Case Report

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Disseminated *Cryptosporidium Parvum* Infection in a Post Renal Transplant Child

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Abstract

Cryptosporidium species are parasitic protozoans causing diarrhoea following the ingestion of oocyst contaminated food or water. Disease severity and duration vary with the host immune status. Cryptosporidiosis has emerged as a cause of severe persistent diarrhoea in solid organ transplant patients. Even though the infection is self-limiting among immunocompetent hosts, it can lead to disseminated disease in immunocompromised persons. Here we report a case of *Cryptosporidium parvum* infection of a 5-year-old boy, 4 months following kidney transplantation, to elaborate the complexities of management.

Keywords: *Cryptosporidiosis, Post kidney transplantation.*

INTRODUCTION

Cryptosporidium species are parasitic protozoans causing diarrhoea following the ingestion of oocyst contaminated food or water [1,2]. Cryptosporidiosis has emerged as a cause of severe persistent diarrhoea in solid organ transplant patients [3]. Even though the infection is self-limiting among immunocompetent hosts, it can lead to disseminated disease in immunocompromised persons [2,4]. Moreover, even in immunocompetent patients, though clinical cure of the infection can be achieved in over 80%, parasite eradication may succeed only in 60-70 %. [1].

CASE REPORT

A 5-year-old live related kidney transplant recipient, on mycophenolate mofetil (MMF), tacrolimus and alternate day prednisolone for immunosuppression, presented with acute severe watery diarrhoea at 3 months post-transplantation. His renal functions had been stable over the 3 months since transplantation

(baseline 80-90 $\mu\text{mol/l}$) without any events of rejection or infection. He was moderately dehydrated on admission with a reduced urine output, but haemodynamically stable.

Initial investigations revealed hyponatraemia, hypokalaemia, hypocalcaemia and hypomagnesaemia with a severe metabolic acidosis. C-reactive protein (CRP) and blood cultures were normal. Serum creatinine was 132 $\mu\text{mol/L}$ with a blood urea of 23mmol/L. The tacrolimus level had risen significantly to 45.6ng/ml, due to the diarrhoea, and tacrolimus was thus withheld with monitoring of levels. Initial stool full report and bacterial culture were normal with no evidence of infection.

He was commenced on empirical broad-spectrum intravenous antibiotics due to the severe nature of his presentation and his immunocompromised state. However, his diarrhoea persisted, unrelenting, and he continued to have frequent episodes of watery bowel motions (more than 500ml per episode) making it a real challenge to maintain his hydration, electrolyte and acid base status. Several rapid corrections of hypokalaemia,

hypocalcaemia and hypomagnesaemia were done while on maintenance infusions. Cytomegalovirus (CMV), Epstein-Barr virus (EBV) and BK virus (BKV) screening were negative. Lower gastrointestinal (GI) endoscopy revealed evidence of ongoing bowel infection with no evidence suggestive of MMF colitis. Ultrasound scan of the abdomen did not reveal any evidence of gall bladder or biliary tract involvement. Despite elevated creatinine level, graft perfusion was satisfactory on Doppler ultrasound scanning with a resistive Index of 0.56 in all three poles.

Around 2 weeks following the initial presentation, his stools were found to be positive for *Cryptosporidium* oocysts. Species was confirmed as *Cryptosporidium parvum* by polymerase chain reaction (PCR) (Figure 1) using species specific primers. He was started on nitazoxanide and azithromycin for one week. The MMF dose was reduced to 250 mg twice a day. Stool culture was repeatedly negative for other infective organisms but was persistently positive for *Cryptosporidium* oocysts. One week later, he developed cough and respiratory distress and deteriorated rapidly needing ventilator support. His chest x-ray revealed evidence of bronchopneumonia. Repeat courses of azithromycin and nitazoxanide were commenced. Possible concomitant infection was covered with broad spectrum intravenous antibiotics despite negative culture. MMF was withheld and his renal functions deteriorated, and he gradually became anuric despite maintained hydration. Peritoneal dialysis was commenced. Regrettably he developed multi-organ failure and subsequently died despite holistic care.

