
An unproven technique with potentially fatal outcome: provocation/neutralization in a patient with systemic mastocytosis

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Objective: To describe the risks associated with use of an unproven technique, provocation/neutralization, in diagnosis and treatment of a putative “food allergy” in a patient with systemic mastocytosis.

Methods: A case report of a 68-year-old woman with mastocytosis is reported. The patient was interviewed, examined, and all medical records were reviewed. Photos were taken, and skin and colonic biopsies were performed.

Results: The patient was previously diagnosed with urticaria pigmentosa but also had significant diarrhea that was well-controlled by oral cromolyn sodium. She saw a physician who practiced provocation/neutralization and was told that food allergies were the cause of her gastrointestinal symptoms. She was placed on “neutralizing” injections of milk and wheat, but experienced flushing, palpitations, and lightheadedness with syncope upon injections into her thigh, which is a skin area highly involved by visible lesions of cutaneous mastocytosis. Later evaluation revealed increased numbers of mast cells in her colonic mucosa as well as confirmation of cutaneous mastocytosis.

Conclusions: The patient’s previous history of urticaria pigmentosa, orally communicated by the patient, documented in medical records, and easily visible on physical examination, was discounted by a practitioner of an alternative and unproven medical treatment, provocation/neutralization. She subsequently had potentially life-threatening reactions to “provocative” skin testing and “neutralizing” injections. Patients with systemic mastocytosis are at risk for significant mast cell mediator release during immunotherapy, conventional or alternative.

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INTRODUCTION

Cutaneous mast cell disorders in adults, which may reflect a disorder of the bone marrow, include urticaria pigmentosa, diffuse cutaneous mastocytosis, and telangiectasia macularis eruptiva perstans (TMEP). Skin testing in patients afflicted by one of these conditions must be undertaken with caution since the trauma of percutaneous

or intradermal skin tests could result in mast cell activation with histamine release, leading to false positive results or even a syndrome of anaphylaxis. The prevalence of atopy in patients with mast cell disorders is no different than in the general population, but the manifestation of allergy may be more severe due to the increased number of effector cells. Immunotherapy can be instituted if absolutely necessary, as for example, in the treatment of Hymenoptera sting anaphylaxis.¹

Provocation/neutralization testing to foods is an unproven technique that involves either sublingual or intracutaneous “provocation” by a test antigen, followed by an observation period of 10 to 20 minutes after each injection, at which time the wheal response is measured and any subjective symp-

toms are reported. Symptoms such as drowsiness or headache may be considered a positive challenge, meaning that the person is “allergic” to the food. The patient is then given a different dose of the antigen as either a sublingual drop or another injection until the “reaction” is “neutralized.” This “neutralization” dose would then be taken before an anticipated exposure, daily, or weekly as deemed best by the practitioner.^{2–5} Recently, there has been a great deal of interest in alternative and complementary medicine practices, some of which may depend on a placebo effect, and can be termed “unproven,” such as provocation/neutralization.^{3,5} Herein, we describe a patient with systemic mastocytosis, who underwent evaluation by a physician practicing this form of alternative medicine with significant morbidity as a result.

CASE REPORT

The patient is a 68-year-old woman with a history of mild allergic rhinitis dating to childhood. Complete medical records from 1988 onward were reviewed. In 1974, at age 44, she had the rapid onset of reddish-brown macules and papules on her thighs and trunk. Over the subsequent years, the macules and papules became more numerous to also involve the arms (Figs 1 and 2). The lesions ranged in size from 2 to 9 mm, and became the central point of developing urticaria. Urticaria was triggered by hot or cold showers, exercise, and sometimes rubbing. Gastrointestinal symptoms, which developed in the late 1970s, consisted of dyspepsia, recurrent abdominal pain, bloating, and chronic watery diarrhea. She had multiple episodes of near-syncope accompanied by flushing but

