



Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.



Melkersson-Rosenthal Syndrome Induced by COVID-19

Bahadır Taşlıdere^{a,*}, Liljana Mehmetaj^a, Ayşe Büşra Özcan^a, Bedia Gülen^a, Nazan Taşlıdere^b

^a Department of Emergency Medicine, Bezmialem Vakıf University School of Medicine, Istanbul, Turkey

^b Department of Dermatology, Bezmialem Vakıf University School of Medicine, Istanbul, Turkey

ARTICLE INFO

Article history:

Received 18 June 2020

Received in revised form 23 July 2020

Accepted 5 August 2020

Keywords:

Orofacial edema

Fissured tongue

COVID-19

Mast cells

ABSTRACT

Melkersson–Rosenthal syndrome is a rare condition characterized by a triad of orofacial edema, facial paralysis, and fissured tongue. Histopathological examination of the disease has demonstrated areas of inflammation involving mast cells. Activated mast cells also play a part in the pathogenesis of COVID-19 infection, as they release cytokines in the lungs. We present a case of a female patient presenting with edema. We present a case of a female patient presenting with edema. Her examination revealed edema in the right lower lip, right facial paralysis, and fissured tongue. COVID-19 may be associated with which was not previously included in the etiology of the disease.

© 2020 Elsevier Inc. All rights reserved.

1. Introduction

Melkersson–Rosenthal syndrome (MRS) is a neuro-mucocutaneous granulomatous disease characterized by a triad of recurrent peripheral facial paralysis, painless and nonpitting orofacial edema, and fissured tongue. This classic triad shows up in only 25% of cases. The incidence of the syndrome in the population of the US has been reported as 0.08%, and it is more common in women than in men [1]. In the clinic, orofacial edema is the most common component of the triad (80–100%). Generally, the upper lip is the site most commonly involved. The edema is painless, nonpitting, and usually unilateral. Peripheral facial paralysis occurs in 47–90% of cases. This paralysis is also often unilateral. It is thought to develop as a result of granulomatous infiltration and edema of the nerve tissue. Tongue fissure is a rare component of the triad and occurs in 8–25% of cases [1,2]. Due to the rarity of the syndrome, the diagnosis is sometimes delayed. Melkersson–Rosenthal syndrome is thought to be triggered by viral infections such as Epstein-Barr, varicella zoster, cytomegalovirus, herpes simplex, and many other factors such as T lymphocyte dysfunction, genetic predisposition, immune deficiency, stress [3]. Histopathological examination of samples taken from the edematous mucosa of patients with MRS has shown areas of inflammation involving granulomas, Langhans cells, mononuclear infiltration, and mast cells. Mast cells also play a role in inducing an inflammatory response in the pathogenesis of COVID-19 infection [4].

In the light of this information, there is a need for further research on the presence of COVID-19 in the etiology of Melkersson–Rosenthal syndrome. Our case report presents a patient with Melkersson–Rosenthal

syndrome induced by COVID-19, who presented with swollen lip and malaise.

2. Case

A 51-year-old female patient presented to our emergency department with malaise and a swollen lip that started a day prior to presentation. The patient, whose medical history included Melkersson–Rosenthal syndrome, had first been admitted for orofacial edema and facial paralysis four years ago and had recovered when treated with steroid and antihistamine therapy. She had had no relapse for the last four years. Her examination revealed hyperemic, firm edema in the right lower lip extending towards the jaw. The right nasolabial sulcus was obliterated and asymmetrical to the right of the mouth corner (Fig. 1). A fissure line was observed on the tongue (Fig. 2). Her oropharyngeal cavity examination was normal. Her neurological and other systemic examinations were normal. The patient's vital signs were as follows: body temperature, 37.9 °C; heart rate, 101/min; respiratory rate, 22/min; oxygen saturation (SpO₂), 91%; blood pressure, 132/76 mmHg; blood sugar level, 139 mg/dL. The laboratory tests were as follows: WBC, 9.1 10³/uL; neutrophil, 75.17%; lymphocyte, 10.77%; monocyte, 12.25%; LDH, 248 U/L; CRP, 32.56 mg/dL. The other laboratory tests conducted, including hemogram, liver, and kidney function tests, serum electrolytes, complete urinalysis, and prothrombin time, were all within normal ranges. Her serological examinations for herpes simplex virus, cytomegalovirus, Epstein–Barr virus, and Coxsackie virus infection were negative. The results of the patient's thoracic computed tomography, which has a sensitivity of 98% for the COVID-19 infection, were positive [6]. Due to locally restricted resources, the patient was diagnosed according to the clinical, laboratory, and thorax tomography results. Some studies have reported that thorax tomography images have a

* Corresponding author.

E-mail address: drbahadir@yahoo.com (B. Taşlıdere).



Fig. 1. Orofacial Edema.



