

## eMedicine Specialties > Dermatology > Diseases of the Oral Mucosa

# Cheilitis Granulomatosa (Miescher-Melkersson-Rosenthal Syndrome)

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Updated: Oct 17, 2008

## Introduction

### Background

Granulomatous cheilitis is a chronic swelling of the lip due to granulomatous inflammation. Miescher cheilitis is the term used when the granulomatous changes are confined to the lip. Miescher cheilitis is generally regarded as a monosymptomatic form of the Melkersson-Rosenthal syndrome, although the possibility remains that these may be 2 separate diseases. Melkersson-Rosenthal syndrome is the term used when cheilitis occurs with facial palsy and plicated tongue.

Melkersson-Rosenthal syndrome is occasionally a manifestation of Crohn disease<sup>1,2,3,4,5</sup> or orofacial granulomatosis (OFG).

The following Medscape CME courses may be of interest:

- Tubulointerstitial Nephritis as an Extraintestinal Manifestation of Crohn's Disease
- Welcome and Introduction: Setting New Treatment Goals for Crohn's Disease in 2008 (Slides With Transcript)

### Pathophysiology

In granulomatous cheilitis, normal lip architecture is eventually altered by the presence of lymphoedema and noncaseating granulomas in the lamina propria. T<sub>H</sub> 1 immunocytes produce interleukin 12 and RANTES/MIP-1alpha and granulomas. Expression of protease-activated receptor 1 and 2 occurs in OFG. HLA typing may show HLA-A2 or HLA-A11.<sup>6</sup>

### Frequency

### International

The frequency is unknown; the condition is rare.

## Mortality/Morbidity

Morbidity depends on whether underlying organic disease, such as Crohn disease or sarcoidosis,<sup>7</sup> is present.

## Race

No racial predilection is recognized.

## Sex

No sexual predilection is known.

## Age

Onset usually occurs in young adult life.

## Clinical

### History

Cheilitis granulomatosa is episodic with nontender swelling and enlargement of one or both lips. Occasionally, similar swellings involve other areas, including the periocular region.

- The first episode of edema typically subsides completely in hours or days. After recurrent attacks, swelling may persist and slowly increase in degree, eventually becoming permanent. Recurrences can range from days to years.
- Attacks sometimes are accompanied by fever and mild constitutional symptoms (eg, headache, visual disturbance).
- Cranial nerve palsies may be associated. Melkersson-Rosenthal syndrome is the association with facial nerve palsy.<sup>8,9</sup>

### Physical

The earliest manifestation is sudden diffuse or occasionally nodular swellings of the lip or the face involving (in decreasing order of frequency) the upper lip, the lower lip, and one or both cheeks. The forehead, the eyelids, or one side of the scalp may be involved (less common). The upper lip is involved slightly more often than the lower lip, and it may feel soft, firm, or nodular on palpation.

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- Once chronicity is established, the enlarged lip appears cracked and fissured with reddish brown discoloration and scaling. The fissured lip becomes painful and eventually acquires the consistency of firm rubber.
- Swelling may regress very slowly after some years.
- Regional lymph nodes are enlarged (usually minimally) in 50% of patients.
- A fissured or plicated tongue is seen in 20-40% of patients.
  - Its presence from birth (in some patients) may indicate a genetic susceptibility.
  - Patients may lose the sense of taste and have decreased salivary gland secretion.
- Facial palsy of the lower motor-neuron type occurs in about 30% of patients.
  - Facial palsy may precede attacks of edema by months or years, but it more commonly develops later.
  - Facial palsy is intermittent at first, but it may become permanent.
  - It can be unilateral or bilateral, partial or complete.
  - Other cranial nerves (eg, olfactory, auditory, glossopharyngeal, hypoglossal) are occasionally affected.
  - Central nervous system involvement has been reported, but the significance of resulting symptoms is easily overlooked because they are very variable (sometimes simulating multiple sclerosis but often with a poorly defined association of psychiatric and neurologic features).
  - Autonomic disturbances may occur.

