

Eosinophilic Airway Disease in a Patient with a Negative Skin Prick Test, but a Positive Patch Test with Platinum Salts - Implications for Medical Surveillance

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We present the case of a 52-year-old woman with a topic dermatitis since adolescence who developed work-related hand eczema, cough and runny nose 12 years after she had started working as a laboratory technician at a precious metals refinery. While skin prick test with sodium hexachloroplatinate (SPT_{Pt}) was negative, patch testing with ammonium tetrachloroplatinate was positive after 24, 48, 72, and 96 hr. Inhalation challenge with sodium hexachloroplatinate yielded cough, mild shortness of breath, and a maximal decrease of FEV₁ of 8% from baseline 24 hr after the challenge. Significant increases of bronchial hyperresponsiveness, exhaled nitric monoxide and sputum eosinophils were documented after the challenge. We conclude that eosinophilic airway disease due to platinum salts may occur in SPT_{Pt} negative subjects. Both, patch testing and inhalation challenge with platinum salts should be considered in SPT negative subjects with occupational exposure to precious metal salts and work-related allergic symptoms. Am. J. Ind. Med. © 2015 Wiley Periodicals, Inc.

KEY WORDS: Asthma; late reaction; platinum salts; sputum analysis; surveillance

INTRODUCTION

Medical surveillance for the early detection of platinum (Pt) salt allergy is implemented in many precious metals refineries and catalyst productions worldwide. The effectiveness of such a program has been shown in a longitudinal nested case-control study [Merget et al., 2001]. Usually, surveillance comprises symptoms suggestive of an immediate-type allergy and skin prick testing with Pt salts (SPT_{Pt}), mostly sodium hexachloroplatinate (International

Platinum Association 1993, unpublished). Whereas specificity of SPT_{Pt} is considered 100% [Merget et al., 1991; Merget et al., 2000], sensitivity is considered high, but cannot be quantified with certainty because inhalation challenges cannot be used as the gold standard in epidemiological studies and work-related symptoms, which are closely linked to a positive SPT_{Pt} in epidemiological studies [Merget et al., 2000], may be nonspecific.

Information about inhalation challenges with Pt salts is sparse, the pattern was an immediate-type reaction in all cases [Merget et al., 1994]. However, two subjects with negative SPT_{Pt}, but isolated late asthmatic reactions were described [Pepys et al., 1972]. Patch testing has not been performed in these cases.

METHODS

Personal data and both work and medical history were obtained by a questionnaire and a physician interview. The

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patient underwent a physical examination, standard blood chemistry, and an electrocardiogram. Chest x-rays were considered normal a few months earlier in another hospital. Lung function was recorded by body plethysmography [Criece et al., 2011] and spirometry [American Thoracic Society, 1995] with a MasterLab (Jaeger, Würzburg, Germany). Methacholine testing was performed with a reservoir method as described recently [Polychronakis et al., 2013]. The dose-response relationship of this test is comparable to the American Thoracic Society's dosimeter test [Merget et al., 2005], but the delivered dose is documented as the dose at the mouthpiece, which is about half of the dose nebulized in the American Thoracic Society's protocol. The cut-off for a positive test is (cumulative) 300 µg methacholine [German Society of Occupational and Environmental Medicine 2006].

Total IgE was measured in sera by ImmunoCAP (ThermoFisher Scientific, Uppsala, Sweden), SPT were performed with a battery of 18 environmental allergens from various manufacturers, including house dust mites, grass and tree pollen, animals and molds, and sodium hexachloroplatinate and palladium chloride, both at a concentration of 1 g/L (provided by Heraeus, Hanau, Germany as 10 g/L solutions, diluted tenfold with saline). SPT with metals were performed in duplicate. Reactions were read at 20 min. Patch testing was performed with the standard series (containing cobalt chloride 1% pet.) and the dental metals series (containing ammonium tetrachloroplatinate 0.25% pet. and palladium chloride 1% aqu), provided by AllergEAZE (SmartPractice, Calgary, Canada) according to the German Contact Allergy Group (DKG). Briefly, contact allergens were applied with Finn Chambers (Epitest Ltd Oy, Tuusula, Finland) on hypoallergenic Fixomull stretch (Baiersdorf Medical GmbH, Hamburg, Germany) to the upper back. The strips were removed after 24 hr. Readings were performed after 1, 24, and 48 hr. The reactions were not followed afterwards because the protocol of an earlier test with reactions to both metal salts at 72 and 96 h was available. Results were evaluated according to the standard scoring system recommended by the European Society of Contact Dermatitis (ESCD).