Fig. 2. Fissured Tongue.

sensitivity of 80–90% and specificity of 82,8–96% for detecting the lung lesions in patients with COVID-19. Thorax tomography has a high sensitivity for the diagnosis of COVID-19 and may be considered as a primary tool for the current COVID-19 detection in epidemic areas [7]. Bilateral,

multilobular ground-glass opacities were typically present (Figs. 3). The patient was admitted to the infectious disease ward with pre-diagnosis of COVID-19 and recurrent MRS. She was initiated on hydroxychloroquine, azithromycin, and steroid therapy. The patient's symptoms resolved almost completely, and she recovered enough to be discharged.

3. Discussion and Conclusion

Melkersson–Rosenthal syndrome is characterized by facial paralysis, orofacial edema, and fissured tongue. Orofacial edema is the most common component of the triad in the clinic, and the upper lip is usually involved. Peripheral facial paralysis is often unilateral. It is thought to develop due to granulomatous infiltration and edema of the nerve tissue. Tongue fissure is a rare component of the triad [5]. In our case, orofacial edema was unilateral and located in the lower lip. Peripheral facial paralysis was present on the right side, and the classic triad of the syndrome was completed by the fissured tongue. Although viral infections such as cytomegalovirus, Epstein Barr, varicella zoster, herpes simplex, and other factors such as adenotonsillitis, allergy, genetics, and T lymphocyte dysfunction are held responsible for the syndrome's etiology, its pathogenesis is not fully known. Langhans giant cells, non-specific inflammation, and fibrosis can be histopathologically identified in patients with Melkersson–Rosenthal syndrome. Analyses of samples taken from the mucosa have demonstrated areas of inflammation involving lymphocytes, plasma cells, and mast cells. Mast cells are particularly present in the lungs and can be activated by many immunological or non-immunological stimuli, especially viruses. Recent studies have shown that mast cells play a role in inducing the inflammatory response sometimes seen in the pathogenesis of COVID-19 infection. The severity of coronavirus infection has been associated with cytokine storms that occur in the lungs after the activation of mast cells. Induced cytokine production causes fever-related upper and lower respiratory tract infections [8,9]. Considering these features, the potential correlation between COVID-19 symptoms and Melkersson–Rosenthal syndrome needs to be investigated. Given the etiopathogenesis, the coexistence of Melkersson–Rosenthal syndrome and a disease such as COVID-19 is not surprising.

In conclusion, the patient with Melkersson–Rosenthal syndrome presented to our emergency department with rare clinical findings of the classic triad. The patient was diagnosed with COVID-19 pneumonia after a series of procedures carried out based on the recent-onset malaise in her history. COVID-19 infection, which was not previously included in the etiology of the disease, can now be considered among the causes of recurrence of the syndrome. Moreover, further research on mast cells will positively contribute to the treatments of both diseases.



Fig. 3. Bilateral, multilobular ground-glass opacities.

Financial support

None.

Declaration of competing interest

None.

Acknowledgement

All Authors have seen and approved the manuscript being submitted. We warrant that the article is the Authors' original work. We warrant that the article has not received prior publication and is not under consideration for publication elsewhere. On behalf of all Co-Authors, the corresponding Author shall bear full responsibility for the submission.

References

- [1] Dhawan SR, Saini AG, Singhi PD. Management strategies of Melkersson–Rosenthal syndrome: a review. *Int J Gen Med.* 2020;13:61–5.
- [2] Lin TY, Chiang CH, Cheng PS. Melkersson–Rosenthal syndrome. *J Formos Med Assoc.* 2016;115(7):583–4.
- [3] Cancian M, Giovannini S, Angelini A, Fedrigo M, Bendo R, Sente R, et al. Melkersson–Rosenthal syndrome: a case report of a rare disease with overlapping features. *Allergy Asthma Clin Immunol.* 2019;15:1.
- [4] Conti P, Ronconi G, Caraffa A, et al. Induction of proinflammatory cytokines (IL-1 and IL6) and lung inflammation by Coronavirus-19 (COVI-19 or SARS-CoV-2): anti-inflammatory strategies. *J Biol Regul Homeost Agents.* 2020;34(2):1.
- [5] Tang J-J, Shen X, Xiao J-J, Wang X-P. Retrospective analysis of 69 patients with Melkersson–Rosenthal syndrome in mainland China. *Int J Clin Exp Med.* 2016;9(2):3901–8.
- [6] Fang Y, Zhang H, Xie J, Lin M, Ying L, Pang P, et al. Sensitivity of chest CT for COVID19: comparison to RT-PCR. *Radiology.* 2020;296(2):115–7.
- [7] Majidi H, Niksolat F. Chest CT in patients suspected of COVID-19 infection: a reliable alternative for RT-PCR. *Am J Emerg Med.* 2020;8(S0735–6757(20)):30244–8.
- [8] Kritas SK, Ronconi G, Caraffa A, et al. Mast cells contribute to coronavirus-induced inflammation: new anti-inflammatory strategy. *J Biol Regul Homeost Agents.* 2020;34:1.
- [9] Marshall JS, Portales-Cervantes L, Leong E. Mast cell responses to viruses and pathogen products. *Int J Mol Sci.* 2019;20(17):4241.