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by [Ørbaek P](#)

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Allergy to the complex salts of platinum

A review of the literature and three case reports

by Palle Ørbaek, MD¹

ØRBAEK P. Allergy to the complex salts of platinum: A review of the literature and three case reports. *Scand j work environ health* 8 (1982) 141—145. The article presents three cases, two certain and one suspected, of allergy to the complex salts of platinum. A review of the literature, with special reference to the possible immunological mechanisms involved, and the possible diagnostic tests are given. The use of platinum antitumor compounds and their allergenic potency are briefly described. Finally, proposals for preemployment examinations and for regular medical checkups of exposed workers are given.

Key terms: immunoglobulin E-mediated metal allergy, occupational asthma, platinosis, platinum antitumor compounds.

Platinum is one of the six elements of group VIII in the periodic system. It occurs in nature together with the other members of the group and with the sulfides of nickel, copper, and iron (5, 6, 7). Floating and smelting the ore produces a mass rich in the group VIII metals and ready for refining, which is principally the same process for the primary extraction of as for the reuse of platinum. During the refining process complex halogenated salts of platinum are always precipitated (5, 6, 7, 11). The mixture of metals is dissolved in aqua regia. After the precipitation of gold and coexisting metals, the solution is treated with ammonium chloride to precipitate platinum as the yellow complex salt ammonium hexachloroplatinate $[\text{PtCl}_6(\text{NH}_4)_2]$ (5, 6, 7, 11). Calcination produces a yellow crude platinum sponge, which is subjected to further refining when redissolved. Finally the pure sponge is condensed to metallic platinum by melting at a high temperature. The dry yellow salt in the sponge is apt to escape into the ambient atmosphere in high concentrations (7).

Metallic platinum is used in the chemical industry as a catalyst, in the electrical

industry, because of its great resistance to corrosion, in dentistry, in jewellery making, and for many other purposes (6, 11). The complex salts of platinum are used in the chemical, photographic, and electroplating industry (6, 7). In the last decade some complex platinum compounds have been tried as antitumor agents (1, 8). This procedure has aroused general clinical interest in their possible tendency to sensitize humans.

Exposure to the complex salts of platinum, especially ammonium hexa- and tetrachloroplatinate, may elicit anaphylactic reactions such as conjunctivitis, rhinorrhea, sneezing, cough, asthma, and urticaria (2, 4, 7, 11, 12, 16, 18). Anaphylactic shock can be provoked by a skin test (4, 9, 11) and by the injection of platinum antitumor agents (8).

The suspicion that a worker has been sensitized is awakened by his work history, in which he can tell exactly at which stage of the refining process the symptoms occur (5, 7). When removed from exposure, the sensitized worker will be relieved of his symptoms (5).

To confirm the diagnosis of hypersensitivity to complex salts of platinum, a skin test is performed, usually as a prick test (2, 5, 15, 18), but even epicutaneous application may be used (18). Inhalation of the dust of ammonium hexachloroplatinate can be used for a definite confirmation of the diagnosis.

¹ Department of Occupational Medicine, University Hospital of Malmö, Sweden.

Reprint requests to: Dr P Ørbaek, Department of Occupational Medicine, University Hospital of Malmö, S-214 01 Malmö, Sweden.

Case reports

Case 1 concerned a 62-year-old man with no known atopy in his family. He smoked 50 g of pipe tobacco a week. In 1920 he suffered from tuberculosis of the spine and secondary thoracic kyphosis, and he has suffered from ischemic heart disease since 1970 and from hypertension treated with a thiazide since 1978. In 1979 he had a myocardial infarction.

He had no history of allergy before 1969, when he was employed by a metal refinery and began to refine old gold-platinum jewellery. After working there for a couple of years he began to feel irritation in his eyes and tightness in his chest. He observed that the symptoms always occurred after working with yellow "platinum powder" (ammonium hexachloroplatinate); this occurrence was followed in the evening by extreme tiredness. Year by year the symptoms became worse with wheezing after about 30 min of exposure. Contact with the platinum sponge was occasionally followed by urticaria.

Auscultation of the chest in January 1980 revealed a few ronchi. Spirometric findings were vital capacity (VC) 4.61 l, total lung capacity (TLC) 8.70 l, volume of first second of a forced expiration ($FEV_{1.0}$) 2.44 l, $FEV_{1.0}/VC$ 53 %, maximal voluntary ventilation (MVV) 82 l, and volume of trapped gas (VTG) 304 ml. There was a small increase in the closing volume and a slight reduction of diffusion capacity. Chest radiographs and computerized tomography demonstrated a pleural density on the right apex and a few emphysematous bullae. The results of the blood analyses were erythrocytes $5.8 \times 10^{12}/l$, leucocytes $8.8 \times 10^9/l$, eosinophils $169 \times 10^6/l$, differential normal, total immunoglobulin (Ig) E 78 ku/l (< 20 ku/l no atopy, > 100 ku/l atopy possible).

