

fore returned the following spring with freshly collected sap, which was used, undiluted, for testing. She had a 1 + reaction. A control subject, not allergic to tree pollen, showed no reaction on skin testing with the sap.

DISCUSSION

This patient's urticarial reaction likely resulted from ingestion of raw maple sap and is probably related to her tree pollen allergy. She clearly produces tree pollen-specific IgE, which then recognizes cross-reacting heat-labile antigenic determinants contained in the fresh fruit and nuts of the trees. This explains her clinical reactions to these foods.¹⁻⁵ Because the relevant antigens are heat-labile, she has no reaction to the cooked fruit. The raw tree sap may contain the same or similar heat-labile allergens as the pollen and fruit. This would explain this patient's reaction to the sap, as well as her ability to tolerate maple syrup. The sap is extensively boiled to produce the final maple syrup product. Any heat-labile antigens originally present in the sap would be denatured during boiling, so that the syrup itself would cause no reaction.

Although this patient's reaction was limited to urticaria, it was clearly systemic in nature. Assuming an underlying IgE-mediated mechanism, the possibility of full-blown anaphylaxis in an appropriately sensitized individual can readily be appreciated.

Manufacture of maple syrup is not a uniquely

Canadian pastime; it is also widely practiced in the northeastern United States. Ingestion of raw sap is commonly performed to estimate its sugar content; it may occur unintentionally if partially processed sap or syrup is "taste-tested." Such exposures are potentially hazardous in individuals with allergy to tree pollen or nuts. These patients should therefore be advised to avoid ingesting raw maple sap.

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Anaphylaxis to methotrexate: A possible IgE-mediated mechanism

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Methotrexate is a folic acid antagonist used in the treatment of several neoplasms and inflammatory diseases. Though it is commonly used, few systemic anaphylactic reactions have been described, the majority of which were produced by

high-dose methotrexate.¹⁻³ The mechanism implicated is not clearly defined. Some authors suggest the possibility that an immunologic mechanism is responsible for these reactions.

This report describes an anaphylactic shock reaction in a patient receiving low-dose methotrexate. Studies performed suggest an IgE-mediated hypersensitivity mechanism.

CASE REPORT

A 60-year-old woman with a diagnosis of breast cancer was treated with partial mastectomy, radio-

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therapy, and six cycles of chemotherapy (cyclophosphamide, 1260 mg; methotrexate, 75 mg; and 5-fluorouracil, 1080 mg) with good tolerance. She was admitted to our hospital for her seventh cycle of chemotherapy. Within a few minutes of the start of methotrexate infusion, the patient complained of itching in palms and soles, and a generalized rash, hypotension, loss of consciousness, and cardiopulmonary arrest developed. She was treated with fluidotherapy, adrenaline, intravenously administered corticosteroids, dopamine, and mechanical ventilation. Assistance in the intensive care unit was required for 24 hours.

A study was carried out to investigate the mechanism of the reaction. Skin prick test with methotrexate (Lederle Laboratories, Pearl River, N.Y.) was performed at a concentration of 10 mg/ml. Positive and negative skin test controls were histamine (10 mg/ml) and saline solution, respectively. The same test was performed on 16 patients with cancer and 10 atopic patients, who were otherwise healthy, and served as control subjects. Five of the patients with cancer had been previously treated with methotrexate.

Total IgE was measured by microparticle enzyme immunoassay with the IMx system (Abbott Diagnostics, Chicago, Ill.) 2 days, 1 month, and 7 months after the anaphylactic reaction. We tried to detect *in vitro* specific IgE by RAST with three different procedures: binding methotrexate to a nitrocellulose membrane, linking methotrexate-human serum albumin and methotrexate-IgG to activated paper discs, and linking MTX 6B-epoxy-activated Sepharose (Pharmacia Diagnostics AB, Uppsala, Sweden). Histamine release test was performed with the Pharmacia Histamine RIA 50 technique.

RESULTS

An immediate positive response was obtained in the methotrexate prick test with a 15 × 10 mm wheal (histamine, 8 × 6 mm; saline solution, 0 mm) and a 20 × 18 mm flare. Prick test results were negative in all control subjects. Prick test results remained positive with a 10 × 9 mm wheal (15 × 17 mm flare) when performed 7 months later.

Measurement of total IgE was 52 IU/ml at 2 days, 28 IU/ml at 1 month, and 19 IU/ml at 7 months after the reaction. No *in vitro* specific IgE was detected. Histamine release curve showed no differences between patient and control subjects. The results were even higher in the control subjects than in the patient, as can be observed in Fig. 1.

