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Case Report

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Agranulocytosis Caused by Voriconazole: A Non DRESS Syndrome Case Report and Literature Review

Shanshan Xie[1], Chunhua Guo[2], Weifang Zhang[1], Jinjin Wan[1], Qiufen Xun[3], Qing Yang[3] and Wei Wang[3*]

[1]Department of Pharmacy, the Second Affiliated Hospital of Nanchang University, China

[2]Department of Pharmacy, TaiHe County People's Hospital, China

[3]Department of Respiratory, the Second Affiliated Hospital of Nanchang University Nanchang, China

[*]**Corresponding author**: Wei Wang, Department of Respiratory, the Second Affiliated Hospital of Nanchang University, Nanchang 330006, China, E-mail: wendy_xi@126.com

Abstract

Background: Voriconazole is an antifungal agent that has been widely used for invasive aspergillosis. In recent years, some new and unexpected adverse reactions of voriconazole have been reported, such as phototoxic skin diseases, periostitis and malignant tumors. However, there are few reports about voriconazole-related agranulocytosis. Therefore, it is necessary to report this severe adverse reaction to highlight such a potentially fatal possibility.

Case presentation: This report describes a 56-year-old male patient diagnosed with invasive aspergillosis and asthma. After one month treatment with voriconazole, he presented with fever, rashes and agranulocytosis (0.01×109/l). Excluded other potential causes of agranulocytosis and distinguished with drug reaction with eosinophilia and systemic symptoms syndrome (DRESS), this patient was considered a rare, severe and non-DRESS adverse drug reaction induced by voriconazole. After voriconazole withdrawal and glucocorticoid treatment, the symptoms ultimately recovered.

Conclusions: According to experience of this case and literature review, physicians should be aware of agranulocytosis when treating patients with voriconazole, especially in patients with neutropenia.

Keywords: Voriconazole; Agranulocytosis; Adverse drug reaction; Drug reaction with eosinophilia and systemic symptoms syndrome (DRESS); case report

Abbreviations: CRP: C-Reactive Protein; BALF: Bronchoalveolar Lavage Fluid; SMZ/TMP: Sulfamethoxazole/Trimethoprim; ADR: Adverse Drug Reaction; DIHS: Drug-Induced Hypersensitivity

Syndrome

Background

Voriconazole is a broad-spectrum triazole antifungal agent. The Infectious Diseases Society of America recommends it as the first-line treatment for invasive aspergillosis [1], also for patients with hematologic malignancies or recipients of hematopoietic stem cell transplantation [2]. In order to prophylaxis and treatment of fungal infections in these patients, the application of voriconazole raises various adverse events. The most common types of events are rash, visual disturbance, hepatotoxicity and phototoxicity [3,4]. However, there is only one case of voriconazole-related agranulocytosis reported. This study reports a 56-year-old Chinese man who developed agranulocytosis after treatment with voriconazole.

Case Presentation

A 56-year-old male patient was admitted to a hospital due to fever, chest tightness and cough with white phlegm for one-week duration. He was a smoker (30 pack-years). He had a history of asthma and had been treated with budesonide/formoterol (320 μg/9μg) (one inhalation twice daily). The patient has no family history. Physical examination revealed fever (38.5°C), tachypnea (21 breaths per minute), normal oxygen saturation (98%) without oxygen supplement, and scattered wheezing sounds in bilateral lungs. The laboratory tests showed neutropenia (10.10×109/l), increased C-Reactive Protein (CRP) (62.3 mg/l) and total serum IgE (161 IU/ml). Cultures of sputum and Bronchoalveolar Lavage Fluid (BALF) detected Aspergillus fumigatus, which was also identified by metagenomic next-generation sequencing later. Chest computed tomography scan revealed bilateral multiple pulmonary nodules **(Figure 1a and b)**. Therefore, the diagnoses were revised to invasive pulmonary aspergillosis and asthma. Correspondingly, the treatment strategy of voriconazole combined with glucocorticoid was formulated. The treatment regimen of voriconazole was as follows: 6 mg/kg every 12 hours for the first 24 hours, then 4 mg/kg Q12h. The treatment regimen of glucocorticoid was as follows: methylprednisolone 40 mg QD for 14 days, switched to prednisone 10 mg QD for seven days, then 5 mg QD till the second admission. In addition, rabeprazole (10 mg QD) was prescribed in case of gastrointestinal adverse reactions for the initial 21 days. The patient began to quit smoking and stopped inhalation of budesonide/formoterol.

