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Short Communication

Myelosuppression-sparing treatment of central nervous system nocardiosis in a multiple myeloma patient utilizing a tedizolid-based regimen: a case report

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ABSTRACT

Central nervous system (CNS) nocardiosis is a recognised opportunistic infection in immunocompromised patients. Treatment involves prolonged institution of antibiotics, making oral agents a convenient and desired option. Unfortunately, devising an effective, well-tolerated antimicrobial for the duration required to treat CNS nocardiosis is challenging owing to treatment intolerance and toxicities. This report highlights myelosuppression-sparing treatment with an oral tedizolid-based regimen following a complicated course with standard agents. A 68-year-old female from Florida (USA) with low-risk lambda light chain multiple myeloma complicated by persistently low CD4 counts, absolute neutrophil counts and IgG levels presented 18 months after diagnosis with fever, pneumonia, new-onset atrial fibrillation, right-sided hemiparesis, encephalopathy and slurred speech. Magnetic resonance imaging (MRI) showed numerous ring-enhancing lesions, and blood cultures were positive for *Nocardia farcinica*. The patient failed initial therapy with trimethoprim/sulfamethoxazole (SXT), linezolid and imipenem plus surgical debridement of the frontal lobe abscess. Intraoperative cultures were positive for *N. farcinica*. The treatment course was also complicated by steadily declining white blood cell and platelet counts despite receiving filgrastim. She was therefore placed on SXT and tedizolid for 6 months. Subsequent brain MRI showed complete resolution of the lesions and thus chemotherapy for multiple myeloma was re-initiated. In conclusion, tedizolid-based regimens may be an option for patients with myelosuppression requiring prolonged antibiotic therapy for CNS nocardiosis.

1. Introduction

Nocardia is a genus of partially acid-fast, weakly Gram-positive staining bacteria with branching filaments. Nocardiosis is a particularly virulent systemic form of *Nocardia* infection often occurring in immunocompromised individuals and characterised by a relapsing, relentless course frequently involving the lung but with potential to affect almost any organ. Fortunately, it is a rare disease; however, with a mortality rate ranging from 7 to 36% and a relapse rate of 13% depending on the treatment regimen, it still poses a challenge to clinicians [1]. The majority of cases are caused by the *Nocardia asteroides* complex consisting of *Nocardia abscessus*, *Nocardia cyriacigeorgica*, *Nocardia farcinica* and *Nocardia nova* [2]. *N. farcinica* is known to have higher rates of antimicrobial resistance and risk of dissemination [3].

Although nocardiosis predominantly occurs in immunosuppressed hosts, immunocompetent patients comprise 25% of reported cases. Risk factors described for central nervous system (CNS) nocardiosis include immunosuppression, prior solid organ and haematopoietic stem cell transplantation, low CD4 count, chronic granulomatous disease, haematological malignancy and pre-existing brain disease [4]. Neurotropism for CNS capillary endothelial cells underlies the pathobiology of CNS nocardiosis, which is mediated by release of catalase and superoxide dismutase that prevent phagolysosomal fusion within macrophages and promote haematogenous spread across the blood–brain barrier to the CNS [5]. CNS involvement can present as either meningitis, cerebral abscess or both. Effective medical therapy for CNS nocardiosis hinges upon achieving high and sustained concentrations of antimicrobial agents in CNS tissues for prolonged durations. Established agents that achieve this include trimethoprim/sulfamethoxazole (SXT), imipenem, amikacin and linezolid. Unfortunately, the prolonged durations required for treatment of CNS nocardiosis predispose to

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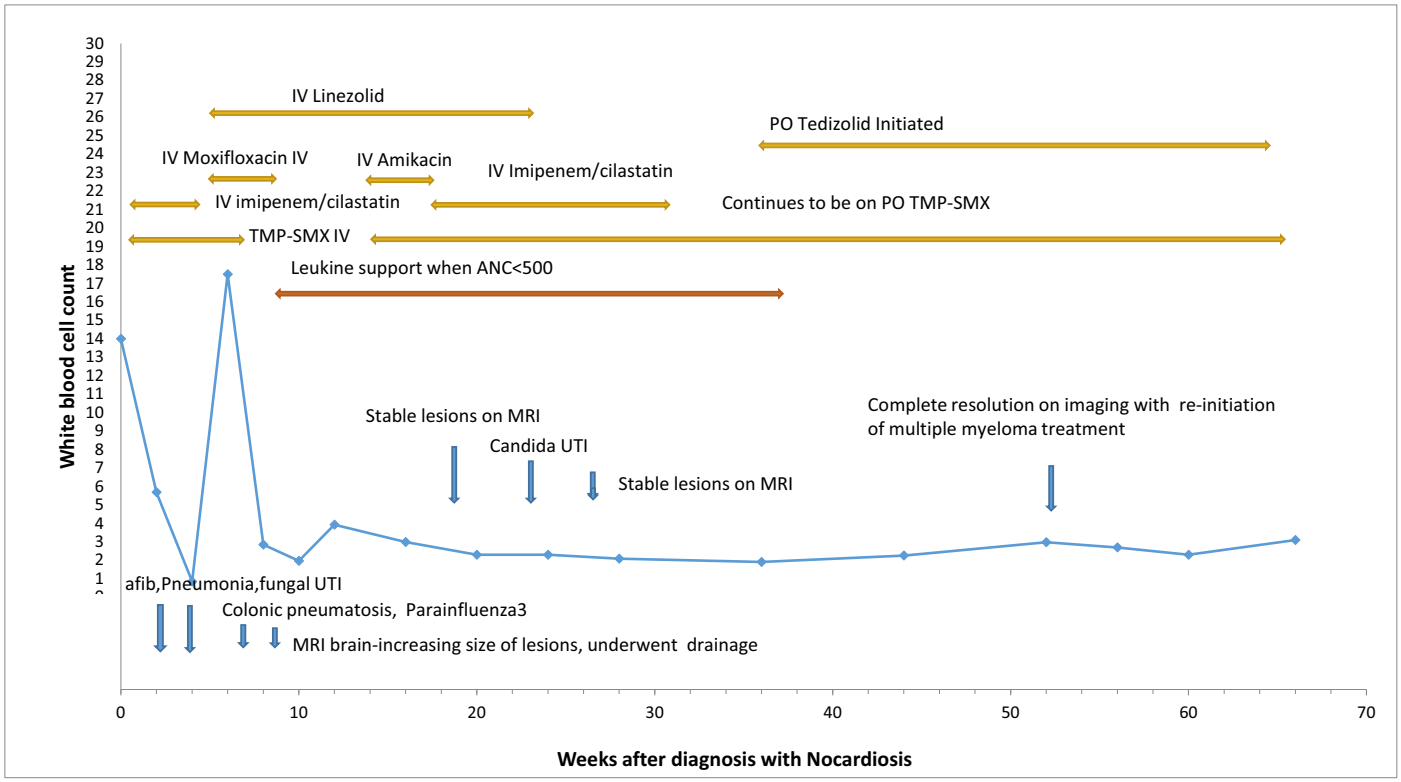