Figure 1: Results of PCR test

DISCUSSION

The prevalence of cryptosporidial infection in Sri Lanka among renal transplant recipients is unknown. A study from India found asymptomatic infection in around 20% of renal transplant recipients and symptomatic disease in about 17% [5]. A Turkish study found 19% prevalence of cryptosporidial infection in faecal samples of renal transplant recipients [5]. Similar estimates have also been found in paediatric renal transplant cohorts [6]. Clinical presentation among solid organ transplant recipients may vary from being asymptomatic to having very severe and prolonged watery diarrhoea, vomiting, severe nausea, fever, and abdominal pain [1,7].

Stool microscopy is the chief diagnostic method, though microscopy has low sensitivity unless high concentrations of oocytes are released in the stools [8]. The oocyte size, too, is important (3-7 μ m) as they can be confused with yeast, so that a modified Ziehl-Neelsen stain or a fluorescent stain can be used to improve detection [9]. However, these tests have poor sensitivity [1]. Molecular methods have transformed the diagnosis with the emergence of PCR testing, which is relatively rapid, is more sensitive and has the major benefit of speciation. Speciation is very important in identifying the possible transmission route [9]. Furthermore, treatment can be challenging because anti-parasitic drugs have only modest activity [10].

Prevention of infection is important. Preventive measures include avoidance of swimming in possibly contaminated lakes and streams, consumption of boiled water or water that is passed through a filter with a pore size of less than 1 μ m and consumption of only hygienically prepared food [11]. Moreover, contact with anyone who has a diarrhoeal illness should be limited [11,12].

It is very important to maintain hydration, electrolyte and nutritional status when patients present with severe watery diarrhoea [11]. Helping to restore immune status is also important by reducing immuno-suppressive drug doses [1,12,13,14]. However, a critical balance needs to be struck here as over reduction can lead to rejection of the transplant [15].

In solid organ transplantation, the response of available drugs used in *Cryptosporidium* infestation is not clearly described in the currently available literature. The optimal duration of therapy and the goal viz. clinical versus parasitological cure, is also not clearly defined in the setting of organ transplantation.

We followed the treatment regime which is described for cryptosporidiosis in HIV patients. The management of cryptosporidiosis in transplant recipients is further confounded due to drug interaction, risk of rejection and alteration in drug levels [16]. The main three groups of drugs recommended for parasite eradication in cryptosporidiosis are the macrolides (azithromycin, spiramycin), aminoglycosides (paromomycin) and nitazoxanide [17]. Aminoglycosides cause nephrotoxicity and should be used with caution especially when drug levels cannot be monitored [18]. The use of a combination of the above drugs in a patient with a high risk of dehydration makes preservation of normal renal function very difficult.

It is also a well-documented fact that tacrolimus levels are elevated during diarrhoea [15] – a feature which was well evident in our patient who had a massively elevated tacrolimus level on presentation. The mechanism for this is thought to be increased gut absorption and reduced gut metabolism of tacrolimus caused by reduced activity of P-glycoprotein and CYP3A4 respectively [19].

Our patient's initial creatinine value was only slightly elevated, and this was attributed to dehydration as well as tacrolimus toxicity. However, with progression of the infection, the creatinine level went up to 350 µmol/l. This could have been due to the infection per se or be due to rejection brought about by the reduction in immunosuppression. Persistent tacrolimus toxicity also needs to be considered.

CONCLUSION

Management of cryptosporidiosis in renal transplant recipients involves striking a critical balance between prevention of rejection, eradication of infection, avoidance of nephrotoxicity and management of dehydration, acid base and electrolyte anomalies. Poor sensitivity in detecting *Cryptosporidium* species via the current freely available investigations and absence of specific and strong anti-parasitic treatment, further contribute to the complexity. It can therefore be an absolute challenge. Hence prevention of cryptosporidiosis is very important.

Author declarations

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Author contributions

All authors contributed to the diagnosis and management of this patient. WALKW drafted the manuscript which was edited by all authors

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Ethics approval and consent to participate

Informed written consent has obtained from the patient

Competing interests

The authors declare no competing interests

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