Muscle toxicity induced by intravenous voriconazole in a cryptogenic organizing pneumonia patient misdiagnosed as suspected pulmonary fungal infection

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Case report

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Abstract

Background Although voriconazole is a widely used azole antifungal agent in clinical practice, its side effect of muscle toxicity is extremely rare. The present study demonstrates an adverse effect of progressive myotoxicity induced by intravenous voriconazole in a cryptogenic organizing pneumonia patient misdiagnosed as suspected pulmonary fungal infection.

Case presentation A 78-year-old male was admitted to our hospital due to recurrent cough and expectoration for four months. His previous chest CT scan indicated alveolar opacities and multiple cavitory nodules in the right lower lobe. Pulmonary fungal infection was considered due to weakly positive results of serum galactomannan and 1,3 β -D-glucan test, with no evidence of malignant tumor, tuberculosis, or Wegener's granulomatosis. The patient experienced diffuse myalgia with significantly elevated muscle enzymes after voriconazole administration for 13 days, and recovered uneventfully due to immediate voriconazole cessation and enhanced intravenous fluid infusion. Furthermore, the pulmonary cavitory nodules were consistent with the pathological findings of cryptogenic organizing pneumonia.

Conclusions Voriconazole-associated myotoxicity should be considered when a patient presents with evidence of muscle injury during voriconazole administration. Moreover, although invasive pulmonary fungal infection can often show multiple nodules with cavities in CT scan, the initiation of anti-fungal agents should be cautious before the pathological features of multiple cavitory nodules are identified, in order to avoid potential serious adverse events.

Background

The common adverse effects of voriconazole include hepatotoxicity, visual disturbances, photosensitivity, fever, nausea, vomiting, and rash[1]. However, voriconazole-associated myotoxicity is rarely reported[2, 3], and can be easily overlooked by clinicians. The delayed treatment of myotoxicity is potentially lethal, resulting in rhabdomyolysis and even acute renal failure. In the present study, we first demonstrate a case of intravenous voriconazole-induced myotoxicity in Asian patient without prior history of drug-induced myopathy, highlighting its presentation and management in clinical practice. Furthermore, a case of cryptogenic organizing pneumonia (COP) showing multiple cavitory nodules on chest CT scan was also presented, which was misdiagnosed as pulmonary fungal infection on admission. To the best of our knowledge, multiple cavitory nodules are rare imaging findings for COP[4].

Case Presentation

A 78-year-old male presented to our department with recurrent cough and expectoration for four months. He reported a history of hypertension for more than 10 years and his daily antihypertensive medications included metoprolol tartrate 100 mg orally, once daily; felodipine 5 mg orally, once daily. The chest CT scan performed three months ago in Hospital A demonstrated alveolar opacities accompanied by two

cavitary nodules in the right lower lobe. The diagnosis of pneumonia was made, and antibiotics were initiated. However, the lesions in the lung gradually progressed (Fig. 1A, 1B, and 1C). During the course, the antibiotics were changed several times by experience (the sputum production was mild and the results of repeated etiological examination were negative). All the medicines except metoprolol tartrate and felodipine were discontinued three days before admission. Vital signs on admission in our hospital were normal, and the physical examination revealed moist rales in the right lower lobe. The level of serum galactomannan and 1, 3 β -D-glucan test was 88.2 pg/ml (normal values < 70 pg/ml) and 0.83 μ g/L (normal values < 0.65 μ g/L), respectively. Accordingly, pulmonary fungal infection was suspected, and intravenous voriconazole was administered on day one after hospitalization, with a loading dose of 800 mg in the first 24 hours, followed by a maintaining dose of 400 mg, daily. Biapenem (0.3 g intravenously, every eight hours) was also prescribed due to the high risk of secondary multi-drug resistant gram-negative bacilli infection. Sputum bacterial culture results on admission were negative. Bronchoscopy was rejected by the patient's relatives because of the caution of intolerance and related complications. During the first week after admission, the serum tumor markers, ANA/ANCA panel, and sputum smear microscopy for mycobacterium tuberculosis were all negative.

