Haemorrhagic cystitis following the administration of voriconazole in the treatment of central nervous system aspergillosis: a case report

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Abstract
Central nervous system aspergillosis (CNS-A) is a rare and fatal fungal infection. Voriconazole is the recommended treatment for CNS-A. The therapeutic effect of voriconazole is good, but its use is limited due to adverse reactions. This case report describes a 37-year-old male patient that had previously been diagnosed with acute lymphoblastic leukaemia. He had received immunosuppressive agents for 1 year following a haematopoietic bone marrow transplant. He presented with a 1-month history of left limb weakness as well as recurrent fever. Brain magnetic resonance imaging showed that he had multiple cerebral infarctions. Subsequently, he was diagnosed with CNS-A by metagenomic next-generation sequencing. Voriconazole was added to his treatment regimen, but it resulted in severe haemorrhagic cystitis and possibly bladder rupture. The dose of voriconazole was adjusted and reparative bladder surgery was undertaken immediately. Eventually, the patient was successfully treated with voriconazole and there was no recurrence of symptoms after 1 year of follow-up. Haemorrhagic cystitis is a rare adverse drug reaction associated with voriconazole use. Based on the experience with this current case, physicians should be aware of urinary tract complications with voriconazole including haemorrhagic cystitis.
Keywords
Central nervous system aspergillosis (CNS-A), cerebral infarction, voriconazole, adverse drug reaction

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Introduction
The central nervous system (CNS) is one of the most common sites of an Aspergillus infection and in rare cases it can cause ischaemic cerebral infarction.\(^1\)\(^-\)\(^3\) The current treatment of CNS aspergillosis (CNS-A) with cerebral infarction aims mainly to eliminate the pathogens. Voriconazole is the correct choice because it effectively kills Aspergillus, which is also recommended by the Infectious Diseases Society of America (IDSA) as the main therapeutic drug for CNS-A.\(^4\) However, when voriconazole is used, the patient can experience some serious medical complications, such as abnormal liver function, visual impairment, acute pancreatitis, bone marrow dysplasia and arrhythmia.\(^5\) Because of these adverse reactions, patients are forced to change drug or terminate their drug treatment.\(^6\) This current case report describes a patient that experienced voriconazole-related haemorrhagic cystitis. The current case was successfully treated with voriconazole monotherapy and achieved individualized management through therapeutic drug monitoring and dose adjustment. After a 1-year follow-up, the patient had almost achieved a curative effect and haemorrhagic cystitis no longer occurred.

Case report
A 37-year-old male was admitted to the Department of Neurology, The First Affiliated Hospital, Jinan University, Guangzhou, Guangdong Province, China on 12 March 2019. The patient had been diagnosed with acute lymphoblastic leukaemia in March 2017 and a haploidentical haematopoietic stem cell transplantation was performed after 5 months. He was treated with 180 mg mycophenolate sodium enteric-coated tablets orally twice a day and 8 mg methylprednisolone tablets orally once a day. The patient was sent to a local hospital in February 2019, 18 months after the haematopoietic stem cell transplant, when he suddenly developed lower limb weakness. Cerebral magnetic resonance imaging (MRI) showed acute cerebral infarction in the right caudate nucleus. For 2 weeks, the patient continuously experienced fever and hiccups so he was transferred to the Department of Neurology, The First Affiliated Hospital, Jinan University, Guangzhou, Guangdong Province, China for further treatment.

On admission in March 2019, the patient presented with hemiparalysis (left upper and lower limbs with grade 3 power), hiccups and fever. According to the clinical manifestations, the patient was suspected of having a CNS infection-related cerebral infarction. Cerebral MRI showed ischaemic lesions in the right basal ganglia and radiating crown. Cerebral magnetic resonance angiography revealed right internal carotid artery occlusion (Figure 1).

On day 7, the patient’s body temperature increased and he experienced a seizure. Cerebrospinal fluid (CSF) from a lumbar puncture showed the following: an intracranial pressure of 310 mmHg; a white blood
cell (WBC) count of $110 \times 10^{9}$/l; a microprotein level of 491 mg/l; a CSF glucose level of 2.33 mmol/l; and a fasting blood glucose level of 9.30 mmol/l (Table 1). On day 8, the patient was unconscious. The CSF sample was sent to the Beijing Genomics Institute for pathogen detection using metagenomic next-generation sequencing (m-NGS). On day 9, 106 unique reads of *A. fumigatus* were identified from the CSF. Considering the patient’s condition, immunosuppressive drug treatment was suspended. Antifungal therapy with 200 mg voriconazole orally every
12 h was started. The patient consented to this treatment and his symptoms slightly improved, but a low fever continued, so the voriconazole dose was adjusted to 300 mg voriconazole orally every 12 h.