## Causes

The cause is unknown.<sup>10</sup> A genetic predisposition may exist in Melkersson-Rosenthal syndrome; siblings have been affected, and a plicated tongue may be present in otherwise unaffected relatives. Crohn disease, sarcoidosis, and orofacial granulomatosis may present in a similar clinical fashion, and with identical histologic findings. Dietary or other antigens are the most common identified cause of orofacial granulomatosis (OFG).<sup>11,12</sup> Contact antigens are sometimes implicated.<sup>13</sup> OFG may result from reactions to some foods or medicaments, such as cinnamon aldehyde and benzoates.<sup>14</sup>

## Differential Diagnoses

Angioedema, Acquired

Angioedema, Hereditary

Leprosy

Sarcoidosis

## Other Problems to Be Considered

Dental abscess

Trauma

Crohn disease

Orofacial granulomatosis

Lymphoma

## Workup

### Laboratory Studies

- Serum angiotensin-converting enzyme test may be performed to help exclude sarcoidosis.
- Patch tests may be used to help exclude reactions to metals, food additives, or other oral antigens. Some cases may be associated with such sensitivities. If found, avoidance of the implicated allergen is recommended.

### Imaging Studies

- Gastrointestinal tract endoscopy, radiography and biopsy may be used to help exclude Crohn disease.
- Chest radiography or gallium or positron emission tomography (PET) scanning may be performed to help exclude sarcoidosis.
- Panorex dental films may be obtained to assess for the presence of a chronic dental abscess.

### Procedures

- A biopsy of the swollen lip or facial tissues is indicated but only shows lymphoedema and perivascular lymphocytic infiltration during the early stages and later shows granulomas.
- A biopsy may be performed to help exclude Crohn disease and sarcoidosis.

### Histologic Findings

Histologic changes are not always conspicuous or specific in many cases of long duration; the infiltrate becomes denser and pleomorphic, and small focal granulomas are formed that are indistinguishable from Crohn disease or sarcoidosis. Small granulomas occur in the lymphatic walls in some cases. Similar changes may be present in cervical lymph nodes.

# Treatment

## Medical Care

Simple compression for several hours daily may produce significant improvement. Compression devices may reduce lip edema. Orofacial granulomatosis may improve with implementation of a cinnamon- and benzoate-free diet. Intralesional corticosteroids may be helpful in some patients.<sup>18</sup> Success with other treatments has been reported anecdotally. None of the agents listed below has been systematically evaluated.

- Nonsteroidal anti-inflammatory agents
- Antibiotic treatment of dental abscess (resulted in remission in anecdotal cases)
- Mast cell stabilizers<sup>16</sup>
- Clofazimine<sup>17</sup>
- Tetracycline (used for anti-inflammatory activity)
- Methotrexate<sup>18</sup>
- Tacrolimus
- Infliximab<sup>19</sup>

## Surgical Care

- Surgery and radiation have been used.
- Surgery alone is relatively unsuccessful.
- Reduction cheiloplasty with intralesional triamcinolone and systemic tetracycline offer the best results.<sup>20</sup> Give corticosteroid injections periodically after surgery to avoid an exaggerated recurrence.

## Consultations

Consult a gastroenterologist, an immunologist, and an oral medicine specialist.

## Medication

Clofazimine or metronidazole may produce resolution in granulomatous cheilitis. Intralesional corticosteroid (triamcinolone) injections may reduce swelling. Systemic corticosteroids are rarely indicated and not all cases respond.

Azathioprine, dapsone, sulfapyridine, or sulfasalazine may be helpful.

Long-term penicillin, tetracycline, erythromycin, and ketotifen are other management approaches that are occasionally helpful.

No RCTs have yet been recorded with possible therapies, such as tacrolimus, thalidomide, or infliximab.

## Antibiotics

Therapy must be comprehensive and should cover all likely pathogens in the clinical setting.

## Clofazimine (Lamprene 50- or 100-mg cap)

Inhibits mycobacterial growth, binds preferentially to mycobacterial DNA. Has antimicrobial properties, but mechanism of action is unknown.

## Dosing

### Adult

100 mg PO bid for 10 d, then twice weekly for 4 mo

### Pediatric

1 mg/kg/d PO qd

## Interactions

Dapsone may inhibit anti-inflammatory activity

## Contraindications

Documented hypersensitivity; breastfeeding; hepatic disease; renal disease

## Precautions

### Pregnancy

C - Fetal risk revealed in studies in animals but not established or not studied in humans; may use if benefits outweigh risk to fetus

### Precautions

Severe abdominal symptoms may require exploratory laparotomies; caution in patients with GI problems (eg, abdominal pain, diarrhea); skin discoloration due to drug may result in depression or suicide; apply oil to skin for dryness and ichthyosis; stains soft contact lenses

## Dapsone (Avlosulfon)

Bactericidal and bacteriostatic against mycobacteria. Mechanism of action is similar to that of sulfonamides where competitive antagonists of PABA prevent formation of folic acid, inhibiting bacterial growth.