The patient reported muscle weakness on day nine, but the muscle strength of the four limbs was normal. The level of muscle enzymes detected on day eight revealed a mild increase, but was still within normal limits. In the following four days, the symptom of muscle weakness exacerbated with concomitant diffuse myalgia. Muscle strength was approximately 3/5 for the four limbs on day 12. Serological examination on day 13 revealed that the level of aspartate transaminase (AST), alanine transaminase (ALT), creatinine kinase (CK), and lactate dehydrogenase (LDH) was 100.9 U/L (15–40 U/L), 45.8 U/L (9–50 U/L), 1465 U/L (50–310 U/L), and 322 U/L (120–250 U/L), respectively (Fig. 2). Furthermore, the level of serum creatinine and electrolyte was within normal limits, which was consistent with the value measured on admission. In addition, urine output was greater than 1,500 ml daily after admission, and the laboratory examination of urine was unyielding. All recent prescribed medicines that had potential adverse effect of muscle toxicity were screened and ruled out, except for voriconazole, in which an independent myotoxic effect has been reported in an American woman[3]. Then, voriconazole was discontinued immediately on day 15 and replaced by caspofungin. The intravenous fluid infusion was enhanced, and both urine output and level of creatinine were monitored. Furthermore, idiopathic inflammatory myositis-associated antibodies were all unyielding. The symptoms of myalgias and muscle weakness alleviated on day 16, and were resolved five days later. CK returned to normal on day 19 and the other three enzymes returned to normal levels two days later (Fig. 2). It was notable that the Naranjo Adverse Drug Reaction Probability Scale presented a probable relationship between muscle toxicity and the administration of intravenous voriconazole (score of 7)(Table 1).

The chest CT scan on February 6, 2017 revealed that the lesion of the right lower lobe progressively enlarged (Fig. 1D). The biapenem was then ceased, and the teicoplanin was prescribed due to the caution of gram-positive cocci infection. The patient discharged at the request of his relatives on February 14, 2017 and visited Hospital B four days later (The detailed medical records cannot be available). The CT scan on March 15, 2017 in Hospital B indicated the lesions remarkably progressed (Fig. 1E), then core

needle biopsy of the nodules was performed, and the pathologic results were consistent with organizing pneumonia (Fig. 3). As a result, the diagnosis of COP was established on the basis of ruling out the possibility of secondary organizing pneumonia. The patient was prescribed with 35 mg of prednisone for four weeks as initial treatment according to the schedule. The symptoms of cough and expectoration alleviated gradually, and the lesions in the right lower lobe were partly absorbed (Fig. 1F). However, the patient lost follow-up since June 2017 and he never visited our hospital again. The timeline of this patient was described in Fig. 4.

Discussion

Azole antifungal agent-induced myotoxicity has been previously reported, and most cases are associated with concomitant statin use because of the suppression of drug metabolism[5–7]. However, as a member of azole antifungal agent, voriconazole has been rarely reported to have independent myotoxic effects[2, 3]. Up to now, the detailed mechanism of voriconazole-induced myotoxicity remains largely unknown. Direct muscle toxicity and immune-mediated inflammatory injury are supposed to be involved in voriconazole-associated muscle toxicity and further research is warranted to reveal the potential mechanism.

It is most likely that the voriconazole had an independent effect of muscle toxicity in the present study. First, voriconazole was not used concomitantly with statins. The concomitant use of these two drugs may increase the risk of myotoxicity due to the pharmacokinetic interactions between these two medicines[8]. Furthermore, voriconazole was not concomitantly used with other drugs that can cause myotoxicity effects, such as corticosteroids, amiodarone, colchicine, cyclosporine, zidovudine, and vincristine[9]. Second, no other medical conditions that could cause myotoxicity were identified, such as idiopathic inflammatory myositis and hypothyroidism. In addition, serologic examinations were unyielding. Third, other medical conditions that could cause the elevation of muscle enzymes or muscle weakness such as hypoxia, prolonged bed rest, serum electrolyte disturbance, or malnutrition were excluded. Fourth, the changing patterns of muscle enzymes, which increased dramatically after the administration of voriconazole and declined after the discontinuation of voriconazole, were consistent with the deduction that the drug was the culprit. Finally, the Naranjo Adverse Drug Reaction Probability Scale presented a score of 7, indicating a probable relationship between muscle toxicity and the administration of intravenous voriconazole.

Non-traumatic rhabdomyolysis has been reported as a severe adverse effect of azole antifungals, which have been used alone or concomitantly with statins[5–7, 10]. Despite the fact that muscle damage occurred in this case, however, severe consequences such as rhabdomyolysis were successfully prevented due to our awareness of the muscle toxicity of azole antifungals and the timely discontinuation of voriconazole. Hepatotoxicity is one of the common adverse effects of voriconazole. However, the elevated transaminases in the present case might also be attributable to muscle toxicity, since both ALT and AST are highly concentrated in muscular cells[11].