DISCUSSION

We described the case of a patient who experienced anaphylactic shock in response to low-dose methotrexate. Twelve anaphylactic reactions to methotrexate have been previously reported. A

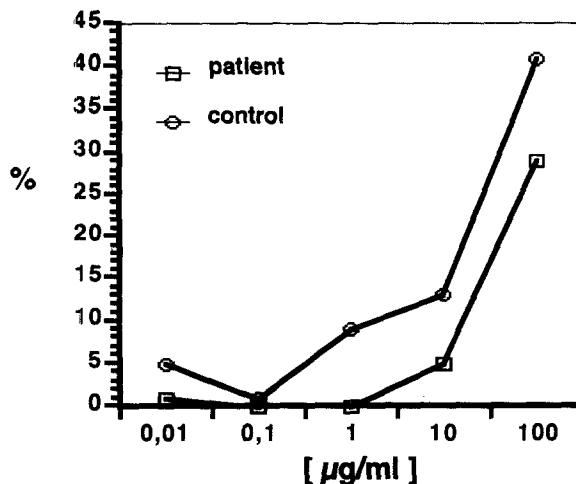


FIG. 1. Histamine release curve with methotrexate.

low dose was used in only one case, as in our patient.⁴

Goldberg et al.² reported two cases of acute reaction in patients receiving the combination of methotrexate and *Bacillus Calmette-Guérin*. They suggest that *Bacillus Calmette-Guérin* could potentiate the development of an immune reaction to methotrexate or to preparation contaminants. Serum antibodies to methotrexate were not found.² Da Costa et al.⁵ isolated protein-methotrexate-IgG complexes in the serum of patients receiving high-dose methotrexate therapy. Although these authors suggest that immunocomplexes could be responsible for hypersensitivity symptoms, this mechanism would justify a semi-acute reaction rather than an acute one. Cohn et al.⁴ report a case of anaphylaxis in a patient receiving 60 mg of methotrexate. The development of symptoms after intradermal injection of methotrexate suggests a hypersensitivity reaction. The prick test result was negative in this case. As in our patient, the investigators could not detect *in vitro* specific IgE by RAST. This can be explained by technical difficulties in binding methotrexate to a solid phase in order to perform the RAST testing, or MTX itself may not be capable of immunologic reactivity if not complexed with another protein, as has been suggested.⁵

The clinical results of the investigations carried out in our patient strongly suggest that the mechanism of the anaphylactic shock reaction to methotrexate was a type I IgE-mediated immune reaction. Of note in this case report is the low dose used and the severe reaction experienced by our patient. To our knowledge, this is the first case reported in the literature in which *in vivo* IgE binding to methotrexate occurred. The negative

results obtained in the control subjects support the specificity of this finding.

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Report of successful desensitization to itraconazole

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Itraconazole, a triazole antifungal agent, has been used effectively in both immunocompromised and immunocompetent patients for the treatment of histoplasmosis, blastomycosis, coccidioidomycosis, paracoccidioidomycosis, sporotrichosis, candidiasis, and infection with several *Aspergillus* species.¹ In patients infected with human immunodeficiency virus, itraconazole has been shown to be effective in both primary treatment and suppressive therapy of histoplasmosis. In general, itraconazole is well tolerated by most patients. The most common adverse reactions to itraconazole are primarily gastrointestinal and include nausea, flatulence, anorexia, and a mild increase in transaminases. Itraconazole has been reported to occasionally cause a generalized maculopapular rash.² Indeed, a patient who had a diffuse maculopapular rash after taking itracona-

TABLE I. Itraconazole desensitization schedule

Dose*	Oral dose of itraconazole (mg)†
1	1
2	2
3	4
4	8
5	16
6	32
7	64
8	128
9	200

*Interval between doses: 30 minutes.

†The itraconazole capsules were crushed; and the contents of the capsule were weighed, mixed in applesauce, and given to the patient.

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zole for 4 months has been reported. The drug eruption disappeared after discontinuation of the itraconazole and reappeared after the drug was reintroduced.² We report a case of a pruritic rash related to itraconazole and subsequent successful desensitization to this medication.

CASE REPORT

A 67-year-old woman was being treated with itraconazole for culture-positive *Coccidiomycosis immitis* tenosynovitis of the left wrist. The patient was not immunocompromised and had no evidence of systemic fungal infection. She was receiving no other medications. Small, discreet, pruritic erythematous papules