Morbihan disease: a case report and differentiation from Melkersson-Rosenthal syndrome

Drew Kuraitis[1] MD PhD, Aimee Coscarart[1,2] MD, Laura Williams[1] MD, Alun Wang[2] MD PhD

Affiliations: [1]Department of Dermatology, Tulane University, New Orleans, Louisiana, USA, [2]Department of Pathology, Tulane University, New Orleans, Louisiana, USA

Corresponding Author: Drew Kuraitis, 1430 Tulane Avenue #8036, New Orleans, LA 70112, Email: dkuraiti@tulane.edu

Abstract

We present a 32-year old woman with a 9-year history of upper facial swelling. A workup by the ophthalmology department led to the diagnosis of Melkersson-Rosenthal syndrome. Re-evaluation in our dermatology clinic confirmed a diagnosis of Morbihan disease. Herein, we review case reports and case series of upper facial swelling in the dermatologic and ophthalmologic literature. Although the two entities share histopathological changes, they tend to have different clinical presentations. Melkersson-Rosenthal syndrome appears to be more likely diagnosed in the ophthalmologic literature when the clinical presentation and histopathology may be more consistent with Morbihan disease. In a patient with upper facial swelling, an absence of orolabial swelling, and lack of facial neuropathy, we argue for a diagnosis of Morbihan disease over Melkersson-Rosenthal syndrome, especially if the patient has a history of rosacea.

Keywords: Melkersson-Rosenthal, Morbihan, rosacea, granulomatous rosacea, granuloma

Introduction

Melkersson-Rosenthal Syndrome (MRS) is a rare disease of unknown etiology, characterized by the classic triad of orofacial swelling, facial neuropathy, and geographic tongue, or lingua plicata; however, this triad is found only in one third of patients [1]. Orofacial swelling usually involving the lips is the dominant feature of this syndrome and is often the initial presenting symptom [2]. Swelling may also occur on sites such as cheeks, chin, and mucosal surfaces. Cheilitis granulomatosa (CG) is a chronic, granulomatous swelling of the lips and has been considered to be a monosymptomatic form of MRS [3, 4]. A third entity, orofacial granulomatosis (OFG) considered to be an umbrella term that can encompass MRS and CG, is characterized by persistent enlargement of orofacial soft tissues in the absence of Crohn disease or sarcoidosis [5]. There is confusion regarding the nomenclature and overlap of these diseases. Clarification regarding the terminology of these entities has recently been discussed in a systematic review [6]. Regardless, all of these entities share similar histopathologic patterns, edema, and non-caseating granulomas in the absence of other identifiable causes. Histopathology of MD varies between patients but is similar to changes seen in MRS and consists of dilated vasculature, dilated and obstructed lymphatic vessels, and nearby non-caseating granulomas [7]. The clinical presentations are similar and exhibit forms of orofacial swelling. Both present with chronic swelling of the upper face, typically the forehead, glabella, eyelids, nose, and cheeks [7, 8]. Morbihan disease (MD) is a rare entity and may be known as rosaceous lymphedema or solid persistent facial edema. The etiology of MD is unclear but some consider it to be an end-stage presentation of rosacea [9].

Case Synopsis

A 32-year old woman presented to our dermatology clinic with the chief complaint of upper facial redness and swelling for 9 years' duration. She reported an

