

ACTAS Derma-Sifiliográficas

Full English text available at
www.elsevier.es/ad



ORIGINAL ARTICLE

Granulomatous Cheilitis: A Report of 6 Cases and a Review of the Literature[☆]

M.L. Martínez Martínez,^{*} J.M. Azaña-Defez, L.J. Pérez-García, M.T. López-Villaescusa, M. Rodríguez Vázquez, C. Faura Berruga

Servicio de Dermatología, Complejo Hospitalario Universitario de Albacete, Albacete, Spain

Received 2 September 2011; accepted 5 February 2012

Available online 27 September 2012

KEYWORDS

Granulomatous cheilitis;
Miescher cheilitis;
Melkersson-Rosenthal syndrome;
Granuloma

PALABRAS CLAVE

Queilitis granulomatosa;
Queilitis de Miescher;

Abstract

Introduction: Granulomatous cheilitis (Miescher cheilitis), a condition characterized by recurrent swelling of the lips, is the most common monosymptomatic form of the Melkersson-Rosenthal syndrome. The aim of this study was to study the characteristics of patients diagnosed with granulomatous cheilitis at the dermatology department of our hospital over a period of 17 years.

Material and methods: We performed a descriptive study of patients diagnosed with granulomatous cheilitis at our hospital between January 1993 and January 2010.

Results: The condition was diagnosed in 6 patients (4 women and 2 men), with a mean age of 49 years at the time of diagnosis. All the patients had recurrent swelling of the upper lip and 2 also had swelling in other parts of the face. The mean time from the onset of symptoms to the initial visit was approximately 16 months. There were no cases of facial palsy, and just 1 patient had a fissured tongue. None of the patients developed Crohn disease or any other granulomatous disorders during follow-up.

Conclusions: Granulomatous cheilitis is a rare disease. None of the patients in our series had gastrointestinal or neurologic symptoms. Accordingly, we believe that granulomatous cheilitis is an independent orofacial granulomatous disease which most often presents without accompanying signs or symptoms

© 2011 Elsevier España, S.L. and AEDV. All rights reserved.

Queilitis granulomatosa. Presentación de 6 casos y revisión de la literatura

Resumen

Introducción: La queilitis granulomatosa (QG) de Miescher representa la forma monosintomática más frecuente del síndrome de Melkersson-Rosenthal, que se caracteriza por una tumefacción labial recurrente. El objetivo de nuestro estudio fue describir las características de los pacientes con QG atendidos en nuestro servicio durante un periodo de 17 años.

[☆] Please cite this article as: Martínez Martínez ML, Azaña-Defez JM, Pérez-García LJ, López-Villaescusa MT, Rodríguez Vázquez M, Faura Berruga C. Queilitis granulomatosa. Presentación de 6 casos y revisión de la literatura. Actas Dermosifiliogr.2012;103:718-724.

^{*} Corresponding author.

E-mail address: mlmartinezm@sescam.jccm.es (M.L. Martínez Martínez).

Síndrome de
Melkersson-
Rosenthal;
Granuloma

Material y métodos: Estudio descriptivo de los pacientes diagnosticados de QG atendidos en el Departamento de Dermatología desde enero de 1993 hasta enero de 2010.

Resultados: Se recogieron un total de 6 pacientes, con un ligero predominio femenino (4 mujeres y 2 hombres), y una media de edad al diagnóstico de 49 años. Todos presentaban una tumefacción en el labio superior, persistente y recurrente, junto con afectación de otras regiones faciales en 2 casos. La media de tiempo desde la aparición de los síntomas a la consulta inicial fue de aproximadamente 16 meses. En ningún paciente se observó la presencia de parálisis facial y únicamente se objetivó lengua fisurada en un caso. Durante los años de seguimiento ningún paciente fue diagnosticado de enfermedad de Crohn ni de otra enfermedad granulomatosa.

Conclusión: La QG es una entidad infrecuente. Ninguno de los pacientes evaluados ha presentado sintomatología gastrointestinal o neurológica asociada, por lo que consideramos la QG de Miescher una patología independiente dentro del grupo de las granulomatosis orofaciales, no asociada a otros síntomas o signos como forma de presentación más frecuente.

© 2011 Elsevier España, S.L. y AEDV. Todos los derechos reservados.

