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Successful oral desensitization to levothyroxine

Hypothyroidism is a common endocrine disease affecting many people worldwide. It was reported that the prevalence of hypothyroidism in women and men is 0.6 to 1.2 and 1.3 to 4.0 cases per 1,000 individuals, respectively.¹ Hypersensitivity reactions to levothyroxine are rare. These reactions generally occur as generalized urticaria, angioedema, eczematiform skin eruption, fever, and liver dysfunction in affected patients.^{2–6} This report presents a successful oral desensitization procedure in a case with levothyroxine hypersensitivity reaction.

A 35-year-old woman presented to the outpatient clinic with symptoms of a systemic reaction due to levothyroxine. She had a known history of multiple drug allergies and was previously followed by our clinic for radiocontrast agent and nonsteroidal anti-inflammatory drug allergies. The patient was diagnosed with Hashimoto's disease and prescribed oral levothyroxine 100 µg daily. During this time she did not have any other medical conditions or medications. During the first week of therapy with levothyroxine the patient experienced a moderate systemic reaction that consisted of generalized itchy rash on the trunk and extremities, dyspnea, and palpitation. These symptoms presented approximately 30 minutes after oral ingestion of the levothyroxine tablet. She presented to the local emergency service, where she was evaluated by a physician and treated with intramuscular antihistamine and corticosteroid therapy with a diagnosis of drug allergy. Levothyroxine treatment was stopped, and she was treated with antihistamine therapy. The symptoms gradually quieted in a short time, and levothyroxine therapy was not reinstated.

One and one-half years later, the patient presented with increased symptoms of hypothyroidism, including fatigue, constipation, unexplained weight gain, muscle weakness, impaired memory, thinning hair, and dry skin. Levothyroxine therapy was selected as a treatment for these symptoms. Before initiation of therapy, her levothyroxine allergy was evaluated with a skin test. The skin test procedure includes preparing a stock solution by dissolving a 25 µg levothyroxine tablet in 1 mL volume of 0.09% phosphate-buffered saline according to a previously published protocol.³ The prick test was performed with undiluted stock solution, and the intradermal test was performed with 1/100 wt/vol concentration. On the intradermal test, 0.01 mL solution was used carefully to not have a deceptive wheal. This concentration proved to be non-irritating in 10 healthy control subjects. Histamine and saline were used as positive and negative controls, respectively.

The skin prick test result was negative, and the intradermal test with 1/100 wt/vol concentration showed a positive result (a wheal 3 × 3 mm and a flare 20 × 15 mm for levothyroxine; a wheal 3 × 4 mm and a flare 6 × 7 mm for histamine). No wheal or flare reaction was induced by saline (negative control). Based on the intradermal test result, it was determined that the previous reaction to levothyroxine was thought to be a type 1 hypersensitivity reaction, and a desensitization protocol was designed. Currently oral levothyroxine desensitization protocols

Table 1

Oral desensitization protocol with levothyroxine

Order	Dose (µg)	Cumulative Dose (µg)
1	0.01	0.01
2	0.02	0.03
3	0.04	0.07
4	0.08	0.15
5	0.16	0.31
6	0.32	0.63
7	0.64	1.27
8	1.28	2.55
9	2.56	5.11
10	5.12	10.23
11	10.24	20.47
12	20.48	40.95
13	40.96	81.91

are not available in the literature. The desensitization scheme was designed according to the general desensitization rules.⁷ No pre-medication was given to the patient. After obtaining the consent of the patient, our desensitization scheme was applied with an initial oral dose of 0.01 µg levothyroxine (1/10,000 of the usual daily total dose) and was gradually increased until a cumulative dose of 81.91 µg was attained (Table 1). The intervals among the doses were 30 minutes. This protocol lasted 2 days, and then she was able to take 75 µg levothyroxine orally without any problem on the third day. In this patient, levothyroxine therapy has been maintained successfully without any further allergic reaction symptoms.

Levothyroxine remains as therapy for the treatment of hypothyroidism. Currently there are no alternative options. A small number of allergic reactions to levothyroxine have been reported in the literature. One report details the intravenous desensitization successfully performed in 1 patient.⁵ As far as we know, no oral desensitization protocol has been defined for levothyroxine. Thus, there is not a standard desensitization scheme. In this case, time of the emergence of symptoms and the positive skin test result were consistent with type 1 hypersensitivity reaction. Considering the necessity of hypothyroidism medication, desensitization with levothyroxine should be done as soon as possible. In this case, oral desensitization was preferred because continuation to levothyroxine therapy was possible only by oral route. This case is of importance in clinical practice, because the first oral desensitization with levothyroxine was applied successfully.

