Case report

Antifungals in a case of basidiobolomycosis: role and limitations

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SUMMARY

A 10-year-old Saudi boy was diagnosed to have basidiobolomycosis after a stormy course of his ailment. Therapy was initiated with intravenous antifungal, voriconazole, which was well tolerated for 6 weeks except for local excoriation at the site of ileostomy. He developed drug-induced hepatitis on oral voriconazole, therefore, switched to oral itraconazole following which he experienced severe chest pain. Alternatively, co-trimoxazole (bactrim) an antibacterial with antifungal activity was prescribed but he had the intolerance to it as well. Unfortunately, posaconazole as an alternative antifungal was not available in our centre. We report here a Saudi boy who developed an intolerance to most common antifungals used clinically 6 weeks after the therapy was initiated.

BACKGROUND

Systemic basidiobolomycosis (BM) is a rare disease in children and usual presentation is very similar to other commonly seen gastrointestinal disorders such as Crohn's disease, intestinal tuberculosis, amoebiasis and abdominal malignancies.¹ The most effective management options for this condition involve surgical resection of the mass along with a prolonged course of antifungal therapy. Monotherapy with voriconazole has proven good results in different studies although previously it used to be combined regimen with amphotericin and itraconazole.² Side effects and untoward reactions are known with antifungals necessitating clinical monitoring employing blood tests as essential components of management. Special considerations are given to liver chemistry, renal functions, ECG and echocardiography if indicated.^{1 3 4} In case of intolerance to one antifungal, other alternatives can be tried but with special precautions. We report here a Saudi boy who developed an intolerance to most common antifungals used clinically after tolerating it well for initial 6 weeks.

CASE PRESENTATION

A 10-year-old Saudi boy had recurrent abdominal pain, fever and weight loss for 1 year, admitted at multiple hospitals and finally diagnosed outside Kingdom as Crohn's disease on the basis of blood tests and colonoscopic findings. Despite good compliance and proper management given, he continued to have the same symptoms and had three more admissions. All the time, he had raised inflammatory markers and negative workup for immune

deficiencies, celiac disease, infectious causes and malignancies. CT was remarkable for intestinal thickening at ileocecal area. Repeated colonoscopy showed pseudo polyps and inflamed terminal ileum but tissue biopsies were of non-specific colitis and negative for fungal stain and tuberculosis. In the last admission, owing to clinical and radiological evidence of intestinal obstruction, exploratory laparotomy was performed. A mass was resected from ileocecal area with hemicolectomy and end to end anastomosis. Histopathological analysis of the resected mass showed the presence of fungus which was compatible with basidiobolomycosis.

He was initiated on intravenous voriconazole with a dose of 7 mg/kg twice a day with consultation of infectious diseases' physician. He did well for the next 7 days, but developed complication with intestinal leak which was corrected surgically with an urgent ileostomy. He started to have excoriation at the site of ileostomy with profound inflammation at the adjacent area just 3 days after the ileostomy and continued throughout with intravenous voriconazole for 42 days. All the supportive measures from stoma care team could not resolve the issue of excoriation unless he was switched to oral voriconazole and it was resolved. His liver functions were stable during intravenous voriconazole but when he was switched to oral therapy with the same drug, his liver enzymes started to rise as shown in [table 1](#). He was discharged from the hospital after liver enzymes showed a downward trend. The patient was called for the follow-up visit after 1 week, unfortunately, his liver enzymes remained persistently deranged with normal bilirubin at follow-up. Oral voriconazole was stopped for 2 days, liver functions were reassessed, and all the enzymes returned to normal values. Low-dose intravenous voriconazole was restarted with the hope that he tolerated it well previously but liver enzymes did not show any improvement and remained elevated.

As an alternative, itraconazole was suggested by the infectious disease team. On the second day of this therapy, the patient started to have very severe central chest pain which required the use of morphine to relieve his symptoms. Other vital signs were stable during the pain attack. He had two more episodes of chest pain and finally itraconazole was stopped. He was suggested to start for another time with the very low dose of oral voriconazole with an increment of therapeutic dose after stabilisation. He showed the same pattern of hepatitis with normal bilirubin on oral low dose of voriconazole; the therapy was therefore stopped again.

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Table 1 Antifungals used with adverse events and management adopted

Antifungal given	Adverse event noted	Management adopted	Result
Voriconazole (IV)	Excoriation at ileostomy site	Stoma care Switched to oral	No effect Excoriation resolved
Voriconazole (oral)	Anicteric hepatitis	Decreased dose of oral voriconazole Stopped oral voriconazole	No effect Resolved hepatitis
Itraconazole	Severe central chest pain	PPI, IV morphine Stopped itraconazole	No effect Chest pain settled
Co-trimoxazole	Persistent vomiting	PPI Stopped co-trimoxazole	No effect Resolved vomiting

IV, intravenous; PPI, proton pump inhibitor

Another antifungal, posaconazole was suggested but unfortunately it was not available in our center because of legal constraints and drug authority regulations. A request was made for the availability of posaconazole to the authorities and meanwhile, he was started on co-trimoxazole (Bactrim) owing to its antifungal properties. Unfortunately, bactrim was also not tolerated because of persistent vomiting and was stopped on fourth day after initiation.