Introduction

Granulomatous cheilitis (Miescher cheilitis) is a rare condition that presents with recurrent swelling of the lips. It is the most common monosymptomatic form of Melkersson-Rosenthal syndrome, which is characterized by edema of the lips, facial palsy, and fissured tongue. In 1985, Wiesendorf et al.¹ coined the term orofacial granulomatosis to describe a series of noninfectious, nonnecrotizing granulomatous disorders of the lips, face, and oral cavity that included granulomatous cheilitis, Crohn disease, and sarcoidosis. Orofacial granulomatosis is therefore an umbrella term that encompasses a number of entities of diverse etiology, pathogenesis, and clinical features.

The aim of this study was to describe the characteristics of patients treated for granulomatous cheilitis in our department over a 17-year period.

Material and Methods

We created a register of patients diagnosed with granulomatous cheilitis at the dermatology department of Hospital General Universitario de Albacete between January 1993 and January 2010. Only cases with both clinical and histologic confirmation were included. A list of patients who satisfied these criteria was obtained from the diagnostic database of the hospital's pathology department. Once the patients had been identified, we reviewed their medical histories and recorded their clinical data and course. Patients with a clinical diagnosis not confirmed by histology were excluded. The variables analyzed included sex, age at diagnosis, past history, family history, site of the lesions, associated signs and symptoms, time from onset to diagnosis, histopathology findings, additional tests (complete blood count; erythrocyte sedimentation rate; C-reactive protein levels; biochemistry; thyroid stimulating hormone levels; autoimmunity studies; immunoglobulin [Ig] levels; angiotensin-converting enzyme levels; serology for hepatitis B and C viruses and human immunodeficiency virus; chest

radiography; and Mantoux test), treatment prescribed, clinical course, and duration of follow-up.

Results

Six patients (4 women and 2 men) were included in the study (Table 1). The mean (SD) age at the time of diagnosis was 49.8 (15.1) years (range, 29-74 years). The mean time from symptom onset to hospital arrival was 15.83 (10.13) months (range, 3-26 months). All of the patients had persistent, recurrent swelling of the upper lip (Figs. 1-3). Two patients (33.33%) also had swelling in other parts of the face: patient 4 had swelling of the gums as well as the upper lip and patient 6 had lesions in the perioral region, cheeks, and submandibular region in addition to the upper lip (Fig. 4). In patient 6, a submandibular ultrasound imaging study showed enlarged cervical lymph nodes greater than 1 cm in diameter but was otherwise normal. A biopsy of 1 of the enlarged nodes was histologically consistent with granulomatous lymphadenitis; all other possible etiologies were ruled out.

None of the patients had facial palsy, and just 1 (16.66%) had a fissured tongue. In all cases, the clinical diagnosis was followed by a biopsy of the lip; the findings were consistent with granulomatous cheilitis and staining was negative for acid-fast bacilli, fungi, and spirochetes. Granulomatous inflammation (Fig. 5) was observed in 4 patients (66.66%) and nonspecific chronic inflammation (Fig. 6) was observed in 2 patients (33.33%). The patients underwent a chest radiograph, a Mantoux test, serology for hepatitis B and C viruses and human immunodeficiency virus, and laboratory tests including angiotensin-converting enzyme levels, erythrocyte sedimentation rate, and IgA levels; all tests were normal or negative. None of the patients had a family history of labial swelling, a personal history of neurologic, digestive, or respiratory symptoms, or a previous diagnosis of a granulomatous disease. One patient had lichen planus with good symptom control and no oral involvement. Another patient had been diagnosed as a child with allergic contact dermatitis due to nickel salts; however, she denied having had contact with nickel, had no dental implants, and presented no skin lesions. The same patient reported having

Table 1 Data on Patients Included in the Study.

Patient	Age	Sex	Past History	Site	Facial Palsy	Fissured Tongue	Onset to Diagnosis, mo	Additional Tests	Histopathology	Treatment	Outcome	Follow-up, y	Subsequent Diagnoses
1	49	Male	None	Upper lip	None	None	26	Normal	Histiocytic granulomas	Infiltration of triamcinolone (0.1%) Sulfone	Improvement	17	Carcinoma of the bladder Ischemic heart disease
2	57	Female	None	Upper lip	None	None	6	Normal	Histiocytic granulomas	Unknown	Unknown	0	Unknown
3	42	Female	Pregnancy	Upper lip	None	Yes	12	Normal	Nonspecific granulomatous inflammation	Oral corticosteroids	Improvement	14	Dermatophytosis of the upper lip
4	74	Female	Diabetes mellitus	Upper lip	None	None	24	Normal	Epithelioid granulomas	Infiltration of triamcinolone (0.1%) Tetracyclines	Improvement	4	Leukocytoclastic vasculitis
5	48	Male	Lichen planus	Gums of the upper jaw Upper lip	None	None	3	Normal	Nonspecific granulomatous inflammation	Oral corticosteroids	Improvement	1	Cholecystitis
6	29	Female	Sensitization to nickel	Upper lip Submandibular region Perioral region Cheeks	None	None	24	Normal	Epithelioid granulomas	Oral corticosteroids Infiltration of triamcinolone (0.1%) Hydroxychloroquine Tetracyclines Antihistamines Amoxicillin-clavulanic acid	Recurrence	8	Hypothyroidism



