

Nickel-elicited systemic contact dermatitis from a peripheral intravenous catheter

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Nickel-elicited systemic contact dermatitis is a well-known entity, although it is far less common than allergic contact dermatitis. In most of the cases, the main way of nickel administration is oral. Clinical manifestations are miscellaneous including pompholyx, diffuse exanthema, flexural dermatitis or baboon syndrome. Systemic nickel dermatitis induced by venous catheters is very uncommon, but it is probably underdiagnosed. We report here 2 patients with diffuse recurrent maculopapular rash corresponding to nickel-elicited systemic contact dermatitis. They were both perfused during the last episode with the assistance of a peripheral polyurethane venous catheter during or just before the cutaneous eruption. At the base of the catheter, there was a small metallic eyelet on which dimethylglyoxime test was positive, indicating a release of nickel. Then, we measured nickel release in normal use conditions and found high nickel levels, although the manufacturer denied that nickel could be released. This diagnosis is important to know because such exanthema often occurred during postoperative or postpartum period. Its frequency is probably underestimated because it is often considered as a cutaneous drug reaction. To our knowledge, only 2 cases have been reported in the literature.

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Systemic contact dermatitis is seen when sensitized individuals by skin contact are systemically exposed to a hapten (1). It is well-known to occur with drugs (2). Certain metals, especially nickel, can also elicit systemic contact dermatitis by an internal systemic way such as oral intake, transfusion, inhalation, implantation of metal medical devices and dental braces (1, 3).

We report 2 cases of systemic contact dermatitis due to a nicked eyelet in a polyurethane peripheral intravenous catheter, although the manufacturer denied any possibility of nickel release.

Case Reports

Case no. 1

A 37-year-old woman had several recurrent episodes of itchy macular exanthema that appeared a few hours after surgical interventions and labours. Antibiotic β -lactams and non-steroid antiinflammatory drugs were initially suspected, although she was not tested for any drug

sensitivity but afterwards she avoided using these drugs. Later on, she noticed the same cutaneous reaction without use of any drugs or any surgical operation, but each time she had a glucose infusion for several hours. Between 1985 and 2004, she had 7 episodes of diffuse exanthema in such conditions. Her past medical history revealed an allergic contact dermatitis to nickel, confirmed by a highly positive patch test to nickel sulfate (+++).

To confirm the possible responsibility of the metallic part of the catheter, we decided to initiate a glucose infusion for 4 hr under medical supervision. We chose a peripheral intravenous catheter 'OPTIVA' 20G with OCRILON polyurethane (Medex, Johnson & Johnson Medical and Vascular Access, Arlington, TX, USA) that is usually used in our hospital. 1 hr after, she underwent an itchy macular and slightly swollen exanthema, predominantly on the flexural folds, which diminished after 2 days of loratidine therapy. There was no cutaneous reaction at the infusion site on the forearm.

Case no. 2

A 33-year-old woman experienced since 2003 recurrent episodes of itchy exanthema, which appeared 10 hr after 3 surgical operations for a pulmonary malignant tumour and ovarian metastases and after an iodine contrast medium injection for a chest scan. They consisted of dark red maculopapular lesions predominantly localized in the periumbilical area and in the folds (Fig. 1) and with no cutaneous lesion at the infusion site on the forearm.

A few months later, she underwent allergological investigations. Concerning the iodine contrast medium, despite the negativity of all skin tests, she was considered to be allergic to this drug and was advised to avoid it. The prick and intradermal tests for β -lactamin drugs and an oral provocation test for ketoprofene were also negative. A few weeks later, she had an intravenous administration test of another suspected drug (cefotaxime) that induced the eruption 3 hr later, and hence the patient was considered to be allergic to this drug. For the next surgical operation, she received a quinolone (ciprofloxacin), but the same rash relapsed 10 hr later. For the last operation, the anaesthetist used the same drugs but he put a central venous catheterization set (Arrow, Arrow International, Reading, PA, USA) instead of the peripheral catheter. The central catheter was made only of polyurethane components. There was no recurrence of the cutaneous eruption during the postoperative period.

The patient had also a past medical history of severe allergic contact dermatitis to nickel, confirmed by highly positive patch tests to nickel sulfate (+ + +).

We contacted the manufacturer to find the composition of the peripheral catheter (OPTIVA,



Fig. 1. Dark red macular exanthema of the trunk, predominant in the periumbilical area.

Table 1. Measures of nickel levels in glucose solution through the catheter at different times

Time (hr)	Nickel release ($\mu\text{g/l}$)
Control	0.4
1	15
2	6.50
3	7
4	6.50
5	6
6	7
24	9

Medex, Johnson and Johnson Medical and Vascular Access). It was latex free, made of polyurethane components, but the eyelet was made of brass (30%) and nickel plated (70%). We realized a nickel spot test on the eyelet (Chemotechnique Nickel Spot Test, Vellinge, Sweden), which consists of an ammoniacal solution of dimethylglyoxime that detects nickel release. A positive spot test produces a bright, reddish-pink insoluble salt with nickel. Here, the spot test was negative. Then, we put the eyelet in a bottle with 10 cm³ of glucose infusion for 48 hr and we realized another spot test, which was positive on the eyelet and with the glucose infusion incubated with the eyelet.

