

Severe hypersensitivity reaction to injectable Gallium 67 in a worker exposed to silica

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Gallium 67 scintigraphy is employed in the evaluation of workers with possible pneumoconiosis. To our knowledge, however, a severe hypersensitivity reaction following the intravenous injection of Gallium 67 has not been described. We report the case of a worker chronically exposed to silica who developed an allergic cutaneous and severe articular reaction following the injection of Gallium 67 while being investigated for possible silicosis. Hilar adenopathy was noted on the chest roentgenogram and, retrospectively, circulating immune complexes were found in the patient's serum. The presence of a positive prick skin test to benzyl alcohol suggests that this preservative caused the hypersensitivity reaction.

Key words: hypersensitivity reaction; injectable Gallium 67; silica; occupational; exposure.

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Gallium (Ga) 67 is a radiopharmaceutical product used in nuclear medicine to study inflammatory diseases. It is employed in the investigation of silicosis because an abnormal uptake in the lungs may herald progressive interstitial lung disease (1).

Side-effects of Ga 67 are rare. One allergic reaction in 300 injections was reported by the company marketing the product. A review of the literature reported 16 adverse reactions in the United States (2). "Nausea, severe itching, erythema and rashes, and hypersensitivity or allergic reactions" have been reported; all seemed mild.

In patients with silicosis, abnormalities in cellular and humoral immunity have been reported. Chronic exposure to silica has also been shown to affect local immunity (3, 4). We report the case of a worker exposed to silica who developed urticaria and severe articular symptoms following the injection of Ga 67 while being investigated for possible silicosis. The results of skin tests suggest that benzyl alcohol, used as a preservative in Ga 67, was the causative agent. Whether prior exposure to silica affected the length or severity of the reaction is left to speculation. The political implications of this adverse reaction are presented.

Case report

A 38-year-old man had been exposed to high concentrations of almost pure silica as a welder in a mine for 15 years. His father had died of unknown lung disease after working in the same mine. He had no pertinent medical history. His chief complaints were progressive dyspnea over the last few years and a cough with daily production of phlegm. He had smoked 20 cigarettes per day for 11 years, was not taking any medication and did not have any allergies.

A prominence of both hila on a routine chest roentgenogram led to an evaluation for possible silicosis. He received for the first time an intravenous injection of Ga 67 and returned home.

In the evening, on the day of the injection, he experienced severe itching and joint pains. The following day, he visited the emergency room for a rash over his entire body. The diagnosis of a severe urticarial reaction following the injection of Ga 67 was entertained. Ten days later, the joint pains increased. They were symmetrical and involved mostly the fingers, hands, elbows, shoulders and knees. Cutaneous signs disappeared progressively but joint pains

persisted for about 5 months. The pains were so severe that the patient was hospitalized, an investigation for possible collagen vascular disease was performed, and the patient was treated with systemic steroids.

Complete blood count and ECG were normal, the sedimentation rate was 18 mm/h, and a tuberculin test was negative. Chest roentgenogram showed bilateral hilar adenopathy but no interstitial changes. Pulmonary function tests showed a mild restrictive impairment with a forced vital capacity of 70% of predicted, forced expiratory volume in 1 s of 66% of predicted, and total lung capacity of 74% of predicted. Lung compliance was $0.171 \times \text{cmH}_2\text{O}^{-1}$. The Ga 67 scan showed an increased uptake in both hila, especially on the right. Mediastinoscopy revealed silicotic lymph nodes. Serum antinuclear antibodies (ANA) and rheumatoid factor were negative.

Complementary tests

Laboratory tests were repeated 3 years later, on low-dose steroid treatment. These tests included sedimentation rate, serum immunoglobulins and protein electrophoresis, C3, C4, CH100, ANA and circulating immune complexes. All were normal, except for an increase in circulating immune complexes, noted by the C1q method. IgG, IgA and IgM were normal. Skin prick and patch tests are presented in Table 1; the patient had a positive skin prick test to benzyl alcohol.

