Am J Cardiovasc Dis 2016;6(4):185-190
www.AJCD.us /ISSN:2160-200X/AJCD0033522

Original Article

Tsutsugamushi disease presenting with aortic valve endocarditis: a case report and literature review

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Received June 9, 2016; Accepted November 24, 2016; Epub November 30, 2016; Published December 15, 2016

Abstract: Tsutsugamushi disease is a zoonotic disease caused by *Orientia tsutsugamushi* in which humans are accidental hosts. Infective endocarditis associated with Tsutsugamushi disease has not been previously reported. We are describing a case of Tsutsugamushi disease presenting with aortic valve endocarditis. The clinical data of a 67-year-old female with *O. tsutsugamushi*-induced aortic valve endocarditis was summarized retrospectively and analyzed with a literature review. Treatment of *O. tsutsugamushi*-induced aortic valve endocarditis with chloramphenicol is recommended.

Keywords: Tsutsugamushi disease, infective endocarditis, excrescence, heart valve

Introduction

Tsutsugamushi disease is a mite-borne infectious disease caused by *Orientia tsutsugamushi*, a gram negative intracellular bacterium. The clinical picture of Tsutsugamushi disease is characterized by the sudden onset of fever with chills and non-specific symptoms that include headache, myalgia, sweating and vomiting. The presence of an eschar, which occurs in approximately one-half the patients with proven scrub typhus infection and usually involves the axilla, groin, or inguinal region, is characteristic of scrub typhus. Complications of Tsutsugamushi disease include pneumonia [1], acute respiratory distress syndrome (ARDS) [2], myocarditis [3] and so on. Of note, heart valve involvement in Tsutsugamushi disease is uncommon. To date, infective endocarditis associated with Tsutsugamushi disease has not been reported. As part of this review article, we report a case of *O. tsutsugamushi*-induced infective endocarditis with involvement of the aortic valve.

Case report

A 67-year-old female was admitted to our hospital for evaluation of recurrent chest tightness, palpitation, shortness of breath and fever of 5 days duration. The highest temperature was 39.7°C. She had been diagnosed with moderate aortic valve incompetence in a local hospital nearly 10 years earlier. Two days prior to this admission, she was seen in the Emergency Department of our hospital and treated with cefmetazole and acetaminophen; however, the fever persisted. A transthoracic echocardiography showed excrescence formation (**Figure 1A**) and moderate regurgitation of the aortic valve, thus she was referred to our cardiovascular department.

On physical examination, the temperature was 38.3°C, the pulse rate was 105 beats/min, the respiratory rate was 22 breathes/min, and the blood pressure was 116/78 mmHg. The patient appeared languorous and acutely ill. The breath sounds in both lungs were normal with a little moist rales in the lower right lung. On palpation, the heart border was not extended, and the liver and spleen were normal. The heart rhythm was completely irregular. A diastolic murmur was present in the third-to-fourth intercostal space at the left of the sternum.

Laboratory testing and imaging examinations showed the following: white blood cell count,

