CASE REPORT

Management of Cheilitis Granulomatosa with Pica Disorder: A Rare Case Report

Usha Dayanarayana[1], Shilpa P Shastry[2], Ramamurthy T Kempegowda[3], Nikitha Sridhar[4], Naveen N Kumar[5], Mahesh B Srinivasreddy[6]

Abstract

Aim: To report a rare case of cheilitis granulomatosa (CG) with pica disorder presented as chronic persistent lip swelling with an unusual eating disorder.

Background: Cheilitis granulomatosa or Miescher's cheilitis is a rare, persistent, or recurring nontender chronic painless swelling of one or both the lips due to granulomatous inflammation, which was first described by Miescher in 1945. It can present as a monosymptomatic form or as a part of other entities of Melkersson–Rosenthal syndrome (MRS).

Case description: A 14-year-old female patient presented with persistent diffuse swelling of the upper lip for 1 year. She also had an unusual habit of eating clay, mud, and potentially harmful items like flakes of paint for 1.5 years. Clinically, chronic persistent lip swelling involving upper lip and gingival enlargements were present along with systemic manifestations. Patient counseling with combination therapy showed excellent response with no signs of relapse at 6 months of follow-up.

Conclusion: Cheilitis granulomatosa is a unique rare inflammatory disorder with many possible contributory factors and exact etiology is poorly understood.

Clinical significance: This case report draws attention to constant exposure to an allergen that could be one of the possible etiological factors to CG secondary to pica eating disorder. Though it is a rare disease, research on the pathogenesis of CG and clinical trials evaluating the efficacy of the various treatments are needed to enhance our understanding of this disease, to improve the quality of life, as patients are very disturbed by the unsightly and distressing nature of macrocheilitis.

Keywords: Case report, Cheilitis granulomatosa, Intralesional steroids, Lip swelling, Melkersson–Rosenthal syndrome, Orofacial granulomatosis, Pica.

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Introduction

Cheilitis granulomatosa (CG) or Miescher's cheilitis is a rare, persistent, or recurring nontender chronic painless swelling of one or both lips due to granulomatous inflammation, which was first described by Miescher in 1945.[1,2] It can present as monosymptomatic or as a part of other entities. It is one of the most common monosymptomatic form of Melkersson–Rosenthal syndrome (MRS), characterized by a systemic granulomatous disease of unknown etiology with the classical triad of swelling of the lips, plicated tongue (lingua plicata), and recurring facial paralysis. MRS occurs in 8–25% of cases, whereas in about 28% of cases, it is presented with few symptoms, which usually include the only finding of CG. Cheilitis granulomatosa and MRS are both considered to be subsets of orofacial granulomatosis (OFG). Orofacial granulomatosis is idiopathic persistent and/or recurrent labial enlargement, along with oral ulcers, and a variety of orofacial features in the absence of any identifiable systemic conditions.[3] Cheilitis granulomatosa can also be seen in other systemic granulomatous conditions such as Crohn's disease or sarcoidosis,[4] or foreign body reactions, allergic reactions, immunological factors, delayed hypersensitivity response to an unrecognized antigen, chronic infections, and genetics.[5] The chronic nature of the inflammation of lips could lead to fibrosis and permanent lip swelling, as the etiology remains unknown, which makes treatment difficult, and relapses frequently. Hence, diagnosis and management remain challenging.

Pica is an unusual habit of eating disorder in which a person craves and consumes nonnutritive items like clay, mud, and flakes of paint. The disorder gets its name from magpie bird (Latin name—"*pica pica*") with the strange behavior of eating a variety of objects out of curiosity.[6] Prevalence rates of pica range from 4% in men, 27.8–68% in pregnant women, and about 25–33% in children. However, most of the patients with pica disorder may hide their behavior or be reluctant to mention it. It has been observed in men and women of all ages and ethnicity, but prevalence is more among lower socioeconomic classes. The etiology of pica remains unknown, but the risk factors for developing this eating disorder include pregnancy, psychological factors associated with stress, child neglect,

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abuse, maternal deprivation, mental health disorder, iron deficiency anemia, nutritional deficiency, autistic disorder, and epilepsy.

