Case Report

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Management of Atypical Peripheral Neuropathy: A Case Report

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Abstract: Introduction: Peripheral neuropathies are very common and occur due to multiple causes including diabetes, tuberculosis, vasculitis, thyroid disorders, immune mediated diseases, vitamin B12 deficiency and drugs. Drug induced peripheral neuropathy (DIPN) is potentially irreversible, resulting in sensory deficits and paraesthesia. DIPN due to anti-tubercular drugs is common and can be implicated on linezolid, cycloserine and isoniazid. **Case**: 40-year-old female, diabetic with MDR-TB presented with severe, sharp, burning pain in her lower limbs. The patient was on all longer acting ATT drug regimen and was suspected with drug induced peripheral neuropathy. **Conclusion**: Linezolid, is used in treatment of tuberculosis and one of the major side effects includes peripheral neuropathy which is usually quite severe, presenting predominantly with sensory symptoms. Cessation of linezolid and neuropathic pain medications reduced the pain of patient from VCPS 8-10 to 1-2. Treatment of DIPN can be challenging as adverse drug reactions while treating tuberculosis should be kept in mind. It also warrants earliest treatment by identification of the drug in disguise and timely discontinuation of the drug.

Keywords: linezolid; tuberculosis; neuropathic pain; drug induced peripheral neuropathy; case report

Introduction

Peripheral neuropathies are complex set of peripheral nervous system disorders. They affect around 2.4% of the population with the prevalence increasing to 8% in older populations [1].

Distal sensory polyneuropathy (DSP) is very common and is characterized by "length-dependent peripheral nerve injury resulting in distal predominant sensory loss, pain, and severe weakness" [2]. The causes of peripheral neuropathy include diabetes, tuberculosis, vasculitis, thyroid disorders, immune mediated diseases and vitamin B12 deficiency. Other causes are attributed to drugs like chemotherapeutic agents, antimicrobials, cardiovascular drugs, psychotropics, anticonvulsants and antitubercular drugs [3].

Drug induced peripheral neuropathy (DIPN) is potentially irreversible, resulting in sensory deficits and paraesthesia. DIPN accounts for 4% of all neuropathies while the incidence in tubercular patients ranges from 13% to 29% with varying rates in different studies [4,5]. Though aetiology is multifactorial, detailed history and workup are required to rule out possible causes of pain due to other comorbidities. We present here a case of painful atypical drug induced peripheral neuropathy incited by antitubercular drugs and their management. Written informed consent was obtained from the patient for publication.

Patient Information

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A 40-year-old female, a known case of type-2 diabetes mellitus (DM) and pulmonary tuberculosis (PTB) with right sided pyopneumothorax presented to the pain clinic with severe, sharp, burning pain in her lower limbs (R>L), severe enough to disturb her sleep and a Verbal Categorical Pain Scale (VCPS) rating of 8-10 on a scale of 0 to 10. It was associated with difficulty in walking and aggravated on standing.

History dates back to five months when the patient presented with the chief concerns of dyspnoea (mMRC grade II) and chest pain for 15 days and was diagnosed with right sided pleural effusion. On evaluation, the aetiology was found to be tubercular and HRCT Chest revealed right moderate hydropneumothorax with minimal left pleural effusion. On CBNAAT and Gene-Xpert, she was diagnosed with Multi-Drug Resistant Tuberculosis (MDR-TB). The patient was started on longer acting oral anti-tubercular drugs which included linezolid 600 mg once daily, bedaquiline 200 mg once daily (thrice a week), levofloxacin 750 mg once daily, cycloserine 750 mg once daily, clofazimine 100 mg once daily, and pyridoxine 100 mg once daily before bed for two months. The effusion was drained via an intercostal drain attached to a negative suction and she was relieved of chest pain and breathlessness.

Clinical Findings

After three months, patient presented again with a complaint of severe, sharp, pricking and burning type of pain in bilateral lower limbs (R>L), starting from feet and radiating till the thighs, which worsened at night and was severe enough to disturb her sleep, causing her to continuously wail in the ward. Her pain aggravated with a fan or with air conditioner (AC) and on standing. The patient faced difficulty in walking due to pain. Initially, it was conservatively managed by the pulmonologist.

However, due to persistent and increasing pain, fatigue, and numbness of bilateral lower limbs, she was referred to the pain clinic. Assessment of neuropathic pain was done using a DN-4 questionnaire which revealed a score of 7/10 as seen in Figure 1. Local examination of bilateral lower limbs was done and observations were recorded as described in Table 1.

Diagnostic Evaluation

Routine blood investigations, thyroid workup and diabetic workup were done and were found to be normal. A nerve conduction study was performed which revealed bilateral sensory motor axonal neuropathy. An MRI spine was performed to rule out discogenic origin of pain and was found to be normal. The patient was also advised a doppler to rule out vascular afflictions and it was found to be normal with no evidence of thrombosis.

Therapeutic Intervention

On presentation to the pain clinic, she was receiving longer acting anti-tubercular treatment (ATT) regimen drugs for three months. The patient was distressed, since she was unable to walk for last one week due to severe burning and pricking pain in her bilateral dorsum and sole of feet, radiating till thighs. After evaluation, it was suspected to be drug induced peripheral neuropathy and linezolid was stopped after discussion with the pulmonologist. Cycloserine induced neuritis was also suspected but it could not be stopped due to lack of alternative drugs with better adverse effect profile.

