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Letter to the Editor

Before Attributing Numbness and Erythema of the Hands and Feet to Doxorubicin, all Alternative Explanations must be Ruled Out

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Letter to the Editor

We read with interest the article by Kumar *et al.* about a 39-year-old patient with metastatic ovarian cancer who developed numbness and erythema on her palms and soles, following treatment with paclitaxel and carboplatin, surgery, olaparib, doxorubicin, and bevacizumab [1]. The patient was treated with high-dose pyridoxine, which resolved the erythema, but the sensory disturbances persisted [1]. She then received lower-dose bevacizumab and third-line chemotherapy [1]. The study is promising, but some points require further clarification.

First, the diagnosis of doxorubicin-associated neuropathy is questionable [1]. Several arguments speak against doxorubicin-induced toxic neuropathy in the index patient. She had previously received several other neurotoxic drugs that could be responsible for her sensory disturbances. Neurotoxic drugs that could also be a cause and that she had received include bevacizumab [2], olaparib [3], paclitaxel [4], and carboplatin [1]. Doxorubicin may have been the final trigger. It is also conceivable that the use of multiple neurotoxic drugs led to cumulative toxicity. Another possible cause of the sensory symptoms is paraneoplastic neuropathy [1]. Therefore, the determination of antineuronal antibodies would have been crucial. It is also conceivable that the neuropathy was caused by malnutrition due to a deficiency of vitamins B12, B1, B3, B6, B9, copper, or vitamin E.

The second point is that other, non-tumor-related differential causes of neuropathy were not sufficiently ruled out [1]. Were all differential causes of secondary neuropathy actually excluded in the index patient? Were the HbA1c values, renal function parameters, serum vitamin levels, hormone levels, infection parameters including virus panels (Zika, Chikungunya, Dengue), ANA, ANCA, antineuronal antibodies, *Borrelia burgdorferi* antibodies, and rheumatological parameters within the normal range?

Third, no nerve conduction studies (NCS) were performed [1]. To determine whether large nerve fibers were indeed affected, NCS of the sensory and motor fibers would have been essential. Involvement of the motor fibers is conceivable, as the patient exhibited marked atrophy of the intrinsic hand and foot muscles [1]. The patient's height, weight, and nutritional status should be known. In the absence of large nerve fiber involvement, small fiber neuropathy (SFN) should be considered and confirmed or ruled out by autonomic function testing and skin biopsy to determine intraepidermal nerve fiber density (IENFD). Palm and sole erythema in association with sensory disturbances are common manifestations of SFN [5].

Fourth, no long-term outcomes were reported [1]. What were the effects of the third-line chemotherapy and the final bevacizumab cycle? Did the neuropathy recur or resolve? The long-term consequences would have been of interest. Overall, doxorubicin should not be considered as a cause of sensory disturbances and erythema until all other causes have been ruled out. The presence of neuropathy should be confirmed by NCSs.

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