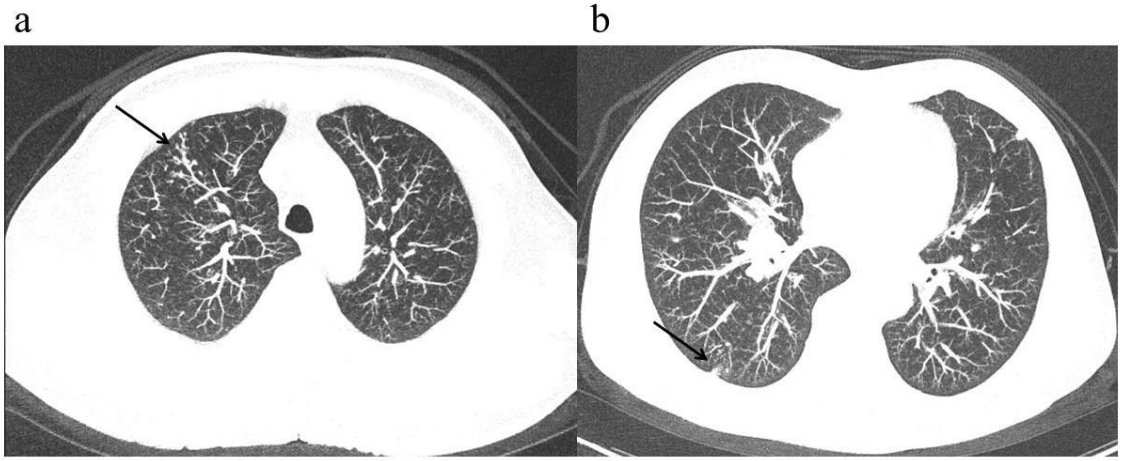

Figure 1: Chest computed tomography scan of the patient. Black arrow showed the multiple nodules in the bilateral lobes of the lung.

After 34 days, the patient was readmitted to the second hospital with right gingival pain and fever (38.5°C). This episode was without chest tightness, and physical examination showed no positive signs. Interestingly, there were a significant reduction in leukocytes (0.68×109/l) and neutrophils (0.01×109/l). Other laboratory test results showed: lymphopenia 0.60×109/l; eosinopenia0.02×109/l; normal hemoglobin 124 g/l; normal platelets 208×109/l; increased CRP (35.7 mg/l); normal total serum IgE (39.4 IU/ml); normal levels of GM and (1-3)-β-D-glucan tests; negative detection of T cell spot test of tuberculosis infection (SPOT. TB); negative detection of Epstein-Barr virus, herpes simplex virus-2 and cytomegalovirus; normal levels of thyroid hormone; normal liver and renal function; negative autoantibodies tests; negative blood culture and bone marrow culture. The bone marrow smear revealed hypocellularity. The bone marrow biopsy found no dysplasia or primitive immature cells. Compared with the previous chest CT scans, the chest and abdominal computed tomography scans showed decreased pulmonary nodules, which suggested an effective treatment with voriconazole.