For the pain, she was started on a multimodal regime of oral medications consisting of pregabalin extended release 75 mg (with mecobalamin) twice daily, amitriptyline 10 mg once daily at bedtime and tramadol 50 mg thrice daily. She was advised to cover her feet and avoid direct blast of air from ceiling fan or AC. After two weeks, the pain in lower limbs decreased but difficulty in walking persisted with a VCPS score of 4. The dose of pregabalin was increased to 150 mg twice daily. A lipid profile was done and oral atorvastatin-aspirin 10/75 mg was added.

Follow Up and Outcomes

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Two weeks later, the burning sensation persisted with a VCPS of 3 at night. Oral duloxetine 20 mg was prescribed at night. Two weeks later, patient could sleep well with a VCPS of 1-2. Eventually, she started walking with baby-steps unsupported and was advised physiotherapy to overcome partial stiffness and weakness that developed due to disuse of bilateral lower limbs. The patient was discharged finally from the hospital and asked to follow-up in the pain clinic for further review and tapering off her medications as and when required.

Patient Perspective

I have been explained about the drug intervention and publication for the case and I willingly provide consent for the same. With the discontinuation of linezolid and starting medications for pain, I felt relieved of the excruciating pain. The pain gradually reduced and I was able to sleep and walk. The doctors advised me to avoid direct air from AC or fan, so I covered my legs and felt better. Physiotherapy sessions are ongoing and helpful. I have been discharged but I continue to visit the hospital for follow up. Overall, I am satisfied with the treatment and there is > 80% reduction in my pain.

Discussion

India has the highest burden of tuberculosis accounting for 26% of the global incidence [6]. Painful peripheral neuropathy is commonly observed among patients with tuberculosis (TB). It occurs due to multiple reasons including the disease itself, co-morbid conditions, substance abuse, malnutrition, and an adverse effect of treatment [7]. More recently, it has been related to radiculopathy because of tuberculous meningitis [8]. Thus, it is essential to screen all tuberculotic patients for peripheral neuropathy.

Most drug-induced peripheral neuropathies (DIPN) cause damage at the dorsal root ganglia. At the cellular level, the mechanisms for DIPN include metabolic dysregulation, covalent modification, organelle damage, intracellular inflammatory signalling, axonal transport defects, and channelopathies [9].

DIPN occurs as an adverse effect of cardiovascular agents (amiodarone, statins), chemotherapeutic agents (platinum compounds, vinca alkaloids, epothilones, taxanes, arsenic trioxides), antitubercular drugs (isoniazid, ethambutol, linezolid, cycloserine, fluoroquinolones, ethionamide, and para-aminosalicylic acid), immunosuppressive drugs (leflunomide, interferons) and anti-retroviral drugs as summarized in Table 2 with their respective incidence [10]. DIPN secondary to ATT requires vigilant screening and if ignored, may prove to be dreadfully painful and irreversible.

Linezolid, an oxazolidinone antibiotic, is used in the treatment of tuberculosis, essentially XDR-TB and one of the major side effects includes peripheral neuropathy which is usually quite severe, presenting predominantly with sensory symptoms. Other adverse effects include myelosuppression, optic neuritis and gastrointestinal reactions [11,12]. Peripheral neuropathy usually occurs at a dose of more than 600 mg per day. Symptomatic relief is observed when the dosage is reduced to 300 mg per day [13–15]. Most patients being treated with linezolid receive pyridoxine as part of the standard of care. As per literature, most cases of linezolid induced peripheral neuropathy were observed in patients with prolonged intake of linezolid, with minimum duration of at least 28 days [16].

We considered various differential diagnosis and ruled out the possibilities of HIV, thyroid anomalies, diabetes, vascular causes and vitamin deficiencies. DIPN due to ATT, particularly linezolid seemed to be a plausible cause due to reduction in pain after discontinuing the drug. Though the patient responded to pharmacotherapy which includes gabapentinoids, SNRIs, TCAs, opioids, and topical applications, there are established interventional modalities available as RFA of bilateral lumbar sympathetic plexus. [12]

The basic management of DIPN in patients with tuberculosis must follow a 2-phased approach. [17]. Phase 1 includes prevention: (i) management of underlying disease (s)- TB, diabetes, HIV infection, etc.; (ii) avoidance of substance abuse; (iii) drug dose adjustments: without bargaining the TB treatment regimen. (iv) pyridoxine supplementation. Phase 2 involves (i) termination of the

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possible offending agent; (ii) vitamin supplementation to counter the deficiencies and supplementation for those with dietary compromise; (iii) rigorous physical therapy; (iv) pain relief; (v) bio-psycho-social support; and (vi) pharmacotherapy: tricyclic antidepressants (amitriptyline), selective serotonin reuptake inhibitors (fluoxetine. paroxetine), serotonin noradrenaline reuptake inhibitors (duloxetine and milnacipran) and gabapentin or pregabalin.

Conclusion

Management of painful DIPN in pain OPD requires a holistic timely and multimodal approach as it is a diagnosis of exclusion. Treatment of DIPN can be challenging as adverse drug reactions while treating tuberculosis should be kept in mind. The aim should be preventing any possible DIPN as it can become irreversible. However, if present, it warrants earliest treatment by identification of the drug in disguise and timely discontinuation of the drug with vitamin supplementation, rigorous physiotherapy, and frequent follow-ups, which help in achieving a good outcome for the patient.

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