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Case Report

Unusual cause of recurrent fever after travel in South America

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ABSTRACT

Fever in returning travelers is a common problem and usually the diagnosis is made within a few days or the traveler recovers.

We present two travelers who presented with fever two weeks after returning from a six week vacation in South America. Over the following 18 months they presented with short attacks of fever, elevated CRP and leukocytosis and the program for investigation became more and more elaborate. A curious and key feature was, that they were completely synchronous both developing symptoms within an hour and presentation with the same laboratory findings of leukocytosis and elevated CRP. Extensive and repeated tests were performed, at our facility and abroad. After a year it was discovered that the uses of aroma oils were associated with the symptoms. No similar case has been found to be reported previously.

These cases emphasize that natural products are not inherently safe. The investigational program was build up over time as new attacks continued to occur and suggestions from different centers which were consulted were followed up. The number of tests performed at different laboratories took an extensive amount of time. These cases emphasize that a panel of analysis in returning travelers in which no clear diagnosis is found should be developed.

Introduction

Fever in returning travelers is a common problem and usually the diagnosis is made within a few days or the traveler recovers [1,2].

We report here two travelers who presented with fever two weeks after returning from a six week vacation in South America. Over the following 18 months they presented with short attacks of fever, elevated CRP and leukocytosis and the program for investigation became more and more elaborate. A curious and key feature was, that they were completely synchronous both developing symptoms within an hour and presentation with the same laboratory findings of leukocytosis and elevated CRP.

Extensive and repeated tests were performed. After about a year it turned out that the couple used aroma oils (Nature and Decouvertes – Fig. 1) in the home applied by a nebulizer placed in the middle of a table. The use of the oil matched perfectly with the fever attacks. The oils were not used during summer, also explaining the absence of symptoms during the summer months.

Aromatic oils have been used for centuries as healing and soothing scents.

Since the use of the oils ended there has been no relapse in any symptoms. It has not been possible to test them with exposure for ethical reasons.

We are not aware of or have found any previous reports, in English or other languages, reporting similar events after the use of similar products.

Case presentation

After traveling to South America for a six weeks tourist holiday the two patients returned home to Denmark. Ten days after returning they were both admitted to hospital with fever, muscle and joint pains and vomiting. From the 8 September 2012 to the 22 October 2012 they spent 3 weeks in Peru, half a week in Bolivia, half a week in Chile and 2 weeks in Brazil. They traveled by local busses, stayed at medium level hotels and were not ill at any time during their travels.

Prior to their travels they had received vaccines against hepatitis A and B, yellow fever and tetanus/diphtheria. Table 1 shows the patients' history and Table 2 lists CRP, white blood cell count and recorded rectal temperatures. Day 0 is defined as the first day the couple was admitted to hospital, 10 days after the

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Fig. 1. Aroma oils used by the patients.

return from South America. There was no eosinophilia at any given time and the total IgE remained normal throughout.

Approximately nine episodes occurred within the following 18 months, all attacks being identical in symptoms, duration and paraclinical results for both patients (Table 2).

Initially the patients were tested negative for malaria and dengue fever. Under the suspicion of a rickettsial infection they were treated with doxycycline 100 mg two times daily initially for one week [3]. This was immediately afterwards repeated again for one week. After the third relapse, Day 20, the patients received 3 months Doxycycline 100 mg two times daily plus moxifloxacin 400 mg × 1, as it was believed they previously had had a good effect.

The patients went through an elaborate program of serological tests and test for nucleic acids of different pathogens, which is summarized in Table 3. Through the whole course a wide range of tests were performed including heart echocardiography, PET-CT and an MRI which were all normal.

Discussion

Definition of travel associated disease "is a patient who has crossed an international boarder within the past 10 years and presents for a presumed travel-related disease" [4]. It is not uncommon for travelers to report an illness associated with their travels (20–70%), but only a small portion of these actually seek medical attention [2,5,6]. A detailed medical history is a very important tool in correct diagnosis, including destinations, risk factors, previous medical history. Incubation time is also important to keep in mind through the process (Table 5) [2,5,7].