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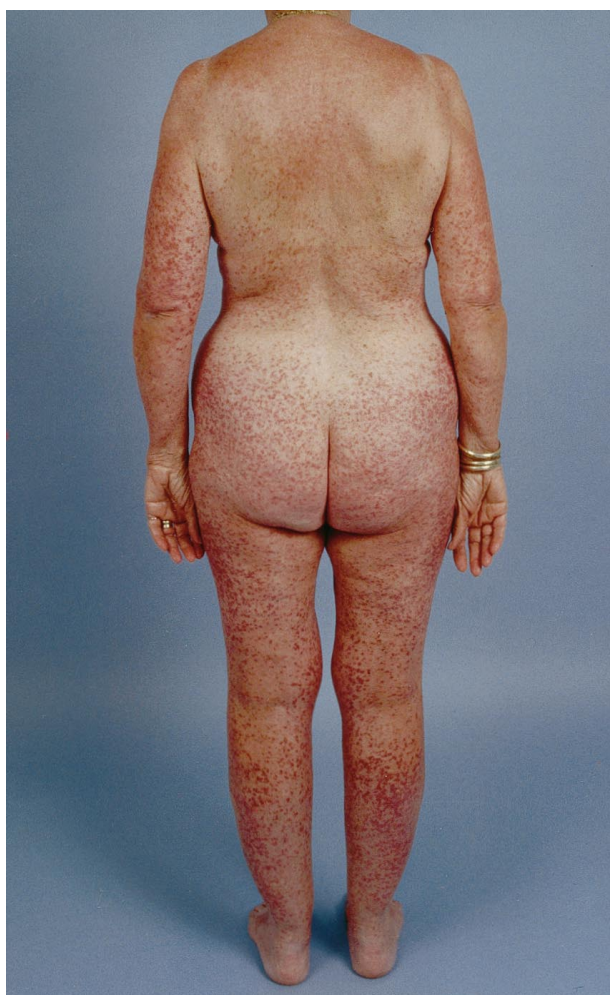


Figure 1. Generalized distribution of the reddish brown macules and papules of cutaneous mastocytosis, photographed in 1992.

without urticaria which occurred almost exclusively after eating food or even drinking water. In 1988 a dermatologist saw her, documented a positive Darier's sign and performed a skin biopsy which was interpreted as urticaria pigmentosa. There was no bone pain or hepatosplenomegaly and a complete blood count with differential was normal. Due to her systemic symptoms, astemizole and oral cromolyn sodium were recommended. She reported almost complete clearing of the gastrointestinal symptoms and episodes of near-syncope on this regimen; however, she could not easily afford the medications and sought another opinion.

In 1991 she saw a physician who practiced allergy. This physician made note in the chart of the diagnosis of urticaria pigmentosa but told her that her gastrointestinal symptoms were explained by food allergies and that she should stop the cromolyn sodium and astemizole and go on a 4-day rotation diet (rotary diversified diet⁵) and injections that he would prescribe. In addition, he advised conventional immunotherapy for pollinosis based on a RAST test performed with her serum (30 antigens screened, all class 0 except class 1 to Bermuda grass, June-Kentucky bluegrass, and meadow fescue, and class 2 to perennial ryegrass and timothy grass pollens). On the sec-

ond visit, she had intradermal testing to foods on her upper arm and was well until the end of the session when she felt flushed and lightheaded. She stood up to open a window, fell to the floor, and was quickly given epinephrine subcutaneously by the nurse. She was told that she was so allergic to two of the foods, wheat and milk, that she should receive regular injections to "neutralize" the reactions. She was also to start pollen extract immunotherapy: both to be self-administered at home.