CK has been considered as a highly sensitive index for detection and monitoring of muscle injury, and in most clinical settings the level of serum CK is positively correlated with degree of muscle damage[12]. In deed, the dynamic changes of serum CK level in our case were compatible with appearance, alleviation, and absence of myotoxicity-related symptoms. Comparing to a study of voriconazole-induced muscle toxicity by Shanmugam, *et al*[3], the level of serum CK in our case elevated in the early stage during voriconazole administration. Although the relationship between muscle toxicity and trough concentration of voriconazole is uncertain, some adverse events (neurotoxicity and hepatotoxicity) are seen in definite correlation with supratherapeutic voriconazole trough level[1]. It seems like that intravenous administration of voriconazole in an elderly patient in our study is more susceptible to get a higher voriconazole trough level, or even cause supratherapeutic voriconazole concentration in a shorter time than that in young patient with oral voriconazole. It is a great pity that trough concentration of voriconazole in our study has not been determined.

The imaging of multiple cavitary nodules is a characteristic of pulmonary fungal infection, which is not specific. Findings on imaging studies usually prompt the differential diagnosis of tumor, pneumonia, Wegener's granulomatosis, and tuberculosis. The common imaging findings of COP include multiple alveolar opacities, solitary opacity, and infiltrative opacities. However, multiple nodules are rare, especially findings on nodules with cavitation[4].

Conclusion

The present study highlights the muscle toxicity of voriconazole, even when it is used alone. The possibility of such adverse effect should be considered when a patient reports muscle weakness or myalgia, or shows elevated muscle enzymes after voriconazole administration. The prompt discontinuation of voriconazole is mandatory to avoid serious consequences. Furthermore, although multiple nodules with cavities are features of invasive pulmonary fungal infection in CT scan, the differential diagnosis of multiple cavitary nodules is warranted before the initiation of anti-fungal agents, in order to avoid potential serious adverse events.

Abbreviations

COP: cryptogenic organizing pneumonia; AST: aspartate transaminase; ALT: alanine transaminase; CK: creatinine kinase; LDH: lactate dehydrogenase.

Declarations

Authors' contributions

Wei Lei was responsible for the organization and coordination of the trial. Jian-an Huang was the chief investigator and responsible for the data analysis. Jiajia Wang, Xingbo Zhou, Nan Su, Xiaofei Wang, and

Xiaohui Zhang developed the trial design. All authors contributed to the writing of the final manuscript and approved the submission.

Availability of data and materials

The data in the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare no competing interests.

Ethics approval

This study was approved by the Institutional Review Board of the First Affiliated Hospital of Soochow University.

Consent for publication

The patient provided a written informed consent for publication and this would be available for review by the Editor-in-Chief.

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Not applicable.

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Table

Table 1. The Naranjo Scale questions and weighted scores				
To assess the adverse drug reaction, please answer the following questionnaire and give the pertinent score	Yes	No	Do not know	Score
1. Are there previous conclusive reports on this reaction?	+1*	0	0	1
2. Did the adverse event appear after the suspected drug was administered?	+2*	-1	0	2
3. Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?	+1*	0	0	1
4. Did the adverse reaction reappear when the drug was readministered?	+2	-1	0*	0
5. Are there alternative causes (other than the drug) that could on their own have caused the reaction?	-1	+2*	0	2
6. Did the reaction reappear when a placebo was given?	-1	+1	0*	0
7. Was the drug detected in the blood (or other fluids) in concentrations known to?	+1	0*	0	0
8. Was the reaction more severe when the dose was increased, or less severe when the dose was decreased?	+1	0	0*	0
9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0*	0
10. Was the adverse event confirmed by any objective evidence?	+1*	0	0	1
Total Score	5	2	0	7
Relationship: total score ≥ 9 , definite; total score 5 to 8, probable; total score 1 to 4, possible; total score ≤ 0 , doubtful. * The items of pertinent score				

Figures

Figure 1

Changes of lesions in the right lower lobe on chest CT scan. (A, B, and C) The lesions gradually progressed. (D) The lesions obviously progressed after voriconazole administration for 12 days. (E and F) Compared to Figure E, lesions in Figure F were partly absorbed after the prednisone administration for four weeks.

Figure 2

Dynamic changes in muscle enzyme level. The serologic level of CK, LDH, AST, and ALT began to increase after voriconazole administration for eight days. The level of the muscle enzymes gradually declined after voriconazole cessation on day 15. The CK level returned to normal on day 19, and the other three enzymes returned to normal levels two days later.

Figure 3

Pathological features of lung tissue collected by core needle biopsy (H&E staining, 100×). Alveolar spaces were filled with granulation tissues, and the alveolar septum mildly thickened, accompanied by fiber tissue hyperplasia.

Figure 4

The timeline of key events for the patient.