Table 1
Symptom history.

Day	Symptoms
0	Fever, joint and muscle pain
10	Vomiting, headache, muscle pain, fever
20	Night sweats, shivering, headache, light respiratory pain
112	Fever, night sweats, shivering, muscle and joint pain, slight non-productive cough
127	Muscle and joint pain
136	Fever, night sweats, shivering, headache
139	Fever, muscle and joint pain
412	Fever, muscle and joint pain
434	Fever, chest pain, dyspnea, tiredness

The GeoSentinel surveillance program has found that the most common causes of fever after traveling is malaria, dengue fever, enteric fever (*Salmonella typhi*) and rickettsioses [2]. Initially malaria and dengue fever were excluded and the patients were treated with doxycycline under the presumption of a rickettsia or bartonella infection. When the fever attacks continued we excluded endocarditis due to *Coxiella burnetii* (Q fever) and looked for South American trypanosomiasis due to *Trypanosoma cruzi* (Chagas disease), which can be transmitted orally through fresh fruit juice. We speculated that *Toxoplasma gondii* was a possibility as *T. gondii* genotypes in South America are more pathogenic compared to Europe [8], but only one of the subjects had antibodies at a low titer, not compatible with an acute infection. Leptospirosis was also a diagnostic option, especially with a second phase of fever shortly after the first; this was however also excluded by a negative serology. Acute schistosomiasis and other parasites were ruled out as there was no eosinophilia or elevated total-IgE in either patient.

Different centers were asked to assist with this case, including Unité Des Rickettsies, France, Porton Down, UK and Center for Disease Control and Prevention (CDC), United States. See Tables 3 and 4 for list of all the test and results found on the patients. Everything that was tested for came out negative, including blood and urine cultures.

Table 2
Biochemical infectious markers.

Day	Patient A			Patient B		
	Temperature (°C)	CRP (mg/l)	WBC (10*9/l)	Temperature (°C)	CRP (mg/l)	WBC (10*9/l)
0	37.5	58	32.2	37.7	67.2	34.9
3		19.9	6.5		26.1	6.7
10	37.1	36.6	25	37.2	40.6	24.8
12					26.8	8.2
13		11	5.3			
24		1	4.6		0.9	6.2
40		4.4	6.3		<0.6	5.9
112		26.3	18.2		59	22.7
119		6.8	5		24.4	5.5
127		5.7	15.8		22.4	18.5
129		24.3	6.4		48.3	5.5
153		<0.6	8.1			
166		<0.6	7.7			
194					1.2	4.8
196		17	5			
395		44.5	17		60.2	18.5
412		0.6	7.6			
434	37.1	20.5	24		15.9	18.6
435		38.1	10.8			

Table 3
Test results.

