Orofacial granulomatosis associated with hypersensitivity to dental amalgam

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Orofacial granulomatosis is a clinicopathologic entity characterized by chronic swelling of the lip and possible soft tissues in the orofacial region owing to granulomatous inflammation of unknown cause. We present 3 cases of orofacial granulomatosis associated with allergic contact dermatitis to dental materials. Previous treatment with corticosteroids did not have any therapeutic effect. Patch testing revealed a positive reaction to several allergens, including dental amalgam and mercury in 2 cases. A lymphocyte transformation test modified for metals was used to evaluate lymphocyte reactivity. After the removal of the suspected allergens, all patients experienced recovery within 1 month, with the exception of the lip swelling, which gradually subsided over several months. (Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2011;112:335-341)

Orofacial granulomatosis (OFG) is a descriptive term proposed by Wiesenfeld et al. in 1985.1 Histologically, it is characterized by noncaseating epithelioid granulomas involving the facial and oral tissues. Clinically, OFG may manifest as localized or generalized erythema and edema of the lips and face. The buccal mucosa and tongue may exhibit enlargement, folding, and occasional ulceration.2,3 This clinicopathologic entity encompasses the clinically recognized Melkersson-Rosenthal syndrome (MRS) and cheilitis granulomatosa. The incidence and prevalence is unknown, and OFG is considered to be an uncommon condition.4 The underlying etiology is unknown, and spontaneous remissions are rare. The proposed causes are genetic predisposition, foreign body reaction, infection, food allergies, and, occasionally, allergy to dental materials. However, OFG lacks specificity, and it may be considered to be an oral manifestation of various diseases, such as sarcoidosis, Crohn disease, or tuberculosis.2,6

Treatment usually consists of a symptomatic therapy of prolonged application of corticosteroids and immunomodulatory agents.3 In persistent cases, surgical intervention with cheiloplasty may be recommended.

In the present publication, we report 3 cases of OFG that were uncommonly associated by delayed hypersensitivity to dental materials.

CASE REPORTS

Case 1

A 32-year-old nonatopic caucasian woman sought treatment for tightening, burning, and persistent swelling of her lower lip occurring over an 11-month duration (Fig. 1, a). The patient described the swelling as permanent and pronounced on the left side of the lower lip with warm sensations. The first symptom she noticed was itching of the gums for 2 weeks; sudden swelling of the lip followed. She was monitored for increased neuromuscular irritability, slight constriction of the visual field, blurred vision, and microprolactinoma of the pituitary gland. She used Dostinex (cabergoline) regularly, as prescribed by her endocrinologist.

Previously, she had undergone many examinations and had been treated by many specialists without satisfactory results. The etiology of the lip swelling was unknown. There was no association with previous dental treatment, medication, oral hygiene, cosmetic products, or foods. Tuberculosis or gastrointestinal problems were not included in her medical history. The diagnoses of hemangioma and lymphangioma were excluded based on magnetic resonance imaging findings. Hereditary angioedema
and food and latex allergy were excluded by biochemical analysis and allergologic tests (prick tests, specific IgE levels, and eosinophil cationic protein (ECP)). Sarcoidosis and Crohn’s disease were excluded based on medical history, chest radiography, biochemical parameters, and immunologic analysis. A complete blood count, erythrocyte sedimentation rate (ESR), and serum levels of vitamin B12, folic acid, iron, albumin, calcium, immunoglobulins, anti–Saccharomyces cerevisiae antibodies (ASCA), and serum angiotensin-converting enzyme (SACE; 37 IU/L) were normal; however, there had been an increase in zinc (18.7 μmol/L). An endoscopic examination was not performed.

A biopsy specimen obtained from the lip showed intradermal noncaseating granuloma and subepithelial lymphocytic infiltrate (Fig. 1, b). Ziehl-Neelsen and periodic acid–Schiff (PAS) stains did not show acid-fast bacilli or fungi in the specimen. Polarizable foreign bodies were not detected. The previous treatment, which consisted of topical corticosteroids and antihistamines, was without any therapeutic effect. A repeated application of intralesional corticosteroids brought only brief alleviation. The patient underwent detailed patch testing with 4 patch series—81 allergens in total. The positive reactions and tested patch series are presented in Table I.