Figure 1 Persistent swelling of the upper lip in patient 6.



Figure 2 Edema of the upper lip in patient 1.



Figure 3 Swelling of the upper lip in patient 5.

had recurrent episodes of periodontitis that were treated with antibiotics, were not associated with the exacerbation of granulomatous cheilitis, and did not coincide with flare-ups of the disease. No foci of infection associated with a worsening of the lesions were detected in any of the other cases.

The patients were prescribed different treatments—including infiltration of triamcinolone (0.1%), sulfone, oral corticosteroids, tetracyclines, hydroxychloroquine, and



Figure 4 Involvement of the perioral region, including the submandibular region and both cheeks in patient 6.

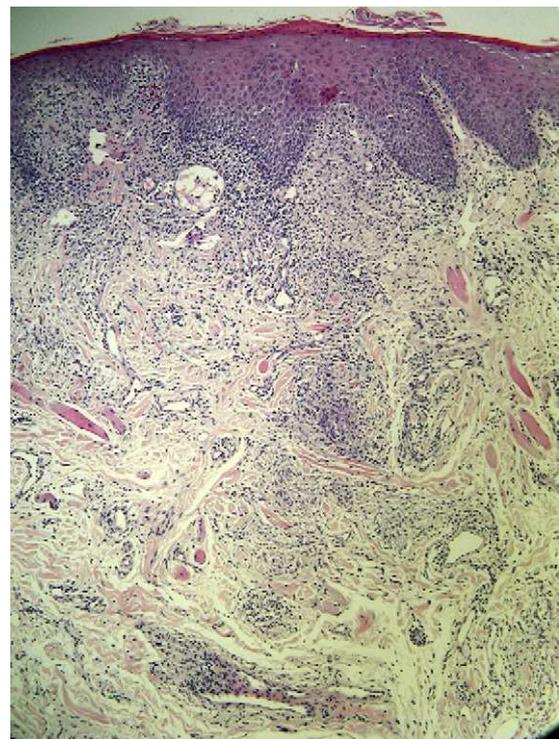


Figure 5 Granulomatous dermatitis with superficial and deep mixed perivascular infiltrate in patient 5 (hematoxylin-eosin, original magnification $\times 40$).

amoxicillin-clavulanic acid—depending on the severity of the manifestations. Improvement was achieved in most of the patients; the manifestations recurred in 1 patient and another patient was lost to follow-up. Excluding the latter patient, the mean follow-up period was 8.8 (6.68) years (range, 1-17 years). None of the patients was diagnosed with

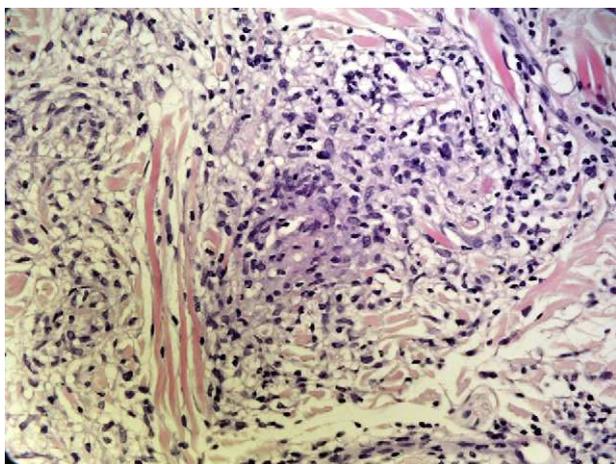


Figure 6 Poorly defined, noncaseating epithelioid granulomas in patient 6 (hematoxylin-eosin, original magnification $\times 400$).

Crohn disease or any other granulomatous disease during the follow-up period.