In the skin test epicutaneous application of 0.1 ml of 0.1 % platinum chloride (PtCl) produced an erythema (20×25 mm) and a wheal (6×6 mm) and systemic reaction with rhinorrhea, cough, and dyspnea after 20 min. There were no reactions to tests with palladium chloride or potassium dicyanoaurate.

Case 2 comprised a 38-year-old man with no known atopy in his family. He smoked 30–40 cigarettes a day. During

military service in 1961 he suffered from rhinitis after exposure to grass. *Pustolosis plantaris* was diagnosed in 1977.

In 1962 he was employed by a metal refinery where he was occasionally exposed to platinum salts. In 1963 he got hand eczema, apparently without urticaria. No relation to his work was suspected. During 1970–1978 he worked in a laboratory where he was not exposed to platinum salts; during this period he was symptom-free. In May 1979 he started work at the same refinery as the patient represented in case 1 and assisted him with the refining process. After a month his eyes began to itch, and after four months urticaria made its first appearance. In October 1979 he got acute urticaria all over his body and a severe cough that prevented him from smoking the next 3–4 h. He was given symptomatic treatment and was later examined at the Department of Occupational Dermatology. Skin tests revealed contact allergy to p-phenylenediamine and an immediate reaction to platinum chloride with wheal and flare. There was no reaction to palladium chloride or potassium dicyanoaurate. Exposure was discontinued and the symptoms ceased.

A clinical examination in April 1980 showed nothing remarkable. The results of spirometry were VC 3.85 l, TCL 5.60 l, $FEV_{1.0}$ 3.55 l, $FEV_{1.0}/VC$ 92 %, MVV 145 l, VTG 164 ml. The lung compliance was subnormal, and the diffusion capacity was reduced but increased on hyperventilation, indicating capillary damage. Control spirometry in July 1981 was status quo. Chest radiographs were normal. The results of the blood analyses were erythrocytes $5.0 \times 10^{12}/l$, leucocytes $8.5 \times 10^9/l$, eosinophils $333 \times 10^6/l$, differential normal, total IgE > 800 ku/l. A skin test in May 1980 gave no reaction.

Case 3 involved a 58-year-old man with no known atopy in his family. He smoked 50 g of pipe tobacco and 20 cigarettes a week. Examinations in 1964, 1972, and 1976 because of hemophysis produced no explanation. Mild, stable diabetes mellitus was diagnosed in 1977; later that year he was treated for a mild depression.

As a foundry worker he was exposed to silica dust in 1936–1968. The next 4 a

he worked in an office. In 1972 he too started work at the same refinery as the patient in case 1; there, he was heavily exposed to ammonium hexachloroplatinate. After having worked for six months he began to suffer from rhinorrhea, cough, and dyspnea, always provoked by the dust of the platinum sponge. In 1976 he was placed on the sick list because of wheeze and dyspnea. After discontinuation of the exposure, his symptoms disappeared. He never suffered from a rash.

Auscultation of his chest in October 1977 revealed a few ronchi. The results of spirometry were VC 3.57 l, TLC 6.09 l, FEV_{1.0} 2.36 l, FEV_{1.0}/VC 70 %, MVV 64 l. The gas distribution was demonstrated to be irregular. Lung compliance was reduced to 0.148 l/cm H₂O, and the diffusion capacity was half of normal. Chest radiographs showed lung silicosis stage I. An electrocardiogram disclosed sinus rhythm, right axis deviation, and pulmonary p-waves. The results of the blood analyses were erythrocytes $5.4 \times 10^{12}/l$, leucocytes $7.4 \times 10^9/l$, eosinophils $75 \times 10^6/l$, differential normal, total IgE 15 ku/l. A skin test in April 1980 gave no reaction.

He was granted a disability pension because of respiratory insufficiency. For confirmation of his suspected allergy an inhalation provocation test was needed, but impossible to perform.

Discussion

Hypersensitivity to the complex salts of platinum has been known since 1911 (4, 7, 11, 12, 16, 17, 18), but apparently never reported in the Scandinavian literature.

Roberts (16) used the term "platinosis," which is semantically unfortunate because it suggests a pneumoconiosis, but a chronic fibrosing lung disease of this etiology has not been reported (5).