## Dosing

### Adult

50-300 mg PO qd (average dose, 100 mg qd)

### Pediatric

Not established

## Interactions

May inhibit anti-inflammatory effects of clofazimine; hematologic reactions may increase with folic acid antagonists, eg, pyrimethamine (monitor for agranulocytosis during second and third mo of therapy); probenecid increases toxicity; trimethoprim with dapsone may increase toxicity of both drugs; because of increased renal clearance, levels may significantly decrease when administered concurrently with rifampin

## Contraindications

Absolute: Documented hypersensitivity

Relative: G-6-PD deficiency (especially in African Americans, Middle Easterners, and Asians), significant cardiopulmonary disease, significant hematologic disease, sulfa allergy (cautious use in patients with sulfa allergy may be attempted; cross-reactivity is relatively rare and mild)

## Precautions

### Pregnancy

C - Fetal risk revealed in studies in animals but not established or not studied in humans; may use if benefits outweigh risk to fetus

### Precautions

Perform weekly blood counts (first mo), then perform WBC counts monthly (6 mo), and then semiannually; discontinue if significant reduction in platelets, leukocytes, or hematopoiesis occurs; caution in methemoglobin reductase deficiency, G-6-PD deficiency, or hemoglobin M because of high risk for hemolysis and Heinz body formation; caution in patients exposed to other agents or conditions (eg, infection, diabetic ketosis) capable of producing hemolysis; peripheral neuropathy can occur (rare); phototoxicity may occur when exposed to UV light

## Anti-inflammatories

These agents decrease inflammatory responses and systemically interfere with events leading to inflammation.

## Sulfapyridine (Dagenan)

Competitive antagonist of PABA. Mechanism of action in linear IgA dermatosis is unknown.

## Dosing

### Adult

Initial dose is 500 mg PO bid; increase by 1 g q1-2wk until disease is controlled; control may require 1-4 g/d

### Pediatric

35 mg/kg PO bid; not to exceed 100 mg/kg/d

## Interactions



Bioavailability of digoxin is reduced (interval of 2-3 h between administrations is recommended)

## Contraindications

Documented hypersensitivity; slow acetylators may require smaller doses or more gradual initial dosage adjustment

## Precautions

### Pregnancy

B - Fetal risk not confirmed in studies in humans but has been shown in some studies in animals

### Precautions

Idiosyncratic reactions, such as hypersensitivity pneumonitis, a lupuslike syndrome, pancreatitis, and toxic hepatitis, may occur; agranulocytosis rarely occurs; both immune hemolytic anemia and nonimmune hemolytic anemia develop (the latter is more common in patients with G-6-PD deficiency); folate deficiency may occur secondary to impaired absorption; nephrolithiasis may occur as with other sulfa drugs; toxic epidermal necrolysis has been reported with medications containing sulfa groups; check CBC count and liver function tests monthly for 5 mo then q6wk thereafter

Risk-benefit analysis should be considered if (1) allergy to sulfapyridine, other sulfonamides, furosemide, thiazide diuretics, sulfonyleureas, or carbonic anhydrase inhibitors; (2) blood dyscrasias (sulfapyridine may cause agranulocytosis, aplastic anemia, or other blood dyscrasias); (3) G-6-PD deficiency (sulfapyridine may cause hemolytic anemia); (4) hepatic function impairment (sulfonamides are metabolized in liver and may cause hepatitis); (5) porphyria (sulfonamides may precipitate acute attack of porphyria); (6) renal function impairment (sulfapyridine excreted primarily through kidneys)

## Sulfasalazine (Azulfidine)

Decreases inflammatory response and systemically inhibits prostaglandin synthesis.

