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Granulomatous cheilitis in a patient after SARS-CoV-2 infection treated with antibiotics: a case report

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Abstract

Granulomatous cheilitis or Miescher's cheilitis is a rare granulomatous disorder defined by recurrent lip swelling or edema of other facial soft tissues. Histopathology shows non-caseous granulomas and multinucleated giant cells. The exact etiology is unknown, although genetic background, immunological irregularities, and systemic or infectious diseases contribute to the onset of disease. There are no treatment guidelines. The usual treatment options include systemic or intralesional corticosteroids, a spectrum of antibiotics, and immunosuppressants. A 63-year-old patient presenting with lip swelling and simultaneous swelling of other facial soft tissues was diagnosed with granulomatous cheilitis. The symptoms occurred 3 weeks after SARS-CoV-2 infection. Initial treatment with systemic corticosteroids and antihistamines was inadequate. Here we report successful treatment with a combination of doxycycline and metronidazole.

Keywords: granulomatous cheilitis, facial edema, antibiotic therapy, SARS-CoV-2

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Introduction

Granulomatous cheilitis (GC) or Miescher's cheilitis is a rare granulomatous disorder characterized by recurrent lip swelling. It can occur as part of Melkersson–Rosenthal syndrome, consisting of orofacial edema, peripheral facial nerve paresis, and fissured tongue. The entire triad rarely occurs in one patient (1). Histopathological examination is necessary to obtain a correct diagnosis and exclude other conditions that cause facial edema. Perivascular lymphocyte infiltrate, non-caseous granulomas, and multinucleated giant cells are usually observed, although only minimal infiltrates and edema can be seen in early stages of the disease (2). GC can be resistant to treatment, and there are no uniform guidelines. Cases of treatment with systemic and intralesional corticosteroids, antileprosy drugs, antibiotics, and immunosuppressants are described in the literature. More prominent swelling sometimes requires surgical correction (3).

We report a case of a patient with GC that occurred 3 weeks after SARS-CoV-2 infection. Initial treatment with systemic corticosteroids was inadequate. Remission was achieved after supplementary antibiotic treatment with doxycycline and metronidazole.

Case report

A 63-year-old patient presented to our emergency department in May 2021. She reported recurrent upper lip, cheek, nose, and forehead swelling for 2 months. The swelling was most prominent during the day; it decreased during the night but never fully disappeared. Worsening of edema appeared approximately once per week. The swelling was most prominent on the upper lip, with the right half being more affected. She reported skin tightness, an occasional tingling sensation, and mild pruritus. She denied having trouble breathing or feeling a lump in her throat. Approximately 3 weeks before the onset of the swelling, she suffered from a 1-week loss of smell that was subsequently diagnosed and confirmed with a PCR test as part of a SARS-CoV-2 infection. Her family doctor prescribed oral methylprednisolone 32 mg per day for 2 days and loratadine 10 to 20 mg per day for 5 days. During that period, the swelling almost disappeared, but it reappeared after a short period of time. Her drug history included rosuvastatin 30 mg OD and occasional paracetamol and ibuprofen. She had no known allergies. Her family history was unremarkable for cutaneous disorders, and her niece had been treated for systemic lupus erythematosus.

Clinical examination revealed firm swelling of the upper lip, more prominent on the right side. Infiltrate with erythema was also present on the cheeks and the forehead, and it was relatively well demarcated (Fig. 1). Other parts of the body were unaffected, and there were no hives. No changes to the tongue and oral mucosa were observed. Neurological examination revealed no deficits.

Differential diagnosis included infectious diseases (erysipelas, leprosy, tuberculosis, histoplasmosis, and cutaneous leishmaniasis), angioedema, urticaria, allergic contact dermatitis, malignancies (lymphoma and sarcoma), systemic diseases (Crohn's disease and sarcoidosis), and oral diseases (dental abscess).

Basic laboratory tests were in the normal range, including total IgE and serum protein electrophoresis. Sedimentation rate (35 mm/h) and triacylglycerides (2.0 mmol/l) were slightly elevated. Tumor markers were negative. C3 was slightly elevated (1.237), whereas C4 and C1-inhibitor of complement were in the normal range. Autoantibodies (ANA, ANCA, and anti-DNA) were negative. Hepatitis serology and QuantiFERON-TB tests were negative. Glucose-6-phosphate dehydrogenase level was reduced (1.68). The angiotensin-converting enzyme level was in the normal range. X-rays of the chest, feet, and hands revealed no pathological changes.

The histology report following a skin biopsy near the border of the upper lip showed spongiosis, focal basal vacuolization, some basal lymphocytes, and mild dermal edema. Distinct perivascular, perifollicular, and interstitial inflammatory infiltrate of lymphocytes and macrophages with associated individual eosinophilic granulocytes was observed in the superficial and deep dermis and in the subcutis. Multinucleated giant cells and poorly demarcated interstitial granulomas were also observed (Fig. 2).