The risk of an exposed worker becoming sensitized is approximately 60 % (7, 16, 18). The duration of exposure before the first symptoms is usually three months to three years (11, 17, 18), sometimes even less than three months (5, 16). The heaviest exposure is found in refineries, and therefore also the greatest risks of sensitization. Workers can be sensitized by splashes of the salt solutions, but the most dangerous step in the process is work with

the dry yellow platinum sponge that may result in a high concentration of ammonium hexachloroplatinate in the ambient atmosphere, especially if the exhaust ventilation is insufficient (7). The hygienic standard of the workshop where the reported patients worked and their work routines were not reasonably safe. Our safety engineer estimated the air concentration of ammonium hexachloroplatinate to be well above the American threshold limit value of 0.002 mg/m³, but analytical problems made it impossible to get an exact measure of the actual air concentration. Two persons had worked with the process for 3 a before 1969, when the man reported in case 1 replaced them. According to the union safety officer they had not suffered from any allergic reaction. During 1979 another two persons were exposed for a period of six months without any disability being reported. The refining laboratory was then closed.

The disease meets the following criteria for an allergic etiology: (i) asymptomatic interval (5, 11), (ii) only a portion of the exposed subjects reacting (5), (iii) reaction to exposure to minimal air concentrations (4, 15), (iv) symptoms more likely to appear in atopic individuals (5, 11, 16), (v) hyposensitization successful (9), and (vi) specific antibodies of the IgE type demonstrated (3, 13, 14).

Nonspecific histamine release by the platinum salts has been found in experimental animals (11). In humans the demonstration of passive cutaneous anaphylaxis by heat-stable antibodies S-TS IgG, and IgG4 (10) and by heat-labile antibodies (IgE) in the Prausnitz-Küstner test has been successful (4, 13). Hexachloroplatinate-mediated histamine release from washed leucocytes of sensitized workers is significantly greater than from the leucocytes of nonexposed subjects (13, 18). Use of the radioallergosorbent test (RAST) has revealed specific IgE antibodies to the complex chloroplatinates (3, 14, 18). The allergenic potency of the platinum salts is determined by their electric charge and the number of reactive halide ligands. Hexa- and tetrachloroplatinates are the most potent (1, 2, 14). No anaphylactic reactions to metallic platinum or the chlorides of the other members of group VIII have been reported (4, 7, 9).

Lung physiological studies of sensitized workers have demonstrated immediate, late, and dual asthmatic reactions, all of which can be inhibited by the inhalation of cromolyn sodium (Lomudal®) before the inhalation provocation test (15). This effect of cromolyn sodium suggests that both the immediate and late reactions are provoked by IgE-mediated mast cell degranulation.

The immunological reaction reviewed can be used for diagnostic purposes (15). It is easy to perform a skin test with platinum chloride or an even more sensitive test with hexachloroplatinate, with either an epicutaneous or a prick test technique (2, 18). Instillation of a platinum salt solution in the nose is another simple possibility (15). If necessary inhalation of dust from a mixture of ammonium hexachloroplatinate and lactose can be safely done (15). RAST discs are not yet commercially available, and the Praustnitz-Küstner test should not be necessary for clinical diagnosis. Since several episodes of anaphylactic shock have been reported (4, 9, 12, 18), adrenaline must always be available during the tests.

Treatment

To relieve a patient from symptoms, avoidance of exposure is the only definite solution. If prolonged exposure is permitted by the use of an effective drug like cromolyn sodium, there is considerable risk of a more generalized asthmatic condition, which would mean chronic disability to the patient due to development of an unspecific bronchial hyperreactivity. Hyposensitization has been successful, but cannot be recommended because of a serum sickness-like complication (9). When the use of platinum compounds in the treatment of cancer is complicated by anaphylactic reactions, the great difference in their allergenic structures could make it possible to switch to a non cross-reacting substance (1, 2, 8).

Conclusions

Sensitization to the complex salts of platinum is a considerable risk for exposed workers. For prevention rigorous hygienic measures should be undertaken. High

standards of engineering to establish enclosure of the process as far as possible are the most important. Contact with the dusty yellow ammonium hexachloroplatinate should be avoided through the installation of sufficient air exhaust. The refinery workers should periodically be given information about platinum salt allergy, as well as instruction about the personal means of prevention of keeping the workshops clean and having a high standard of personal hygiene (5, 7, 17). Any potential employee who may be exposed to the complex salts of platinum should be examined by medical history, prick tests to common allergens, radiography, and spirometry to exclude atopy or any previous chest disease (5, 11, 16). If the worker has been previously exposed, a prick test with platinum salts should be done.

During employment all workers at risk should regularly be checked by spirometry and, eventually, by prick tests. The intervals between the medical checkups should be decided upon after an evaluation of the degree of exposure.

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