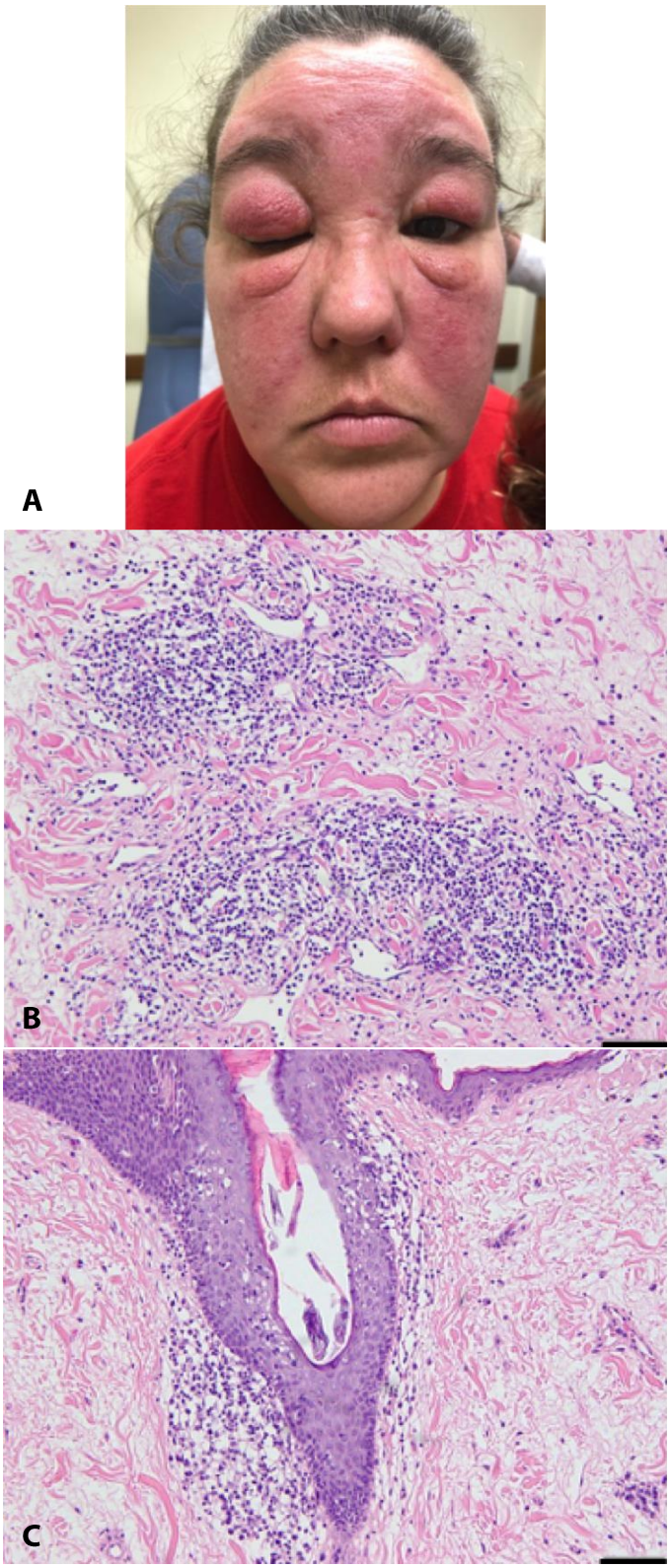

Figure 1. ***A)*** *Well demarcated erythematous, indurated woody plaques of the forehead, cheeks and upper eyelids.* ***B)*** *Dermal edema with lymphangiectasia, perivascular lymphocytic infiltrate, and intralymphatic histiocytosis. H&E, 200×.* ***C)*** *Folliculitis with Demodex, dermal edema, and telangiectasia. H&E, 200×.*

acute onset of skin changes with redness and progressive swelling over time. She denied pain, tenderness, weeping, lip swelling, and symptoms suggestive of facial neuropathy. She denied having textural changes to her tongue. Her physical examination was notable for well-demarcated erythematous, indurated, woody plaques on her forehead, bilateral cheeks, and upper eyelids with scattered erythematous papules and pustules (**Figure 1A)**. Pustule scraping was positive for *Demodex*. She reports having a biopsy many years prior and was told she had rosacea. In 2017, she was diagnosed with Melkersson-Rosenthal syndrome (MRS) by an ophthalmology consultant after an eyelid biopsy that was notable for "dermal edema with lymphangiectasia, perivascular lymphocytic infiltrate, and intralymphatic histiocytosis" (**Figure 1B)**. She reported trying topical corticosteroids and topical antibiotics in addition to independent, multi-month courses of systemic therapies (dapsone, high dose ibuprofen, doxycycline, hydroxychloroquine, methotrexate) without symptomatic improvement.

On presentation to our dermatology clinic in 2018, biopsy of the forehead revealed "perivascular and perilymphatic non-caseating granulomas accompanied by prominent telangiectasia, edema of the dermis, lymphangiectasia, and intravascular histiocytosis, rosacea-like sebaceous hyperplasia, folliculitis with *Demodex*, and telangiectasia" (**Figure 1C)**. Based on biopsy results, clinical presentation and her history of rosacea, a diagnosis of MD was rendered.