The next visit therefore, was to learn how to give herself the two separate antigen injections (milk + wheat and pollen, respectively) in her thigh, which is a skin area nearly confluent with reddish-brown macules. Within 10 minutes of the milk and wheat "neutralizing" injection (the grass pollen extract was to have been administered at 15 minutes), she felt extremely hot, passed out, and was incontinent of stool. She was noted in the medical record to have peripheral cyanosis and the pulse was recorded as "palpitations." The physician supervised treatment of this reaction: she was first given heparin 10,000 units IV according to the record. She then received 0.3 mL of epinephrine 1:1000 SQ. She remained poorly responsive, so the physician gave her glycerol SQ to "neutralize" a putative "glycerol allergy." She slowly recovered after 5 hours in the physician's office and felt ill and fatigued for days. The physician suggested that she pretreat herself with glycerol sublingually to "neutralize" her "glycerol allergy" and that she could then continue on the injections. He also recommended that she obtain a MedicAlert bracelet listing glycerol as an allergy. She declined, but did stay on a diet eliminating milk and wheat with return of her gastrointestinal, cutaneous, and systemic symptoms off of the cromolyn sodium and astemizole.

In 1992, she sought evaluation at our university. She again denied bone pain and had no hepatosplenomegaly. Her blood count was normal and no specific IgE was detectable to wheat or cow milk. She was advised that she

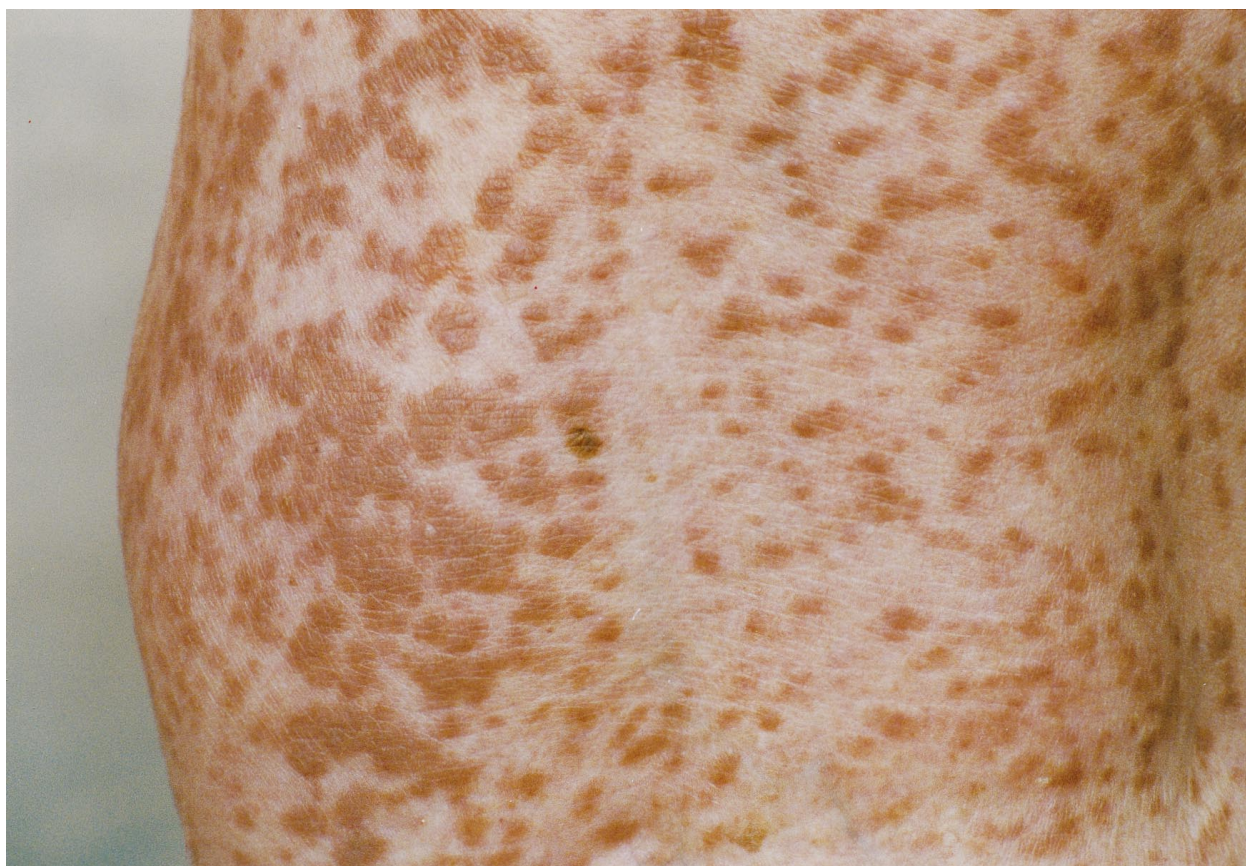


Figure 2. A magnified view of the left popliteal fossa photographed in 1998 that clearly shows the papular nature of most of the lesions.