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A case of relapsing polychondritis and hypogammaglobulinemia

Relapsing polychondritis (RP) is a rare immune-mediated disease of unknown origin that causes recurrent cartilage inflammation. Its peak incidence is in the 4th or 5th decade of life with a female to male ratio of 3:1. Whereas auricular cartilaginous inflammation is the most common presentation, relapsing polychondritis can also involve cartilaginous components of the respiratory tract, joints, heart, and blood vessels. Corticosteroids are the first line of treatment. Immunosuppressants such as cyclosporine, azathioprine, methotrexate, and cyclophosphamide are possible alternatives. Additionally, the biologic agent antiCD20 monoclonal antibody (rituximab) has been found to be helpful in treating RP.¹

Relapsing polychondritis is suspected to be autoimmune in origin, and other systemic autoimmune phenomena have been linked with this condition. Immunodeficiency, however, is rarely associated with RP. Furthermore, RP has not yet been reported in an adult patient with hypogammaglobulinemia. We report a case of a 37-year-old Hispanic man referred to the allergy and immunology clinic with a 3-year history of recurrent ear inflammation and superimposed secondary infections. There was no shortness of breath, stridor, wheezing, or hoarseness to suggest tracheal involvement. His medical history was significant for controlled asthma, seasonal allergies, recurrent sinusitis, and nasal polypectomy. There was no family history of immunodeficiency. Over the course of the duration of his condition he received multiple, intermittent courses of oral amoxicillin and prednisone for infections and chronic swelling of his ears. This treatment was temporarily beneficial. Prior investigations failed to identify a definitive cause. At the time of presentation, the patient's medications were prednisone 20 mg by mouth daily, fluticasone/salmeterol 500/50 dry powder inhaler twice daily, and albuterol metered dose inhaler as needed. Physical examination findings included erythema and swelling of bilateral pinna, with sparing of the earlobes. There was no evidence of otitis media or nose involvement on examination. Based on the patient's clinical presentation, the diagnosis of RP was made.

At the time of evaluation, the patient's workup showed negative antibody for double-stranded DNA, rheumatoid factor, Sjogren's syndrome antibodies, Smith antigen antibody, and ribonucleoprotein antibody. Complete blood count and basic metabolic studies results were normal. The erythrocyte sedimentation rate was 4 mm/hr. A chest X-ray obtained at the time of initiating follow-up with the clinic was without any evidence of tracheobronchial involvement or fibrosis. A subsequent unenhanced computed tomography image of the chest identified biapical pleural thickening and did not identify any pulmonary nodules, mediastinal adenopathy, interstitial fibrosis, or evidence of a thymoma. Pulmonary function test inspiratory and expiratory loops were unremarkable and showed forced vital capacity 118%, forced expiratory volume in 1 second

115%, forced expiratory volume in 1 second/forced vital capacity 81%, forced expiratory flow 25–75% 90%. Complement levels were within normal limits, specifically C3 119 mg/dL (normal: 90–180 mg/dL) and C4 24 mg/dL (normal: 10–40 mg/dL). Immunoglobulin levels on 2 occasions, which were predated by treatment with corticosteroids but obtained before starting immunosuppressants such as methotrexate, showed consistent hypogammaglobulinemia (Table 1). The patient was therefore evaluated for possible causes of hypogammaglobulinemia, including primary immunodeficiency, protein-losing diseases, and hematologic malignancies. Lymphocyte subsets were within normal limits (Table 1). Serum protein electrophoresis was consistent with hypogammaglobulinemia but did not identify a monoclonal spike. Urinalysis did not identify any proteinuria. Infectious causes were ruled out, including tuberculosis. The patient's condition failed a course of azathioprine but demonstrated significant clinical improvement on treatment with prednisone 15 mg by mouth daily and methotrexate 20 mg by mouth weekly.

Relapsing polychondritis is primarily a clinical diagnosis usually made in the presence of 3 out of 6 of the following criteria: chondritis of pinna, nasal chondritis, nonerosive inflammatory polyarthritis, ocular inflammation, respiratory tract chondritis, and cochlear or vestibular dysfunction.^{2,3} Laboratory findings are not diagnostic, and histologic confirmation may not be necessary. Relapsing polychondritis is most prevalent among whites, with the typical age of onset being between the ages of 40 and 60 years. Its hallmark feature is intermittent inflammation and destruction of cartilaginous structures such as the ear, nose, trachea, bronchi, and joints. Involvement of the respiratory tract, specifically the tracheobronchial tree, can present as wheezing that can be misinterpreted as asthma. Keratouveitis, albeit rare, can also be an initial presentation of RP.⁴ Although auricular chondritis is the most common presentation, involvement of the respiratory tract carries the greatest risk for mortality.⁵ Approximately 30% of patients have additional autoimmune or hematologic disease.³

Corticosteroids are the mainstay of treatment of RP, with immunosuppressive agents serving as possible corticosteroid-sparing alternatives. Biologic agents such as tumor necrosis factor alpha inhibitors and interleukin-1 receptor antagonists can be effective for refractory RP.⁶ Tocilizumab, an anti–interleukin-6 agent, has also been used in cases of refractory RP.⁷

Hypogammaglobulinemia is a form of immunodeficiency marked by antibody deficiency. This condition can be primary or acquired, with causes ranging from primary immunodeficiencies such as common variable immunodeficiency to acquired conditions such as drug-induced hypogammaglobulinemia or nephrotic syndrome–associated hypogammaglobulinemia. The clinical complications of hypogammaglobulinemia are increased risk of infections with encapsulated bacteria, and it is therefore important that clinicians recognize this clinical entity.⁸ Treatment ranges from