Torsades de Pointes by Azithromycin in Scrub Typhus and Review on Cardiac Manifestations of Scrub Typhus

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Azithromycin shows a comparable therapeutic efficacy to doxycycline against mild to moderate scrub typhus. It is safe enough to use in pregnant women or children less than 8 years of age, but may be associated with fatal cardiac dysrythmia. Herein we report a case of scrub typhus in which torsades de pointes developed during treatment with intravenous azithromycin. A 63-year-old man with a history of hypertension and prolonged QT interval was admitted because of fever with duration of 13 days, rash, an eschar, and delirium. An initial electrocardiography showed atrial fibrillation with rapid ventricular response. Scrub typhus complicated by meningoencephalitis, pneumonitis, and possible myocarditis was diagnosed. Two 500 mg doses of azithromycin were infused over 30 minutes, 12 hours apart. The patient developed a cardiac arrest due to torsades de pointes 30 minutes after the second dose of azithromycin. After the patient was resuscitated successfully and the antibiotic was change to doxycycline. The patient eventually improved and was discharged without any sequelae.

Key Words: Scrub typhus, tsutsugamushi disease, azithromycin, torsades de pointes, ventricular tachycardia

INTRODUCTION

Scrub typhus is endemic in Southeast Asia, including Korea. Doxycycline has been the drug of choice for the treatment of scrub typhus, however its becoming less effective due to the emergence of strains, resistant to doxycycline. Treatment of scrub typhus in children and pregnant women is a situation in which doxycycline is contraindicated. Azithromycin may be an ideal antibiotic for the treatment of scrub typhus because it is safe even in pregnant women and has good activities against doxycycline-resistant Orientia tsutsugamushi. In clinical studies, the efficacies of azithromycin for the treatment of scrub typhus of mild to moderate severity are comparable to those of doxycycline(1-3). These studies reafirm that azithromycin is not associated with serious adverse effects. Reports of scrub typhus occurring during pregnancy also show the efficacy and safety of azithromycin. Further studies on the efficacy of azithromycin in treating severe scrub typhus are anticipated. Meanwhile while we want to mention a serious adverse effect that may be associated with the treatment of scrub typhus with azithromycin.
CASE REPORT

A 63-year-old man was admitted to our hospital because he had a fever lasting 13 days, myalgia, rash, and delirium. The patient had a history of uncontrolled hypertension, obesity, and fatty liver. The electrocardiography checked four years ago showed the left ventricular hypertrophy, T-wave abnormalities suggesting lateral ischemia, and prolongation of the corrected QT (QTc) interval (453 ms).

On admission, the body temperature was 37.5°C and blood pressure was 185/89 mmHg. An eschar at the left inguinal area and regional lymphadenopathies were noted. Chest PA showed pulmonary congestion or interstitial pneumonitis. An initial ECG showed atrial fibrillation with rapid ventricular response and QTc interval of 442 ms. Serum potassium and ionized calcium levels were 4.8 mmol/L and 1.11 mmol/L, respectively. Arterial blood gas analysis revealed that the pH was 7.40: PCO₂, 3.9 kPa; PO₂, 7 kPa; and HCO₃⁻, 18 mmol/L. The cerebrospinal fluid showed a white blood cell count of 0.064 × 10⁷/L with 44% lymphocytes, and protein and glucose levels of 1.83 g/L and 2.6 mmol/L, respectively. Brain CT revealed senile changes.

Scrub typhus complicated by encephalitis, pneumonitis and possible myocarditis was suspected, and two 500 mg doses of azithromycin were infused over 30 minutes, 12 hours apart over a period of 30 min. The patient developed a cardiac arrest 30 minute after the second infusion of azithromycin, and torsades de pointes was recorded in the electrocardiography (Fig. 1). The patient was successfully resuscitated with cardioversion. Because azithromycin was suspected of causing torsades de pointes, the antibiotic was changed to oral doxycycline. Other medications that were administered concomitantly were midazolam, furosemide, cimetidine, dopamine, and methylprednisolone. The subsequent clinical course was uneventful, and scrub typhus was confirmed by the fourfold increase in the antibody titers of O. tsutsugamushi. ECG findings at discharge were the same to those checked 4 years ago—QTc of 452 ms, left ventricular hypertrophy, and abnormal T waves.

DISCUSSION

Torsades de pointes (TdP) is a polymorphic ventricular tachycardia that is related with the prolongation of the corrected QT interval. It is rare, but fatal if it is not promptly identified and managed. Congenital long QT syndromes and class IA & III antiarrhythmic drugs are well-known causes of TdP. Recently, TdP by non-cardiovascular drugs, including antihistamines, cisapride, and antibiotics (the macrolides/ketolides, certain fluoroquinolones and antimarialids, pentamidine, and theazole antifungals) are increasingly recognized; although these drugs usually cause clinically unnoticeable delays of mild degree in ventricular repolarization, they may amplify the risk for torsades de pointes (TdP) when prescribed in the presence of other risk factors. Among antibiotics, macrolides have greatest potential to induce QT prolongation. The exact incidence of TdP associated with the use of macrolides is not known, but a postmarketing analysis estimated the adjusted report–utilization ratio of TdP in erythromycin is 0.07, clarithromycin 0.18, and azithromycin 0.06 reports per 1 million recommendations. The rate of TdP in cefuroxime, as a control, is 0.02 (4). Risk factors for the development of TdP by macrolides include increasing age, female sex, and structural heart diseases/co–administered drugs known to prolong the QT interval(4). Though the risk of the development of TdP by azithromycin seems to be 3 times higher than that of cefuroxime, the incidence of TdP is too low to estimate the actual risk of TdP by azithromycin, and this data are unable to establish causation of the administration of macrolides and the development of TdP. Actually reviewing the published reports, azithromycin has questionable or at least minimal risk of proarrhythmic po-

![Fig. 1. The electrocardiography of the patient shows torsades de pointes.](image-url)
potential, and does not alter the metabolism of other pro-
arrhythmic drugs: in an experimental study, azithro-
mycin prolongs QT interval, but shows no proarhythmic
effects(5); evaluation of the repolarization and pro-
arrhythmia effects of azithromycin using the TdP–suscep-
tible animal model does not reveal prolongation of QT
interval(6); in a human volunteer study, azithromycin
does not prolong QT interval(7); and there are only three
case reports of TdP(8–10) and one case of QT pro-
longation(11), after use of azithromycin, exclusively in patients
with underlying cardiac diseases.