had cutaneous and systemic mastocytosis based on her previous skin biopsy and her gastrointestinal symptoms. She declined biopsies of the bone marrow, upper and lower gastrointestinal tract. In 1997, she agreed to a repeat skin biopsy and to flexible sigmoidoscopy. The skin biopsy was consistent with cutaneous mastocytosis but the mast cell infiltrate was sparse, with prominent capillary dilatation, suggestive of TMEP (Fig 3). The biopsies taken of the sigmoid colon showed multiple nests of mast cells (Fig 4). Review of the previous skin biopsy from 1989 showed features suggestive of TMEP also, however, the clinical appearance of the lesions has always been characteristic of urticaria pigmentosa. It is possible that she may have some overlapping features. Since continuing on oral cromolyn sodium and non-sedating antihistamines, she has had good control of the gastrointestinal symp-

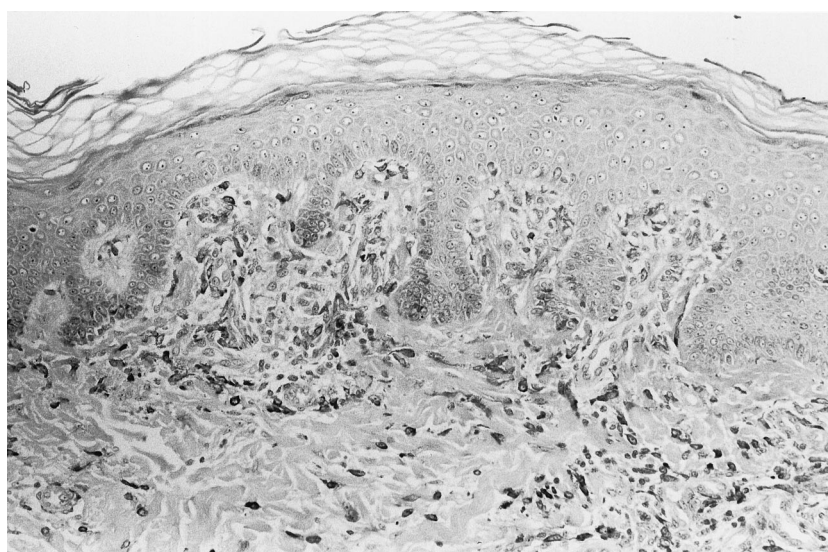


Figure 3. Skin biopsy 1997. Papillary dermal telangiectasia with a mild perivascular and interstitial infiltrate of mast cells with dark staining cytoplasmic granules (Giemsa stain $\times 50$).

toms (with occasional flares) and near-syncope events, as well as excellent prevention of urticaria. Her diet liberally includes wheat and milk products.

DISCUSSION

Although there is no way to prove in retrospect what exactly occurred during the intradermal testing with foods and later during the antigen injections, one plausible explanation is that food extract injections in the region of her mast cell collections in her arm and thigh caused release of mast cell mediators with resultant hypotension and the anaphylaxis syndrome. The physician involved had believed that she must be allergic to glycerol, but there are no documented cases of IgE directed to glycerol in the literature. Therapy for her reactions should have consisted of epinephrine as the primary agent;^{6,7} there is no currently accepted role for heparin in the treatment of anaphylaxis, although there is ongoing interest in heparin as an anti-inflammatory medication and mast cell stabilizer.⁸⁻¹⁰

Provocation/neutralization has been shown to be ineffective as a treatment for adverse reactions to foods in a double-blind, placebo-controlled challenge study.¹¹ This type of procedure relies on a placebo response for effectiveness.^{11,12} It has been touted in the otolaryngology and clinical ecology literature as a safe, effective therapy.^{3,4} There is, however, a report of angioedema following application of sublingual drops when a patient had an IgE-mediated food hypersensitivity.¹³ Practitioners normally avoid this by not testing patients who have a history suggestive of an IgE-mediated reaction. Practitioners of alternative medicine, including provocation/neutralization therapy, may not come from an internal medicine or pediatric background, and may not be aware of medical conditions responsible for a patient's symptom complex, instead attributing symptoms to "allergy."

