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Immunological characterization of the allergic contact mucositis related to the ingestion of nickel-rich foods

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ABSTRACT

Background: The ingestion of nickel (Ni)-rich foods may result in allergic contact mucositis (ACM), a not yet well defined condition identifiable by oral mucosa patch test (omPT). Our aim was to characterize immunologically the ACM taking advantage from the allergen exposure that occurs during the omPT for Ni.

Methods: Thirty-seven symptomatic patients underwent to omPT for Ni. Before and after omPT, serum and urine Ni concentrations were determined by mass spectrometry, the white blood cells were counted by hemochromocytometric assay, the peripheral lymphocyte typing was carried out by flow cytometry, total IgE and cytokine serum concentrations were measured by immunoenzymatic assays. The local lymphocyte typing was performed by immunohistochemistry only after omPT.

Results: According to the omPT outcomes, 25 patients were defined as Ni-sensitive and the remaining 12 as controls. After omPT, serum and urine Ni concentrations increased significantly in all patients, while a significant increment of circulating lymphocytes and neutrophils was highlighted, respectively, in Ni-sensitive and control patients. Consistently, the Th and Tc circulating lymphocytes, as well as the Th/Tc ratio increased significantly in Ni-sensitive patients after omPT. No noteworthy increment in serum concentrations of total IgE and selected cytokines was observed in any patient after omPT. The presence of CD3+, CD4+, and CD8+ cells was highlighted on the oral mucosa biopsy samples taken from Ni-sensitive patients after omPT.

Conclusions: In patients with ACM, a local adaptive response with increased lymphocyte trafficking appears to be the most likely mechanism of reaction to Ni administered with the omPT.

Abbreviations: A_{450nm}, absorbance at 450 nm; ACD, allergic contact dermatitis; ACM, allergic contact mucositis; Ags, antigens; ANOVA, analysis of variance; APC, allophycocyanin; DTH, delayed-type hypersensitivity; EDTA, ethylenediaminetetraacetic acid; ELISA, enzyme-linked immunosorbent assay; ePT, epicutaneous patch test; EQA, external quality assessment; FACS, fluorescence-activated cell sorter; FITC, fluorescein isothiocyanate; HRP, horseradish peroxidase; ICDRG, International Contact Dermatitis Research Group; ICP-MS, inductively coupled plasma-mass spectrometry; IQA, internal quality assessment; mAbs, monoclonal antibodies; Ni, nickel; NK, natural killer; omPT, oral mucosa patch test; PBS, phosphate buffered saline; PE, phycoerythrin; PerCP, peridinin chlorophyll protein; SD, standard deviation; SSc, side light scatter; Tc, T suppressor/cytotoxic; Th, T helper/inducer; TLR, Toll-like receptor; WBC, white blood cells.

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Introduction

Nickel (Ni) is a transition metal widespread in the environment, foods, drugs, chemicals, and metallic utensils which absorption may occur by inhalation, ingestion, or through the skin. In the blood, Ni is mainly bound to albumin while kidneys are the primary route of elimination (Barceloux, 1999).

This metal is an essential microelement for the homeostasis of the human organism however, it has also carcinogenic properties, can act as contact allergen and high concentrations may cause an acute toxic reaction (Barceloux, 1999; Magaye et al., 2012). In 2008, the American Contact Dermatitis Society has defined Ni as the "Contact Allergen of the Year" (Kornick and Zug, 2008). The prevalence of Ni allergy is indeed growing in many countries and represents a major health and socioeconomic issue. Researches published over the last forty years from North America to Western Europe highlight a median prevalence of 8.6%, with values higher among women than men (17.1% vs. 3%) (Darlenski et al., 2012; Schram et al., 2010; Thyssen et al., 2007).

The main clinical manifestation caused by skin contact with Ni is an allergic contact dermatitis (ACD), for which the epicutaneous patch test (ePT) is considered the gold standard for diagnosis (Mark and Slavin, 2006). Similarly, Ni exposure through the intestinal mucosa can result in a systemic hypersensitivity with dermatologic manifestations or symptoms such as diarrhea, headache, and general discomfort (Darlenski et al., 2012; Hsu et al., 2011; Matiz and Jacob, 2011). The allergic contact mucositis (ACM) has been recently described as a systemic Ni hypersensitivity identifiable by the oral mucosa patch test (omPT). In patients with ACM, the ingestion of Ni-rich foods causes the onset of intestinal and/or extraintestinal manifestations while, after a reasonable period of low-Ni diet, they report an improvement in symptoms and restoring of well-being (Picarelli et al., 2011). Nevertheless, further studies are necessary to confirm and extend these findings and their implications on human health.