Then, the patient received recombinant human granulocyte-colony stimulating factor, and imipenem/cilastatin (1.0g Q8h) plus sulfamethoxazole/trimethoprim (SMZ/TMP) (0.96g Q6h) for empirical anti-infection therapy. After four days of observation, the fever and neutropenia were not recovered. Moreover, erythematous rashes on the patient's extremities unexpectedly appeared, which presented a possibility of an allergic disease consulted by the dermatologist. Therefore, the suspected allergic drug SMZ/TMP was stopped using. During the following five days, the temperature was almost normal, but neutropenia and rashes persisted. Excluding hematological diseases, the patient's leukocytes might be due to adverse reactions caused by voriconazole. On the 44th day of voriconazole administration, it was discontinued and methylprednisolone (60 mg QD for ten days) was prescribed. At 36 hours of drug withdrawal, the plasma voriconazole concentration was measured at 2.37 mg/l (1.0-5.5 mg/l). Ten days after voriconazole withdrawal, the neutropenia was ultimately recovered (28.16×109/l) **(Figure 2)** and the rashes gradually disappeared. In addition, the CYP2C19 genotype was tested to evaluate the

metabolism of voriconazole. The result revealed an Intermediate Metabolizer (IM, *1/*2 636 GG, 681 GA). Considering invasive aspergillosis, the patient received posaconazole (10 ml Q12h) as an alternative treatment when he was discharged from the hospital. During the subsequent follow-up, the number of neutrophils did not decrease. Within one month, methylprednisolone gradually reached the withdrawal standard by reducing the dose to 4mg daily. After two months, the blood test re-examination showed normal leukocytes (4.09×109/l) and neutrophils (2.85×109/l). Moreover, the patient had no complaints of discomfort.

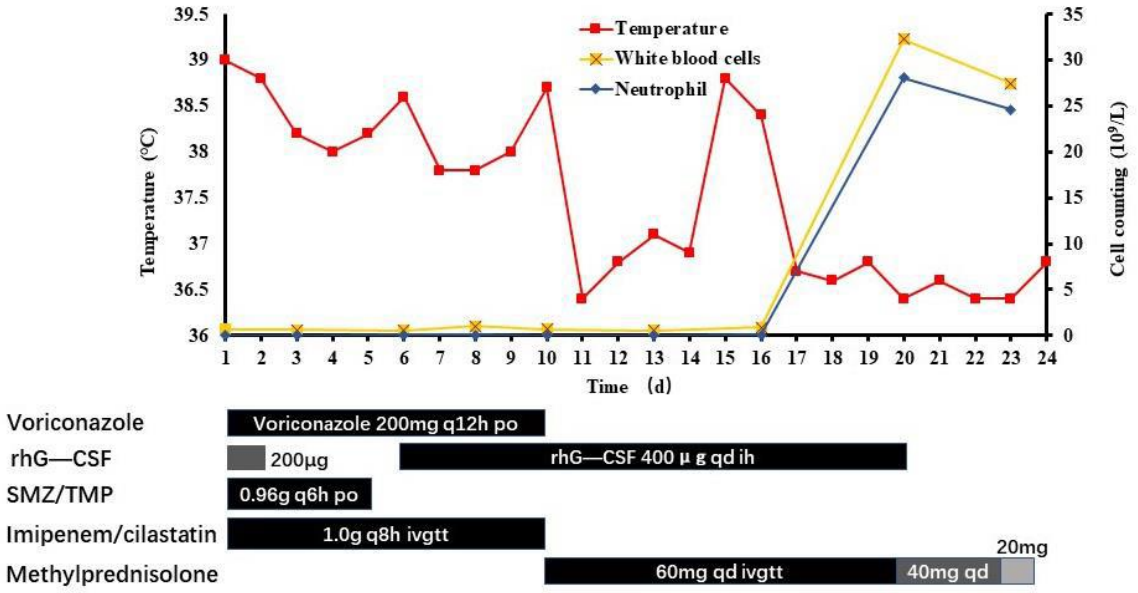

Figure 2: Clinical course at the second admission. rhG-CSF: Recombinant Human Granulocyte Colony Stimulating Factor; SMZ/TMP: sulfamethoxazole/trimethoprim.

