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'THE YEAR OF LIVING DANGEROUSLY': SUCCESSFUL *RHODOCOCCUS EQUI* THERAPY IN AN IMMUNOSUPPRESSED PATIENT WITH MINIMAL TOXICITY BY ONE YEAR OF CONTINUOUS INTRAVENOUS VANCOMYCIN THERAPY COMBINED WITH ORAL LEVOFLOXACIN AND RIFAMPICIN

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ABSTRACT

Background: *Rhodococcus equi* is a Gram-positive microorganism that causes infections, particularly in immunocompromised patients. Treatment duration can be prolonged. While vancomycin is an effective drug in this scenario, its use may lead to renal damage. Studies have shown that continuous vancomycin infusion appears to be a safe strategy in terms of adverse effects compared to bolus administration.

Case description: We present the case of a 71-year-old female liver transplant recipient. After being diagnosed with a mediastinal infection caused by *Rhodococcus equi* with poor response to initial therapy, she required 12 months of continuous intravenous domiciliary infusion of vancomycin combined with oral levofloxacin and rifampicin. There was no drug-related complication throughout the follow-up.

Conclusions: The use of continuous vancomycin infusion has emerged as a safer, more efficient, and cost-effective alternative to intermittent administration. We want to emphasise the uniqueness of this case, where despite the unprecedented treatment duration, no adverse effects occurred.

KEYWORDS

Vancomycin, domiciliary antibiotic continuous infusion, *Rhodococcus equi*, home hospitalisation, immunocompromised patient.

LEARNING POINTS

- Vancomycin therapy based on continuous infusion represents a safer and cheaper strategy than classic intermittent administration.
- The use of continuous infusion facilitates the management of complex infections with outpatient antimicrobial therapy.

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INTRODUCTION

Rhodococcus equi is a Gram-positive, intracellular and zoonotic pathogen that can cause unusually severe disease in humans, particularly in immunocompromised individuals. Pulmonary infection is the most common clinical form. The duration of treatment in immunocompromised patients is not standardised, although a combination of two agents for months or even years is recommended depending on the nature of the lesion and clinical and radiographic assessments during follow-up[1]. In the majority of cases, *R. equi* is susceptible to vancomycin, imipenem, rifampicin, quinolones or macrolides[2], but antibiotic choice should be established based on susceptibility testing results.

CASE DESCRIPTION

A 71-year-old woman with a history of cryptogenic cirrhosis underwent a liver transplant in October 2020 due to refractory ascites, requiring ongoing immunosuppressive therapy with tacrolimus. Mycophenolate, initially included in the immunosuppressive regimen, was discontinued in December 2020 due to myelotoxicity. In February 2021, the patient presented with dissociated cholestasis attributed to the presence of a duodenal diverticulum and a plastic biliary stent was placed. A follow-up endoscopic examination in May 2021 showed an oesophageal mass characterised by a partially obstructive, vegetative appearance, with a central ulcerated and fistulising component *(Fig. 1)*. A previous oesophagogastroduodenoscopy in 2019 had only revealed two sub-5 mm varicose cords in the distal oesophagus. When asked, the patient admitted to having experienced dysphagia for solid food during the previous month.

Subsequent diagnostic evaluations, including endoscopic ultrasound (EUS) and computed tomography scans (CT), showed a lesion extending into the mediastinal region *(Fig. 2)*. Fine-needle aspiration cytology failed to detect any malignancy sign, but biopsies taken during a previous upper endoscopy revealed subepithelial histiocytic proliferation of likely reactive nature. In addition, the anatomopathological report described small, rounded formations resembling microorganisms within the sample tissue.

Due to persistent symptoms and an elusive diagnosis, the patient underwent another upper endoscopy in June 2021 with targeted sampling of the ulcerated region, with the suspicion of an infective nature of the oesophageal lesion. Eventually, blood cultures revealed the presence of *R. equi*, which showed sensitivity to cotrimoxazole, levofloxacin and rifampicin. The same specimen was isolated from the oesophageal tissue culture obtained during endoscopic studies.

Finally, the patient was diagnosed with an oesophageal/mediastinal infection with concomitant bacteraemia caused by *R. equi*, and a combined therapeutic approach was initiated. This regimen included daily administration of oral levofloxacin (500 mg) and cotrimoxazole (800/160 mg) every 12 hours. The patient was readmitted to hospital in January 2022 due to progression of the oesophageal lesion *(Fig. 3)*, despite undergoing an extended course of antibiotic therapy. This evolution prompted the introduction of vancomycin, initially through bolus therapy (15 mg/kg), followed by continuous infusion (750 mg) using an elastomeric pump for 24 hours (Dosi-Fuser® 100 ml/24h, 4.1 ml/h). Concurrent administration of oral levofloxacin (500