Thus, azithromycin per se has a questionable asso-
ciation with TdP, but there is a possibility that it con-
tributes the development of TdP by other proarhythmic
drugs or underlying cardiac diseases(12, 13). In our pa-
tient, other known proarhythmic drugs are not admini-
stered, so underlying QT prolongation is the major cause
of the TdP. However, development of TdP in patients
with underlying QT prolongation after receiving azithro-
mycin has been reported in only three cases, so its oc-
currence is a very rare event. Thus, we guess scrub typhus is an additional contributing factor for develop-
ment of TdP in our patient.

Scrub typhus is a relatively benign disease in the antibiotic era. However, if the appropriate treatment is
delayed or missed, the mortality rates reach up to 30%
(14). Severe scrub typhus is characterized by involvement
of multiple organs, including liver, lung, brain, kidney,
and heart. The frequencies of involvement of these organs vary according to the duration of scrub typhus:
generally the longer the duration of the illness, higher
the frequent the incidence of complications. In studies
performed in Korean, pneumonic involvement occurs in
34–69%, hepatic involvement in 90%, and azotemia in
15%. Pneumonitis can cause hypoxia that alters serum
electrolytes level, especially potassium, and consequently
contributes to the development of cardiac dysrhythmia.
Hepatic dysfunction and azotemia can be associated with
the development of cardiac dysrhythmia by altering the
metabolism of proarrhythmic drugs. Furthermore, other
risk factors, such as electrolytes imbalance, that can
prolong the QT interval are frequently observed in scrub
typhus. In addition, in Korea, scrub typhus occurs more
frequently in elderly women, which is a risk factor for
development of TdP during use of macrolides. Elderly
people have many underlying illnesses and take several
types of medications, such as anti–hypertensive medica-
tions and diuretics, which can contribute to the develop-
ment of TdP. In addition, chronic B viral hepatitis or
alcoholism is prevalent in the elderly in Korea, and may
result in altered drug metabolism. Alcoholism is
common in men residing in urban areas, which is associ-
ated alcoholic liver diseases and alcoholic cardiomyop-
athy.

About the heart involvement in scrub typhus, patho-
logic examination of the heart performed in era before
the introduction of tetracycline or chloramphenicol
reveals the following abnormalities(15): perivascular and
intramyocardial infiltration of leukocytes in about 50% of
the autopsied patients; mild inflammatory reactions in
the Purkinje tissue of the papillary muscles in certain
portion of the patients; and subepicardial petechial he-
norrhages in about half of the patients. Myocardial
involvement by scrub typhus is usually not evident
clinically, but in certain patients death may occur due to
congestive heart failure or serious dysrhythmia: conges-
tive heart failure occurs only in severe cases and begins
in second or third week(16). Clinical features of myo-
cardial involvement are cardiac enlargement, persistent
gallop rhythm, apical systolic murmur: heart failure and
resultant pulmonary edema at the terminal phase; and
serious dysrhythmia usually occurred concomitantly with
myocardial failure. The ECG findings representing myo-
cardial injury are low voltage, slurring and notching of
QRS complexes, and atrial fibrillation(17). Sharp T wave
inversion or notching in lead CR–3 may also be another
finding suggesting myocardial involvement(16). Thus,
atrial fibrillation in our patient is certainly thought to be
an evidence of myocardial involvement of scrub typhus.
In post–antibiotic era, with the decrease of the number
of patients with severe scrub typhus, are rare. However
there have been reports of: myocarditis(17), pericarditis
or pericardial effusion(18), and acute myocardial infarction
(19). One study shows 3% of incidence of myocarditis
(20). Various electrocardiographic abnormalities are re-
ported, but, they are usually not specific to scrub typhus.
(21, 22). In a Korean study, the incidences of QT prolongation and the first degree AV block in scrub typhus are 5.1% and 5.1% each. A study from China showed ECG abnormalities of benign significance: one case showed QTC interval prolongation only during acute phase(21). A study from Thailand reports nonspecific electrocardiographic abnormalities that are those expected in other febrile illnesses(22); but the duration of the illness of the enrolled patients are 4 days (mean), which means that they include the early phase of scrub typhus and may not be adequate for studying cardiac complications of scrub typhus.

Thus, because the risk of fatal cardiac dysrhythmia may be substantial in severe scrub typhus, the use of azithromycin for the treatment of scrub typhus is better to be reserved to cases in which the disease severity is mild to moderate until further studies confirm the safety of azithromycin in severe scrub typhus. If its use is inevitable, electrocardiography, serum level of electrolytes, and liver and renal function tests should be checked before the administration of intravenous azithromycin. Administration via oral route might be preferred. In addition, concomitant administration of medications that potentially prolong QT intervals should be avoided.

요 약

Azithromycin

Azithromycin doxy-

cyline

torsades de pointes

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