Fig. 1. White blood cell counts during treatment of central nervous system nocardiosis. IV, intravenous; PO, oral; TMP-SMX, trimethoprim/sulfamethoxazole; ANC, absolute neutrophil count; MRI, magnetic resonance imaging; afib, atrial fibrillation; UTI, urinary tract infection.

toxicities such as acute kidney injury and myelosuppression. Several antimicrobial agents have recently received US Food and Drug Administration (FDA) approval after being rigorously evaluated for indications such as skin and soft-tissue infections and intra-abdominal infections. However, these agents are unlikely to be evaluated for relatively uncommon infections such as nocardiosis owing to accrual challenges. This paper provides some insight into the therapeutic utility of one of these novel agents that could expand our armamentarium for the treatment of CNS nocardiosis.

Here we report successful treatment of CNS nocardiosis with tedizolid, a second-generation oxazolidinone, after the patient had received a prolonged course with other agents that was fraught with complications.

2. Materials and methods

The patient was a 68-year-old female who was a resident of Florida (USA) and who was diagnosed with low-risk lambda light chain multiple myeloma in February 2012. She received induction chemotherapy with melphalan, bortezomib, thalidomide, adriamycin, cyclophosphamide, cisplatin and etoposide (MVDTPACE) with plans for stem cell collection aborted thrice secondary to metapneumovirus infection and consequently failed mobilisation even with granulocyte-colony stimulating factor (G-CSF), plerixafor and hyperbaric oxygen. Maintenance therapy consisted of bortezomib, thalidomide and dexamethasone (VTD), with very good partial response as per the International Myeloma Working Group (IMWG) criteria. Her bone marrow cellularity prior to acquiring *Nocardia* was 40%. After ca. 16 months of VTD maintenance therapy, she developed respiratory symptoms requiring hospitalisation and was treated for bacterial pneumonia. She then developed atrial fibrillation with rapid ventricular rhythm and right-sided facial palsy with right-sided hemiplegia.

Her workup included brain magnetic resonance imaging (MRI), which revealed multiple ring-enhancing lesions in the parietal lobe (measuring 15.3 mm × 15 mm), bilateral occipital, temporal and frontal lobes with surrounding oedema, a 2-mm midline shift and leptomeningeal enhancement. Chest computed tomography (CT) confirmed left multisegmental pneumonia. She was initiated on SXT [15 mg/kg/day intravenous (i.v.)] and imipenem/cilastatin 1 g i.v. every 8 h empirically for *Nocardia* along with dexamethasone and levetiracetam. Her blood cultures confirmed *N. farcinica* sensitive to linezolid, moxifloxacin and amikacin. She was then placed on linezolid 600 mg i.v. twice daily and moxifloxacin 400 mg i.v. once daily, and i.v. SXT was continued. After receiving 19 days of SXT, linezolid and moxifloxacin, her haemoglobin level, white blood cell (WBC) count and platelet count started decreasing and SXT had to be discontinued (Fig. 1). Atrial fibrillation was pharmacologically cardioverted to normal sinus rhythm with dronedarone. Serial MRIs initially showed improvement in oedema but unchanged lesions and only partial resolution of the slurred speech and right-sided hemiplegia. After 25 days of treatment with linezolid and moxifloxacin, repeat MRI worsened with an increase in size and enhancement of lesions and oedema. She underwent surgical drainage of two abscesses and intraoperative cultures were positive for *N. farcinica*. She was started on amikacin, re-started on i.v. SXT and continued on linezolid, with the absolute neutrophil count being maintained >1000 cells/mm^3 responsive to sargramostim.

After a 3-month course of amikacin, SXT and linezolid, surveillance MRIs revealed stable to minimal improvement in the size of the lesions. Her hospital course was then complicated with parainfluenza 1, pulmonary aspergillosis, urinary tract infection and pneumatosis intestinalis. She was managed medically with i.v. and later oral (p.o.) voriconazole for 3 weeks to treat her pulmonary aspergillosis. She was discharged on linezolid (600 mg p.o. twice daily) and SXT (800/160 mg p.o. three times daily), which was cycled with