Discussion

Melkersson-Rosenthal syndrome is a systemic granulomatous disease of unknown etiology characterized by the triad of orofacial edema, facial palsy, and fissured (or scrotal) tongue. The complete triad is present in 8% to 25% of patients diagnosed with Melkersson-Rosenthal syndrome, while oligosymptomatic forms of the condition account for 47% of cases. In 28% of cases, orofacial swelling or granulomatous cheilitis is the sole manifestation of the disease. Granulomatous cheilitis is the most common form of presentation of Melkersson-Rosenthal syndrome, observed in 80% of cases.²⁻⁵ Five of our patients (83.33%) had a monosymptomatic form of Melkersson-Rosenthal syndrome (granulomatous cheilitis), whereas just 1 patient (16.66%) had an oligosymptomatic form of the condition (swelling of the lips with fissured tongue). None of our patients had the complete form of the syndrome, nor did any of them present evidence of facial palsy or other neurologic signs or symptoms.

The etiology of granulomatous cheilitis is poorly understood but has been associated with genetic,⁶ allergic,⁷⁻¹² and infectious¹³ factors. There are several reports in the literature that associate the pathogenesis of granulomatous cheilitis with odontogenic infection and that describe remission or improvement after treatment of the infection.¹⁴⁻¹⁶ In our study, patient 6 was diagnosed with recurrent episodes of odontogenic infection. Although these infections resolved with antibiotic treatment, the patient continued to have acute episodes of granulomatous cheilitis. The same patient showed sensitization to nickel salts, although she had no dental implants and had had no contact with any instruments containing this substance. Both odontogenic infection and nickel sensitization are possible etiologies of the patient's granulomatous cheilitis; however, no temporal or causal relationship supporting either of these hypotheses has yet been established. Various substances including chocolate,¹¹ food additives, cinnamon compounds, and benzoates have been implicated as possible etiologic agents

of granulomatous cheilitis; elimination diets have led to improvement in some patients.^{7,8} Sensitization to metals such as gold and mercury has also been linked to the pathogenesis of the disease.¹⁰

Granulomatous cheilitis is a rare disease. Although it can appear at any age, including in childhood,¹⁷ it occurs most frequently in the second or third decade of life.¹⁸ In our study, the patients were aged between 29 and 74 years. As in previous studies,¹⁹⁻²¹ there were no childhood cases and a majority of the patients (66.66%) were women. We identified a total of 6 patients with granulomatous cheilitis over a period of 17 years.

Granulomatous cheilitis usually affects the upper lip and, less frequently, the lower lip. However, as was the case in 2 of our patients (33.33%), the disease can also affect other oral and facial regions, including the face, oral mucosa, gums, tongue, pharynx, and larynx.¹⁸ The most common presentation is acute, asymptomatic swelling of the lips lasting hours to days. Initially, the episodes of swelling are self-limiting and resolve completely; after several recurring episodes, however, the lips retain some degree of firm, indurated edema. Patients may report pain or a burning sensation, especially if the oral involvement is associated with erythema, fissures, erosions, or scaling of the lips. When other areas of the face are involved, there may be enlarged regional lymph nodes, as occurred in one of our patients.²² None of the patients in our study presented systemic symptoms, although flare-ups of granulomatous cheilitis can be associated with fever and general malaise.^{18,22}

Diagnosis of granulomatous cheilitis is based on clinical findings confirmed by histology. Histopathology reveals nonnecrotizing granulomas, edema, lymphangiectasia, and perivascular lymphocytic infiltration. Noncaseating granulomas are not always present in the dermis, especially in the early stages of granulomatous cheilitis, so their absence does not rule out the condition. Therefore, granulomatous cheilitis is not always associated with specific histological changes.²⁰ The differential diagnosis should include diseases that involve facial edema, conditions caused by granulomas, and, generally, all chronic forms of macrocheilia.

Several studies have linked granulomatous cheilitis to Crohn disease.^{23,24} In a series of 14 patients with granulomatous cheilitis, an association with Crohn disease was found in 30% of the patients and minor gastrointestinal symptoms without detectable signs of inflammatory bowel disease were found in 43%.²³ None of the patients in our study presented gastrointestinal disorders or were diagnosed with Crohn disease during the follow-up period. None of our patients underwent an endoscopic examination because there were no clinical findings to justify such a procedure; the decision not to perform endoscopy was consistent with the recommendations of previous studies.²⁰