During an examination that was performed in the outpatient clinic of our institute, the lower lip was markedly edematous, firm to palpation and indurated without erythema or dermatitis (Fig. 1, a). The tongue was fissured, and few petechiae were found on the hard palate. A lymphocyte transformation test modified for metals (LTT-MELISA) that was performed in the immunologic laboratory was used to evaluate lymphocyte reactivity toward metals. An increased lymphocytic activity against tested antigens and mercury was found (Fig. 2).

The removal of 10 amalgam fillings (19 surfaces) took place over 3 appointments at 1-month intervals. The tightening and swelling of the lip worsened for a short period after each appointment, and perioral eczema also appeared (Fig. 1, c).

Mercury in the blood and urine was measured before and after the removal of the last 3 amalgam fillings (6 surfaces). Thereafter, the patient underwent unithiol treatment for 2 days (Dimaval cps; 10 mg/kg body wt.) at the Department of Occupational Medicine. Her urine output of Hg2+, Cu+, and Zn2+ increased to 850%, 600%, and 180%, respectively; Ca2+, PO4 3−, and Fe3+ were within the normal range without substantial change; Na+, K+, Cl-, and Mg+ urine output decreased after the treatment to 44%, 5%, 6.5%, and 21%, respectively. Blood parameters did not substantially change. Mercury output in the urine increased from 0.8 μg/24 h before the amalgam removal to 70 μg/24 h on both the first and the second day, respectively, of the antidote treatment. The mercury level in the whole blood was 0.4 μg/L initially, 0.3 μg/L after amalgam removal, and 0.4 μg/L after antidote treatment. Neutrophilia and increased C-reactive protein were observed at the end of unithiol treatment.

One month after the last amalgam removal, most of the symptoms diminished, with the exception of lip swelling,

Fig. 1. Clinical features of case 1. a, Swelling of the lower lip 3 months after the last application of intralesional corticosteroids. b, Biopsy of the lip: intradermal noncaseating granuloma without necrosis. c, Circumoral dermatitis appeared 24 hours after the removal of amalgam fillings. d, Eight months after the removal of all amalgam fillings.
which gradually subsided within 8 months. LTT-MELISA results were in agreement with these clinical improvements; lymphocyte reactivity to mercury and all other tested metals was decreased (Fig. 2). Twenty-four months after the last amalgam removal, the patient had not experienced any relapse or worsening (Fig. 1, d).

Table 1. Positive results of patch testing with allergens of European baseline series and metal series (29 and 28 allergens; Chemotekhnic Diagnostics, Malmö, Sweden), bakery allergens and dental materials (13 and 11 allergens; Trolab, Hermal, Reinbek, Germany)

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pet., Petrolatum; ND, not done.

Fig. 2. Results of the LTT-MELISA. Case 1, before amalgam fillings removal and 8 months after. Case 2, before amalgam fillings removal and 8 and 30 months after; at 8 months, the lymphocyte reactions intensified, which was probably due to exposure to the allergen. Case 3, before amalgam fillings removal and 5 months after. (x axis: metals tested; y axis: stimulation index.)
Case 2

An otherwise healthy 23-year-old atopic woman presented with long-standing edema of her upper lip with a ∼3-year history (Fig. 3, a). She reported recurrent edema during the first year, which became more persistent and firm thereafter. Furthermore, she complained of soreness, burning, and itching of the lips, tongue, and gums. Recurrent right-sided facial paresthesia accompanied the symptoms as they worsened. All symptoms were aggravated by psychologic and physical stress.

The cause of her symptoms was unknown. There was no association with cosmetic products or foods. A dentist treated the patient ∼4 months before the onset of the symptoms; during that appointment, 1 tooth was reconstructed by an amalgam filling. Tuberculosis or gastrointestinal problems were not in her medical history. The diagnosis of hereditary angioedema was excluded by biochemical analysis. Allergic reaction was not supported by biochemical analysis (immunoglobulins, specific IgE levels). Diagnosis of sarcoidosis and Crohn disease was excluded based on medical history, chest radiography, biochemical parameters, and immunologic analysis. The complete blood count, ESR, and levels of vitamin B12, folic acid, iron, albumin, calcium, immunoglobulins, ASCA, and SACE (45 IU/L) were normal; however, zinc was increased slightly (17.8 μmol/L). An endoscopic examination was not performed. A lip biopsy was completed at another clinic, and we obtained the specimen for a second reading. The specimen included only superficial layers of the lip with a perivascular infiltrate of lymphocytes (Fig. 3, b). The patient refused to undergo another biopsy due to the pain experienced during the first biopsy. Ziehl-Neelsen and PAS staining did not show acid-
fast bacilli or fungi in the specimen. Polarizable foreign bodies were not detected. Previous treatment of the symptoms by topical corticosteroids and an intraleisional corticosteroid had no effect. Patch test results are presented in Table I. The series of allergens used were identical to those used in case 1.