She started isotretinoin 40mg daily and stopped after four months when she failed to improve. She then started methotrexate 15mg weekly which was continued for 8 months, similarly without improvement. She has since been taking pulsed oral ivermectin, 21mg every two to four weeks, and receiving intralesional Kenalog (5mg/mL) injections to the upper and lower eyelids bilaterally approximately every 6 to 8 weeks. She reports rapid improvement of facial erythema and pustules after ivermectin dosing and we have noted objective improvement in swelling and induration of upper eyelids (**Figure 2**). If she does not continue to

improve on the current therapy, we plan to discuss surgical debulking for symptomatic relief.

Case Discussion

We found similar cases reported in the literature discussing patients with chronic, indurated, edematous upper facial plaques that were diagnosed as MRS in the ophthalmologic literature and as MD in the dermatologic literature. As both entities are rare occurrences, we sought to summarize the described differences in both fields. We searched PubMed for case reports and case series with keywords Morbihan, Morbihan's, or Melkersson-Rosenthal and recorded the journal source, patient characteristics, pathology findings, and history of rosacea. Reports that were included were those published in English, those that reported chronic upper facial swelling, and those with histopathologic descriptions. Exclusion criteria included reports of MRS that detailed neuropathy and/or orolabial swelling.

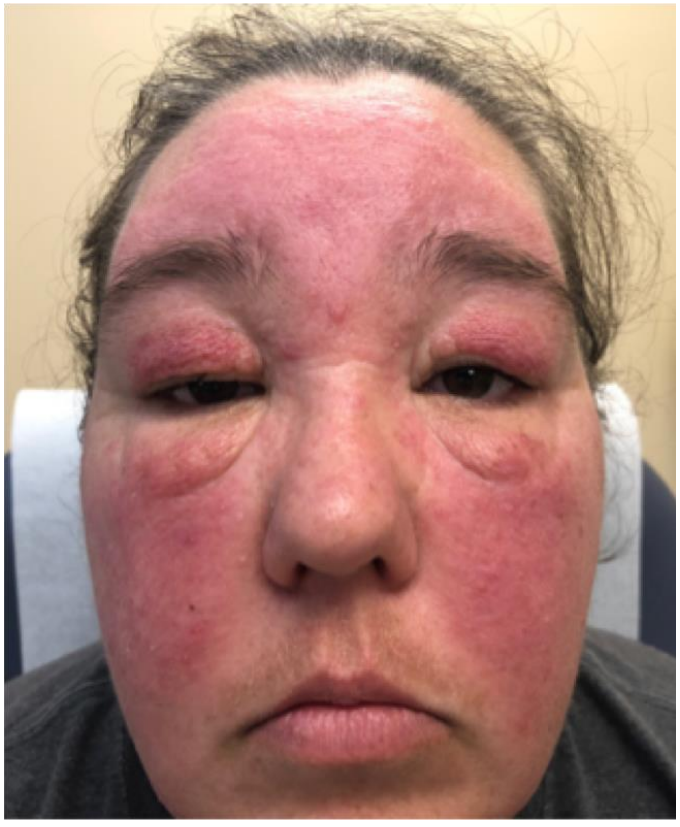

Figure 2. *Improved upper eyelid induration and swelling after four treatments of intralesional Kenalog at 5mg/mL.*

From 9 studies in the ophthalmologic literature, we identified 19 patients with chronic upper facial swelling and no report of neurologic or orolabial swelling (**Table 1**). Of these 19 patients, 6 were diagnosed with MD and the remainder with MRS or OFG. From 15 studies in the dermatologic literature, we identified 18 patients with chronic upper facial swelling and no report of neurologic or orolabial swelling (**Table 2**). Based on clinical descriptions alone, we believe that all these patients' described pathology may fit the diagnosis of MD better than another diagnosis, which is better reflected in the dermatologic literature. This opinion is based on the history and presentation of chronic upper facial swelling without oral involvement. Histopathologic descriptions for all cases were similar and generally reported edema, non-caseating granuloma formation adjacent to dilated lymph channels, and/or lymphatics containing granulomas.

A majority of the studies did not report whether or not there was a history of rosacea, but four of 19 patients in the ophthalmologic literature carried this diagnosis or had a presentation consistent with rosacea, compared to 7 of 18 patients in the dermatologic literature. To establish an association between rosacea and MD it would be helpful to be able to collect this data, which has been approximated to be about one third of MD patients [6]. Similarly, few studies mentioned whether or not *Demodex* mites were visible on histopathology. As *Demodex* have been implicated in the development of rosacea, this may also be helpful in establishing associations [10].