The difficulty of managing granulomatous cheilitis is reflected in the variety of treatments that have been used and the lack of consensus regarding the preferred treatment. Moreover, because granulomatous cheilitis is a rare disease, there have been no placebo-controlled studies to evaluate the effectiveness of the various treatments. Combination therapy with intralesional triamcinolone and clofazimine or dapsone is one of the most commonly used treatment options.^{25,26} Other reported treatments include prednisone, hydroxychloroquine, sulfasalazine,²⁰

antihistamines, tetracyclines,²⁷ metronidazole,²⁸ macrolides,²⁹ thalidomide,³⁰ and infliximab.³¹ Cheiloplasty is reserved for treatment-resistant cases in which major deformity develops. However, the clinical course and therapeutic response of patients with granulomatous cheilitis are often unpredictable, and spontaneous remissions and recurrences are common. In our series, 4 of the 6 patients (66.66%) responded to medical treatment, 1 patient did not attend subsequent appointments and was lost to follow-up, and the final patient developed recurrence despite the use of various treatment regimens. The most common treatment was intralesional corticosteroids; in cases that required prolonged therapy, however, this treatment was accompanied by other drugs in order to lower the corticosteroid dosage.

Our study has several limitations. The sample of patients was small and the clinical data were reviewed retrospectively; both of these facts may have influenced our results to some extent. Additionally, granulomatous cheilitis may have been underdiagnosed in our study because we only included cases with a clinical and histological diagnosis and excluded patients in whom histologic confirmation was not obtained.

In conclusion, our findings in this study support previous reports that granulomatous cheilitis is an independent entity within the group of orofacial granulomatoses, that it is rare and difficult to diagnose and treat, and that it usually does not present with accompanying signs or symptoms or as part of Melkersson-Rosenthal syndrome. Further research on the pathogenesis of granulomatous cheilitis and clinical trials evaluating the efficacy of the various treatments are needed in order to enhance our understanding of this disease.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