On day 36, the patient developed reddish bloody urination at night. Blood clots were seen after the catheter was inserted, which repeatedly obstructed the urethra. Abdominal colour ultrasound showed a haemorrhagic bladder mass. Since the patient was suffering from abdominal distension, emergency bladder surgery was performed to remove the blood clot. Unfortunately, bladder rupture was found during the operation and an open operation was required to repair it. The patient was transferred to the intensive care unit after surgery. As a result of excessive blood loss, the patient developed hypovolaemic cerebral infarction. This event was suspected to have been caused by an adverse reaction to voriconazole. On day 37, the voriconazole dose was reduced to 200 mg voriconazole orally every 12 h. After the patient’s condition stabilized, he was transferred back to the Department of Neurology, The First Affiliated Hospital, Jinan University for further treatment.

The CSF was analysed again on days 45 and 58 (Table 1), but the patient continued to have severe haematuria and decreased haemoglobin levels. The dose of voriconazole was adjusted again on day 60 to 150 mg voriconazole orally every 12 h and soon the patient’s haematuria decreased, but he developed a fever again. On day 77, the dose of voriconazole was adjusted again to 175 mg voriconazole orally every 12 h. Fortunately, the patient had no fever and only intermittent haematuria. Meanwhile, 7.5 mg succinic acid tablets orally once a day were added to relieve the bladder spasm. After that, the patient had no haematuria and the haemoglobin level gradually returned to normal. No lesions were found on bladder ultrasonography.

Table 1. Changes in the biochemical characteristics of the cerebrospinal fluid of a male patient suspected of having a central nervous system infection-related cerebral infarction during the course of his treatment.

| Date       | Hospitalization duration, day |
|------------|-------------------------------|
| WBC, 10^6/l | RBC, 10^6/l | Multinucleate cells, % | Mononuclear cells, % | Immunoglobulin, mg/l | Chloride, mmol/l | ADA, U/l | Microprotein, mg/l | CSF glucose, mmol/l | Synchronous blood glucose, mmol/l | Fungal dextran, pg/ml | m-NGS reading number |
| 7.19       | 20.03.19 | 45 | 210 | 3 | 100 | – | – | 161.77 | 124.1 | 169.01 | 122.38 | 73.85 |
| 11.05.19   | 05.06.19 | 85 | 170 | 11 | 0 | – | – | 194.71 | 126.8 | 186.86 | 0 | 0 |

WBC, white blood cells; RBC, red blood cells; ADA, adenosine deaminase; CSF, cerebrospinal fluid; m-NGS, metagenomic next-generation sequencing.
The CSF was re-examined on day 85 and the intracranial pressure had dropped to 170 mmHg. The m-NGS reported that the unique reading number of \textit{A. fumigatus} was 0 (Table 1). The patient was unable to undergo a brain MRI examination until day 103 due to his unstable condition. On day 103, the brain MRI showed a massive infarction of the right frontotemporal parietal occipital lobe, right basal ganglia, radial crown and thalamus (chronic stage). Cerebral magnetic resonance angiography showed right internal carotid artery occlusion (Figure 1). The brain MRI results on day 103 demonstrated that the cerebral infarction area was larger than before and it was suspected to be related to the recurrence of cerebral infarction caused by hypovolaemia on day 36. The infection was well controlled and the patient was gradually able to walk and eat by himself. As his condition improved, he was sent to a local hospital for rehabilitation. No recurrence of his symptoms has occurred after 1 year of follow-up. The patient provided informed consent for publication of the case.