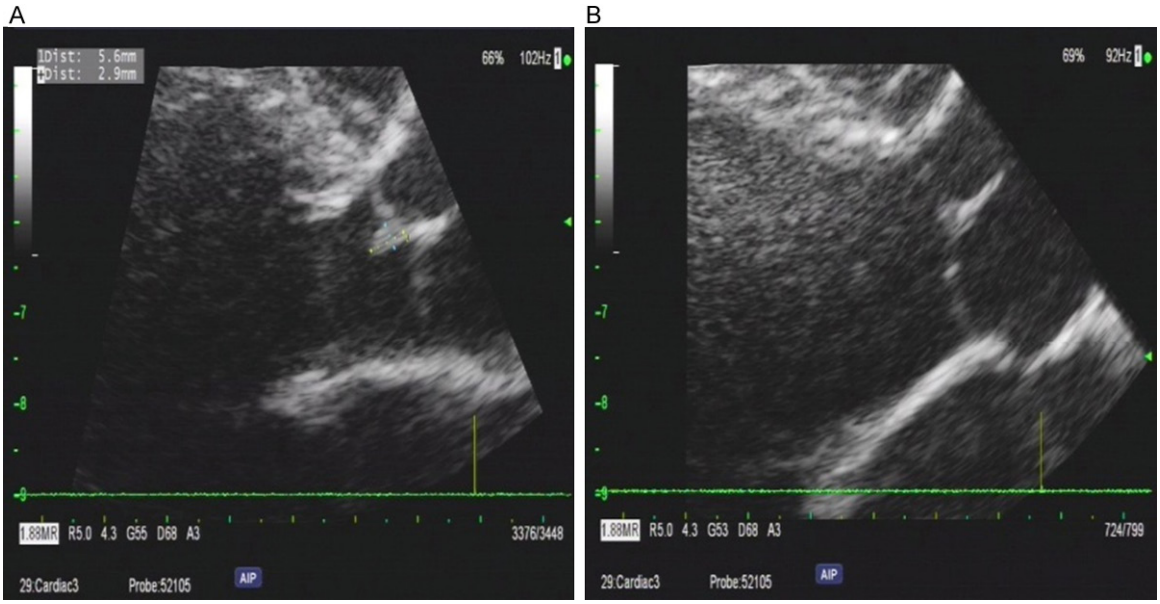

Figure 1. A: Transthoracic echocardiography showed the excrescence with a maximal diameter of 5.6 × 2.9 mm on the right coronary valve. B: The excrescence resolved after treatment with chloramphenicol.

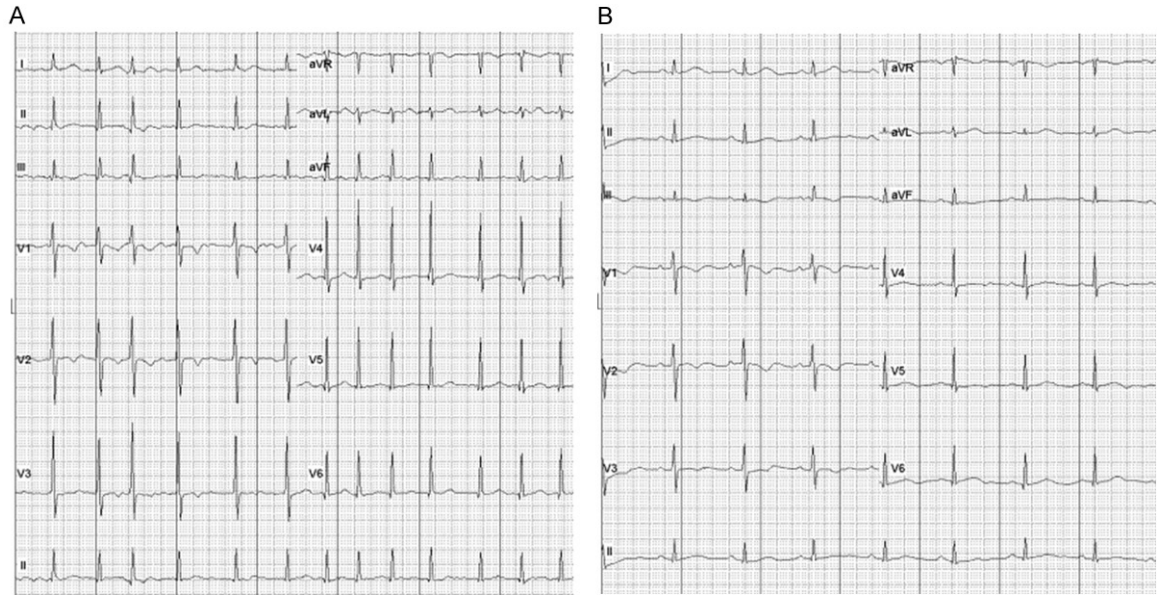

Figure 2. A: ECG on admission showed atrial fibrillation (about 105 beats/min) and T waves depression in leads II, III, aVF and V3 to V6. B: ECG after treatment with chloramphenicol revealed a sinus rhythm (68 beats/min) and T waves depression in leads II, III, aVF and V3 to V6.