During the examination performed in the outpatient clinic of our institute, the upper lip was markedly edematous, firm to palpation, and fissured with scaling. The lower lip was slightly edematous on the right side (Fig. 3, a). The intraoral examination revealed gingival erythema, a fissured tongue (Fig. 3, c), and numerous petechiae on the hard palate (Fig. 3, d). The clinical presentation was compatible with clinically recognized MRS.

Based on our recommendation, the patient’s dentist replaced all 9 amalgam fillings (13 surfaces), after which the patient reported a short-term worsening of the lip edema. The symptoms subsided within 4 weeks, with the exception of swelling of the upper lip, which gradually subsided within 18 months. LTT-MELISA was used to evaluate the lymphocytic reactivity before and after the amalgam removal (Fig. 2). Forty-five months after the amalgam removal, the patient had not reported any worsening (Fig. 3, e).

Case 3

A 50-year-old nonatopic caucasian woman sought treatment for perioral erythema and persistent swelling of the lips that had lasted >4 years (Fig. 4, a). She described the edema as permanent without improvements. The symptoms appeared after dental treatment during which 1 amalgam filling (3 surfaces) was replaced.

The cause of the lip swelling was unknown. Association of the lip swelling with dental treatment was considered to be a coincidence. There was no association with medication, oral hygiene, cosmetic products, or foods; her medical history did not include tuberculosis or gastrointestinal problems. Erysipelas was suspected, and the patient was treated with antibiotics but without effect. The blood examination for Lyme disease, including lymphocytoma was negative. Sarcoidosis and Crohn disease were excluded based on medical history, chest radiography, biochemical parameters, and immunologic analysis. A complete blood count, ESR, and levels of vitamin B12, folic acid, iron, albumin, calcium, immunoglobulins, ASCA, and SACE (46 IU/L) were normal, except for a slight increase in zinc (15.1 μmol/L). An endoscopic examination was not performed. Allergic reaction was not supported by biochemical analysis (immunoglobulins, specific IgE levels), except for a slight increase of ECP (25.4 μg/L). A biopsy specimen obtained from the lip showed numerous intradermal noncaseating granulomas and subepithelial lymphocytic infiltrate (Fig. 4, b). Ziehl-Neelsen and PAS stainings did not show acid-fast bacilli or fungi in the specimen. Polarizable foreign bodies were not detected. The treatment by oral corticosteroids brought alleviation; however, relapse occurred while she was taking a dosage of prednisone <20 mg. The patient underwent detailed patch testing (European baseline series and cosmetic series; Chemotechnique Diagnostics, Malmö, Sweden; Dental Materials; Trolab, Hermal, Reinbek, Germany), and all of the results were negative.
the urine was 1 μg/g creatinine. Increased lymphocytic reactivity against mercury and silver was found in the LTT-MELISA (Fig. 2).

The time coincidence of the patient’s symptoms with her dental treatment was verified in the documentation provided by the dentist. The patient was informed about the possible association, and she decided to remove the amalgam fillings. Seven amalgam fillings (11 surfaces) were removed during 3 appointments. Shortly thereafter, the patient decided to stop taking oral corticosteroids due to her weight increase. At the time of writing, 6 months after the removal of amalgam, the patient had not reported any relapses or aggravation, and the symptoms had partially subsided (Fig. 4, c). Lymphocyte reactivity against the mercury and silver had decreased (Fig. 2).