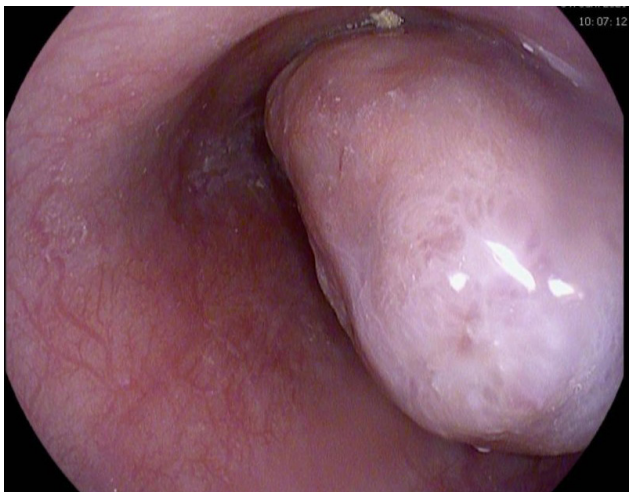

Figure 1. Endoscopic appearance of the lesion

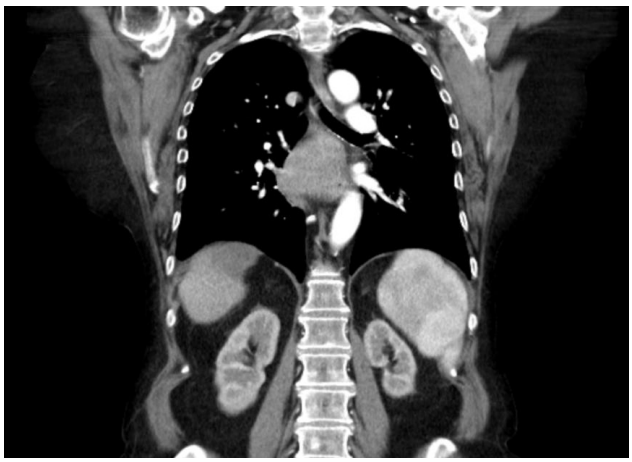

Figure 2. CT scan at the moment of diagnosis

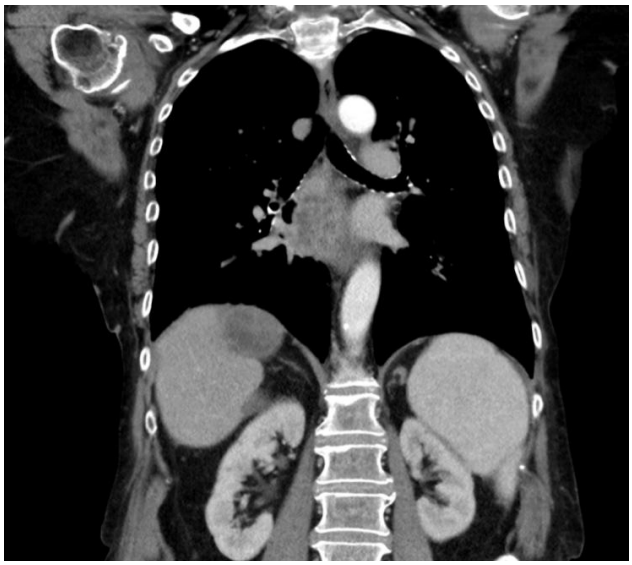

Figure 3. Follow-up CT scan showing progression of the oesophageal mass

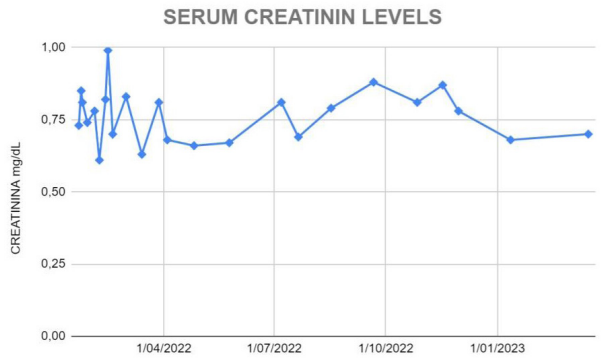

Figure 4. Evolution of creatinine levels throughout the treatment with vancomycin