The objective of this paper is to present a rare case of CG associated with pica, its clinical presentation, and systematic investigations that helped us to diagnose this condition. Also, treatment efficacy to the series of intralesional dexamethasone injections to the lips along with systemic steroids and other treatments for pica disorder with 6 months follow-up are discussed.

Case Description

A 14-year-old female patient presented with persistent diffuse swelling of the upper lip for 1 year and diffuse gingival enlargement along with bleeding gums of the upper and lower anterior gums for 2 months. There was no other facial involvement. Her personal history revealed that she had an unusual habit of eating clay, mud, and potentially harmful items like flakes of paint for 1.5 years. Her medical history revealed high serum immunoglobulin E (IgE) levels and puberty menorrhagia from the past 1 year. There were no other systemic symptoms noted, including respiratory and gastrointestinal symptoms. She had no family history of atopy, Crohn's disease, and was not under any medications.

Upon clinical examination, there was a localized symmetrical swelling of the upper lip with a slight pale pink color. The upper lip tissues had a uniform smooth surface, firm in consistency, nontender without any nodular formations (Fig. 1). Intraoral examination revealed diffuse gingival enlargement (involving marginal, interdental, and attached gingiva) in the anterior compartment of maxillary and mandibular gingiva extending and covering two-thirds of the labial aspect of the tooth structures (Fig. 2). There was no evidence of facial nerve palsy, fissured tongue, cobblestone appearance of the oral mucosa, or oral ulcers. Regional lymph nodes were not enlarged. Based on the history and clinical findings, a provisional diagnosis of CG of the upper lip conditioned gingival enlargement along with pica was given. Differential diagnosis of cheilitis glandularis and Crohn's disease was considered.

The patient had initially been prescribed with an antihistamine—fexofenadine 180 mg for 7 days (considering increased IgE levels and constant exposure of allergens), and anthelmintic—albendazole 400 mg (for deworming). The patient was then referred for a series of serological investigations, incisional biopsy, and radiological and gynecological evaluation.

Serological investigations: Complete hemogram, peripheral blood smear, erythrocyte sedimentation rate, liver function test, and serum IgE levels were advised. Blood chemistry analysis revealed low hemoglobin levels 8.9 gm/dL with high total white blood count and absolute neutrophil count. Peripheral