DISCUSSION

Orofacial granulomatosis is a clinicopathological entity characterized by chronic swelling of the lip and soft tissues in the orofacial region owing to granulomatous inflammation of unknown cause. A differential diagnosis based on biopsy should include sarcoidosis and Crohn disease. Increased SACE levels may be useful in the diagnosis of sarcoidosis and OFG. In sarcoidosis, the most common finding is pulmonary infiltration and hilar lymphadenopathy (90% of cases). Extrathoracic manifestations occur in approximately one-half of the cases. However, oral involvements are infrequent, and a recent review of the English-language literature found only 68 cases of oral sarcoidosis. The lips and palate were involved in only 6 and 3 cases, respectively. Regarding Crohn disease, the disease can be excluded by biochemical analysis, negative ASCA titers, and normal results of gastrointestinal tract investigation in patients without specific symptoms. The association between OFG and Crohn disease should not be overstated, as discussed by Pryce and King. Intestinal disease usually follows the onset of oral lesions within a few months. There were no clinical manifestations of sarcoidosis or Crohn disease in cases 1, 2, or 3 from the onset of oral symptoms to 3, 6, and 4 years, respectively (up to the time of writing). An endoscopic examination and endoscopic biopsy were considered to be redundant and unethical regarding the biochemical and immunologic findings and clinical manifestations.

Recent studies have identified monoclonal lymphocytic expansion in OFG lesions; this finding is probably a consequence of chronic antigenic stimulation and increased cytokine production. An allergic response to a broad spectrum of antigens was found in ~20%-30% of the cases; the commonly identified allergens included foodstuffs, flavoring agents, and preservatives. Furthermore, allergen elimination resulted in recovery. Occasionally, delayed hypersensitivity to dental materials was implicated in the etiology of OFG. In the cases presented in the present report, association with only 1 complex antigen was found. It is probable that only patients with suspicious reactions to dental materials were sent to our department. In case 3, the patch tests were negative, which was probably owing to the previous administration of oral corticosteroids. The patients presented in cases 1 and 2 experienced complete recovery over an 8-month period and an 18-month period, respectively. The patient in case 3 observed a significant improvement and we expected a complete recovery during the next months. The resolution of symptoms over the course of several months is consistent with previously published case reports.

Granulomatous reactions were found in amalgam tattoos and in subcutaneous deposits of inorganic mercury. However, it is assumed that these granulomas were induced by a reaction to foreign body material. In cases 1 and 3, the granulomas were probably associated with a delayed-type hypersensitivity reaction. In case 2, the specimen included only superficial layers of the lip with perivascular infiltrate. This was probably the reason why granulomas, which are usually located in the lamina propria, were not found.

The cause of sensitization remains unclear. We did not presume significant exposure to mercury in presented patients. They chewed chewing gum approximately once a week, and they did not use any mercury-containing cosmetics or drugs. We decided to measure mercury levels, because the possible toxic reaction may be suggested in the debate over the amalgam controversy. We found that the mercury levels were within population values (mercury median values in blood of women 0.89 μg/L and in urine of adults 1.10 μg/g creatinine); however, the measurements in case 2 were not completed owing to technical reasons. In case 1, the patient agreed to undergo unithiol treatment. The total mercury output does not indicate increased elimination of mercury compared with other studies. It should be noted that the chelating agent unithiol (dimercaptopropan sulfonate) is not indicated as a common treatment; it is indicated in cases of life-threatening intoxication with mercury. Chelation therapy performed by inexperienced physicians may lead to unwanted symptoms. Unithiol treatment had no effect in patients who subjectively attributed their symptoms to the toxicity of dental amalgam. LTT was found to be a useful method in the diagnosis of allergic reactions to drugs; however, its reliability in diagnosing a metal allergy is still questionable. The LTT-MELISA was developed as an optimized LTT, and it was validated by Valentine-Thon et al. However, several previous studies have questioned the LTT-MELISA, and therefore controversy remains. Based on our clinical experience, LTT-MELISA may be helpful in certain cases, and the
results should be interpreted individually. In the cases presented in this report, the immunologic response assessed by LTT-MELISA reflected the observed improvements throughout the course of treatment.

Detailed allergy testing that includes dental materials may help to identify a subgroup of patients with OFG who may benefit from the allergen elimination. The results of the LTT-MELISA and the possible clinical effects of unithiol treatment should be confirmed in future clinical trials.

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REFERENCES