5.08 × 10^9/L; hemoglobin, 130 g/L; platelet count, 78 × 10^9/L; alanine aminotransferase level, 74 U/L; aspartate aminotransferase level, 101 U/L; albumin level, 26.6 g/L; C-reactive protein level, 110.72 mg/L; rheumatoid factor, 41.08 IU/mL; erythrocyte sedimentation rate, 74 mm/h; complement C3, 490 mg/L; procalcitonin level, 2.1 ng/mL, brain natriuretic peptide level, 701 pg/mL, and troponin I was negative. Urinalysis revealed 2+ proteinuria, 2+ occult blood without significant casts and an erythrocyte count of 1305.5/μL. The 24-hour urinary protein excretion was 2.72 g. The ECG on admission showed atrial fibrillation with ventricular rate of about 105 beats/min and T waves depression in leads II, III, aVF and V3 to

Figure 3. A: An ecchymotic 30 × 20 mm plaque with a 20 × 10 mm black eschar was present in the right lateral inguinal region. B: An ecchymotic 15 × 15 mm plaque without a black eschar was present in the same region after treatment with chloramphenicol.

V6 (**Figure 2A**). A chest X-ray revealed increased and thickened markings in the lungs bilaterally. Transthoracic echocardiography indicated the following: (1) excrescence formation on the right coronary valve (**Figure 1A**) and moderate regurgitation of the aortic valve; (2) mild mitral regurgitation; (3) mild regurgitation of the tricuspid and pulmonary valve; and (4) an ejection fraction of 60%. Computed tomography indicated mild inflammation in both pulmonary lower lobes and a small of bilateral pleural effusion.

On the basis of the heart valve disease history, clinical manifestations, laboratory findings, and imaging examinations, the patient was diagnosed with acute infective endocarditis. Blood was collected at 1, 6, and 12 h after admission for bacterial and fungal cultures. Pending cultures, empirical intravenous administration of piperacillin-tazobactam was initiated. Because the patient had a persistent fever 3 days after admission, the antibiotics were changed to imipenem and cilastatin sodium. Subsequently, vancomycin and fluconazole were added. However, her fever was unremitting. At that time, the results of the blood cultures were still negative. The peripheral smear for *Plasmodium* and the Weil-Felix tests were also negative. Seven days following admission, the patient was re-examined and an eschar was noted in the right lateral inguinal region (**Figure 3A**). On further questioning, the patient acknowledged doing field work 2 weeks prior to admission. Therefore, a tentative diagnosis of Tsutsugamushi disease was made based on the clinical and laboratory findings. This finding further suggested that *O. tsutsugamushi* might induce infective endocarditis with involvement of the aortic valve. Thus, the treatment regimen was changed to chloramphenicol (1g iv drip q12h). After 3 days of treatment with chloramphenicol, the clinical symptoms and signs, including fever, weakness, and shortness of breath, improved greatly. After 10 days of treatment, the aortic valve excrescence was no longer present (**Figure 1B**) and the clinical symptoms, including fever, palpitation, chest tightness and shortness of breath resolved. An ECG after treatment revealed a sinus rhythm with ventricular rate of 68 beats/min and T waves depression in leads II, III, aVF and V3 to V6 (**Figure 2B**). The patient recovered and was discharged to home without complications. She was followed up for nearly 2 years and her general health was favorable.

Discussion

Scrub typhus, which is caused by *O. tsutsugamushi* (tsutsuga means small and dangerous, and mushi means insect or mite), is a zoonotic infectious disease that is transmitted to humans by an arthropod vector of the trombiculid family. The term scrub is used because of the type of vegetation that harbors the vectors. Typhus is derived from the Greek word meaning fever with stupor or smoke [4]. Scrub typhus is endemic in many Asian countries, including China, India, Japan, Korea, and others regions in East and South East Asia [5]. Scrub typhus can manifest with a variety of complications including encephalitis [6], hepatitis [7], DIC [8], and hemophagocytic lymphohistiocytosis [9]. Scrub typhus can also lead to myocardial damage such as fulminant myocarditis [3]. However, heart valve involvement in scrub typhus is rare. This is the first reported case of infective endocarditis associated with scrub typhus.

Orientia tsutsugamushi is an obligate intracellular, gram-negative organism that grows freely in the cytoplasm of infected cells. The life cycle of *O. tsutsugamushi* is maintained by the trans-

ovarian transmission in trombiculid mites. After hatching, the infected larval mites (chiggers, the only stage that feeds on the host) inoculate the skin of infected hosts. Infected chiggers are particularly found in dense areas of scrub vegetation during the wet season, which is when the mites lay their eggs [10]. The incidence of scrub typhus increased in the southern Chinese city of Guangzhou from 3.29 per 100,000 in 2006 to 9.85 per 100,000 in 2012. A summer peak was observed in June and July with the exception of year 2009 and 2011. The majority of cases (71.4%) involved those ≥ 40 years of age, and the incidence in females was higher than males in persons ≥ 50 years [11]. The patient described herein is female, 67 years of age, and had a history of field work in July (the rainy season) in Guangzhou city.