It appears that upper facial swelling without orolabial or neurologic involvement is being more likely diagnosed as MRS in the ophthalmologic literature when compared to the dermatologic literature. Although these diseases are rare, there does not appear to be clear histopathologic evidence to differentiate between MRS and MD. The shared histologic features are lymphedema with scattered non-caseating granulomas adjacent to or inside of lymphatics. Lymphedema is the likely cause of the shared clinical presentations of facial swelling. Therefore, we propose that MRS and MD lesions are part of the spectrum of "persistent lymphedema of

the face," with MD presenting as upper and bilateral facial lymphedema and often affecting eyelids and MRS as lower facial lymphedema with a tendency for affecting lips and tongue. The former entity's lesions are often localized and could affect the facial nerve leading to classic neuropathic findings. In the absence of facial neuropathy and/or orolabial swelling, a diagnosis of MD should be considered when persistent upper facial swelling is the predominant finding.

Despite both entities being difficult to treat, there is evidence supporting similar treatments for both conditions. MRS has been treated with surgery, corticosteroids, and oral antibiotics [6], whereas MD has been treated with surgery, corticosteroids, oral antibiotics, and isotretinoin [7], with differing rates of success.

Conclusion

To initiate the most appropriate treatment for MRS or MD, it is imperative that a proper diagnosis is made. Our recommendations are two-fold: (1) upper facial swelling with histologic evidence of edema, lymphangiectasia, and granulomatous changes are not sufficient to make the diagnosis of MRS, but may represent an entity on the "persistent lymphedema of the face" spectrum; (2) predominant upper facial swelling, and the absence of orofacial and neurologic involvement should lead to consideration of MD, especially if the patient has a history of rosacea.

Potential conflicts of interest

The authors declare no conflicts of interests.

