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CASE REPORT

Severe medication-induced peripheral neuropathy treated with topical doxepin cream in a paediatric patient with leukaemia

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SUMMARY

A 17-year-old female with recently relapsed acute lymphoblastic leukaemia and a treatment course complicated by rhinocerebral mucormycosis infection developed severe peripheral neuropathy during the treatment for mucormycosis infection. This was felt to be a medication side effect. Her peripheral neuropathy was refractory to many well-established treatments, but ultimately responded dramatically and consistently to a novel therapy, topical doxepin cream (5%). This case report is the first published report of the application of topical doxepin cream for treatment of peripheral neuropathy in a paediatric patient.

BACKGROUND

Peripheral neuropathy can be caused by a variety of aetiologies, including medications, poorly controlled diabetes and idiopathic hereditary and acquired causes. Regardless of the cause, it can be notoriously difficult to treat and contribute to significant patient suffering. Common therapies include gabapentin, pregabalin and duloxetine as well as more traditional analgesics such as non-steroidal anti-inflammatory medications and opioids.[1] As none of these therapies have proven to be universally efficacious, research continues to search for additional treatment options.

CASE PRESENTATION

The patient is a 17-year-old female who experienced a combined bone marrow and central nervous system relapse 6 months after completing a 2½ year course of chemotherapy for pre-B acute lymphoblastic leukaemia (ALL). She received reinduction chemotherapy consisting of dexamethasone, mitoxantrone, PEG-asparaginase, vincristine and intrathecal chemotherapy (methotrexate, hydrocortisone and cytarabine). She developed a mild tingling in fingers and toes consistent with vincristine-associated peripheral sensory neuropathy, which was well controlled with gabapentin. Midway through her 4 week reinduction course, she was admitted for management of febrile neutropaenia and was found to have invasive rhinocerebral mucormycosis requiring multiple sinus and brain debridements, intravenous amphotericin and posaconazole. During this time, she received 13 days of blinatumomab for continued treatment of her ALL. The blinatumomab was discontinued when she needed to have a craniotomy for further debridement of the mucormycosis. Two weeks later, posaconazole was switched to micafungin as it was found to have in vitro synergy with amphotericin and an Ommaya reservoir was placed for the administration of intrathecal amphotericin.

Approximately two and a half months after starting reinduction therapy, she acutely developed severe pain in all the toes and arches of both feet without proximal radiation. Occasionally her hands would also have the burning pain and tingling also. The foot pain was constant and severe and kept her awake at night. There were no associated skin changes or rashes. There was some relief with heat packs, but no relief with morphine or gabapentin. The pain was worse when standing or walking.

INVESTIGATIONS

Neurology was consulted and on examination found her to have decreased vibratory sensation at the great toes and decreased deep tendon reflexes bilaterally at the ankles. Examinations of cranial nerves 2–12, proprioception, perception of light touch, cerebellar function, motor strength and mental status were normal. The clinical history and examination were felt to be most consistent with a small fibre, length dependent, sensory polyneuropathy. The symptoms were not thought to be consistent with a radiculopathy or myelopathy.

Her painful distal sensory polyneuropathy was felt to be most likely medication related, with potential causes including chemotherapeutic agents, especially vincristine and blinatumomab and antifungals, especially posaconazole. To rule out other aetiologies, evaluations including thyroid stimulating hormone, free T4 and vitamin B12 levels were sent and a MRI of lumbar spine was performed, all of which were unremarkable.

TREATMENT

The patient's severe peripheral neuropathy associated pain in her feet continued to worsen and proved increasingly difficult to treat, despite aggressive medical management, leading to readily apparent suffering for the patient. She was unable to walk and would spend much of the days and nights writhing in severe pain in bed. Gabapentin was gradually increased to a dose of 900 mg twice during the day and 1200 mg at night. Lorazepam, short-acting opioids and lidocaine patches were used with increasingly high doses; however, she had persistent, severe

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pain despite these treatments. Oral ketamine was administered for pain control, but she did not tolerate the treatment due to medication-induced dysphoria. As an adjunct treatment for her rhinocerebral mucormycosis, she began daily hyperbaric oxygen treatments, shortly after which her neuropathic pain improved significantly for a few days. Unfortunately, her pain worsened again to unbearable levels despite continued hyperbaric oxygen treatments and thus, with the aid of our pain management service, she was started on methadone and amitriptyline with doses gradually increased without any significant improvement in her pain. She was then started on duloxetine. Several days after duloxetine was started, but before one would expect it to have any effect, the pain continued to be severe causing much suffering for the patient.[2] At this point, 5% topical doxepin cream was applied to the feet with reported significant improvement in her pain within 20 min of an application. The next day she was able to ambulate comfortably for the first time in weeks. Though she was continued on her other medications, doxepin cream became the mainstay of her treatment. She received up to three applications a day with significant improvement in her pain control allowing her to be comfortable and ambulate freely.