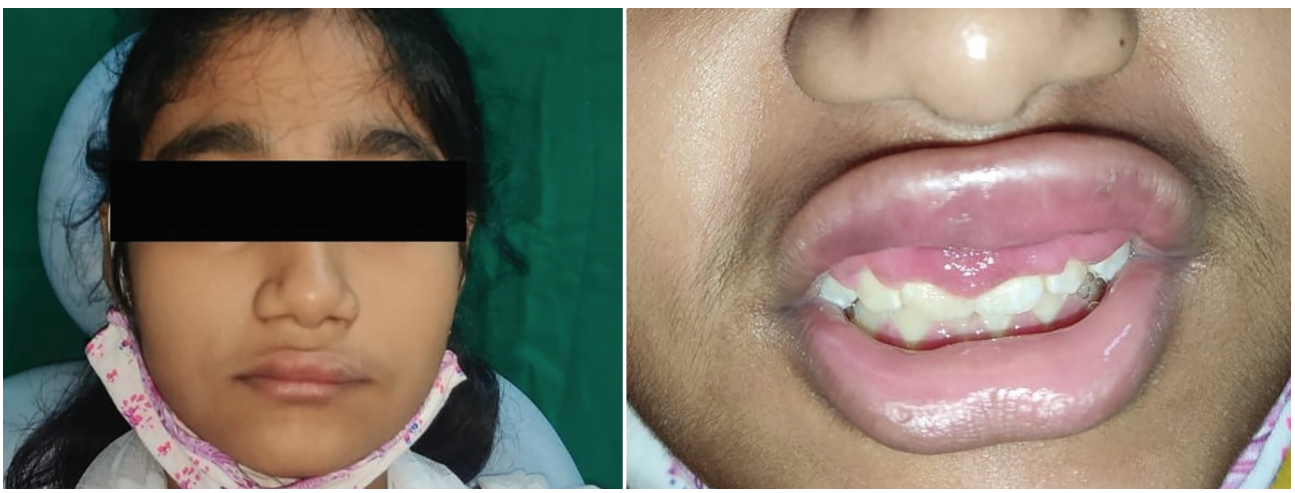

Fig. 1: Preoperative photograph showing diffuse swelling of the upper lip

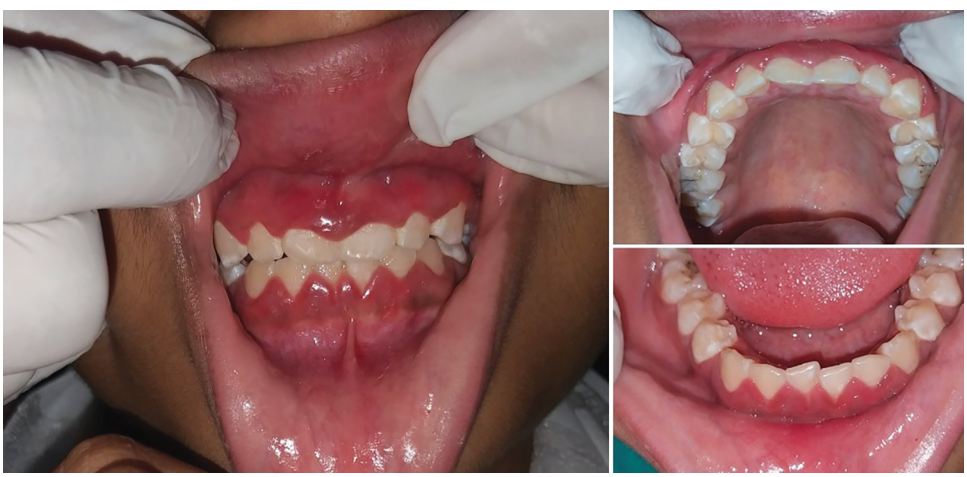

Fig. 2: Preoperative photograph showing maxillary and mandibular anterior gingival enlargement; no enlargement seen in the maxillary and mandibular posterior teeth

smear showed dimorphic anemia of moderate degree with a characteristic sign of two deficiencies—iron deficiency and nutritional macrocytic anemia, with neutrophilic leukocytosis. The absolute eosinophil count and serum IgE were at a higher range. There were no hemoparasite seen. Vitamin B_{12} was within normal levels but toward the lower range. Hormonal assays including thyroid function tests, follicular-stimulating hormone (FSH), and luteinizing hormone (LH) were within the normal limits. Gynecologist evaluation revealed the normal structure of the uterus and pelvis without any evidence of local causes for menorrhagia.

Ultrasonography: Abdomen and pelvis ultrasound revealed no abnormalities in the liver, gall bladder, spleen, pancreas, kidney, stomach, intestines, ovaries, and uterus.

Orthopantomography: It revealed interdental horizontal bone loss in the maxillary anterior region with no gross bony pathology (Fig. 3).

Incisional biopsy: Biopsy samples were taken from the upper lip and gingiva to confirm the diagnosis. The microscopic analysis provided a histopathological report with marked hyperplastic parakeratotic stratified squamous epithelium with underlying connective tissue containing perivascular aggregates of lymphocytes and plasma cells. A well-formed noncaseating granuloma containing lymphocytes, macrophages, and a few multinucleated giants were seen along with a discrete collection of lymphocytes which is suggestive of CG. Biopsy of gingival tissue on H&E staining at ×40 showed the presence of hyperplastic nonstratified squamous epithelium with underlying connective tissue. The connective tissue showed diffuse chronic inflammatory cells chiefly lymphocytes and plasma cells with few collagen fiber bundles suggestive of inflammatory gingival enlargement (Fig. 4).

