Case Report

Unusual cause of recurrent fever after travel in South America

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A R T I C L E   I N F O

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A B S T R A C T

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 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
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 border 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].

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 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 |

Table 2
Biochemical infectious markers.

| Day | Patient A |                  | Patient B |                  |
|-----|-----------|-----------------|-----------|-----------------|
|     | Temperature (°C) | CRP (mg/l) | WBC (10⁹/l) | Temperature (°C) | CRP (mg/l) | WBC (10⁹/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 | <0.6      | 1.2            |           |                |             |
| 196 | 17        | 5              |           | 60.2           | 18.5        |
| 395 | 44.5      | 17             |           |                |             |
| 412 | 0.6       | 7.6            |           | 15.9           | 18.6        |
| 434 | 37.1      | 20.5           |           |                |             |
| 435 | 38.1      | 10.8           |           |                |             |
Table 3
Test results.

| Day | Test                                                                 | Patient A | Patient B |
|-----|----------------------------------------------------------------------|-----------|-----------|
| 12  | Borelia burgdorferi (IgM + IgG)                                      | Negative  | Negative  |
|     | Bartonella henselae and B. quintana (IgM + IgG)                      | Negative  | Negative  |
|     | Ehrlichia (IgG)                                                      | Positive  | Negative  |
|     | Francisella tularensis                                              | Negative  | Negative  |
|     | * Tested rickettsii, R. typhi (IgM + IgG)                            | Negative  | Negative  |
|     | Brucella melitensis and B. abortus                                   | Negative  | Negative  |
| 40  | Bartonella henselae and B. quintana                                  | Negative  | Negative  |
| 112 | Francisella tularensis                                              | Negative  | Negative  |
|     | * Tested rickettsii, B. burgdorferi (IgM + IgG)                      | Negative  | Negative  |
|     | Rickettsia DNA                                                       | Negative  | Negative  |
|     | * Tested 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  |
|     | * Tested Coxielia burnettii (IgM + IgG phase I and II)               | Inconclusive | Negative |
|     | Rickettsia conori, 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  |
|     | * Tested Borrelia burgdorferi*                                       | Negative  | Negative  |
|     | Chikungunya Virus                                                   | Negative  | Negative  |
| 188 | Orotophous Virus                                                     | Negative  | Negative  |
| 196 | Leishmaniasis + Trypanosoma cruzi antibodies                         | Negative  | Negative  |
| 395 | Bacterial DNA (PCR) + Parasite DNA (PCR)                             | Negative  | Negative  |
| 434 | Bartonelle henselae (IgM + IgG), B. quintana (IgM + IgG)             | Negative  | Negative  |
|     | Rickettsia                                                          | Negative  | Negative  |
|     | Trypanosoma cruzi, Trypanosoma brucei gambiensis, T. brucei rhodensiense | Negative | Negative  |
|     | Leishmania antibodies                                                | Negative  | Negative  |
|     | * Tested Coxielia burnettii (Q-feve) 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                                                                 | 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 Chlamidia + gonococci PCR and culture                       | Negative  | –         |
| 119 | Microscopy for malaria                                               | Negative  | –         |
| 127 | Blood cultures × 2                                                   | Negative  | Negative  |
| 129 | * Tested 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  | –         |
| 395 | * Tested Toxoplasma gondii IgM + IgG                                | Negative  | Positive (IgG 92 UI/ml) |
| 412 | Swap for Chlamidia DNA + Gonococci culture                           | Negative  | –         |
| 434 | Mycobacterium tuberculosis                                           | Negative  | Negative  |
| 434 | HIV antibody and antigen test                                        | Negative  | –         |
| 434 | * Tested 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, chron: >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.

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