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ORIGINAL ARTICLE

COEXISTENCE OF SJOGREN'S SYNDROME AND FAMILIAL MEDITERRANEAN FEVER: A RARE COMBINATION

Ginosyan Knarik,[1]* Ghazinyan Irina,[2] Nazaretyan Eduard,[3] Eghiazaryan Nikolay,[4] Efremidu Maritsa,[5] Sevoyan Lilit,[4] Osipyan Magda[5]

[1] Associate professor, Head of Department of Rheumatology, Yerevan State Medical University after M. Heratsi, "Heratsi" University Hospital, Yervan, Armenia
[2] Lecturer of Department of Propaedeutics of Internal Diseases, Yerevan State Medical University after M. Heratsi, Yervan, Armenia
[3] Professor of Department of Propaedeutics of Internal Diseases, Yerevan State Medical University after M. Heratsi, Yervan, Armenia
[4] Lecturer of Department of Rheumatology, Yerevan State Medical University after M. Heratsi, "Heratsi" University Hospital, Yervan, Armenia
[5] Assistant Department of Rheumatology, Yerevan State Medical University after M. Heratsi, "Heratsi" University Hospital, Yervan, Armenia

** Corresponding author: Knarik Ginosyan, Head of the Department of Rheumatology, Yerevan State Medical University after M. Heratsi, Armenia;*
e-mail: kginosyan@gmail.com

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Abstract

Sjogren's syndrome is a chronic autoimmune disorder characterized by dry eyes, dry mouth and musculoskeletal involvement. Familial Mediterranean fever (FMF) is an autosomal recessive disease characterized by recurrent episodes of fever, peritonitis, synovitis, pleuritis, and erysipelas-like skin lesions. An increased prevalence of systemic autoimmune diseases has been reported in FMF. There are a lot of cases about coexistence of FMF-ankylosing spondylitis, vasculitis, Behcet's disease and others. In this article we present a rare combination of FMF and Sjogren's syndrome.

Keywords: *familial Mediterranean fever; Sjogren's syndrome; autoinflammation; autoimmunity.*

Introduction

Sjogren's syndrome (SS) is a chronic autoimmune disorder of exocrine glands with associated lymphocytic infiltrates of the affected glands characterized by dry eyes, dry mouth, and musculoskeletal involvement.[1]

Familial Mediterranean fever (FMF) is an autoinflammatory disorder which is caused by

mutations in Mediterranean fever (MEFV) gene which is located on the short (p) arm of chromosome 16. It's an autosomal recessive disease characterized by recurrent episodes of fever, peritonitis, synovitis, pleuritis, and erysipelas-like skin lesions. It is common in Turkish, Armenian, Arabic, and Sephardic Jewish populations.[2]

Diseases that have been proposed to be associated with FMF include Behcet's disease, inflammatory bowel disease, vasculitis, ankylosing spondylitis.[3-8]

In this article we report an unusual case of coexistence of FMF and Sjogren's disease.

Case report

A 58-year-old female with 35 years history of periodic severe attacks of abdominal and chest pain, accompanying by high fever 39-40^{0}C with duration of 2 days admitted to our outpatient clinic. These attacks were repeated 1-2 times per month. In her medical history molecular-genetic examination of MEFV gene revealed 2 mutations in compound-heterozygote form – M694V/V726A and she was diagnosed with FMF. She had been on colchicine treatment for 30 years. In 2022 year, she noticed dryness of eyes and mouth and enlargement of salivary glands. High ESR and C-reactive protein levels, elevated levels of circulating immune complexes, rheumatoid factor, antinuclear, anti-SSA/Ro and anti-SSB/La antibodies were revealed in laboratory analysis. Other examinations such as complete blood count and biochemistry test results were unremarkable. Schirmer's test was < 5 mm. The lip biopsy of minor salivary glands was carried out. Histopathological findings were typical for Sjogren's syndrome. Taking into account clinical findings (dry mouth, dry eyes, enlargement of salivary glands), laboratory data (specific for SS anti-SSA/Ro and anti-SSB/La antibodies, also positive rheumatoid factor and elevated markers of inflammation), results of Schirmer's test (confirm dry eyes symptom) and histopathological findings the diagnosis of Sjogren's syndrome was established. She was prescribed prednisone-15 mg/day with tapering dosage to 5 mg/day, hydroxychloroquine 400 mg/day, colchicine 1.5 mg/day and lubricant eye drops.

Discussion

Autoinflammatory diseases, the typical representative of which is FMF, and autoimmune diseases such as Sjogren's syndrome have common features but different mechanisms of development.

While autoimmunity involves adaptive immune activation, autoinflammation involves innate immune activation. Both diseases share some characteristics: they start with the prefix "auto" to define a pathological process directed against self, they are systemic diseases, frequently involving the musculoskeletal system, gastrointestinal tract, kidneys, skin, both include monogenic and polygenic diseases.[9] An increased prevalence of systemic autoimmune diseases has been reported in FMF. There is some evidence about the coexistence of FMF-ankylosing spondylitis, vasculitis, Behcet's disease and others.[3-8]

To our knowledge, three cases of the coexistence of FMF and SS have been reported in the literature. Tanaka et al. reported a 42-year-old female Japanese patient with FMF who complained of dry mouth and dry eye[10]. She had a homozygous M6491 mutation and experienced recurrent attacks of chest pain, fever, and knee arthritis. Specific antibodies for SS (anti-Ro and anti-La) weren't detected, but the antinuclear antibody was positive at high titers. Schirmer's test was positive. Findings of sialography were consistent with SS.