Inhalation challenge with Pt salts comprised 13 steps of quadrupling concentrations of sodium hexachloroplatinate diluted in phosphate buffer from 60 pg/ml to 1 mg/ml (cumulative doses of 2.7 pg to 60 µg). Pt salt solutions were aerosolized by a DeVilbiss 646 nebulizer and an APSpro dosimeter (Jaeger, Würzburg, Germany). The application of Pt salt was adapted to the American Thoracic Society's protocol for methacholine testing [American Thoracic Society, 2000] with minor modifications [Merget et al., 2009]. Briefly, the nebulizer was actuated 0.5 s after the start of inspiration to ensure a significant airflow upon nebulization. Secondly, we omitted breathholds after inhalation. Lung function measurements after each step

started about 10 minutes after the end of inhalation. The interval between inhalations was about 15 min.

On the first day the patient underwent all baseline examinations, methacholine testing, and serial lung function measurements to ensure a stable condition. On the 2nd day inhalation challenge with Pt salt was performed. Serial methacholine testing, exhaled nitric oxide (eNO; Niox Mino, Aerocrine, Solna, Sweden) and differential cell counts in induced sputum [Raulf-Heimsoth et al., 2011] were assessed before and about 24 hr after challenge as secondary outcomes. Sputum analysis and eNO measurements were repeated 48 hr after the challenge.

This case study was part of a study about noninvasive methods during specific inhalation challenges. It was approved by the ethics committee of the Ruhr-University Bochum and the patient gave written informed consent.

CASE REPORT

The 52-year-old laboratory technician worked in the laboratory of a precious metals refinery with exposure to various precious metals including Pt and palladium and irritants since 12 years. The work had been terminated due to allergic symptoms about 9 months prior to the examination.

The patient reported a history of mild atopic dermatitis with predominant involvement of the hands and forearms since adolescence. An exacerbation occurred about 3 years previously, again with predominant involvement of the hands and forearms. Two years later the patient developed work-related cough and runny nose. Soon after exposure cessation she was free of airway symptoms, and hand eczema had subsided almost completely. A diagnosis of atopic dermatitis and contact sensitizations to ammonium tetrachloroplatinate, palladium chloride, and cobalt chloride was previously made by a dermatologist (ammonium tetrachloroplatinate and palladium chloride: + reactions after 48, 72, and 96 hr; cobalt chloride: + reactions after 72 and 96 hr), but a causal link between skin disease and positive patch test reactions was not assumed. IgE-mediated sensitization to tree pollen without asthma was diagnosed by a pneumonologist.

At the time of the examination the patient was without allergic symptoms and did not use any medication. Physical examination of the patient did not show any abnormal findings, and there was neither atopic dermatitis nor hand eczema. Blood count as well as blood chemistry were normal. Total IgE was 140 kU/L (slightly elevated). Lung function was normal, and bronchial hyperresponsiveness was absent. SPT showed a 5 mm wheal with tree pollen, but no reaction with sodium hexachloroplatinate and palladium chloride. In contrast, repeated patch testing gave positive reactions with ammonium tetrachloroplatinate and palladium chloride already after 24 and 48 hr (ammonium

tetrachloroplatinate: +++/+++, palladium chloride: ++/++ and a + reaction with cobalt chloride after 48 h (later readings see above). Inhalation challenge with sodium hexachloroplatinate was performed because the patient reported work-related cough. The challenge produced symptoms (cough, itching of the throat, dyspnea) which started after the second step, but testing was not terminated earlier than after the ninth step with a maximal concentration of 3.9 $\mu\text{g/ml}$ (a cumulative dose of 235 ng) due to symptoms. Although a significant asthmatic reaction was not seen, a decrease of FEV₁ of 8% from baseline and a decrease of the forced midexpiratory flow (FEF₅₀) from 3.2 to 2.3 L/s after 24 hr (maximal reaction) indicated an airways reaction. Airway symptoms were maximal about 24 hr after challenge testing and improved afterwards without medication. Whereas bronchial hyperresponsiveness was not documented at baseline, this was the case 24 hr after the challenge with a PD₂₀FEV₁ of 270 μg methacholine. eNO increased from 15 ppb to 86 ppb (24 hr) and 125 ppb (48 hr) and sputum eosinophils increased from 1% (0.7×10^5) to 10% (9×10^5) 48 hr after challenge. Sputum neutrophils increased from 34% to 56% 24 hr after challenge.

DISCUSSION

The major finding of this case study is an eosinophilic airways reaction to Pt salts after challenge in combination with a negative SPT, but a positive patch test.