Discussion

People with low levels of immunity are susceptible to being infected with \textit{Aspergillus}.\textsuperscript{7} For example, people that have had antitumour chemotherapy, organ transplantation, those on long-term immunosuppressive agents, HIV-positive patients and those with severe immunodeficiency.\textsuperscript{8} \textit{Aspergillus} can invade the intracranial blood vessel wall or the hyphae can extend to the lumen.\textsuperscript{9} They cause thrombosis \textit{in situ} or embolism of the hyphae, which eventually leads to cerebral infarction.\textsuperscript{10,11} It is rare that aspergillosis of the CNS is characterized by ischaemic cerebral infarction. The current case had experienced immunodeficiency due to the long-term use of immunosuppressive agents following a bone marrow transplant as part of his treatment for prior leukaemia. This probably resulted in intracranial \textit{Aspergillus} infection and the multiple cerebral infarctions seen on the MRI scans.

Voriconazole was the first second-generation triazole approved by the US Food and Drug Administration in May 2002. It is indicated for the treatment of invasive aspergillosis and fungal infections caused by \textit{Scedosporium apiospermum} and \textit{Fusarium} spp.\textsuperscript{12} Also, the IDSA advised that voriconazole is the main treatment for CNS-A.\textsuperscript{4} Voriconazole can cross the blood–brain barrier and its concentration in the CSF can exceed its minimum inhibitory concentration, which significantly improves the therapeutic effect on cerebral aspergillosis.\textsuperscript{13} Other anti-aspergillus drugs such as amphotericin B, itraconazole and caspofungin produce negligible concentrations in the CSF or brain tissue.\textsuperscript{14} The minimum inhibitory concentration of voriconazole was lower than that of amphotericin B and itraconazole.\textsuperscript{15} \textit{Aspergillus} infection of the CNS is characterized by high mortality, as research has shown that if left untreated, the mortality rate of CNS aspergillosis can be as high as 88%.\textsuperscript{16} A retrospective study that included 48 patients with a confirmed diagnosis and 33 patients with CNS aspergillosis demonstrated that at a median observation time of 390 days, 31% of patients receiving voriconazole were still alive.\textsuperscript{6} Another study showed that the remission rate was 47% and the median survival was 159 days in 120 patients with \textit{Aspergillus} infection that were treated with voriconazole.\textsuperscript{15} Therefore, the use of voriconazole significantly improves the survival rate of CNS-A patients and can help control the progression of the disease. In most cases, voriconazole shows positive effects on CNS-A, but the long-term toxic effects cannot be ignored. Patients may experience adverse reactions after treatment with voriconazole. For example, common adverse
reactions include abnormal liver function, visual impairment, acute pancreatitis, bone marrow dysplasia and arrhythmia. Cutaneous malignancies, arrhythmias, neurological toxicity, alopecia, nail changes and electrolyte abnormalities are some of its recently reported and rarer adverse effects. A retrospective study showed that 147 cases of allogeneic haematopoietic cell transplantation used voriconazole for a long time and up to 68.7% of patients were forced to discontinue using such drugs due to adverse drug reactions. The treatment process of CNS-A should be highly alert to the occurrence of adverse drug events. Once adverse drug reactions occur, the prognosis should be evaluated in a timely manner and the treatment plan adjusted accordingly.

To the best of our knowledge, this is the first report of haemorrhagic cystitis as a serious side-effect following the use voriconazole to treat CNS-A. Because of the Aspergillus infection, the patients suffer from vascular occlusion, which then leads to ischaemic cerebral infarction. During the early stage, the use of voriconazole is usually associated with good results, but the unpredictable occurrence of haemorrhagic cystitis along with a large volume of blood loss caused the patient’s blood volume to drop. Finally, a hypovolaemic cerebral infarction occurred, which made the patient’s condition worse. However, through the gradual reduction of voriconazole and the use of next-generation sequencing analysis, it was possible to find the dose balance point where the patient could tolerate the adverse drug reactions whilst maintaining the therapeutic effect. Eventually, the patient’s condition recovered significantly with the use of voriconazole monotherapy. There was not any recurrence within 1 year of follow-up. These current findings suggest that voriconazole-related haemorrhagic cystitis was linked to drug dosage.

In conclusion, haemorrhagic cystitis caused by voriconazole treatment is very rare. Voriconazole is the recommended treatment for CNS-A, but adverse reactions are possible. In this current case, haemorrhagic cystitis appeared to be due to the use of voriconazole. This case enlightens the need for clinicians to be alert to uncommon adverse reactions and to try to reduce the impact of the side-effects of voriconazole on the original disease.

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