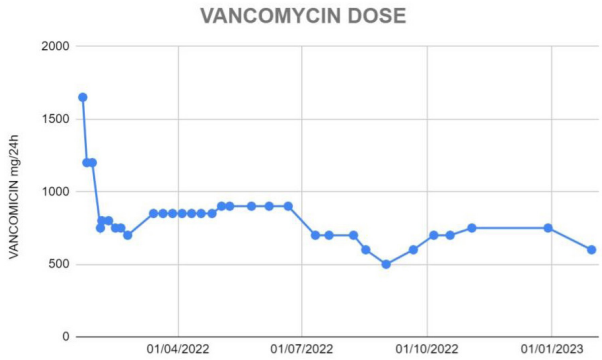

Figure 5. Vancomycin dosage during 12 months continuous infusion therapy

mg daily) and rifampicin (900 mg daily) was also maintained. The surgical committee decided that an intervention was not feasible due to the patient's characteristics and the nature of the lesion. The immunosuppressive treatment could not be changed because of a lack of a safe alternative. The patient was discharged from hospital and the follow-up continued in a home hospitalisation unit. A rigorous regimen of serial drug level monitoring and periodic laboratory assessments was implemented, with particular attention directed toward renal function (*Fig. 4 and 5*). For the first two months, analytical assessments were conducted every 5 days, transitioning to a weekly schedule thereafter. During the last 6 months, due to clinical stability analyses were performed at intervals of 10–14 days. In anticipation of a prolonged treatment, a subcutaneous reservoir was implanted prior to hospital discharge and weekly reviews of the access port were carried out. A dedicated team, consisting of a physician and a nurse, conducted daily home visits. Regarding resource consumption, the estimated cost of home healthcare is six times lower than that associated with hospital management. The patient successfully completed 12 months of intravenous vancomycin treatment and 14 months of oral levofloxacin 500 mg per day, in conjunction with oral rifampicin 300 mg every 8 hours. The control CT scan performed then demonstrated the resolution of the mediastinal infection. Notably, despite the prolonged treatment period, the patient remained free of any treatment-related complications. The patient's physical condition was excellent, maintaining an active lifestyle during follow-up without experiencing muscle discomfort or symptoms of tendinopathy. Periodic analyses did not show any abnormal results in liver function tests. Renal function, which is the most frequently described altered parameter during long-term vancomycin administration, remained unchanged throughout the course, with an average creatinine level of 0.76 mg/dl ± 0.01 mg/dl. Currently, the patient is being followed up in hepatology consultations without any clinical incidence, awaiting a new CT scan for re-evaluation.

DISCUSSION

Vancomycin, an antibiotic from the glycopeptide family, has been traditionally used in the treatment of infections caused by gram-positive bacteria. It has a high volume of distribution, which confers a great capacity for it to penetrate tissues effectively. Its pharmacokinetic properties depend largely on various factors (such as age, obesity, neutropenia, sepsis, renal function) that often determine dosing failure[3] and its antimicrobial capacity depends on the time its concentration remains above the minimum inhibitory concentration (MIC). Thus, monitoring peak and trough levels has traditionally been employed as a dosing adjustment method when vancomycin is administered through a bolus regimen. However, it has been observed that the ideal pharmacodynamic target is not the time above the MIC but a value of AUC24/MIC (area under the curve over 24h/MIC) ratio ≥ 400, with a target trough level of 15–20 mg/l. This is the point at which vancomycin demonstrates maximum bactericidal capacity against *Staphylococcus aureus*[4].

Acute kidney injury is a significant complication that can occur during vancomycin treatment. Its incidence, according to meta-analyses, varies between 5% and 43%[5]. Although the pathogenic mechanisms leading to its occurrence are unknown, the risk increases with elevated trough concentrations (above 15–20 mg/l) or when the daily AUC exceeds 600 mg x h/L[6].

Continuous intravenous infusion (CII) is an alternative that simplifies the monitoring process, since plasma antibiotic concentrations are more stable once the steady-state is reached, which allows for less frequent vancomycin level determinations, and only one sample is needed for them. Also, CII achieves target serum concentrations more rapidly than intermittent intravenous administration. However, there is lack of evidence regarding the comparison of both treatment regimens and the different parameters used to estimate AUC24, as continuous infusion uses steady-state serum concentration as a reference, while intermittent infusion measures peak and trough serum levels[6].

Therefore, the available scientific evidence seems to agree on the greater safety of continuous vancomycin administration, both in hospitalised and outpatient patients, showing a lower risk of nephrotoxicity by reducing peak concentrations of this antibiotic[7–8]. This lower risk of nephrotoxicity, explained by a low incidence of supratherapeutic serum levels, can be

especially relevant in prolonged treatments, as in our case. In terms of efficacy, it appears to be similar in both intermittent and continuous infusion strategies[9].

Other advantages of using elastomeric pumps in continuous vancomycin infusion compared to intermittent infusion are the resource savings involved, both for use in home care units and for the ease of sample collection during monitoring (one single steady-state concentration measurement can be taken every 2 to 5 days if levels are within range). As a result, less manipulation of venous access means a lower incidence of catheter-related complications. Moreover, the home hospitalisation regimen improves patients' quality of life, minimises adverse events and allows relatives and caregivers to continue with their daily activities.

Disadvantages of continuous infusion seem to include greater endothelial damage, requiring the use of a central line, reservoir or similar vascular access[10]. Additionally, the incompatibility of this antibiotic with other drugs demands separate IV lines or catheters for treatment co-administration.

Our patient is a clear example of all the aforementioned benefits, with the peculiarity of the long duration of treatment, which reached 12 months without presenting any complications, both in terms of renal damage and less common ones such as fever, *Clostridioides difficile* infection, allergic reaction or haematological toxicity.

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