Treatment: After the initial prescription of antihistamines and albendazole, the patient was reviewed after 1 week but the swelling was persistent and did not subside. On histopathological confirmation of CG, intralesional injection corticosteroid (dexamethasone 8 mg/mL, 2 mL every 15 days once for 45 days) for upper lip was injected (Fig. 5). Systemic prednisolone was also prescribed, 20 mg per day for the 1st week followed by 10 mg per day for 2nd week, and then tapering off the dose in the subsequent weeks. The lip swelling reduced markedly after the first 15 days course of treatment. Then after the two sessions of intralesional injection along with a tapered dose of tablet wysolone, there was complete resolution of lip swelling noted and the patient was happy with the results (Fig. 6). Iron sucrose (200 mg/100 mL) intravenous (IV) infusion twice a week for 2 weeks, oral ferrous ascorbate with folic acid, vitamin supplements with zinc were prescribed for

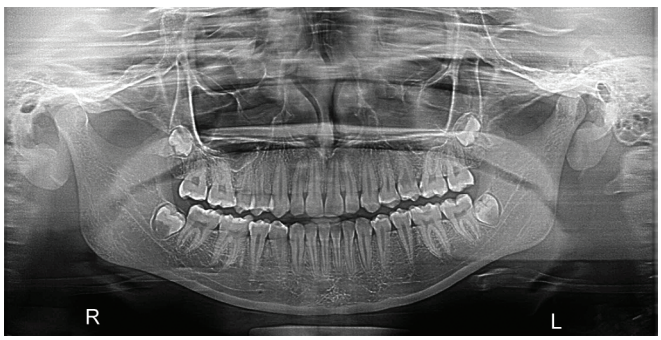

Fig. 3: Panoramic radiograph showing mild bone loss in the maxillary anterior region