Day	Test	Result	
		Patient A	Patient B
12	*Borellia burgdorferi* (IgM + IgG)	Negative	Negative
	Bartonella henseale and *B. quintana* (IgM + IgG)	Negative	Negative
	Ehrlichia (IgG)	Positive	Negative
	Francisella tularensis	Negative	Negative
	Rickettsian rickettsii, *R. typhi* (IgM + IgG)	Negative	Negative
	Leptospira (patoc, icterohaemorrhagiae, interro. Copenhageni, canicola, interro. Autumnalis, Hardjo, Pomona, Bataviae, Borgpeters. Tarassovi, Borgpeters. Ballum, Broomii)	Negative	Negative
	Brucella melitensis and *B. abortus*	Negative	Negative
40	*Bartonella henselae* and *B. quintana*	Negative	Negative
112	*Francisella tularensis*	Negative	Negative
	Borellia burgdorferi (IgM + IgG)	Negative	Negative
	Rickettsia DNA	Negative	Negative
	Rickettsian rickettsii and *R. typhi* (IgM + IgG)	Positive IgM for *R. rickettsii*	Negative
	Bacterial DNA (PCR)	Negative	Negative
	Ehrlichia (IgG)	Positive	Negative
	Bartonella henselae, *B. quintana*, *B. bacilliformis*[*]	Negative	Negative
	Coxiella burnetii (IgM + IgG phase I and II)	Inconclusive	Negative
	Rickettsia conorii, *R. felis*, *R. typhi*[*]	Negative	Negative
	Bartonella PCR[*]	Negative	Negative
	Brucella melitensis, *B. abortus*	Negative	Negative
129	Bacterial DNA (PCR)	Negative	Negative
164	Mayaro Virus RNA[**]	Negative	Negative
	Borrelia burgdorferi[**]	Negative	Negative
	Chikungunya Virus[**]	Negative	Negative
	Rickettsia[**]	Negative	Negative
188	Oropouche Virus[**]	Negative	Negative
196	Leishmaniasis + *Trypanosoma cruzi* antibodies	Negative	Negative
395	Bacterial DNA (PCR) + Parasite DNA (PCR)	Negative	Negative
	Bartonelle henselae (IgM + IgG), *B. quintana* (IgM + IgG)	Negative	Negative
434	Rickettsia	Negative	Negative
	Bacterial DNA (PCR)	Negative	Negative
	Trypanosoma cruzi, *Trypanosoma brucei gambiense*, *T. brucei rhodensiense*	Negative	Negative
	Leishmania antibodies	Negative	Negative
	Coxiella burnetti (Q-fever) antibodies	Negative	Negative

[*] Tested at Unité Des Rickettsies, France.
[**] Tested at Porton Down, UK.

Table 4
Laboratory results from Aarhus University Hospital, Denmark.

Day	Test	Result	
		Patient A	Patient B
0	Microscopy for malaria	Negative	Negative
0	Dengue rapid test	Negative	Negative
0	Blood cultures × 4	Negative	Negative
10	Microscopy for malaria and *Borrelia recurrentis*	Negative	Negative
10	Blood cultures × 2	Negative	Negative
11	Microscopy for malaria and *B. recurrentis*	Negative	Negative
12	Microscopy for malaria and *B. recurrentis*	Negative	Negative
112	Blood cultures × 2	Negative	Negative
112	Cervical swab	Negative	–
112	Swap for Chlamydia + gonococci PCR and culture	Negative	–
119	Microscopy for malaria	Negative	Negative
127	Blood cultures × 2	Negative	Negative
129	*Toxoplasma gondii* IgM + IgG	Negative	Positive (IgG 85 UI/ml)
129	Mycobacterium tuberculosis interferon release assay	Negative	Negative
129	Blood cultures × 2	Negative	Negative
129	HIV antibody and antigen test	Negative	Negative
129	Syphilis	Negative	Negative
129	EBV serology	Previous infection (EBNA IgG positive)	Negative
129	CMV serology	Previous infection (IgG positive)	Negative
304	HIV antibody and antigen test	Negative	–
304	HAV, HBV; HCV	Negative	
395	HIV	Negative	Negative
395	*Toxoplasma gondii* IgM + IgG	Negative	Positive (IgG 92 UI/ml)
412	Swap for Chlamydia DNA + Gonococci culture	Negative	–
434	*Mycobacterium tuberculosis*	Negative	Negative
434	HIV antibody and antigen test	Negative	–
434	*Toxoplasma gondii* IgM + IgG	Negative	Positive (IgG 84 UI/ml)

Table 4 (*Continued*)

Day	Test	Result	
		Patient A	Patient B
435	Urine culture	Negative	–
435	Blood culture × 2	Negative	–
440	HIV (routine test in pregnancy)	Negative	–
440	Syphilis (routine test in pregnancy)	Negative	–

Table 5
Incubation period.