Discussion and Conclusions

Agranulocytosis is a severe form of neutropenia. It is defined as a significant reduction of neutrophils (less than 0.5×109/l). Idiosyncratic drug-induced agranulocytosis is caused by a causative drug. Many drugs could cause agranulocytosis, such as aspirin, diazepam, carbamazepine, phenytoin, valproate sodium, propylthiouracil, digoxin, flucytosine, SMZ/TMP, omeprazole and so on [5]. However, agranulocytosis caused by voriconazole is very rare. In this case, the patient developed severe agranulocytosis after one month of treatment with voriconazole and neutrophils recovered ten days after drug withdrawal. Based on a systematic review, voriconazole trough blood concentration was significantly associated with treatment response rate and some side effects [6]. The trough blood concentration of voriconazole is recommended to be maintained at 0.5-5.0 mg/l for the Chinese population [7]. Unfortunately, the voriconazole valley concentration of this patient was not available for some reason. However, the concentration at 36 hours after drug withdrawal still revealed 2.37 mg/l. According to the pharmacokinetic profile of voriconazole [8], the trough concentration of voriconazole may be above 5 mg/l in this patient. Moreover, the intermediate metabolizer genotype of CYP2C19 probably contributed to the delayed metabolism of voriconazole [9]. As for the interaction between voriconazole and other drugs, prednisone and rabeprazole were involved in the initial treatment strategy. It has been reported that rabeprazole has a low affinity with CYP isoenzymes [10], and there is no appreciable change in voriconazole

plasma exposure after being combined with rabeprazole [11]. Indeed, rabeprazole did not show drug-drug interaction with voriconazole. Moreover, prednisone did not affect voriconazole plasma concentration [12]. Thus, to evaluate the possibility of adverse reactions caused by voriconazole, the Naranjo Scale score of this patient is applied. A score of 7 suggested that the agranulocytosis probably be caused by voriconazole (Table 1).

Table 1: The weighted scores of the patient on the Naranjo Scale [13].

To assess the adverse drug reaction (ADR), please answer the following questionnaire and give the pertinent score.	Yes	No	Do not know
1. Are there previous conclusive reports on this reaction?	1		
2. Did the adverse event appear after the suspected drug was administered?	2		
3. Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?	1		
4. Did the adverse reaction reappear when the drug was readministered?			0
5. Are there alternative causes (other than the drug) that could on their own have caused the reaction?		2	
6. Did the reaction reappear when a placebo was given?			0
7. Was the drug detected in the blood (or other fluids) in concentrations known?	1		
8. Was the reaction more severe when the dose increased, or less severe when the dose decreased?			0
9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure?			0
10. Was the adverse event confirmed by any objective evidence?		0	
Total score	7		

The total score ≥ 9 was empirically defined as “definitely” having caused the ADR; the total score 5–8 was defined as “probably” caused the ADR; the total score 1–4 was defined as “possibly” and the total score ≤ 0 indicated association with the drug was “doubtful”.

Voriconazole has been widely used because of its good efficacy and safety. However, more and more new adverse reactions have been verified recently. Some reported unexpected reactions were phototoxic skin diseases, periostitis, malignant tumors, alopecia, hyperlipidemia and nail changes [14,15]. Among these reports, there is only one case of agranulocytosis caused by voriconazole to date [16]. It was reported that a 68-year-old female patient who had pulmonary aspergillosis was also treated with voriconazole. After one-month, severe agranulocytosis occurred. The other two weeks of cessation of voriconazole and seven days of treatment with glucocorticoid later, the disorders recovered completely. These two cases had in common with similar symptoms, such as fever, rashes and agranulocytosis, time to onset of voriconazole treatment and resolution time. However, the differences in this female patient included: multiple lymphadenopathies, eosinophils infiltrating around blood vessels in skin histology, liver dysfunction and significant proliferative response in the lymphocyte stimulation test with voriconazole. Therefore, the diagnosis of DIHS/DRESS (Drug-Induced Hypersensitivity Syndrome/ Drug Reaction with Eosinophilia and Systemic Symptoms Syndrome) was evident. Different from the previous case report, the DRESS validation score [17] of our patient turned out to be 1 (Table

2). The most noticeable skin rashes accounted for 68% of the body surface area (both upper extremities 14%, both thighs 18% and the trunk 36%). However, there were no enlarged lymph nodes, eosinophilia, atypical lymphocytes and other potential causes. The recovery took about ten days. As for the lung involvement, the DRESS syndrome includes impaired pulmonary function tests, interstitial lung infiltrates, pneumonia, pulmonary nodules, pleural effusion, or acute hypoxemic respiratory failure [18]. However, the multiple pulmonary nodules of this patient were related to aspergillosis infection, which were also decreased after voriconazole treatment. As a result, this patient was a non-DRESS case.