OUTCOME AND FOLLOW-UP

One week after the initiation of doxepin cream treatment, intra-Ommaya amphotericin treatments were stopped due to eradication of any evidence of central nervous system mucormycosis. The patient's neuropathic pain improved significantly thereafter and she was gradually weaned off methadone, amitriptyline and topical doxepin over the following 3 weeks. She remained on duloxetine and gabapentin with good control of her neuropathic pain.

DISCUSSION

There are many aetiologies of peripheral neuropathy, including medications, with common culprits including chemotherapeutic and anti-infective agents.[3] Potential causes of our patient's peripheral neuropathy included her exposure to vincristine and blinatumomab as well as more recent exposure to sulfonamides. She briefly received posaconazole as well, though this is typically associated with peripheral neuropathy only after prolonged courses.[4] On literature review, there was no clear association found between peripheral neuropathy and the other medications she was receiving at the time of onset of symptoms, including amphotericin, both intravenous and intrathecal, micafungin, meropenem and vancomycin. However, as her symptoms developed within 2 weeks of initiating intra-Ommaya amphotericin treatments and improved significantly within days of cessation of these treatments, we hypothesise that this treatment may have contributed to her neuropathy.

As detailed above, our patient's pain was refractory to many of the first-line treatments for neuropathic pain. The first intervention that showed promise was hyperbaric oxygen treatments, with transient relief in her pain after only several treatments. Previous studies have shown reduction in neuropathic pain in animal models.[5–10] Another study, although small, showed significant improvement in antiretroviral-induced neuropathy after hyperbaric oxygen therapy.[11] Unfortunately, her improvement was short-lived and her neuropathic pain worsened again despite continued treatments with hyperbaric oxygen.

In the search for other treatment options, we found that topical doxepin cream had been shown to reduce neuropathic pain in prior studies.[12 13] Those studies found that doxepin, a tricyclic antidepressant, exerted an analgesic effect with topical application. This use of doxepin cream is an off-label use as the US Food and Drug Administration-approved indication for this formulation is for the short-term management of pruritus in adult patients with atopic dermatitis or lichen simplex chronicus. While some of the pain control effect could be due to the well-described central nervous system efficacy of tricyclic antidepressants in neuropathic pain management from systemic absorption of topically applied doxepin, in our case she was already on therapeutic oral doses of amitriptyline prior to starting doxepin and the immediacy of pain relief suggests a separate local analgesic effect. One study suggested that this peripheral activity of topical tricyclic antidepressants could be mediated through peripheral adenosine receptors.[13] In our patient, topical doxepin cream proved to be the most effective treatment, with relief consistently reported within 20 min of application.

In conclusion, neuropathic pain of all aetiologies can be incredibly difficult to treat and can be a source of great patient suffering. Many of the first-line therapies take several weeks to take effect. For patients who need additional pain control while awaiting relief from traditional treatments, or for patients with pain refractory to traditional treatments, a trial of 5% topical doxepin cream may be beneficial.

Patient's perspective

- Written by the mother who is an oncology nurse practitioner.
- My daughter was suffering from severe neuropathic pain despite receiving many conventional neuropathic pain treatments. I thought the methadone helped initially, but the pain continued to worsen. The ketamine could have helped somewhat also, but it caused dysphoria (hallucinations and an uncomfortable feeling). I think lorazepam could have helped manage the dysphoria in retrospect, but we did not pursue this at the time and instead discontinued the ketamine. By contrast the doxepin cream had very rapid efficacy with pain relief within twenty minutes. This really was a huge improvement and alleviated what to that point had been very severe and intractable pain and suffering for my daughter.

Learning points

- Painful peripheral neuropathy is a significant medication side effect, which can be synergistically worse in patients who receive multiple neurotoxic medications.
- The response of neuropathic pain to treatments such as gabapentin, duloxetine and amitriptyline can be slow to develop.
- Topical doxepin cream (5%) may be beneficial in patients who need immediate additional pain control while awaiting relief from other neuropathic pain treatments or for those patients with pain that is refractory to traditional therapies.

Contributors All the authors (ZD, RB, JMK, DJK) have cared for the patient and contributed to the conception, design, writing and editing of this manuscript. All the authors have reviewed the manuscript and agree to its content for submission.

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