We took samples of glucose infusion through the catheter and measured nickel release at different times (Table 1).

As nickel is a ubiquitous element, great care was taken at all stages of preparation to avoid any risk of contaminations. Details of procedure have been described by Pineau et al. (4) concerning sampling conditions for trace elements. Nickel levels were determined by electrothermal atomic absorption spectrometry using a longitudinal 4110ZL Zeeman and equipped with an AS72 autosampler (all from Perkin-Elmer, Norwalk, CT, USA). Nickel measurements were performed in triplicate. The detection limit was 0.0038 $\mu\text{g/l}$.

Each nickel calibration was monitored with one quality control (Serionorm, Nycomed, Oslo, Norway). The results obtained were 5.2 $\mu\text{g/l}$.

There was a significant elevation of nickel level after the 1st hour (15 $\mu\text{g/l}$). After that, it was relatively stable, the medium concentration being about 7 $\mu\text{g/l}$.

We measured the nickel level in the tube that contained the eyelet and the glucose solution during 2 days and 7 days. It was an impressive level of about 600 $\mu\text{g/l}$ and 11 000 $\mu\text{g/l}$ or 11 mg/l, respectively.

We were surprised because the manufacturer ensured that the nickel atoms were chemically alloyed by electroplating and hence they could

not be released. Furthermore, on the manufacturer web site, presence of metal in the base of the catheter was not mentioned.

We concluded that both patients presented with systemic contact dermatitis due to release of nickel that was present in the eyelet of the polyurethane peripheral venous catheter. In the second case, we cannot exclude also an allergic reaction to cefotaxime because it was a concomitant intravenous provocation test with a glucose infusion during the test.

Discussion

Systemic contact dermatitis may occur in contact-sensitized individuals when these are exposed to the hapten orally, transcutaneously, intramuscularly, intravenously or by inhalation (1). This eruption has a latency period of a few hours or a few days after exposure, and it is a benign and often underdiagnosed eruption.

The most specific cutaneous reactions include flare-up reactions in previously positive patch tests and/or flares of previous sites of contact dermatitis, symmetrical erythema of the gluteal and in the flexural or intertriginous folds resembling the dark red gluteal areas of baboons. The term 'baboon syndrome' was introduced 20 years ago (5).

Vesicular hand eczema (pompholyx or dyshidrotic eczema), flexural dermatitis, maculopapular rash, urticarial reactions, vasculitis like lesions and rarely general symptoms have also been reported (1). Recently, Hausermann et al. (6) proposed the term of symmetrical drug-related intertriginous and flexural exanthema or SDRIFE, for this distinctive clinical pattern of drug eruption. Histologically, there are spongiosis, dermal lymphocytic infiltrate, sometimes a focal vacuolar degeneration, rarely pustules or leucocytoclastic vasculitis.

Pathogenesis of systemic contact dermatitis is not very clear. Some studies have concluded that this reaction may be mediated by both a type III and a type IV mechanism (7).

The most frequent causes of systemic contact dermatitis are drugs such as aminopenicillins, neomycin, terbinafine and pseudoephedrine (2). Nickel, more rarely, can also elicit widespread dermatitis by an internal systemic route, for example, oral intake, transfusion, inhalation, implantation of metal medical devices and dental braces (1, 3). Systemic nickel dermatitis has been seen following accidental intravenous exposure to micrograms of nickel in 2 old case reports (8, 9). In our cases, the manufacturer told us that these intravenous catheters complied to the

requirements of toxicology tests such as systemic injection test (ISO 10993-11), intracutaneous reactivity and skin sensitization tests (ISO 10993-10), tests for *in vitro* cytotoxicity (ISO 10993-5) and haemocompatibility testing (ISO 10993-4). These polyurethane peripheral catheters are used all over the world.

However, we demonstrated that there was an important nickel release from the metallic eyelet of the catheter when it was in contact with a glucose solution. We think that investigations of nickel release by the manufacturer are improper and should be re-evaluated.

In a recent study, nickel-sensitive individuals whose dermatitis flared after oral challenge with nickel showed significant decreases in fractions of $CD3^+ CD45RO^+ CLA^+$ and $CD8^+ CD45RO^+ CLA^+$ blood lymphocytes, suggesting migration of $CD8^+$ 'memory' CLA^+ T lymphocytes from the blood to peripheral tissues. Only nickel-sensitive individuals reacting to high nickel doses had significantly elevated levels of IL-5 in the serum after oral exposure, indicating an activation of type 2 T lymphocytes in the peripheral blood (10).

In conclusion, we have described 2 patients with systemic contact dermatitis due to nickel release from a peripheral intravenous catheter. In 18 months, we have observed 5 other patients (all women) perfused with the same catheter presenting with recurrent postoperative or postpartum cutaneous eruption, with different drugs at each episodes. All of them had a past history of severe allergic contact dermatitis to nickel. 3 of them presented with a maculopapular exanthema and the 2 others had also pompholyx. Systemic contact dermatitis to nickel was highly suspected but could not be yet proved absolutely because these persons refused any allergological explorations.

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