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Letter to the Editor

A case of systemic nickel allergy with diarrhea-predominant irritable bowel syndrome in which nickel intake restriction and administration of a probiotic formulation were effective

Dear Editor,

In 2017, nickel restriction was reported to improve irritable bowel syndrome (IBS)¹; however, the relationship between nickel allergy and IBS has been reported only recently.^{2,3} Here we report a case of nickel allergy with IBS along with skin lesions in which eruption improved by treating the IBS with nickel restriction and a probiotic formulation.

We describe the case of a 47-year-old woman who smoked 10 cigarettes a day and enjoyed eating chocolate. She had diarrhea-predominant IBS, weighed 39 kg, and had no history of allergic disease. She had suffered from erythema with itching on her palms and feet for the past year. She was treated with topical steroids, oral antihistamines, and oral prednisone at a local clinic, but the skin rash gradually expanded to her forearms and trunk. Therefore, she was referred to our department. Pruritic erythema with irregular margins and partial pigmentation was observed on her forearms and trunk (Fig. 1A). Her palms were severely itchy and appeared to be swollen due to inflammation, and she showed overall erythema with partial scales (Fig. 1B). The hyperkeratosis was prominently observed on her soles (Fig. 1C). The small tense vesicles on the ventral surface of the palmoplantar were associated with dyshidrotic eczema like-rash.⁴ Laboratory blood tests did not reveal any abnormalities. A skin biopsy was taken from the palm. The stratum corneum was hyperkeratotic and parakeratotic, the epidermis was thickened with a club-like appearance, and spongiosis was observed (Supplementary Fig. 1A). The upper dermis was infiltrated with lymphocytes and showed a small number of eosinophils. No dysplasia was noted in the infiltrating lymphocytes (Supplementary Fig. 1B). In the patch test (Torii Pharmaceutical, Tokyo, Japan), a positive result (48 h: +, 72 h: +++, 1 week: +++) to nickel sulfate was confirmed according to the criteria of the International Contact Dermatitis Research Group.⁵ The result of the nickel patch test carried out after a week is shown in Supplementary Figure 1C. We advised the patient to avoid contact with nickel-containing substances, and restricted intake of nickel-containing substances (cigarettes and chocolate, etc.) improved the eruptions in the trunk (Fig. 2A). However, the rashes on the palm did not show complete remission (Fig. 2B). In the nickel load test conducted according to a previously described protocol,⁶ we confirmed the reappearance of the eruptions in the trunk and palm at day 3 after a supplementary diet of 10 µg of nickel in chocolate for 2 days. She was diagnosed



Fig. 1. Clinical images. Erythema with pruritus, scales, and itching was observed on the trunk (A) and palms (B). Hyperkeratosis was prominently observed on the patient's soles (C).

with a systemic metal allergy, but nickel restriction did not contribute to complete remission of skin lesions. Regarding diarrhea-predominant IBS, the polycarbophil calcium was administered but that was ineffective. However, the patient's condition with respect to both skin lesions and diarrhea improved with the administration of a probiotic formulation (3 tablets/day; Bifidobacterium, Takeda Pharmaceutical, Osaka, Japan) in addition to a

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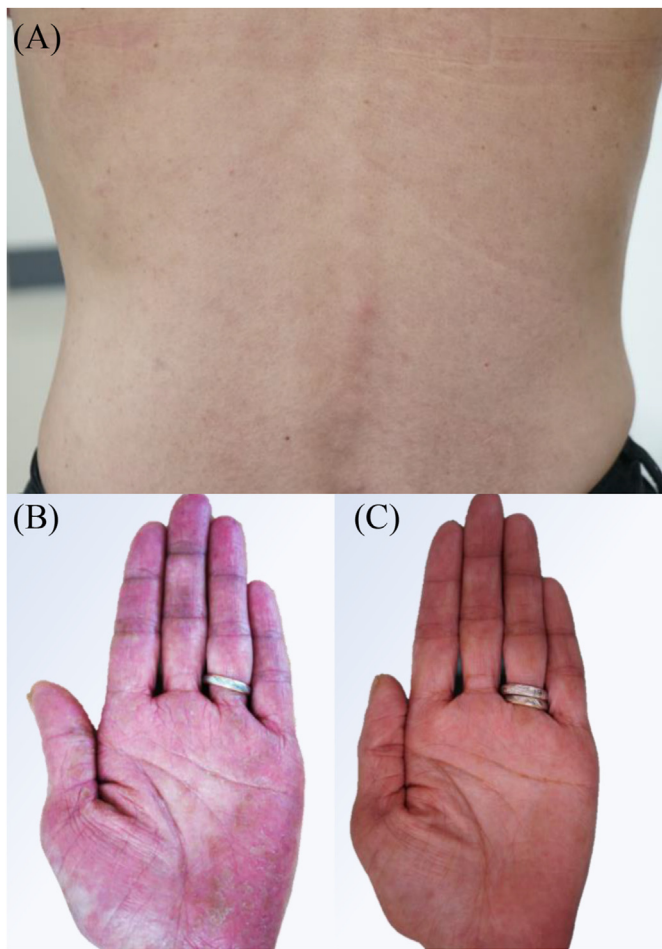


Fig. 2. After restricting the intake of nickel-containing foods, the eruptions in the trunk improved (A) but were still present on the palms (B). Although the area of erythema was shrinking, nickel restriction alone did not cause complete remission of the palm rash. When a probiotic formulation was administered, the skin rash was alleviated, and erythema almost disappeared (C).

restricted nickel diet. She gained 5 kg of body weight after 4 months and the skin rash subsided (Fig. 2C).