References

1. Greene RM, Rogers RS, 3rd. Melkersson-Rosenthal syndrome: a review of 36 patients. *J Am Acad Dermatol*. 1989;21:1263-70. [PMID: 2584463].
2. Zimmer WM, Rogers RS, 3rd, 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. [PMID: 1437063].
3. Rogers RS, 3rd. Melkersson-Rosenthal syndrome and orofacial granulomatosis. *Dermatol Clin*. 1996;14:371-9. [PMID: 8725591].
4. Rogers RS, 3rd. Granulomatous cheilitis, Melkersson-Rosenthal syndrome, and orofacial granulomatosis. *Arch Dermatol*. 2000;136:1557-8. [PMID: 11115174].
5. Grave B, McCullough M, Wiesenfeld D. Orofacial granulomatosis--a 20-year review. *Oral Dis*. 2009;15:46-51. [PMID: 19076470].
6. Wehl G, Rauchenzauner M. A Systematic Review of the Literature of the Three Related Disease Entities Cheilitis Granulomatosa, Orofacial Granulomatosis and Melkersson - Rosenthal Syndrome. *Curr Pediatr Rev*. 2018;14:196-203. [PMID: 29766816].
7. Boparai RS, Levin AM, Lelli GJ, Jr. Morbihan Disease Treatment: Two Case Reports and a Systematic Literature Review. *Ophthalmic Plast Reconstr Surg*. 2018. [PMID: 30252748].
8. Nagasaka T, Koyama T, Matsumura K, Chen KR. Persistent lymphoedema in Morbihan disease: formation of perilymphatic epithelioid cell granulomas as a possible pathogenesis. *Clin Exp Dermatol*. 2008;33:764-7. [PMID: 18627384].
9. Wilkin JK. Rosacea. Pathophysiology and treatment. *Arch Dermatol*. 1994;130:359-62. [PMID: 8129416].
10. Moran EM, Foley R, Powell FC. Demodex and rosacea revisited. *Clin Dermatol*. 2017;35:195-200. [PMID: 28274359].
11. Archibald CW, Punja KG, Oryschak AF. Orofacial granulomatosis presenting as bilateral eyelid swelling. *Saudi J Ophthalmol*. 2012;26:177-9. [PMID: 23960989].
12. Belliveau MJ, Kratky V, Farmer J. Melkersson-Rosenthal syndrome presenting with isolated bilateral eyelid swelling: a clinicopathologic correlation. *Can J Ophthalmol*. 2011;46:286-7. [PMID: 21784219].
13. Carruth BP, Meyer DR, Wladis EJ, et al. Extreme Eyelid Lymphedema Associated With Rosacea (Morbihan Disease): Case Series, Literature Review, and Therapeutic Considerations. *Ophthalmic Plast Reconstr Surg*. 2017;33:S34-S8. [PMID: 26505236].
14. Chen X, Jakobiec FA, Yadav P, et al. Melkersson-Rosenthal syndrome with isolated unilateral eyelid edema: an immunopathologic study. *Ophthalmic Plast Reconstr Surg*. 2015;31:e70-7. [PMID: 24853119].
15. Pierre-Filho Pde T, Rocha EM, Natalino R, et al. Upper eyelid oedema in Melkersson-Rosenthal syndrome. *Clin Exp Ophthalmol*. 2004;32:439-40. [PMID: 15281985].
16. Rawlings NG, Valenzuela AA, Allen LH, Heathcote JG. Isolated eyelid edema in Melkersson-Rosenthal syndrome: a case series. *Eye (Lond)*. 2012;26:163-6. [PMID: 22056858].
17. Reddy DN, Martin JS, Potter HD. Melkersson-Rosenthal Syndrome Presenting as Isolated Eyelid Edema. *Ophthalmology*. 2017;124:256. [PMID: 28126075].
18. Sabet-Peyman EJ, Woodward JA. A case series of patients diagnosed with orofacial granulomatosis presenting primarily with dense infiltrates and severe periorbital edema. *Ophthalmic Plast Reconstr Surg*. 2014;30:e151-5. [PMID: 24836447].
19. Bechara FG, Jansen T, Losch R, et al. Morbihan's disease: treatment with CO_2 laser blepharoplasty. *J Dermatol*. 2004;31:113-5. [PMID: 15160865].
20. Cabral F, Lubbe LC, Nobrega MM, et al. Morbihan disease: a therapeutic challenge. *An Bras Dermatol*. 2017;92:847-50. [PMID: 29364446].
21. Chaidemenos G, Apalla Z, Sidiropoulos T. Morbihan disease: successful treatment with slow-releasing doxycycline monohydrate. *J Eur Acad Dermatol Venereol*. 2018;32:e68-e9. [PMID: 28833773].
22. Vasconcelos RC, Eid NT, Eid RT, et al. Morbihan syndrome: a case

report and literature review. *An Bras Dermatol.* 2016;91:157-9. [PMID: 28300928].
23. Fujimoto N, Mitsuru M, Tanaka T. Successful treatment of Morbihan disease with long-term minocycline and its association with mast cell infiltration. *Acta Derm Venereol.* 2015;95:368-9. [PMID: 25510871].
24. Hu SW, Robinson M, Meehan SA, Cohen DE. Morbihan disease. *Dermatol Online J.* 2012;18:27. [PMID: 23286817].
25. Kabuto M, Fujimoto N, Honda S, Tanaka T. Successful treatment with long-term use of minocycline for Morbihan disease showing mast cell infiltration: A second case report. *J Dermatol.* 2015;42:827-8. [PMID: 25917342].
26. Mazzatenta C, Giorgino G, Rubegni P, et al. Solid persistent facial oedema (Morbihan's disease) following rosacea, successfully treated with isotretinoin and ketotifen. *Br J Dermatol.* 1997;137:1020-1. [PMID: 9470933].
27. Okubo A, Takahashi K, Akasaka T, Amano H. Four cases of Morbihan disease successfully treated with doxycycline. *J Dermatol.* 2017;44:713-6. [PMID: 28150340].
28. Ranu H, Lee J, Hee TH. Therapeutic hotline: Successful treatment of Morbihan's disease with oral prednisolone and doxycycline. *Dermatol Ther.* 2010;23:682-5. [PMID: 21054712].
29. Rebellato PR, Rezende CM, Battaglin ER, et al. Syndrome in question. *An Bras Dermatol.* 2015;90:909-11. [PMID: 26734879].
30. Tsiogka A, Koller J. Efficacy of long-term intralesional triamcinolone in Morbihan's disease and its possible association with mast cell infiltration. *Dermatol Ther.* 2018;31:e12609. [PMID: 29687653].
31. Veraldi S, Persico MC, Francia C. Morbihan syndrome. *Indian Dermatol Online J.* 2013;4:122-4. [PMID: 23741671].
32. Yu X, Qu T, Jin H, Fang K. Morbihan disease treated with *Tripterygium wilfordii* successfully. *J Dermatol.* 2018;45:e122-e3. [PMID: 29165836].