The histopathology in this case is also of interest. Telangiectasia macularis eruptiva perstans accounts for less than 1% of cutaneous mastocytosis cases in adults and has only been de-

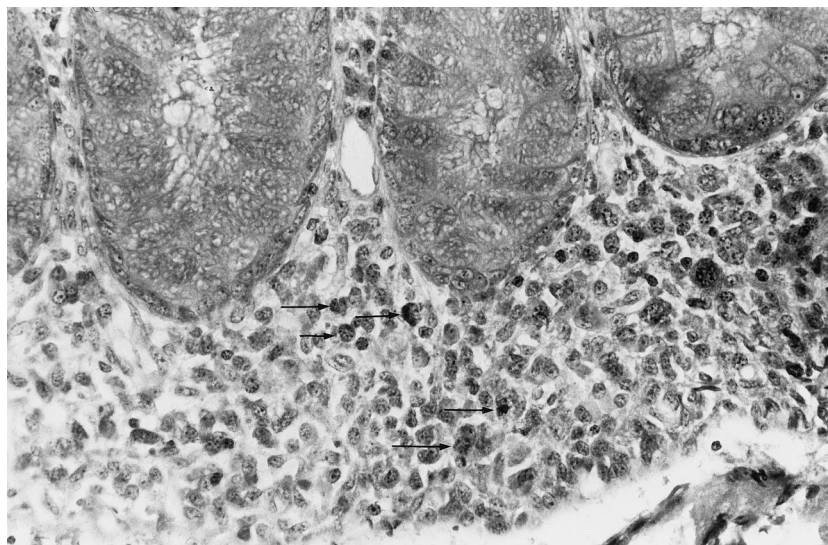


Figure 4. Sigmoid colon biopsy 1997. Lamina propria hypercellularity including macrophages and mast cells with dark staining cytoplasmic granules (arrows indicate examples of mast cells) (Giemsa stain $\times 100$).

scribed once in a child.¹⁴ This rare form of mastocytosis presents as red telangiectatic macules occurring on a tan to brown background, without sharp definition and has traditionally been thought to be limited to the skin but isolated cases may have systemic features.¹⁵ Histopathologically, TMEP is characterized by telangiectases with mild to moderate perivascular and interstitial infiltrates comprised mostly of mast cells in the papillary and upper reticular dermis. Eosinophils may be present in small numbers if the lesion was rubbed before biopsy. In contrast, the other forms of mastocytosis are characterized by diffuse infiltrates of mast cells. Histologic overlap in the papular lesions can exist, as seen in this case. By current mastocytosis classification criteria, our patient would be described as having indolent systemic mastocytosis with gastrointestinal and skin involvement.¹⁶

The medical management in this case is noteworthy for three reasons. (1) A thorough history and physical can prevent morbidity from immunotherapy (traditional or alternative). In this case, the physician dismissed the known history of mast cell disease. (2) Physicians who give immunotherapy in their offices, whether prescribed by

themselves or another physician, need to be knowledgeable in the treatment of anaphylaxis, which was mismanaged in this case.^{6,7} (3) Alternative and complementary medical practices are generally considered to be benign, but that is not always so as supported here. In summary, provocation/neutralization is not without risk in certain patients, including those with IgE-mediated sensitivity to foods and the rare patient with a mast cell disorder as illustrated by this case. In view of the explosion of interest in alternative and complementary medicine, allergy specialists need to continue taking an active role in educating the public, medical community and in these times, insurance groups, about procedures that are unproven or scientifically without foundation.

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