Whereas the results of the secondary outcomes and thus an eosinophilic airway reaction are unequivocal, it may be questioned whether the patient had asthma. The patient reported work-related cough, but no previous variable shortness of breath. Shortness of breath during the challenge may also be interpreted by psychological factors. Due to airways symptoms challenge testing was terminated after a concentration of 3.9 μg Pt salt per ml, and the dose was not increased on the second day because the secondary outcomes indicated a positive result. However, changes in spirometry and the development of bronchial hyperresponsiveness corroborate the view that the patient would have developed a significant asthmatic reaction with higher allergen doses.

The discussion about changes in sputum cell counts during inhalation challenges focusses on eosinophils [Quirce et al., 2010]. Increases of neutrophils in induced sputum after inhalation challenges with diisocyanates were reported [Lemiere et al., 2002], but the increase was moderate and was also observed in pulmonary nonresponders and non-exposed controls [Raulf-Heimsoth et al., 2013]. Increased sputum neutrophils after inhalation challenges with environmental high-molecular allergens were not reported [Gauvreau et al., 1999]. In this patient we observed a large increase of eosinophils (10-fold), but only a small relative increase of neutrophils (1.6-fold) after inhalation challenge.

Whether neurophilia represents a feature of a specific mechanism in this case remains unknown.

A false negative SPT in this patient is not probable as the test was performed in duplicate and according to internationally accepted recommendations. We cannot exclude that the discrepant results of a negative SPT_{Pt} and a positive patch test were due to the fact that different Pt salts were used. However, both test materials are standardized and SPT testing with Pt salts with similar halide ligand numbers yielded only minor differences [Cristaudo et al., 2005].

There is little information about patch testing in workers with exposure to Pt salts. Positive patch tests with Pt salt were described in four out of 153 refinery workers. Two of the patch test positive workers had hand eczema, but only one non-asthmatic worker with hand eczema was SPT_{Pt} negative [Santucci et al., 2000]. Thus workers with airway disease, negative SPT_{Pt}, but positive patch test with Pt salts as in this case have not been described previously.

The causal link between a positive patch test suggesting allergic contact sensitization and the airways reaction remains hypothetical. Whether patch testing is of additional diagnostic value in Pt salt induced airway disease can only be evaluated by testing a number of similar patients (with positive inhalation challenge but negative SPT_{Pt}), but such data will be difficult to obtain due to the sparseness of such cases. Similar cases of occupational asthma associated with positive epicutaneous tests, but negative SPT were described for persulfates [Harth et al., 2006; Polychronakis et al., 2013], chromium [Olaguibel and Basomba 1989; Park et al., 1994] and paraphenylene diamine [Helaskoski et al., 2014].

Positive challenges with Pt salts were described in three subjects who converted from a positive to a negative SPT_{Pt} after exposure cessation [Merget et al., 1994]. It cannot be excluded that the patient reported here lost SPT_{Pt} reactivity after a period of nine months since exposure cessation. However, the simultaneous occurrence of exacerbation of skin disease and rhinoconjunctivitis, the absence of asthmatic symptoms which are the main manifestation of immediate type Pt salt allergy, and the persistence of symptoms after the inhalation challenge until the next day argue for an atypical, non-immediate type airway reaction. Such late reactions are known from two case reports with negative SPT_{Pt} [Pepys et al., 1972], but this is the first case which provides information about an eosinophilic mechanism in combination with a positive patch test.

Patch tests were positive with ammonium tetrachloroplatinate, palladium chloride and cobalt chloride. It is known that subjects with Pt salt allergy occasionally show concomitant immediate type sensitizations to palladium, whereas the association with cobalt sensitization is unknown. Sera from Pt-sensitive, palladium-exposed workers also elicited a positive passive cutaneous anaphylaxis response to palladium in subhuman primates [Biagini et al., 1985]. In a study of 306 South African refinery workers, 38 had positive

SPT_{Pt}. Out of these one subject was positive to palladium and six subjects to rhodium salts [Murdoch et al., 1986]. Also a case with positive patch tests to both metals has been described [Santucci et al., 2000]. Generally, these reactions are interpreted as cross-sensitizations. Pt salts are considered the primary sensitizer because sensitizations to palladium were less pronounced and exposure to palladium was estimated to be lower. Both arguments were suitable also in this case.

The presented case has important implications for surveillance of workers with exposure to Pt salts. Usually the surveillance program comprises medical history, spirometry and SPT_{Pt}. As only SPT_{Pt} has high specificity, the plant physicians rely more on this test than on the other tools. This case demonstrates that Pt salt allergy may occur in spite of a negative SPT_{Pt}, thus workers with exposure to Pt salts and work-related airway symptoms should be submitted to further evaluation by inhalation challenge and patch testing. We recommend to diagnose patients with suspected occupational allergic airways symptoms due to metals and further low molecular weight substances in a setting where both immediate- and delayed-type hypersensitivity can be investigated.

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