Table 1. *Reported cases of upper facial swelling in the ophthalmologic literature with reported presence (+) or absence (-) of clinical and histopathologic characteristics.*

			Patient Characteristics				Histopathologic Characteristics		
Study	Journal	Diagnosis	Age	Sex	Periorbital or eyelid edema	History of rosacea	Peri- or intra-lymphatic granulomas	Lymphan-giectasia	Demodex
Archibald 2012 [11]	*Saudi J Ophthalmol*	OFG	69	F	+		+	+	
Belliveau 2011 [12]	*Can J Ophthalmol*	MRS	60	M	+		+	+	
Boparai 2018 [7]	*Ophthal Plast Reconstr Surg*	MD	40	F	+	-			
		MD	61	M	+	+		+	+
Carruth 2017 [13]	*Ophthal Plast Reconstr Surg*	MD	54	M	+	+		+	
		MD	74	M	+	+		+	
		MD	64	M	+	-		+	
		MD	62	M	+	+		+	
Chen 2015 [14]	*Ophthal Plast Reconstr Surg*	MRS	45	M	+		+	+	
Pierre-Filho 2004 [15]	*Clin Exp Ophthalmol*	MRS	54	F	+		+		
Rawlings 2012 [16].	*Eye*	MRS	73	M	+		+	+	
		MRS	71	M	+		+		
		MRS	59	M	+		+	+	
		MRS	52″	M	+		+		
		MRS	46	F	+		+		
Reddy 2017 [17]	*Ophthalmology*	MRS	75	M	+		+		
Sabet-Peyman 2014 [18].	*Ophthal PlastReconstr Surg*	OFG	57	M	+		+	+	
		OFG	51	M	+		+	+	
		OFG	33	M	+		+	+	

Abbreviations: OFG = orofacial granulomatosis; MRS = Melkersson-Rosenthal syndrome; MD = Morbihan's disease; M = male; F = female.

Table 2. *Reported cases of upper facial swelling in the dermatologic literature with reported presence (+) or absence (-) of clinical and histopathologic characteristics.*

Study	Journal	Diagnosis	Patient Characteristics				Histopathologic Description		
			Age	Sex	Periorbital or eyelid edema	History of rosacea	Peri- or intra-lymphatic granulomas	Lymphan-giectasia	Demodex
Bechara 2004 [19]	*J Dermatol*	MD	67	M	+	+	-	+	
Cabral 2017 [20]	*An Bras Dermatol*	MD	61	F	+	+	+	+	
Chaidemenos 2018 [21]	*Eur Acad Dermatol Venereol*	MD	63	M	+	-			
Vasconcelos 2016 [22]	*An Bras Dermatol*	MD	39	M	+		+	+	+
Fujimoto 2015 [23]	*Acta Derm Venereol*	MD	74	M	+	-	+		
Hu 2012 [24]	*Dermatol Online*	MD	54	F	+	+	+		
Kabuto 2015 [25]	*Japanese Dermatol Assoc*	MD	64	M	+	-	-		
Mazzatenta 1997 [26]	*Brit Assoc Dermatol*	MD	45	M	+	+			
Nagasaka 2008 [8]	*Clin Exper Dermatol*	MD	70	M	+	+	+	+	
Okubo 2017 [27].	*J Dermatol*	MD	56	M	+	-		+	
		MD	32	M	+	-	+	+	
		MD	63	M	+	-			
		MD	67	M	+	+	+		
Ranu 2010 [28]	*Dermatol Ther*	MD	45	M	+	+			
Rebellato 2015 [29]	*An Bras Dermatol*	MD	38	M	+				
Tsiogka 2017 [30]	*Dermatol Ther*	MD	44	M	+	-	-		
Veraldi 2013 [31]	*Indian Dermatol Online J*	MD	60	M	+		+		
Yu 2018 [32]	*J Dermatol*	MD	42	M	+				

OFG = orofacial granulomatosis; MRS = Melkersson-Rosenthal syndrome; MD = Morbihan's disease; M = male; F = female.