Systemic nickel allergy can be suspected following detailed interviews and assessment of nickel-containing substances favored by the patient, and it can be definitely diagnosed using a nickel load test.⁶ Unfortunately, if nickel allergy is diagnosed, it is impossible to completely eliminate nickel from the patient's diet because of its presence in many foods.¹ Thus, nickel intake restriction will not lead to complete remission, even if shrinkage of the rash occurred, as in our case.

In 2017, Rizzi *et al.* reported that a nickel-restricted diet improved diarrhea-predominant IBS.¹ Additionally, in 2020, Borghini *et al.* reported that oral nickel consumption might elicit systemic reactions in patients affected by systemic nickel allergy syndrome, including gastrointestinal symptoms.² In an *in vivo* study, oral nickel administration led to abnormal changes in the intestinal flora of mice.⁷ Recently, Caruso *et al.* reported that abnormalities in the gut flora caused nickel allergy in patients, and DNA analysis of their feces demonstrated that administration of a probiotic formulation, in addition to restricted nickel, significantly improves the abnormal dysbiosis index, rather than nickel

restriction alone.⁸ The probiotic formulation might be able to exert a beneficial influence on pathogenetic pathways of IBS with nickel allergy, including restoration of altered gut microbiota.⁸

Because the association between nickel allergy and IBS was only recently reported, most dermatologists probably do not ask the patient about abdominal symptoms when treating for systemic metal allergy. Conversely, even if the patient visits the internal medicine department for abdominal symptoms of IBS with skin rash, the presence of systemic nickel allergy might be overlooked. Therefore, physicians must be made aware that nickel allergies can cause IBS as well as skin lesions. In cases with refractory eczema like-lesions, suspicion of metal allergy, interviews about abdominal symptoms, and patch test are essential. Further, if nickel restriction alone is ineffective in cases of systemic nickel allergies, additional use of probiotic formulation could not only improve IBS but also be effective in improving skin rash.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.alit.2021.03.004>.

Conflict of interest

The authors have no conflict of interest to declare.

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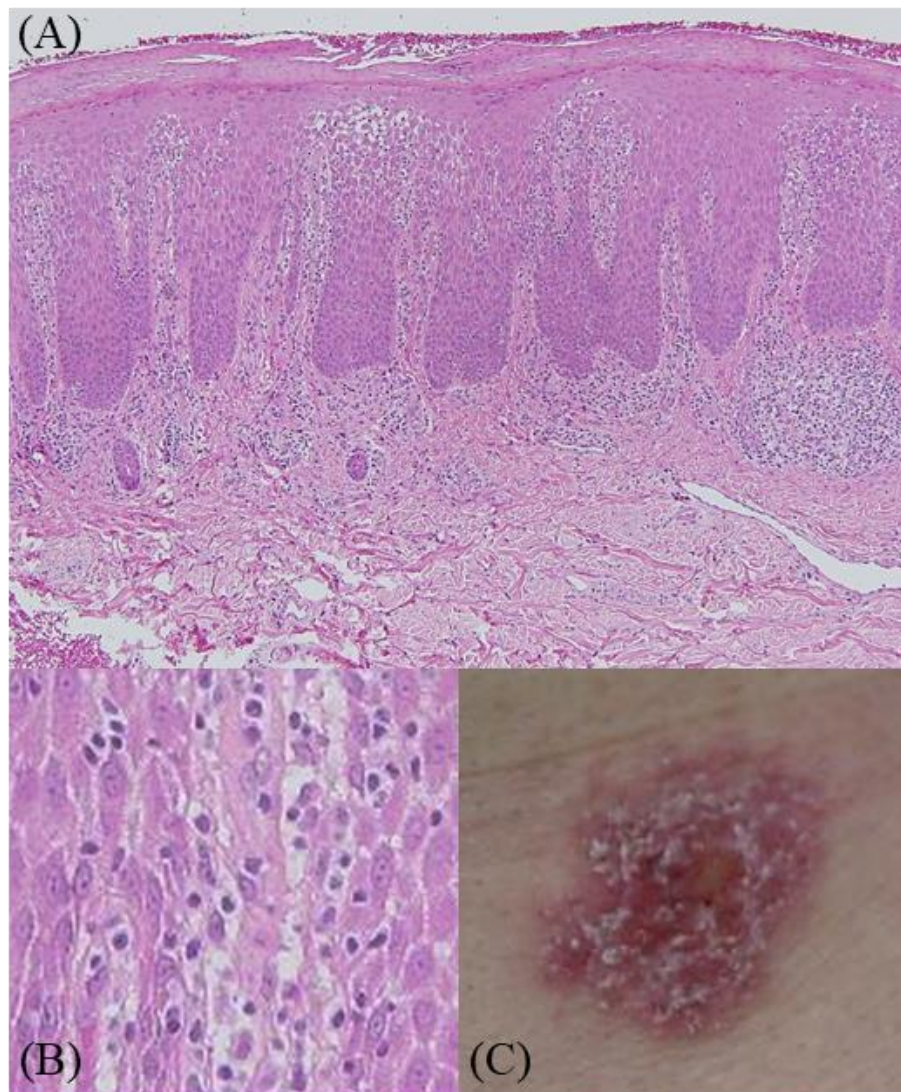
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Supplementary Fig. 1. Histopathological finding in the palm: the epidermis was thickened with spongiosis, H&E staining; magnification, $\times 100$ (A) and $\times 400$ (B). The nickel patch test demonstrated a positive result. The result of the patch test after a -week period is shown (C).