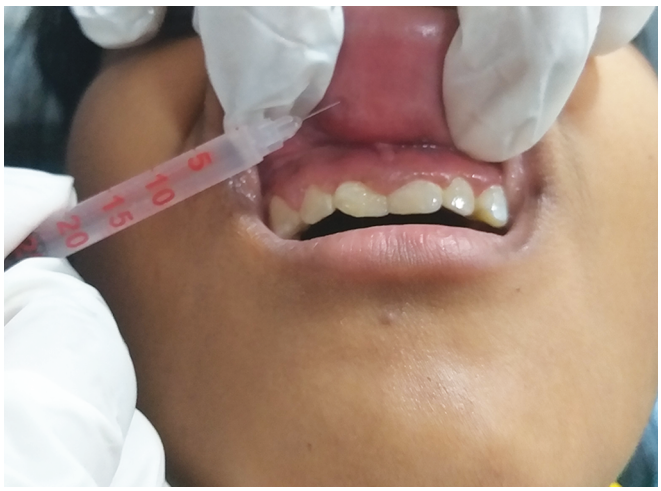

Fig. 5: Intralesional corticosteroid injection to the upper lip

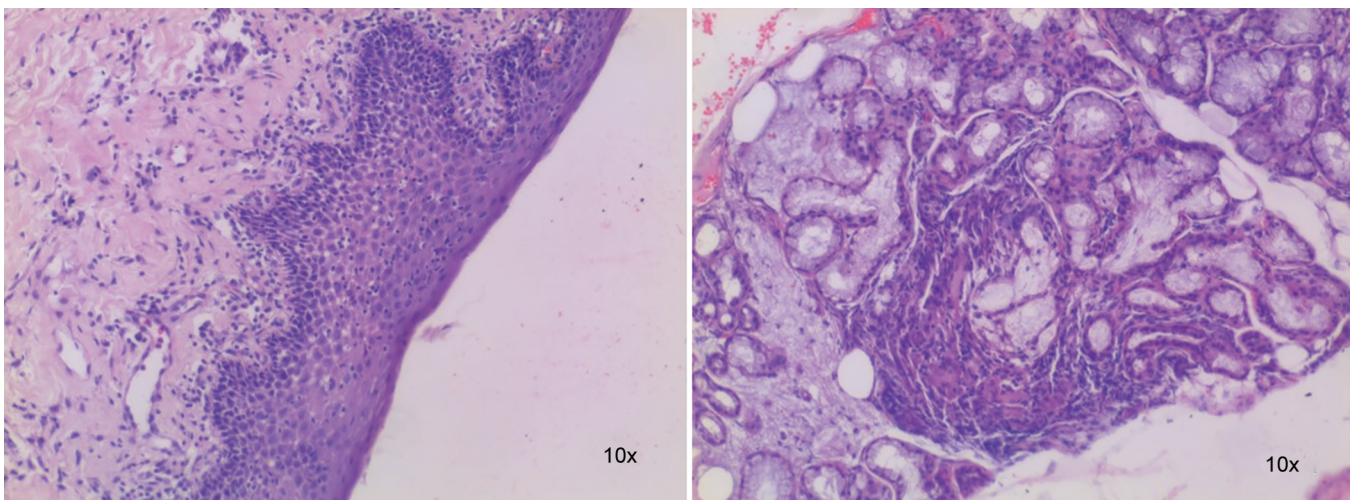

Fig. 4: Histopathology showed noncaseating granuloma along with macrophages, multinucleated giant cells, and lymphocytes

3 months to restore the balance of her systemic condition. For stabilization of menstrual cycles, oral contraceptive pills containing progesterone were advised for 3 months.

For gingival enlargement, treatment of scaling and root planning was done initially. After 14 days of phase I therapy, the gingival tissue became more firm due to the reduction of the edematous component of the enlargement. Then, her hemoglobin and serum IgE levels reports revealed an increase in hemoglobin (Hb 11.3 gm%) percentage, and serum IgE levels were 46.40 IU/mL within the biological reference value. Thereafter, a laser gingivectomy and gingivoplasty was done in the anterior region of the maxilla and mandible under local anesthesia, and the periodontal dressing was placed for 1 week. After gingivoplasty, the size and contour of the gingiva was restored (Fig. 7).

Discussion

The etiology of CG remains unknown or poorly understood; many factors have been implicated including genetic predisposition, mycobacterial infection, foreign body reactions, allergy to foods, additives, cinnamon compounds, benzoates, dietary factors, and atopy. CG has no predisposition to race and gender.[7,8] The incidence has been estimated at 0.08% in the general population and can occur at any age, including childhood, but most frequently in the 2nd or 3rd decade.[2] It is difficult to diagnose and treat CG due to unknown etiology, highly varied clinical presentation, and recurrence.

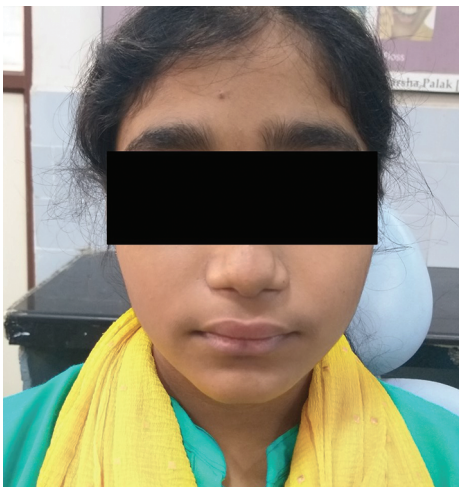

Fig. 6: Postoperative photograph

Our case presented with swelling of the upper lip as a single sole manifestation not accompanied by any other signs like fissured tongue, facial paralysis, facial involvement, or systemic involvement, ruling out MRS, OFG, or other disease entities. The differential diagnosis for diffuse swelling of the upper lip includes CG, cheilitis glandularis, angioedema, foreign body reaction, and sarcoidosis. In our case, based on history and clinical findings, we considered only CG and cheilitis glandularis as differential diagnoses. Differentiating each entity and diagnostic protocol is explained in Table 1 and Figure 8, respectively.