Patch tests were performed 3 years after the alleged hypersensitivity reaction to Gallium 67. Substances studied by patch-test were balsam of Peru, fragrance mix, benzyl alcohol, and citrate of sodium. The test results were determined 48 h following application of an occlusive dressing. Prick tests were performed 2 weeks after the patch tests. Allergens studied by prick test were: cat, dog, horse, feathers, dust, dust mite, aspergillus, trees, grass, ragweed and molds (Hollister Stier). Only positive results and negative pertinent results are presented.

Table 1. Results of skin tests in a worker exposed to silica

Patch tests*	Prick tests**
Balsam of Peru: neg.	Benzyl alcohol (7 mm): pos.
Fragrance mix: neg.	Citrate of sodium: neg.
Benzyl alcohol: neg.	
Citrate of sodium: neg.	

* Standard dilutions: balsam of Peru 25%, fragrance mix 8%, benzyl alcohol 5%, citrate of sodium 0.2% and 1%.

** 11 common pneumoallergens at standard dilutions, benzyl alcohol 5%, citrate of sodium 0.2% and 1% in phosphate buffered saline.

Discussion

This worker presented with urticaria and articular symptoms following the intravenous injection of Ga 67 while being investigated for possible silicosis. The worker had bilateral hilar adenopathy (silicotic lymph nodes) which was consistent with stimulation of local immunity. He also had retrospective signs of abnormal regulation of his systemic immunity with circulating immune complexes. The urticarial reaction developed within 12 h of the injection of Ga 67 and the joint symptoms, one day after the injection.

The signs and symptoms are compatible with a hypersensitivity reaction following the intravenous injection of Ga 67. This may have been a rare, isolated reaction, but it is interesting to question whether prior exposure to silica, which can modify several aspects of immunity, may have affected the onset or the length of this immune reaction.

In animals and in humans, silica has been shown to modify several aspects of cellular immunity. An increase in alveolar macrophages retrieved in lung lavage (3), complement activation in the lungs (4), and an increase in circulating T lymphocytes have been described. Silica can also affect humoral immunity in man by causing an increase in circulating IgG and IgM, antinuclear antibodies, rheumatoid factor, and circulating immune complexes (3, 4). An association has also been shown between silicosis, autoimmune diseases, and tuberculosis (8). A prolonged exposure to silica may affect immunological reactions to sensitizing agents. However, hypersensitivity reactions in workers exposed to silica or suffering from silicosis have not been reported.

The signs and symptoms presented by the worker could conceivably be explained by other illnesses. Influenza, for example, could explain the arthralgias and weakness but no epidemic was reported in the mine at that time. The worker was not taking medication, and retrospectively we did not find any toxic substance in the workplace at the time of the symptoms.

Injectable Ga 67 contains 74 MBq Ga 67, sodium chloride, sodium citrate and 9 mg/ml of benzyl alcohol. Gallium and its derivatives are toxic at high doses. The toxicity of Ga 67 is mostly due to the radioactivity emitted and absorbed with no allergic reactions reported. Sodium citrate can cause allergic reactions but the patch and prick skin tests were negative in this patient.

Benzyl alcohol, used as a preservative in Ga 67, is known to cause toxicity and hypersensitivity at injectable concentrations (2). Weakness, malaise and skin rashes (7), nausea and angioedema, positive patch tests (5), exacerbation of asthma (6) and, finally, cutaneous reactions (9) have all been reported. An immune complex mediated hypersensi-

tivity reaction to the benzyl alcohol found in injectable Ga 67 may explain the signs and symptoms reported by this patient.

It seemed unethical to re-expose the worker to intravenous benzyl alcohol because of the severity and length of the reaction. The political implications of this reaction have been important. Two workers from the same mine reported severe joint symptoms after injection of Ga 67. Interestingly, both workers had positive patch tests to fragrance mix and/or balsam of Peru, which cross-react with benzyl alcohol (5). These complaints have led the local and provincial trade unions to oppose the use of Ga 67 in the investigation of silicosis.

In conclusion, we have presented the case of a worker heavily exposed to pure silica with abnormal local (hilar adenopathy) and systemic (immune complexes) immunity. This worker developed a severe hypersensitivity reaction following the intravenous injection of Ga 67. Skin tests suggest that benzyl alcohol, contained as a preservative in Ga 67, may have caused these reactions; whether prior exposure to silica may increase the incidence or the severity of hypersensitivity reactions to Ga 67 remains unanswered.

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