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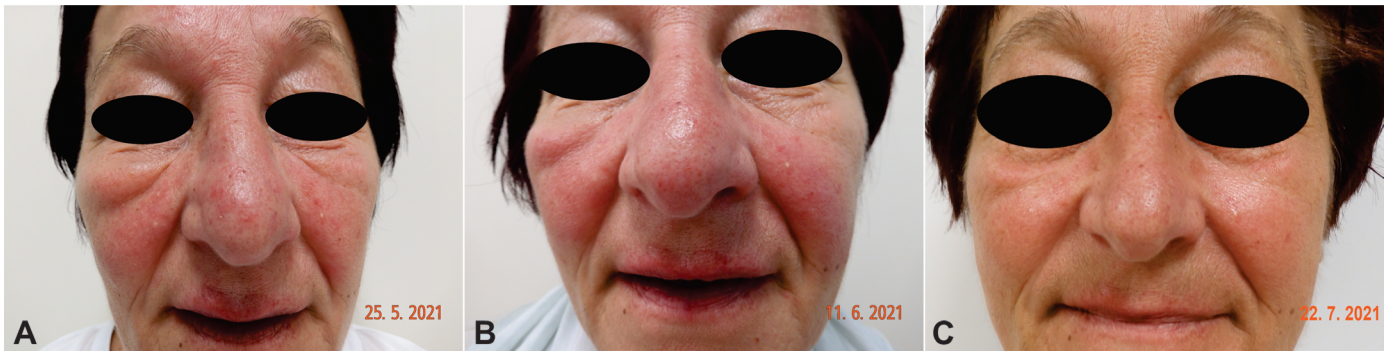

Figure 1 | a) Facial swelling and erythema in the patient at first presentation, b) after 2 weeks of treatment with methylprednisolone, c) 6 weeks after treatment with a combination of antibiotics and oral corticosteroid.

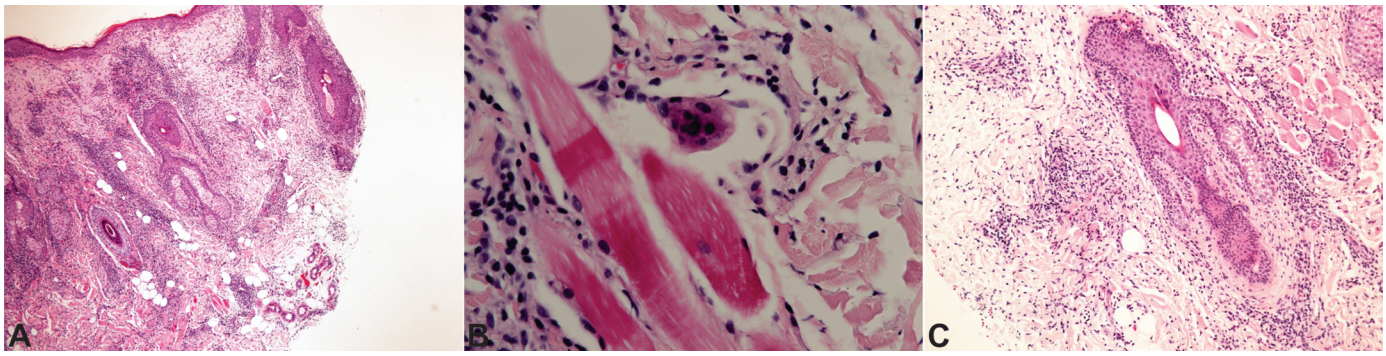

Figure 2 | Histological findings in skin biopsy: a) epidermal changes, mild dermal edema, inflammatory cell infiltrate, b) multinucleated giant cell, and c) interstitial granuloma.

The findings described are usually not present in urticaria or Quincke's edema (a more prominent edema, no granulomatous component, no epidermal changes, and fewer inflammatory cells would be observed here), and so we excluded these two diagnoses. The findings were consistent with GC.

Treatment with fexofenadine 180 mg QDS was initiated at the first visit in May 2021; no improvement was observed at the patient's subsequent follow-up appointment after 3 weeks. The patient was then administered 4 mg/kg clemastine intravenously for 3 days. Reduction of tension on the facial skin was reported, but facial edema and erythema persisted. Subsequently, oral methylprednisolone 20 mg per day was commenced. The patient was instructed to eat a healthy diet and to monitor her blood pressure daily. Three days later, a reduction in cheek swelling and erythema was observed, and other parts of the face improved as well.

