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Letter to the Editor: New Observation

Pemphigoid-like Skin Lesions Following Introduction of Safinamide

Lucie Lachance[1] and Philippe Huot[1,2,3]

[1]Movement Disorder Clinic, Division of Neurology, Department of Neurosciences, McGill University Health Centre, Montreal, QC, Canada, [2]Neurodegenerative Disease Group, Montreal Neurological Institute-Hospital (The Neuro), Montreal, QC, Canada and [3]Department of Neurology and Neurosurgery, McGill University, Montreal, QC, Canada

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Safinamide is a monoamine oxidase B inhibitor and glutamate release inhibitor[1] that is recommended by the International Parkinson and Movement Disorder Society for the treatment of motor fluctuations in Parkinson's disease.[2] The drug was approved in Europe in 2015, in the United States in 2017 and in Canada in 2019. The drug is usually well tolerated in the clinic,[3] however, because the drug was marketed relatively recently, it is possible that some adverse events linked to its use may not have been reported yet. Here, we present the case of a woman with Parkinson's disease who developed pemphigoid-like skin lesions after being started on safinamide therapy.

A 72-year-old lady of Caucasian ancestry had been suffering from Parkinson's disease for 6 years. Her medication consisted of levodopa/carbidopa, pramipexole, domperidone and rasagiline. She also took zopiclone, apixaban, calcium, vitamin D, dexlansoprazole and intra-nasal momethasone. In addition to Parkinson's disease, she had a history of atrio-ventricular dysrhythmia, for which she had a pacemaker implanted, as well as gastro-oesophageal reflux disease. She also had a history of bullous pemphigoid, which had been quiescent for years, without any active skin lesions or on-going therapy. The previous pemphigoid episode had occurred 15 years before, without any precise trigger, and resolved after several months of treatment with topical corticosteroids.

The patient was experiencing severe dyskinesia and motor fluctuations with the drug regimen described above. We elected to replace rasagiline by safinamide, while leaving the other drugs unchanged. Safinamide 50 mg daily was prescribed for 2 weeks, after which it was increased to 100 mg daily.

Safinamide was initially well tolerated and reduced her motor fluctuations and mildly attenuated her dyskinesia. However, approximately 7 weeks after taking safinamide, she noted the appearance of tense reddish itchy blisters of about 1 cm diameter covering her whole body, akin to those she had experienced years ago. Mucosae were spared. The Nikolsky's sign was reportedly negative. She was seen by a dermatologist and a clinical diagnosis of bullous pemphigoid was made. Topical clobetasol 0.05% twice daily was prescribed. When she informed us of the situation, we considered safinamide as a possible aetiological factor and elected to stop it. The itchy bullous lesions healed over approximately 2–3 months following discontinuation of safinamide and did not recur, although red lesions where the blisters were located have remained. Topical clobetasol therapy was continued until the lesions had healed. The figure illustrates some pictures that were taken by the patient and shared with us (Figure 1).

The case presented above has a few limitations. Firstly, the diagnosis was made clinically, and no histopathological tests were performed. Secondly, we did not observe the bullous lesions ourselves, as they occurred between two visits at the clinic, although a dermatologist made the diagnosis. Nevertheless, the situation was brought to us by the patient, and we felt that it might be useful to the community to be aware of this case of presumptive drug-induced bullous pemphigoid caused by safinamide. Thirdly, whereas the lesions improved with the discontinuation of safinamide, the patient was also treated with topical corticosteroids, which makes it impossible to conclude that the improvement was solely due to the cessation of safinamide. It is unfortunately impossible to gather additional information from the patient, as she has passed away since this episode.

Bullous pemphigoid is an auto-immune disorder caused by auto-antibodies that attack proteins at the junction of the dermis and epidermis, which results in blisters and skin erosions.[4] Several drugs and several drug classes have been associated with the onset of bullous pemphigoid, e.g. angiotensin-converting enzyme inhibitors, non-steroidal anti-inflammatory drugs, antibiotics, calcium-channel blockers, etc.[5,6] However, to the best of our knowledge, none of the drugs she was taking have been reported to cause pemphigoid and she had been taking them for years, without developing any skin condition, which makes safinamide the likely cause, as it was introduced a few weeks before the bullous skin lesions appeared. Drug-induced pemphigoid may appear up to 3 months after the introduction of the aetiological agent; here, safinamide has been introduced less than 3 months prior to the lesion onset, which strengthens the possibility of its causative role.[6] In addition, drug-induced pemphigoid tends to appear in younger patients than the spontaneously occurring condition.[6]

Interestingly, Parkinson's disease may be a risk factor for bullous pemphigoid, as the condition is more frequently encountered in Parkinson's disease patients than in the general population.[7] We

Corresponding author: Philippe Huot: Montreal Neurological Institute-Hospital (The Neuro), 3801 University St, Montreal, QC, H3A 2B4, Canada. Email: philippe.huot@mcgill.ca
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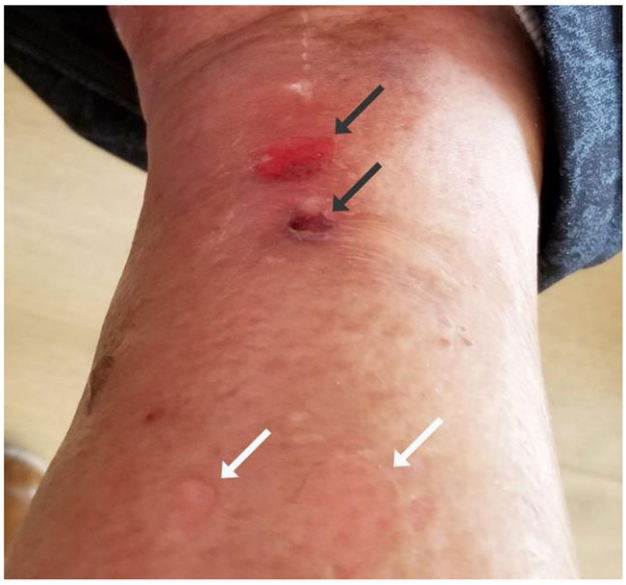

Figure 1: Figure depicting blisters (white arrows) and reddish ulcerated skin lesions (dark grey arrows) at the back of the patient's left calf. The image was provided to us by the patient.

can therefore not rule out that the blisters were caused by Parkinson's disease, although the occurrence after the introduction of safinamide and the improvement after its discontinuation strongly point to safinamide as the culprit factor. We also note that the blisters did not occur while the patient was taking rasagiline, which suggests that not all monoamine oxidase B inhibitors may trigger bullous skin lesions. Of note, a recent meta-analysis discovered that dopaminergic drugs were associated with higher risks of developing drug-induced pemphigoid.[8]

In summary, we have presented the case of a woman who developed a bullous skin condition, diagnosed as drug-induced bullous pemphigoid by a dermatologist. Whereas no histopathological examination was performed to confirm the diagnosis, it nevertheless raises the possibility that safinamide may cause drug-induced pemphigoid. Further case reports like this one, with histopathological confirmation, are necessary to confirm this possibility. Meanwhile, clinicians should be aware that safinamide may lead to bullous skin lesions akin to bullous pemphigoid and adjust their treatment accordingly.

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Conflict of Interest. None.

Statement of Authorship. LL and PH both contributed to the writing of this manuscript.

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