Therapeutically, a wide range of treatment modalities has been implemented for CG. Elimination diets have also been advocated in many cases to identify and eliminate food allergens. Antihistamines, topical, intralesional, and systemic corticosteroids, or combination therapy have been used for the treatment of CG. In our case, the first line of treatment included intralesional steroid injection and oral-systemic corticosteroid administration. Rapid improvement was noted within 3 weeks and the patient showed no recurrence at 1, 3, and 6 months' follow-up. Bacci and Valente had excellent success in one patient with intralesional injections of 40 mg triamcinolone once a week for a total of three administrations; there was a fast improvement with no recurrence at 1, 3, 6, or 12 months' follow-up.[9] Other alternative therapeutic agents include hydroxychloroquine, clofazimine, methotrexate, azathioprine, metronidazole, thalidomide, minocycline, dapsone, danazol, and tumor necrosis factor alpha blocking agents such as infliximab and adalimumab.[10–14] Cheiloplasty is useful in patients with severe disfigurement of the lips for esthetic improvement. Worsaae and Pindborg in 1980 noted that gingival swelling manifestation which may precede the lip swelling in their reported cases. Similarly, in our case, CG affected the upper lip first, followed by the anterior

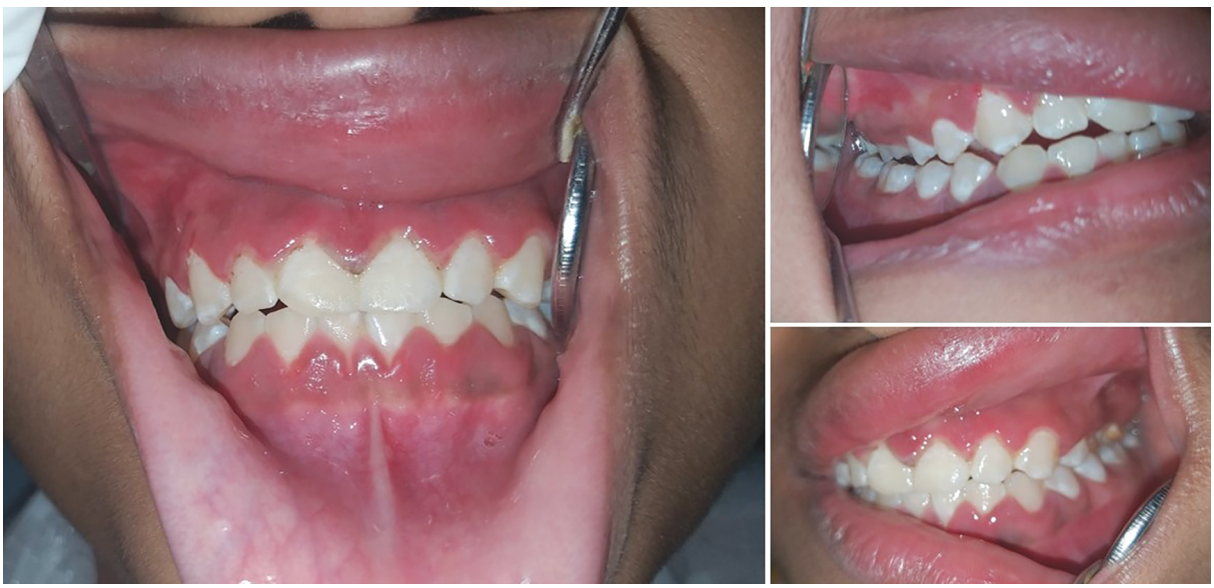

Fig. 7: Postoperative photograph after gingivectomy and gingivoplasty

Table 1: Differential diagnosis of CG

Feature	*CG*	*Cheilitis gladularis*	*Angioedema*	*Crohn's disease*	*Sarcoidosis*
History	Recurrence, rate of episodes, duration of swelling of lips. Based on this, lip could become persistent and indurated	Lip swelling produces beads of mucus on the surface, sometimes with pain and a purulent discharge	Allergic reactions to food or dental materials, infectious agents, and immunologic dysfunction, history of atopy	The detailed history of gastrointestinal symptoms of abdominal pain, distress, loose stools, anemia	History of cough, dyspnea, chest pain, fever, malaise, fatigue, arthralgia, weight loss, visual alteration
Clinical feature	Firm swelling of one or both lips	Swelling and eversion of the lower lip with hyperplasia of the salivary glands; secretion of a clear, thick mucus lower lip leading to erosion, ulceration, crusting, infection	Nonpitting edema of lips, tongue, pharynx, face	Inflammatory bowel disease with inflammation	A multisystem granulomatous disorder of lungs, liver, lymph nodes, skin, and eyes
Oral manifestation	Swelling of the upper lip, and less frequently, the lower lip. Changes in the buccal, palatal, sublingual, and gingival mucosa are anecdotally seen	Firm swelling of the lip with dilation of the orifices of the minor salivary gland ducts	Nonpitting edema of lips, tongue, pharynx, face	Diffuse lip swelling, linear ulcerations with a cobblestone appearance involving the buccal vestibule and mucogingival fold, aphthous-like ulcerations, or small suppurative ulcers such as pyostomatitis vegetans	Lip swelling or a submucosal nodule or multinodular swelling, isolated papule or ulceration, salivary gland enlargement, and xerostomia