Ni allergy is a T lymphocyte-driven delayed-type hypersensitivity (DTH) characterized by leukocyte infiltration at sites of allergen exposure. In detail, Ni ions bind directly to Toll-like receptor 4 (TLR4) expressed on monocytes, dendritic and endothelial cells providing a molecular signal that, in synergy with the DTH response triggered by Ni-haptenated proteins, leads to Ni allergy (Rothenberg, 2010; Schmidt and Goebeler, 2011; Wang and Dai, 2013). However, the current knowledge come from studies performed on patients with ACD and therefore, the immunological mechanisms underlying systemic Ni hypersensitivity still need to be characterized.

Based on these observations, our aim was to characterize immunologically the ACM related to the ingestion of Ni-rich foods by evaluating the DTH response typical of ACD, an eventual immediate hypersensitivity reaction, and the expression of TLR4 and specific cytokines after the allergen exposure that occurs during the omPT for Ni.

Materials and methods

Patients

A total of 37 consecutive outpatients (2 males/35 females, mean age 37.5, range 19–58 years), who from January to December 2012 were referred to our Gastroenterology Unit with intestinal and/or extraintestinal symptoms (e.g. diarrhea, abdominal pain and swelling, hives, itching, and headache) referable to the ingestion of Ni-rich foods, were enrolled in the study. In detail, the relationship between reported symptoms and Ni-rich food ingestion was highlighted by an anamnestic card that every patient has compiled at the time of study entry. The presence of pathological conditions that could justify the clinical picture, such as celiac disease, lactase deficiency, and allergic disorders (from the classic IgE-mediated allergies to ACD caused by metals other than Ni), was also considered.

The main clinical data of the patients being studied are summarized in Table 1.

Study design

For diagnostic purposes, each patient underwent to omPT for Ni. Both before and immediately after the omPT, every patient was submitted to blood sampling to assess the amount of Ni absorbed during the test as well as the cellular, humoral, and cytokine systemic response induced by Ni exposure. In order to evaluate the amount of Ni cleared following its eventual absorption, an urine/24 h collection was prescribed to each patient before and after the omPT. In 10 patients with positive omPT results, who have agreed to be subjected to additional procedures, a blood sample was also obtained at 48 h from the test to monitor the systemic cellular response induced by Ni exposure. In 4 patients with positive and another one with negative omPT results, who have agreed to be submitted to further procedures, an oral mucosa biopsy sample was taken immediately after the test to evaluate the local cellular response induced by Ni exposure. As a Ni-unexposed negative control, an oral mucosa biopsy sample was also taken from 3 healthy volunteers not subjected to omPT.

Table 1
Main clinical data of the patients being studied.

Intestinal symptoms		Extraintestinal symptoms		Other diseases	
	Pts/total (%)		Pts/total (%)		Pts/total (%)
Abdominal swelling	21/37 (56.8%)	Asthenia	16/37 (43.2%)	LD	12/37 (32.4%)
Abdominal pain	15/37 (40.5%)	Headache	15/37 (40.5%)	CD	7/37 (18.9%)
Meteorism	15/37 (40.5%)	Itching	12/37 (32.4%)	OAs	7/37 (18.9%)
Belching	14/37 (37.8%)	Hives	11/37 (29.7%)	T	7/37 (18.9%)
Diarrhea	13/37 (35.1%)	Dermographia	10/37 (27.0%)	ACD	5/37 (13.5%)
Dyspepsia	12/37 (32.4%)	Dizziness	10/37 (27.0%)	IgAD	2/37 (5.4%)
Stomatitis	11/37 (29.7%)	Conjunctivitis	7/37 (18.9%)	P	2/37 (5.4%)
Constipation	10/37 (27.0%)	Erythema	7/37 (18.9%)	AA	1/37 (2.7%)
Nausea	7/37 (18.9%)			V	1/37 (2.7%)
Vomiting	5/37 (13.5%)				

Each patient presented at least one intestinal symptom referable to the ingestion of Ni-rich foods, but not everyone had an extraintestinal Ni-related symptom or were suffering from another disease.
AA, alopecia areata; ACD, allergic contact dermatitis (to iron, nickel, palladium, and silver); CD, celiac disease; IgAD, IgA deficiency; LD, lactase deficiency; OAs, other allergies (to casein, cat's hair, dust, grains, latex, mites, parietaria, and pollen); P, psoriasis; T, thyreopathy; V, vitiligo.