Disease	Incubation time
Dengue fever	3–14 days
Leptospirosis	4–14 days
Borrelia	5–15 days
Francisella	1–14 days
Bartonella bacilliformis/Oroya fever	1–3 weeks
Rickettsia	10–14 days
Malaria	8–30 days
Q fever/Coxiella	2–3 weeks
Brucella	2–4 weeks
Syphilis	Primary 3–90 days
Chagas disease/*Trypanosoma cruzi*	Acute: immediate, chronic: >8 weeks
Leishmaniasis	>1 week
Epstein Barr virus	
HIV	
Tuberculosis	
Cytomegalovirus	

Cytomegalovirus and Epstein–Barr virus were also considered as they are a common cause to fever of unknown origin in adults [9]. HIV and other sexually transmitted diseases were also screened for and these results were also negative. The patients were not tested for histoplasmosis as this rarely causes a prolonged course of disease in immunocompetent patients [10].

Throughout the long period of symptoms with this couple it became more and more apparent that it was not an infectious agent at play. Their symptoms and blood test were too synchronized. The attacks were short lived and the CRP and leukocytosis normalized within a few days. Malignancy and inflammatory diseases were also ruled out as the cause of the recurrent fever. Both patients had a slight dry cough and small, non-tender, lymph glands at several stations. There was no rash. One would expect the patients to react differently to the same infectious agent as their immune systems are different as they differ genetically.

We, therefore, started searching for an agent they could both be exposed to in the home. All the symptoms seemed to occur during autumn, winter and spring – during which the windows are closed. It is therefore believed to be repeated exposure to aroma oils (Nature and Decouvertes) that is the cause of the symptoms. Since the exposure has stopped there have been no more events. For ethical reasons it has not been possible to test with expose.

The story emphasizes that natural products are not inherently safe. The oils used here were nebulized and we assume that the two patients inhaled a high concentration of the nebulized oils over a short time. This was actually recommended by the manufacturer and the oils and table top nebulizer was purchased together. As mentioned earlier, we are not aware of reports of any similar events after using other similar products.

The investigational program was build up over time as new attacks continued to occur and suggestions from different centers which were consulted were followed up. The number of tests performed at different laboratories took time and emphasizes that a panel of analysis in returning travelers with continued symptoms but without a clear diagnosis should be developed.

Conflicts of interest

None declared.

Patient consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

References

[1] Harvey K, Esposito DH, Han P, Kozarsky P, Freedman DO, Plier DA, et al. Surveillance for travel-related disease – GeoSentinel Surveillance System, United States, 1997–2011. MMWR Surveill Summ 2013;62(July):1–23.
[2] Kotlyar S, Rice BT. Fever in the returning traveler. Emerg Med Clin North Am 2013;31(November (4)):927–44.
[3] Dworkin MS, Shoemaker PC, Fritz CL, Dowell ME, Anderson Jr DE. The epidemiology of tick-borne relapsing fever in the United States. Am J Trop Med Hyg 2002;66(June (6)):753–8.
[4] Freedman DO, Weld LH, Kozarsky PE, Fisk T, Robins R, von Sonnenburg F, et al. Spectrum of disease and relation to place of exposure among ill returned travelers. N Engl J Med 2006;354(January (2)):119–30.
[5] House HR, Ehlers JP. Travel-related infections. Emerg Med Clin North Am 2008;26(May (2)):499–516.
[6] Schwartz MD. Fever in the returning traveler: Part I. A methodological approach to initial evaluation. Wilderness Environ Med 2003;14(Spring (1)):24–32.
[7] Schwartz MD. Fever in the returning traveler: Part II. A methodological approach to initial management. Wilderness Environ Med 2003;14(Summer (2)):120–30.
[8] Sibley LD, Khan A, Ajioka JW, Rosenthal BM. Genetic diversity of *Toxoplasma gondii* in animals and humans. Philos Trans R Soc Lond B: Biol Sci 2009;364(September (1530)):2749–61.
[9] Shah R, Castillo C, Burgess M. Fever of unknown origin in the hospitalized patient. Hosp Med Clin 2014;3(2):162–72.
[10] Catania J, Martin SS, Corey GR, Sexton DS. Diagnostic dilemma in a returning traveler with fever. Diagn Microbiol Infect Dis 2013;77(September (1)):85–6.