References

1. Wiesenfeld D, Ferguson MM, Mitchell DN, McDonald DG, Souly C, Cochran K, et al. Orofacial granulomatosis. A clinical and pathological analysis. *Q J Med*. 1985;54:101–13.
2. Martínez-Menchón T, Mahiques L, Pérez-Ferriols A, Febrer I, Vilata JJ, Fortea JM, et al. Síndrome de Melkersson-Rosenthal. *Actas Dermosifiliogr*. 2003;94:180–3.
3. Hornstein OP. Melkersson-Rosenthal syndrome: A challenge for dermatologists to participate in the field of oral medicine. *J Dermatol*. 1997;24:281–96.
4. Greene RM, Rogers III RS. Melkersson-Rosenthal syndrome: A review of 36 patients. *J Am Acad Dermatol*. 1989;21:1263–70.
5. Worsaae N, Christensen KC, Schiodt M, Reibel J. Melkersson-Rosenthal syndrome and cheilitis granulomatosa. A clinicopathological study of thirty-three patients with special reference to their oral lesions. *Oral Surg Oral Med Oral Pathol*. 1982;54:404–13.
6. Smeets E, Frys JP, Van den Berghe H. Melkersson-Rosenthal syndrome and de novo autosomal t(9;21)(p11;p11) translocation. *Clin Genet*. 1994;45:323–4.
7. McKenna KE, Walsh MY, Burrows D. The Melkersson-Rosenthal syndrome and food additive hypersensitivity. *Br J Dermatol*. 1994;131:921–2.
8. Fitzpatrick L, Healy CM, McCartan BE, Flint SR, McCreary CE, Rogers S. Patch testing for food-associated allergies in orofacial granulomatosis. *J Oral Pathol Med*. 2011;40:10–3.
9. Guttman-Yassky E, Weltfriend S, Bergman R. Resolution of orofacial granulomatosis with amalgam removal. *J Eur Acad Dermatol Venereol*. 2003;17:344–7.
10. Lazarov A, Kidron D, Tulchinsky Z, Minkow B. Contact orofacial granulomatosis caused by delayed hypersensitivity to gold and mercury. *J Am Acad Dermatol*. 2003;49:1117–20.
11. Taibjee S, Prais L, Foulds I. Orofacial granulomatosis worsened by chocolate: results of patch testing to ingredients of Cadbury's chocolate. *Br J Dermatol*. 2004;150:595.
12. Morales C, Penarrocha M, Bagán JV, Burches E, Peláez A. Immunological study of Melkersson-Rosenthal syndrome. Lack of response to food additive challenge. *Clin Exp Allergy*. 1995;25:260–4.
13. Muellegger RR, Weger W, Zochling N, Kaddu S, Soyer HP, El Shabrawi-Caelen L, et al. Granulomatous cheilitis and *Borrelia burgdorferi*: Polymerase chain reaction and serologic studies in a retrospective case series of 12 patients. *Arch Dermatol*. 2000;136:1502–6.
14. Kawakami T, Fukai K, Sowa J, Ishii M, Teramae H, Kanazawa K. Case of cheilitis granulomatosa associated with apical periodontitis. *J Dermatol*. 2008;35:115–9.
15. Takeshita T, Koga T, Yashima Y. Case report: cheilitis granulomatosa with periodontitis. *J Dermatol*. 1995;22:804–6.
16. Tadokoro T, Ozawa K, Muso Y, Ito H, Itami S, Yoshikawa K. Melkersson-Rosenthal syndrome caused by saproductia: a case report. *J Dermatol*. 2003;30:679–82.
17. Dodi I, Verri R, Brevi B, Bonetti L, Balestrieri A, Saracino A, et al. A monosymptomatic Melkersson-Rosenthal syndrome in an 8-year old boy. *Acta Biomed*. 2006;77:20–3.
18. Van der Waal RI, Schulten EA, van de Scheur MR, Wauters IM, Starink TM, van der Waal I. Cheilitis granulomatosa. *J Eur Acad Dermatol Venereol*. 2001;15:519–23.
19. Camacho-Alonso F, Bermejo-Fenoll A, López-Jornet P. Queilitis granulomatosa de Miescher. Presentación de cinco casos. *Med Oral Patol Oral Cir Bucal*. 2004;9:425–9.
20. Van der Waal RI, Schulten EA, van der Meij EH, van de Scheur MR, Starink TM, van der Waal I. Cheilitis granulomatosa: overview of 13 patients with long-term follow-up—results of management. *Int J Dermatol*. 2002;41:225–9.
21. Zimmer WM, Rogers RS, Reeve CM, Sheridan PJ. Orofacial manifestations of Melkersson-Rosenthal syndrome. A study of 42 patients and review of 220 cases from the literature. *Oral Surg Oral Med Oral Pathol*. 1992;74:610–9.
22. Hornstein OP. Melkersson-Rosenthal syndrome: a neuromucocutaneous disease of complex origin. *Curr Probl Dermatol*. 1973;5:117–56.
23. Ratzinger G, Sepp N, Vogetseder W, Tilg H. Cheilitis granulomatosa and Melkersson-Rosenthal syndrome: evaluation of gastrointestinal involvement and therapeutic regimens in a series of 14 patients. *J Eur Acad Dermatol Venereol*. 2007;21:1065–70.
24. Álvarez-Garrido H, Pericet-Fernández L, Martínez-García G, Tejerina-García JA, Peral-Martínez I, Miranda-Romero A. Crohn's disease and cheilitis granulomatosa: Role of silicone fillers. *J Am Acad Dermatol*. 2011;65:239–41.
25. Sobjanek M, Włodarkiewicz A, Zelazny I, Nowicki R, Michajłowski I, Sokolowska-Wojdyło M. Successful treatment of Melkersson-Rosenthal syndrome with dapsone and triamcinolone injections. *J Eur Acad Dermatol Venereol*. 2008;22:1028–9.
26. Sobjanek M, Michajłowski I, Zelazny I, Medrzycka-Dabrowska W, Włodarkiewicz A. What is the most effective treatment of cheilitis granulomatosa in Melkersson-Rosenthal syndrome? *J Eur Acad Dermatol Venereol*. 2010;24:364–5.
27. Pigozzi B, Fortina AB, Peserico A. Successful treatment of Melkersson-Rosenthal Syndrome with lymecycline. *Eur J Dermatol*. 2004;14:166–7.

28. Coskun B, Saral Y, Cicek D, Akpolat N. Treatment and follow-up of persistent granulomatous cheilitis with intralesional steroid and metronidazole. *J Dermatolog Treat.* 2004;15:333–5.
29. Ishiguro E, Hatamochi A, Hamasaki Y, Ishikawa S, Yamazaki S. Successful treatment of granulomatous cheilitis with roxithromycin. *J Dermatol.* 2008;35:598–600.
30. Thomas P, Walchner M, Ghoreschi K, Röcken M. Successful treatment of granulomatous cheilitis with thalidomide. *Arch Dermatol.* 2003;139:136–8.
31. Barry O, Barry J, Langan S, Murphy M, Fitzgibbon J, Lyons JF. Treatment of granulomatous cheilitis with infliximab. *Arch Dermatol.* 2005;141:1080–2.