Table 2: DRESS validation score, known as RegiSCAR (adapted from Kardaun).

Score	-1	0	1	2	Actual Score
Fever≥38.5°C	No/U	Yes			0
Enlarged lymph nodes		No/U	Yes		0
Eosinophilia		No/U			0
Eosinophils			0.7-1.499×109 L-1	≥1.5×109 L-1	
Eosinophils, if leucocytes <4.0×109 L-1			10-19.9%	≥20%	
Atypical lymphocytes		No/U	Yes		0
Skin involvement					
Skin rash extent (% body surface area)		No/U	＞50%		1
Skin rash suggesting DRESS	No	U	Yes		0
Biopsy suggesting DRESS	No	Yes/U			0
Organ involvementa					0
Liver		No/U	Yes		
Kidney		No/U	Yes		
Lung		No/U	Yes		
Muscle/heart		No/U	Yes		
Pancreas		No/U	Yes		
Other organ		No/U	Yes		
Resolution ≥ 15 days	No/U	Yes			-1
Evaluation of other potential causes					
Antinuclear antibody					
Blood culture					
Serology for HAV/HBV/HCV					
Chlamydia/mycoplasma					
If none positive and ≥ 3 of above negative			Yes		1
Total score					1

U, unknown/unclassifiable; HAV, hepatitis A virus; HBV, hepatitis B virus; HCV, hepatitis C virus.

[a]After exclusion of other explanations: 1, one organ; 2, two or more organs. Final score < 2, no case; final score

2–3, possible case; final score 4–5, probable case; final score > 5, definite case.

The mechanism of voriconazole-induced agranulocytosis is not clear yet. Generally, agranulocytosis could result from multiple heterogeneous factors, including immune-mediated mechanism, genetic polymorphism involved in metabolic pathways of drugs, decreased production from the hypoplastic bone marrow, autoimmunity, and oxidative modification of the drugs [19]. Old age (>65 years), septicemia or shock, metabolic disorders such as renal failure or a neutrophil count below 0.1×109/l are poor prognostic factors [5]. The management of idiosyncratic drug-induced neutropenia begins with the withdrawal of the responsible drugs, empiric broad-spectrum antibacterial or antifungal therapy, and hematopoietic growth factors therapy. Our patient's severe agranulocytosis was unexpected. In the absence of other causes, it is probably caused by voriconazole. However, there were some limitations in this case. The voriconazole valley concentration did not test in time. The biopsy for rashes did not operate. However, according to the experience of the current case, clinicians need to be alert to this uncommon adverse reaction, especially in patients with hematologic malignancies or hematopoietic stem cell transplantation, who are usually accompanied by neutropenia. When treating with voriconazole for fungal infection, the severe adverse reactions such as agranulocytosis, should be aware. Both trough concentration monitoring and regular blood testing were essential to avoid the ADR in clinical use.

Declarations

Acknowledgements

Not applicable.

Authors' Contributions

SSX analyzed the data and drafted the manuscript; WFZ and JJW collected the pharmaceutic data; WW and QY treated the patient; QFX collected the clinical data and reviewed the literature; WW contributed to manuscript drafting and was responsible for the revision of the manuscript. All authors read and approved the final version.

Ethics approval and consent to participate

The described patient provided written consent to publish this case report.

Consent for publication

Written informed consent was obtained from the patient to publish this report and any accompanying images.

Availability of data and materials

All data generated or analyzed during this study were included in this published article.

Competing interests

The authors declare that they have no competing interests.

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Authors' information

Not applicable.

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