Therapy Letters

Gabapentin for the management of vismodegib-induced muscle cramps

Sir,

Muscle cramps due to vismodegib treatment may be challenging and can cause treatment discontinuation in patients with basal cell carcinoma.[1] Therefore, symptomatic approaches to relieve muscle cramps are necessary. With this regard, we report our findings from an incidental case with intractable cramps who presented to thedepartment of dermatology.

The patient was an 83-year-old man with a history of radiation exposure to scalp for tinea capitis in his childhood. He was treated many times with surgical excisions and twice with radiotherapy for multiple basal cell carcinomas on the scalp previously. On admission, we performed dermoscopy and detected 11 distinct lesions of obviousbasal cell carcinoma on scalp region. A crusted ulcerwas seenon the vertex. After confirming the diagnosis of basal cell carcinoma with biopsy for this lesion, vismodegib treatment was started [Figure 1]. One month after the initiation of treatment, the patient reported severe disturbing cramps in his hands, legs and flanks, 2–4 times a day, mostly in the night, leading to sleep disturbance. He did not report any aggravating or relieving factor associated with the cramps. We intended to use amlodipine for his cramps, but the drug was contraindicated due to co-existing heart failure. Hence, magnesium was initiated at a dose of 365 mg/day. However, magnesium supplementation did not improve the symptoms even after 3 weeks. Approximately after 10 weeks of treatment with vismodegib, he presented with herpes zoster on his trunk. In addition to his antiviral treatment with valacyclovir, gabapentin 600 mg thrice a day was prescribed due to severe pain. One week after the treatment, he noticed aremarkable improvement in muscle cramps. To test any causal relationship between gabapentin use and cramp relief, we interrupted and re-initiated the treatment twice and observed cessation and alleviation of the cramps. Consequently, gabapentin was reduced to 600 mg once a day as the adequate dose and cramp frequency decreased to once or twice a week. Pigmented basal cell carcinomas disappeared clinically and dermoscopically nearly by the 6th month of treatment. Dermoscopic improvement of the lesions during the treatment course revealed the efficasy of vismodegib. However, we continued this treatment for the ulcerated lesion on vertex. Clinical improvement was confirmed with the absence of basal cell carcinoma histologically and vismodegibwas terminated by the 9th month of treatment. After the cessation of vismodegib treatment, the patient required gabapentin less frequently for another month and he was free of cramps for the next 5 months in the follow-up period.

Pathophysiology of muscle cramps caused by vismodegib has not been defined clearly. Cell membrane calcium channel activation by the drug was proposed[2] and some benefits from amlodipine treatment were reported in a vismodegib-treated case series.[3]

Muscle cramps arise from discharges of motor nerves rather than within the muscle itself.[4] High-frequencydischarges leading to cramps can be driven by the central nervous system or generated spontaneously within the peripheral nervous system. Despite the facts that support the involvement of both central and peripheral nervous systems, evidence favors a peripheral origin.[4] Previously, regulation of myelin formation in the peripheral nervous system by hedgehog signaling has been shown.[5] Recently, theimportance of sonic hedgehog and its receptor complex has been documented in adult peripheral nerve regeneration.[6] Moreover, sonic hedgehog and smoothened transcript levels were found increased after injury and the knockdown of sonic hedgehog resulted in impaired regeneration. Considering the importance of hedgehog signaling in nerve regeneration and myelination, inhibition of this pathway might be associated with the onset of crampsand/or neuropathy.

Indeed, drug-related peripheral neuropathies were recordedin more than 5% ofpatients receiving vismodegib.[7] However, neuropathy may not be evident in all cases. In another study, it was concluded that 60% of patients reporting muscle cramps without manifesting neuropathic complaints have smallfiber neuropathy.[8]

Mechanism of action of gabapentin for muscle cramps has not been clearly defined, but it probably has effects on both central and peripheral nervous systems.[9] In an open-label trial, 2-week gabapentin treatment reduced the number of cramps by more than a half in 85.7% of patients. Moreover, after 3 months, cramps disappeared in 100% of the patients.[9] Although such a benefit from gabapentin was not specifically tested in randomized controlled trials, it is commonly prescribed for muscle cramps by neurologists. In addition, disabling cramps were reported in up to two-thirds of the patients with some sort of neuropathy which is the primary clinical indication for gabapentin.[10]

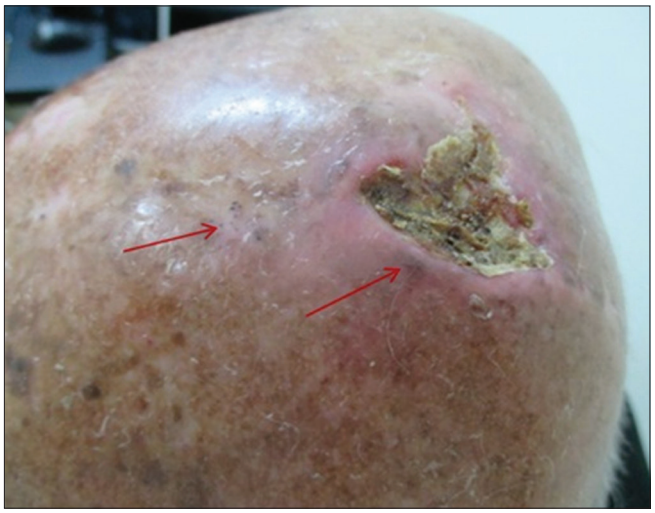

Figure 1: Pretreatment image of the patient with pigmented and ulcerated basal cell carcinomas

In conclusion, central and peripheral nervous system injury might be involved in the mechanism of vismodegib-induced muscle cramps, suggesting the need for clinical research with the available options for neuropathies. In the meantime, we believe that gabapentin can be considered an option for the patients with intractable cramps so that treatment discontinuation could be prevented. However, further randomized trials are needed to prove this theory.

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Conflicts of interest
There are no conflicts of interest.

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