## Dosing

### Adult

500 mg PO qd

### Pediatric

Not established

## Interactions

Decreases effects of iron, digoxin, and folic acid; conversely, increases effect of oral anticoagulants, oral hypoglycemic agents, and methotrexate

## Contraindications

Documented hypersensitivity; sulfa drugs or any component; those diagnosed with GI or GU obstruction

## Precautions

### Pregnancy

B - Fetal risk not confirmed in studies in humans but has been shown in some studies in animals

### Precautions

Caution in patients with renal or hepatic impairment, blood dyscrasias, or urinary obstruction

## Corticosteroids

These agents have anti-inflammatory properties and cause profound and varied metabolic effects. In addition, these agents modify the body's immune response to diverse stimuli.

## Triamcinolone (Aristocort)

For inflammatory dermatosis responsive to steroids. Decreases inflammation by suppressing migration of polymorphonuclear leukocytes and reversing capillary permeability.

## Dosing

### Adult

2.5-40 mg (10 mg/mL or 40 mg/mL formulations; intralesional); repeat prn but not to exceed q4-6wk

### Pediatric

2.5-15 mg (10 mg/mL or 40 mg/mL solutions; intralesional); repeat prn but not to exceed q4-6wk

## Interactions

None reported

## Contraindications

Documented hypersensitivity; fungal, viral, and bacterial skin infections

## Precautions

### Pregnancy

C - Fetal risk revealed in studies in animals but not established or not studied in humans; may use if benefits outweigh risk to fetus

### Precautions

Do not use in decreased skin circulation; prolonged or frequent use may result in Cushing syndrome, reversible HPA-axis suppression, hyperglycemia, and glycosuria

## Immunosuppressants

These agents inhibit key factors that mediate immune reactions, which, in turn, decrease inflammatory responses.

### Azathioprine (Imuran)

Antagonizes purine metabolism and inhibits synthesis of DNA, RNA, and proteins. May decrease proliferation of immune cells, which results in lower autoimmune activity.

### Dosing

#### Adult

1 mg/kg qd/bid (empiric) or by TPMT level; increase by 0.5 mg/kg q4wk until response, not to exceed 2.5 mg/kg/d  
TPMT testing not entirely reliable; involves testing activity of TPMT activity in RBCs, which correlates with systemic TPMT activity; functional enzyme test has been shown to have variability between test sites, and kits may contain varying amounts of enzyme inhibitor; starting at low doses, monitoring for pancytopenia, then increasing the dose is an alternative; if clinical response is not good, patient may be a homozygote for high activity and may need increased dose; some references recommend checking before treatment in all patients

TPMT <5 U: No treatment with azathioprine

TPMT 5-13.7 U: Not to exceed 0.5 mg/kg

TPMT 13.7-19 U: Not to exceed 1.5 mg/kg

TPMT >19 U: Not to exceed 2.5 mg/kg

#### Pediatric

Safety and efficacy not established

### Interactions

Allopurinol increases risk of pancytopenia; captopril/ACE inhibitors may increase risk of anemia and leukopenia; warfarin dose may need to be increased; pancuronium dose may need to be increased for adequate paralysis; live virus vaccines and cotrimoxazole increase risk of hematologic toxicity; rifampicin may cause transplants to possibly be rejected; clozapine may increase risk of agranulocytosis

### Contraindications

Absolute: Documented hypersensitivity, pregnancy or attempting pregnancy, clinically significant active infection

Relative: Concurrent use of allopurinol; prior treatment with alkylating agents (eg, cyclophosphamide, chlorambucil, melphalan, others [high risk of neoplasia])

### Precautions

#### Pregnancy

D - Fetal risk shown in humans; use only if benefits outweigh risk to fetus

## **Precautions**

Increased risk of neoplasia; caution in liver disease and renal impairment; hematologic toxicities may occur; rarely, patients may develop fever without associated infections; measure thiopurine methyltransferase level prior to treatment; periodically monitor CBC count and liver function

## **Follow-up**

### **Further Outpatient Care**

Follow-up care is indicated to exclude the development of Crohn disease or sarcoidosis in patients.

### **Complications**

Complications depend on the underlying pathogenesis.

### **Prognosis**

Swelling is typically chronic.

## **Miscellaneous**

### **Medicolegal Pitfalls**

Failure to obtain adequate biopsy specimens, resulting in a possible misdiagnosis, is a pitfall.

## **Multimedia**



**Media file 1: Labial swelling and angular cheilitis.**

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