Investigations	Biopsy	Reflectance confocal microscopy (RCM), biopsy	Serum IgE levels, patch test	Serum angiotensin-converting enzyme (ACE) levels erythrocyte sedimentation rate (ESR), and complete blood count (CBC), purified protein derivative (PPD) testing count, gastrointestinal tract evaluation, colonoscopy or gastroduodenoscopy	ESR to rule out sarcoidosis high-resolution computed tomography scan of the chest, serum ACE levels and PPD testing, Kveim test

maxillary and mandibular gingival enlargement. However, the therapeutic response of patients with CG is often unpredictable and spontaneous remissions and recurrences are common.

The presence of iron deficiency in our case might have led the patient to the unusual craving of eating habit of clay, mud, and flaking paint nonnutritive items as the body was trying to replenish low iron and nutrient levels. The etiology of pica remains unclear, but it is significantly associated with iron deficiency anemia. After patient counseling for discontinuing of habit and dietary modification along with iron supplements and injections, the patient's unusual behavior was ceased. Many studies and case reports show an association between iron deficiency anemia and pica similar to our case.[15–18]

So far, to the best of our knowledge, there is no case of CG associated with pica disorder that has been reported in the literature. Attributing allergy to be one of the etiological agents in causing CG, the patient's eating habit might have one of the allergens as contributing factor to initiate CG. The fact that her high serum IgE levels also indicated the allergic reaction in this patient. Along with this, eosinophil counts were at the higher end, again pointing out to allergic response. The patient responded well to the corticosteroids therapy indicating a decrease in absolute eosinophil count, and serum IgE levels in the patient. After iron therapy and nutritional supplements, the patient discontinued the unusual eating habit thereby restoring her hemoglobin levels to normal. The patient did not give a history of recurrence in a 6-month follow-up, further substantiating that all these were interrelated and one of the allergic factors in her pica disorder-induced CG in our case.

Increased white blood cell (WBC) and neutrophil count are suggestive of infection. In our case, both were elevated, possibly because of low-grade infection that the body was suffering secondary to the consumption of clay. Parasites like *Toxocara* and *Ascaris*[19–21] present in the clay could have initiated this low-grade infection leading to increased counts. Hence, an anthelmintic agent, albendazole 400 mg was prescribed to eliminate these infectious agents.

Clinical Significance

Cheilitis granulomatosa is a unique rare inflammatory disorder with many possible contributory factors and exact etiology is poorly understood. Hence, treatment outcome is few and could be challenging. This case report draws attention to constant exposure to an allergen that could be one of the possible etiological factors secondary to pica eating disorder. Compounded to this, iron deficiency and malnutrition further increased her craving leading to cycles of events. With appropriate medical therapy, corticosteroids

