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Teaching Point
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Friendly fire

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Introduction

Pneumocystis jirovecii pneumonia (PJP) is a rare but feared complication in immunocompromised patients. Most experience with PJP stems from patients with the human immunodeficiency infection (HIV) although nephrologists see the occasional case, usually in renal transplant patients during the first post-transplant year. The diagnosis requires a high degree of suspicion and treatment is with high-dose trimethoprim–sulfamethoxazole (TMP–SMX), which is usually safe and effective. We recently encountered severe life-threatening side effects in two renal patients treated for proven PJP. We present the cases and provide a brief review of TMP–SMX, with an emphasis on side effects, and its use in renal patients.

Cases

Case 1

A 55-year-old man with end-stage renal failure due to IgA nephropathy received a first renal transplant from a live donor in June 2006. His graft function was good [estimated glomerular filtration rate (eGFR) 55 mL/min] while on steroid-free immunosuppression with tacrolimus (target levels 6 μg/L) and enteric-coated mycophenolate mofetil (540 mg twice a day). In the recent past, he had always been very well, with stable graft function and had worked full time. He now presented in September 2010 with cough. Examination showed a few crackles on the right side but X-ray was normal. Oral amoxicillin/clavulanate was begun. Lactate dehydrogenase was elevated at 569 U/L (normal, 240–480). A computed tomography (CT) of the chest was performed, showing widespread opacities bilaterally. Bronchio-alveloar lavage confirmed *Pneumocystis jirovecii* pneumonia. The patient was admitted and intravenous high-dose TMP–SMX was begun, together with oral prednisolone (40 mg daily). Enteric-coated mycophenolate mofetil was paused. The patient made an excellent recovery and was discharged on oral TMP–SMX. He was seen in clinic 5 days later and complained about hallucinations and pain in his mouth. On examination, he looked unwell and had gait ataxia. Intra-oral examination revealed severe glossitis and stomatitis. The dose of TMP–SMX was reduced but laboratory results received the same day showed marked hyperkalaemia (6.9 mmol/L). The patient was admitted immediately elsewhere; by that time his serum potassium was 7.5 mmol/L and he required emergency treatment for life-threatening hyperkalaemia. Cotrimoxzole was stopped. Atovaquone (750 mg BD) was begun, leading to a complete recovery within a week. Serum potassium returned to normal (Figure 1). There was a minor, unexpected decrease in serum tacrolimus levels. The patient was well when last seen in January 2011 and repeat CT showed resolution of all abnormal findings.

Case 2

A 42-year-old woman presented with nephrotic syndrome caused by biopsy-proven idiopathic membranous nephropathy. Renal function was normal. After initial observation and symptomatic treatment with diuretics, her nephrotic syndrome became worse and justified immunosuppressive therapy. She improved on treatment with steroids and tacrolimus but soon developed reduced renal function in the face of tacrolimus target levels between 6 and 8 μg/L. Renal function recovered on withdrawal of tacrolimus. She was then exposed to a planned course of monthly bolus cyclophosphamide with continued steroids. By an oversight, she was not put on PJP prophylaxis. After the fourth bolus treatment, she developed a non-productive cough and dyspnoea. She was treated with oral antibiotics by her primary care physician but showed only a partial response. On review in the clinic, she had a temperature of 37.5°C. Examination of chest and chest X-ray were both normal. Oxygen saturations were 92.5% on air. PJP polymerase

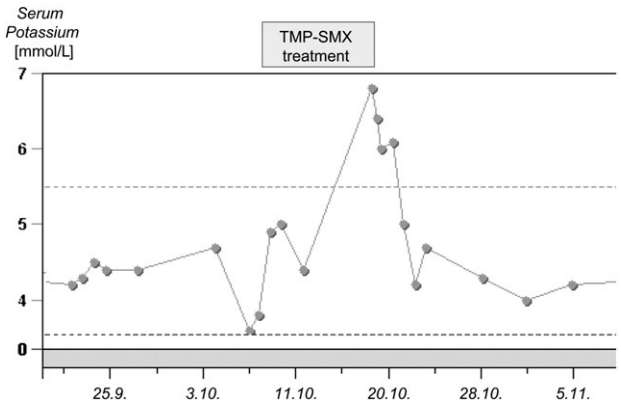

Fig. 1. Time course of hyperkalaemia in Case 1. (The highest serum potassium of 7.5 mmol/L is not included as this was obtained in the emergency room in another hospital).

