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Response to Letter to the Editor entitled "Adding Cases to the Study of Bucillamine-Associated Neural Epidermal Growth Factor Like1-Positive Membranous Nephropathy"

The Author Replies: We thank Takahashi-Kobayashi *et al*. for reporting the additional Japanese case regarding bucillamine-associated neural epidermal growth factor-like 1 (NELL1)-positive membranous nephropathy (MN) in response to our report titled "Neural Epidermal Growth Factor-Like 1–Positive Membranous Nephropathy with Rheumatoid Arthritis.[1]" Of the 88 patients diagnosed with MN between 2013 and 2022, they found 8 (9.1%) with NELL1-positive MN, including 1 (12.5%) with a history of bucillamine-treated rheumatoid arthritis (RA). The frequency of cases with bucillamine-associated NELL1-positive MN was lower than that reported in our study (30%). It is worth noting that the 2 cohorts differed in the time periods. Our cohort included patients with MN diagnosed between 2005 and 2018, and 3 patients with bucillamine-associated NELL1-positive MN were diagnosed in 2005, 2011, and 2013. Therefore, our patients with bucillamine-associated NELL1-positive MN were earlier cases. The difference in the time periods between the cohorts may have influenced the frequency of bucillamine-associated MN because the frequency of bucillamine use may have differed. Proteinuria is now a well-known side effect of bucillamine, which has led to closer monitoring and fewer cases that result in kidney biopsy. Around the same time as our report, Tsuji *et al*.[2] reported Japanese cases of bucillamine-associated NELL1-positive MN. In this cohort of patients diagnosed with RA-complicated MN between 2004 and 2020, 27 of 34 (79%) patients with RA-complicated MN had NELL1-positive MN, and 19 cases (56%) had a history of bucillamine treatment.[2] Collectively, these studies suggest a relatively high prevalence of bucillamine-associated MN among Japanese patients with NELL1-positive MN even though the prevalence may vary during different time periods. Importantly, the cohorts included patients with NELL1-positive MN complicated by RA without bucillamine treatment. Therefore, factors other than bucillamine use may contribute to the development of NELL1-positive MN, such as the genetic background or osteogenic properties of NELL1 in the joint involvement of patients with RA. A larger collection of cases and genetic background studies are warranted in the future.

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