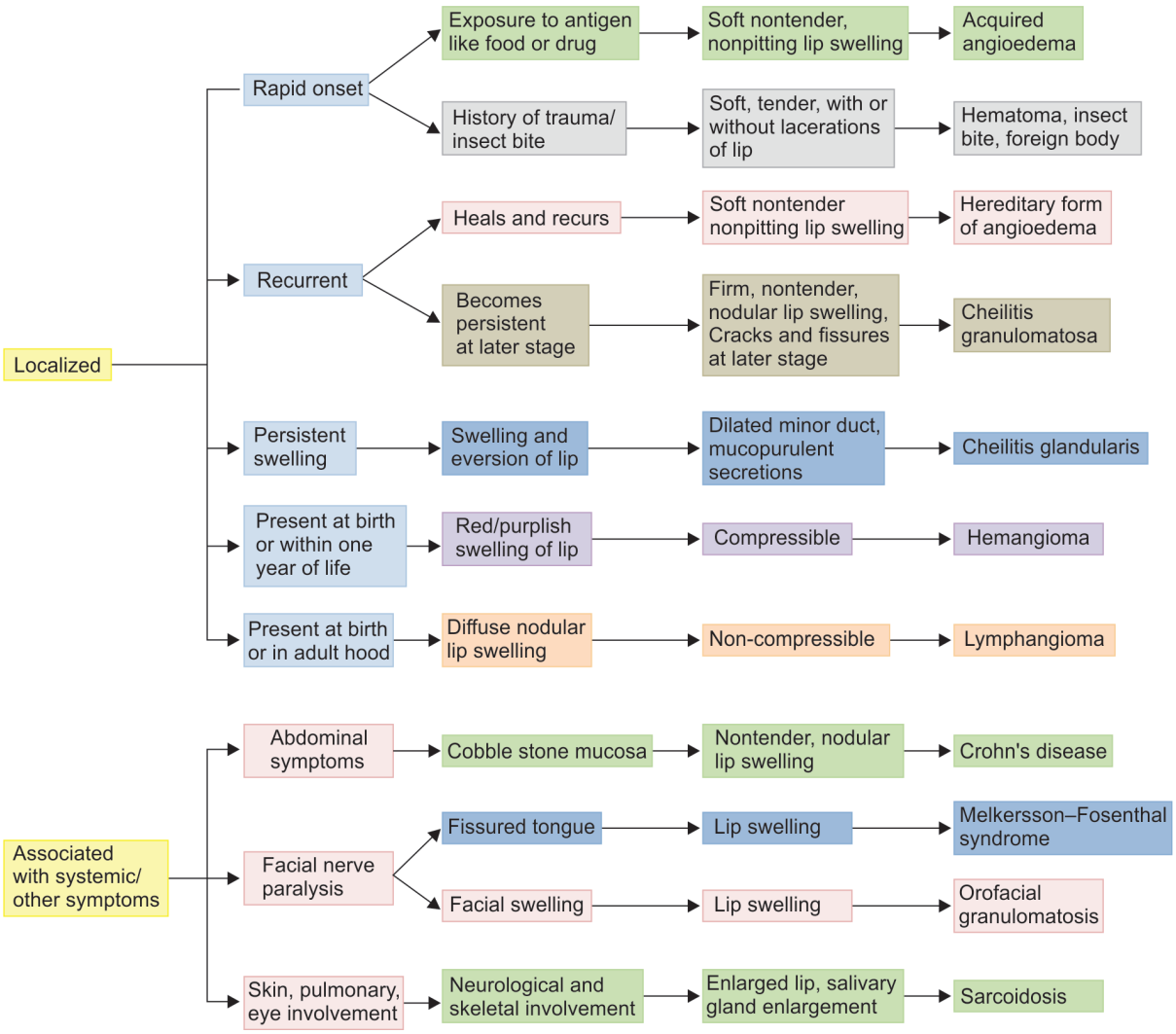

Fig. 8: Diagnostic protocol for diffuse lip swelling

therapy, dietary modifications, and counseling of patient and parents, the symptoms diminished with resultant improvement in her blood parameters. Hence, correct timely diagnosis is necessary keeping in mind that it is based on the correlation of patient's dietary, personal and medical history, clinical features, investigations, and histopathological findings which are crucial for appropriate treatment.

Conclusion

Though it is a rare disease, research on the pathogenesis of granulomatous cheilitis and clinical trials evaluating the efficacy of the various treatments are needed to enhance our understanding of this disease, to improve the quality of life, as patients are very disturbed by the unsightly and distressing nature of macro cheilitis.

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