chain reaction (PCR) was strongly positive. Cytomegalovirus PCR was negative. A diagnosis of PJP was made. Steroids were increased and treatment dose of TMP–SMX started at 120 mg/kg/day in 4 divided oral doses. After the second dose, she developed a rash over the face and chest. This was followed by generalized facial swelling and oedema of the oral mucous membranes. This was accompanied by tachypnoea, dyspnoea and a tight sensation in the throat but no stridor. She also experienced epigastric discomfort, tachycardia and chest tightening but ECG was normal. A clinical diagnosis of anaphylactic reaction was made and she received intravenous hydrocortisone, oxygen and adrenaline. She responded well and did not require ventilation. The respiratory symptoms settled within 6 h but the swelling and rash persisted for 2 days. Her treatment was changed to clindamycin 600 mg three times daily and primaquine 30 mg daily both for 4 weeks. She has made a full recovery from the PJP pneumonia. She has continued on low-dose prednisolone without further immunosuppression. Nine months after the pneumonia, renal function and serum albumin are normal but she has continued proteinuria.

Discussion

PJP is a rare but feared infectious complication in renal transplant recipients [1]. We have seen a minor outbreak in the north-west of England with some 25 cases in the local population of renal transplant recipients (unpublished data). Such outbreaks are common [1, 2] and environmental factors may play a role. Interestingly, the mortality of PJP in renal transplant patients is higher than in the HIV population. A high degree of suspicion is required to make the diagnosis of PJP. CT and sputum testing, or better, bronchio-alveolar lavage, will lead to the correct diagnosis. Serum serum lactate dehydrogenase (LDH) is often used as a serum marker although data are sparse. While the two cases described here posed a significant clinical challenge, they also provided some opportunity to learn.

Case 1 describes a patient who received a course of intravenous TMP–SMX without any adverse events and then suddenly developed life-threatening hyperkalaemia as well as ataxia, hallucinations and glossitis while receiving the drug orally. The temporal association with the drug as well as the resolution after its withdrawal give us confidence in our interpretation. Although the clinical presentation of PJP has traditionally been a renal transplant recipient within the first year, Case 1 demonstrates that PJP can occur late.

Case 2 illustrates that any renal patient on immune modulating therapy can be at risk. Here, facial swelling and rash developed after the second oral dose and the clinical presentation resembled an anaphylactic reaction. We must, of course, be chastized for the fact that the patient had not received prophylactic TMP–SMX, and Case 2 reiterates that really all patients on cyclophosphamide should receive such prophylaxis.

Alternatives to TMP–SMX include atovaquone (as used in Case 1), dapsone, primaquine (as used in Case 2) and pentamidine. The latter is considered relatively toxic and nephrotoxicity is also reported. Expert advice should be sought.

TMP–SMX contains sulfamethoxazole and trimethoprim [3]. Sulfamethoxazole is almost the only sulfonamide still in use [4]. These drugs have a wide range of bacteriostatic antimicrobial activity against both Gram-positive and Gram-negative bacteria and also against other infectious agents, such as Pneumocystis, Isospora and Nocardia. TMP is another bacteriostatic drug and the combination TMP–SMX benefits from synergistic effects. Both components undergo hepatic metabolism and are excreted in the urine. The dose of TMP–SMX needs to be adjusted in renal failure, particularly if the glomerular filtration rate (GFR) is <30 mL/min [5]. TMP–SMX also interacts with a variety of drugs, such as oral anticoagulants and cyclosporine.