The patient showed an intolerance to most of antifungal drugs, except for intravenous voriconazole which he tolerated well for initial 42 days. The family of the patient was concerned with the outcome due to the serious intolerance to most of antifungal drugs therapy he received. After consultation with multidisciplinary team, his therapy was all stopped and follow-up monitoring of liver enzymes, magnetic resonance enterography (MRE) and repeat colonoscopy was suggested. The patient started to gain weight with normal family diet. Liver enzymes, MRE and colonoscopy, all were normal on different occasions. Finally, it was decided to close the ileostomy surgically after a week.

OUTCOME AND FOLLOW-UP

He was switched off from all the medications and called for follow-up with monitoring of liver enzymes, MRE and repeat colonoscopy. He started to gain weight with normal family diet. Liver enzymes, MRE and colonoscopy, all were normal on different occasions. Surgical intervention was decided to close the ileostomy in a week time.

DISCUSSION

Systemic basidiobolomycosis caused by *Basidiobolus ranarum* is a rare disease in children. Generally, its distribution is worldwide but most of the cases were reported from tropical, subtropical regions and especially Saudi Arabia and Iran have made the largest contribution.^{5–7} BM usually causes subcutaneous infection of the trunk and extremities, however, it may involve other organs such as palate, sinuses and rarely visceral organ such as gastrointestinal tract. The usual presentations of gastrointestinal basidiobolomycosis are abdominal pain with constipation or diarrhoea, palpable mass, fever and weight loss. Surgical resection of the mass and antifungal therapy are the most effective therapeutic strategies for this condition.¹⁵

The currently available pharmacotherapy includes amphotericin B, itraconazole, voriconazole and posaconazole either in combination or monotherapy. The azole group of antifungal drugs such as itraconazole, fluconazole had been successfully

used in the management of systemic basidiobolomycosis. Monotherapy with voriconazole has proven good results in different studies although previously it used to be a combined regimen with amphotericin and itraconazole.³ A case of gastrointestinal BM in a Saudi patient was successfully treated with voriconazole.^{2,8}

Side effects and untoward reactions are known with antifungals so therapeutic drug monitoring along with clinical observation is an essential component of management. Special considerations are given to liver functions, renal functions, ECG and echocardiography if indicated.^{1,3,4} In the current case, the patient was initiated on intravenous voriconazole which he tolerated well for initial few days but developed excoriation at the site of ileostomy, profound inflammation at adjacent area and was switched to oral voriconazole. His liver functions were stable during intravenous infusion but when he was switched to oral, liver enzymes started to rise with normal bilirubin. The oral voriconazole was immediately stopped that resulted in the normalisation of liver enzymes.

Most of antifungal drugs from the azole group undergo extensive first-pass metabolism producing hepatotoxic effects. Hepatitis observed in the current case may have occurred due to toxic metabolites of voriconazole generated due to first-pass metabolism of the drug after oral administration. Earlier reports have shown the effectiveness of the voriconazole in children with gastrointestinal BM without serious adverse reaction.² Due to serious hepatotoxicity potential of voriconazole, the alternative medication, oral itraconazole was initiated. Our patient developed severe chest pain and it was stopped because of fear of serious cardiac effects. Earlier reports have also revealed the itraconazole-induced chest pain and heart failure.⁴ Low doses of oral voriconazole were restarted with the intention to increase the dose after being stabilised. However, as observed before similar hepatotoxic effect occurred even with low doses of voriconazole and the drugs was stopped immediately.

Basidiobolomycosis cases have successfully been treated with posaconazole, the drug is well tolerated in most patients without any dose adjustment in hepatic or renal insufficiency.^{9,10} Therefore, this drug was also considered for our current case, but unfortunately, it could not be available in our centre due to legal constraints and drug authority regulations. Owing to the antifungal properties of co-trimoxazole (bactrim), the drug was started for the patient but it could not be continued longer due to serious adverse reactions.

Learning points

- ▶ Long-term antifungals are the mainstay of treatment for gastrointestinal basidiobolomycosis. To our knowledge, this is the first case of gastrointestinal basidiobolomycosis treated with voriconazole, itraconazole and co-trimoxazole and none of the treatment could be continued for longer due to an intolerance to these drugs.
- ▶ This case warrants renal, liver and cardiovascular monitoring from the very start with such therapies to prevent therapeutic failure and complications.
- ▶ This case used multiple drug therapy and expertise that will help clinicians to deal with such cases diligently.
- ▶ Moreover, the case demonstrates the challenge being faced by the physicians dealing with such subjects.
- ▶ The choice of alternative medications for such a case is an area that warrants concerted research to avoid complications.

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