-steroidal drugs. Symptoms subside slowly over weeks to months. Permanent damage of the affected joints is not reported.

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. Schmitt SK. Reactive Arthritis. Infect Dis Clin North Am 2017; 31(2):265–77.
3. Suhrbier A, Jaffar-Bandjee MC, Gasque P. Arthritogenic alphaviruses-an overview. Nat Rev Rheumatol 2012;8(7):420–9.
4. Acosta-Ampudia Y, Monsalve DM, Rodríguez Y, et al. Mayaro: an emerging viral threat? Emerg Microbes Infect 2018;7(1):163.
5. Blohm G, Elbadry MA, Mavian C et al. Mayaro as a Caribbean traveler: Evidence for multiple introductions and transmission of the virus into Haiti. Int J Infect Dis 2019;87:151–3.