After 2 weeks (in mid-June 2021), we observed further improvement of the patient's condition (Fig. 1). The methylprednisolone dose was subsequently reduced to 16 mg per day, and instructions were given for gradual reduction of the dose at home. Subsequently we performed *Borrelia burgdorferi* serology, and the results showed negative IgM but positive IgG antibodies (17 points). We therefore initiated treatment with metronidazole 400 mg BD for 10 days and doxycycline 100 mg BD for a month.

At a 6-week follow-up visit (at the end of July 2021), minimal erythema of the lips and lower half of the forehead and very subtle upper lip swelling persisted. Methylprednisolone was gradually discontinued by the end of September. At her last follow-up appointment in November 2021, no swelling was observed, and only minimal erythema of the cheeks and forehead (Fig. 1). The patient stated that she had these symptoms before the onset of GC.

Discussion

GC is a rare granulomatous disorder characterized by recurrent lip swelling. However, patients can present with edema of the cheeks, chin, eyelids, and oral mucosa. Over time, the swelling can persist and become indurated. The approximate incidence of disease is 0.08%. It occurs more commonly in adults 20 to 40 years old. Children are rarely affected. Women are believed to be more prone to the disease. Cases of multiple patients from the same family have been described (1).

Other nomenclature is often used for the same condition in the literature. Melkersson–Rosenthal syndrome consists of recurrent or permanent facial edema, fissured tongue (*lingua plicata*), and peripheral facial nerve palsy. The classic triad occurs in one-third of patients. GC can be considered a monosymptomatic form of the syndrome. *Orofacial granulomatosis* is another term, defined as persistent edema of the orofacial soft tissues with histological evidence of non-caseous granulomas in the absence of other systemic disorders; for example, sarcoidosis or Crohn's disease. It can be used to describe both GC and Melkersson–Rosenthal syndrome.

Clinically, it is difficult to differentiate GC from Morbihan disease, a rare type of lymphedema or chronical facial swelling associated with rosacea. The histological picture is similar to that in GC (edema, non-caseous perilymphatic granulomas, and dilated or obstructed lymph vessels). *Demodex* spp. mites can sometimes be seen. Bilateral lymphedema on the upper half of the forehead without lip swelling or facial nerve involvement can lead to a diagnosis of Morbihan disease (1, 4).

The literature shows that GC could be of multifactorial origin. Studies associate the disease with some genetic variants of human leukocyte antigen (HLA) or irregular immunological T lymphocyte response. Allergies to dental materials or food, hypersensitivity to ultraviolet B radiation, and underlying Crohn's disease are also described as triggers of the disease. Some studies describe GC as an extraintestinal manifestation of Crohn's disease, which can develop in those patients after a long period of time, although less than 1% of patients with Crohn's disease have concurrent GC.

Moreover, mycobacterial, fungal, or viral infections (cytomegalovirus, Epstein–Barr, varicella-zoster, and herpes simplex virus) are all associated with onset of the disease. Infection with spirochetes has been described in some patients with GC, but opinions on the correlation differ. However, a good response to treatment with penicillin has been described (5).

Our patient reported being infected with SARS-CoV-2 virus 3 weeks before the onset of the first symptoms. At the time of writing this article, there is only one case report in the literature describing a patient with Melkersson–Rosenthal syndrome that occurred after a mild infection with SARS-CoV-2. The disease in this patient occurred earlier and was in remission for years. Further studies are required, but, as far as it is currently known, SARS-CoV-2 can induce different skin disorders, and therefore we cannot exclude a possible correlation (6).

GC can be very resistant to therapy, and there are no uniform guidelines. Systemic corticosteroids are often used; the symptoms improve in 50 to 80% of cases, and recurrences are reduced in 60 to 75% of patients. They are often observed in cases with simultaneous palsy of the facial nerve. Successful treatment with infliximab and adalimumab has been reported, especially in patients with underlying Crohn's disease, oral mucosa involvement, and high C-reactive protein levels. Localized edema responds well to intralesional corticosteroids (e.g., triamcinolone acetonide), and recalcitrant cases sometimes require surgery. Moreover, dapsone is thought to inhibit prostaglandins and leukotrienes, and to lower neutrophil activation, but our patient had low glucose-6-phosphate dehydrogenase, and this was not an option for her (7). Tetracyclines and metronidazole have been mentioned as successful therapy for GC, either in various combinations, as monotherapy, or in combination with oral corticosteroids. Their anti-inflammatory action can lead to rapid improvement, and they are widely available and cost-effective (8).

Conclusions

GC is a rare granulomatous disorder. One possible factor that caused the disease in our patient could be a SARS-CoV-2 infection or *Borrelia burgdorferi* infection. Other etiological factors or systemic diseases that could have triggered the disease were unknown to us. Therapy with systemic corticosteroids and antihistamines was inadequate. Lip and facial swelling improved satisfactorily with doxycycline and metronidazole, leading to full remission.

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