Scrub typhus has a large number of clinical manifestations, which include fever, myalgia, headache, rash, and a pathognomonic eschar. The eschar is formed when an infected chigger, the larval stage of trombiculid mites bites while feeding on human skin, usually in warm, damp areas where pressure from clothing occurs but can sometimes occur in unusual sites such as the ear lobes, wrists and forearm [12]. The border of the eschar may be surrounded by erythema. The eschar resolves in 3-4 weeks with no sequelae, but may occasionally cause scarring or hyperpigmentation. A study had shown an eschar prevalence of 20%-87% among scrub typhus patients [13].

Overall, the most common area affected by eschar formation is the groin (17.8%), followed by the abdomen (17.3%) [14]. Eschars are frequently missed on routine physical examination because the vector bite is painless and the patient does not notice the lesion. In the present case, a typical eschar was noted in the right lateral inguinal region during re-examination on the 7th day after admission. This finding played a key role in the diagnosis and management of *O. tsutsugamushi*-induced infective endocarditis. Therefore, an eschar may be the most useful diagnostic clue in patients with an acute febrile illness; patients should be thoroughly examined for the presence of an eschar, especially over covered areas, such as the groin, genitalia, and axilla.

Under the majority of conditions, infective endocarditis is caused by common pathogens such as *Staphylococcus aureus* and *Streptococcus viridans*. Blood culture is the most important method for the diagnosis of infective endocarditis, but sometimes pathogenic microorganisms can be difficult to identify. In our case, six blood cultures were obtained, the results of which were all negative 7 days after admission. This is called “blood culture-negative infective endocarditis (BCNIE)”. BCNIE can occur in up to 31% of all patients with infective endocarditis and often poses considerable diagnostic and therapeutic dilemmas. BCNIE most commonly arises as a consequence of previous antibiotic administration. It can also be caused by fastidious bacteria, notably obligatory intracellular bacteria [15]. The Weil-Felix test was performed three times for our patient; however, all of the results were negative. Other serologic testing methods for scrub typhus were unavailable in our hospital and the Guangzhou Center for Disease Control in China. So we speculate that *O. tsutsugamushi* might lead to infective endocarditis based on the typical eschar, which existed in our patient. Recently a study also confirmed the same problem that scrub typhus is an important public health concern in Guangdong province in China. Because laboratory diagnostics are commonly lacking for the detection of the disease in Guangdong, it is necessary to improve diagnostic methods to confirm cases of scrub typhus in hospitals [16].

Conventionally, the treatment of scrub typhus involves the use of these antibiotics which include doxycycline, chloramphenicol, quinolones, azithromycin, rifampicin, roxithromycin and tetracycline. In the four studies that have compared azithromycin with chloramphenicol, chloramphenicol treatment was associated with a significantly shorter median time to clearance of fever and lower adverse events when compared with azithromycin [17]. Although there is some evidence for the use of quinolones in scrub typhus, recent reports of quinolone resistance suggest that this treatment should not be used in critically ill patients [18]. As far as our patient was concerned, she belonged to the critically ill patient. Because she was diagnosed with *O. tsutsugamushi*-induced infective endocarditis and at the same time had cardiac insufficiency and hepatic injury. So we chose chloramphenicol (1g q12h iv drip for 10 days) to treat our patient and

achieved satisfactory results. Chloramphenicol as the treatment of scrub typhus-associated infective endocarditis may be an appropriate choice; however, large, prospective randomized controlled trials are needed for confirmation.

Conclusion

Orientia tsutsugamushi-induced infective endocarditis has not been reported previously. Thus, *O. tsutsugamushi* may be added to the list of pathogens in patients with infective endocarditis. As shown in our patient, there is no good substitute for a thorough clinical re-examination in patients with unexplained fever. One should keep in mind the etiology of common febrile illnesses locally and seasonally when evaluating patients with fever.

Acknowledgements

This work was supported by the National Natural Science Foundation of China (81370447) (http://www.nsfc.gov.cn/) and the PhD Start-up Fund of Natural Science Foundation of Guangdong Province (2016A030310203).

Disclosure of conflict of interest

None.

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