Sulfonamides are generally safe but a variety of side effects have been described (Table 1) [6, 11]. It is not always clear which moiety of the combination is causing the side effect. Interestingly, the incidence of side effects is 6–8% in immunocompetent individuals [12] but it as high as 25–50% in HIV-infected patients [11]. The incidence of adverse effects in transplant patients is unknown. Many of the untoward effects involve the skin [12]. Nausea and vomiting are also common. Hypoglycaemia also occurs and monitoring should be in place when patients receive the drug intravenously. The most severe side effects include cytopaenia, exfoliative dermatitis and the Steven–Johnson syndrome [12]. Hallucinations, ataxia and glossitis are also well described although uncommon. TMP–SMX should not be given to patients who are folic acid deficient or who are pregnant or to patients with glucose-6-phosphate dehydrogenase deficiency. Alternative drugs for PJP include pentamidine, dapsone and atovaquone. Pentamidine is considered relatively toxic. We would recommend seeking expert advice from a seasoned infectious disease physician.

Hyperkalaemia with TMP–SMX [13] is thought to be due to blockade of the collecting tubule sodium channel by TMP and may be associated with tubular acidosis. The occurrence of hyperkalaemia is not related to the dose [14]. True nephrotoxicity is rare with TMP–SMX but decreased tubular secretion of creatinine is common [15], which may lead the clinician to erroneously suspect a decline in GFR. Finally, it is worthwhile to note that crystalluria has been described as a side effect of TMP–SMX [5]. Adequate hydration should be maintained. It is difficult to formulate a good recommendation as to how often potassium should

Table 1. Side effects of TMP-SMX [3, 6]

Ataxia
Diarrhoea
Hyperkalaemia [7]
Depression
Glossitis, stomatitis (very rare)
Hallucinations
Hypoglycaemia [8]
Hyponatraemia
Hepatitis, acute liver failure (rare)
Interaction with oral anti-coagulant drugs (warfarin)
Interstitial nephritis
Myocarditis
Pancreatitis
Pancytopenia [9]
Rash (very rarely including Stevens–Johnson syndrome, toxic epidermal necrolysis, photosensitivity)
Rhabdomyolysis
Tinnitus, vertigo
Vasculitis, cryoglobulinaemia [10]

be checked in outpatients on treatment dose of TMP–SMX. However, based on the experience with Case 1, we will monitor potassium twice weekly immediately after discharge and at least weekly thereafter.

Conclusions

Unlike chest physicians and infectious disease specialists, most nephrologists are not very familiar with PJP, its treatment and possible side effects. Making a timely diagnosis of PJP is difficult enough. Another pitfall is to assume, erroneously, that PJP will only occur during the early post-transplant period or that it will not affect immunosuppressed patients with glomerulonephritis. Next, one may be tempted to assume that TMP–SMX is a rather harmless drug, based on experience with its use for PJP prophylaxis. These two cases described here made a narrow escape from 'friendly fire' and provided a harsh reminder of the potential dangers associated with TMP–SMX treatment.

Teaching points

(1) *Pneumocystis jirovecii* pneumonia is a rare but feared infectious complication in renal transplant recipients and patients who receive immunosuppression for glomerulonephritis. Clinical signs and symptoms can be subtle and a high degree of suspicion is required. Serum LDH, chest CT and broncho-alveolar lavage are useful for the diagnosis.

(2) TMP–SMX has a number of side effects, such as rash, bone marrow depression as well as nausea and vomiting. Glossitis and stomatitis are rare, as are ataxia and hallucinations. Toxic epidermal necrolysis is very rare but associated with high morbidity and mortality.

(3) Renal side effects of TMP–SMX include hyperkalaemia and increase in serum creatinine due to reduced tubular secretion. True nephrotoxicity is rare.

(4) Patients on high-dose TMP–SMX require careful clinical monitoring, and also their serum potassium should be monitored, even in a patient who has previously tolerated the drug and has not shown any hyperkalaemia.

(5) Alternative drugs for PJP include atovaquone, clindamycin, dapsone, pentamidine and primaquine.

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Conflict of interest statement. The authors declare no conflict of interest. They have no affiliation with Glaxo Smith Kline, the manufacturer of Septrin™ (TMP–SMX), nor with any of its competitors.

See related article by Eitner *et al.* Risk factors for Pneumocystis jiroveci pneumonia (PcP) in renal transplant recipients. *Nephrol Dial Transplant* 2011; 26:

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