Similarly, Kobak et al. reported a 42-year-old male Turkish patient with a 20-year history of FMF, who presented with complaints of dry eyes and mouth.[11] In this case anti-Ro and anti-La antibodies were negative, but the antinuclear antibody was positive at 1:160. Minor salivary gland biopsy showed grade IV sialoadenitis according to Chisholm grading criteria. His genetic analysis revealed compound heterozygosity for M694V mutation.

Dortbas et al. reported an unusual case of coexistence of FMF, SS and ankylosing spondylitis.[12] A 34-year-old female patient with a 14-year history of FMF with M694V and R202Q mutations of the MEFV gene complained of severe pain in the lower back and hips. The patient presented with a two-year history of inflammatory low back pain and morning stiffness lasting more than one hour. The patient reported that she was diagnosed with SS five years ago when she

complained of dry mouth and eyes. At the time, the antinuclear antibody was positive at 1:320 granular pattern. Anti-Ro/SSA, anti-La/SSB and anti-Ro52 antibodies were also positive. Salivary scintigraphy showed reduced concentration, which was consistent with the findings of SS. Physical examination revealed limitations in the lumbar spine. Flexion and external rotation of the left hip were limited in the mid-range of motion. Modified Schober test was 3 cm. Lumbosacral X-ray of the spine showed bilateral sacroiliitis: grade III on the right side and II-on the left.

Haznedaroglu et al. reported increased IL-18 levels in patients with FMF.[13] They suggested that IL-18 might contribute to the cytokine network in the inflammatory cascade of FMF. Also, Tanaka et al. detected higher IL-18 levels in their patient with concomitant SS and FMF, and reported that FMF-related dysregulated IL-18 production and chronic inflammation might be linked with the occurrence of SS.[10]

Conclusion

A remarkable overlap was highlighted between autoinflammatory (FMF) and systemic autoimmune diseases of connective tissue: both diseases have such common features as arthralgia, myalgia, arthritis, fever, skin involvement, serositis, hepato-splenomegaly and renal involvement. MEFV mutations appear to modify systemic connective tissue diseases phenotype. Further observations are needed to explain the role of MEFV mutations in developing systemic autoimmune disease.

Declarations

Conflict of interest and financial disclosure

The author declares that he has no conflict of interest and there was no external source of funding for the present study. None of the authors have any relevant financial relationship(s) with a commercial interest.

Ethical approval

Research protocol was approved by the local Ethical Committee (2018/23) and in accordance with those of the World Medical Association and the Helsinki Declaration.

Informed consent

Informed consent was obtained from all individual participants included in the study.

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Availability of Data and Materials

Not applicable.

REFERENCES

1. Ramos-Casals M, Brito-Zerón P, Bombardieri S, et al. EULAR recommendations for the management of Sjögren's syndrome with topical and systemic therapies. *Annals of the Rheumatic Diseases*. 2020;79:3-18. doi:10.1136/annrheumdis-2019-216114

2. Sarı İ, Birlik M, Kasifoğlu T. Familial Mediterranean fever: An updated review. *Eur J Rheumatol*. 2014;1:21-33. doi:10.5152/eurjrheum.2014.006

3. Aksu K, Keser G. Coexistence of vasculitides with Familial Mediterranean fever. *Rheumat. Int.* 2011;31(10):1263-1274. doi:10.1007/s00296-011-1840-z

4. Watad A, Tiosano S, Yahav D, et al. Behçet's disease and familial Mediterranean fever: Two sides of the same coin or just an association? A cross-sectional study. *Eur J Intern Med*. 2017;39:75-78. doi:10.1016/j.ejim.2016.10.011

5. Yazici A, Cefle A, Savli H. The frequency of MEFV gene mutations in Behcet's disease and their relation with clinical findings. *Rheumatol*
6. Seyahi E, Ugurlu S, Amikishiev Sh, et al. Behcet disease, familial Mediterranean fever and MEFV variations: more than just an association. *Clinical Immunology*. 2023;251:109630. doi:10.1016/j.clim.2023.109630

7. Akkoc N, Gul A. Familial Mediterranean Fever and Seronegative Arthritis. *Curr Rheumatol Rep*. 2011;13:388–394. doi:10.1007/s11926-011-0191-9

8. Kasifoglu T, Calisir C, Cansu DU, Korkmaz C. The frequency of sacroiliitis in familial Mediterranean fever and the role of HLA-B27 and MEFV mutations in the development of sacroiliitis. *Clin Rheumatol*. 2009;28:41–46. doi:10.1007/s10067-008-0980-3

9. Doria Z, Zen M, Bettio S, et al. Autoinflammation and autoimmunity: bridging the divide. *Autoimmune Rev*. 2012;12(1):22-30. doi:10.1016/j.autrev.2012.07.018

Int. 2012;32:3025-3030. doi:10.1007/s00296-011-2011-y

10. Tanaka M, Migita K, Miyashita T, et al. Coexistence of familial Mediterranean fever and Sjögren's syndrome in a Japanese patient. *Clin Exp Rheumatol*. 2007;25:792–792.

11. Kobak S, Kobak AC, Aksu K, Keser G, Oksel F. Coexistence of Sjogren's syndrome and familial Mediterranean fever. *APLAR Journal of Rheumatology*. 2007;10:244–245. doi:10.5606/ArchRheumatol.2016.5671

12. Dörtbaş F, Garip Y, Güler T, Karci AA. Coexistence of Familial Mediterranean Fever with Ankylosing Spondylitis and Sjogren's Syndrome: A Rare Occurrence. *Arch Rheumatol*. 2015;31(1):87-90. doi:10.5606/ArchRheumatol.2016.5671

13. Haznedaroglu S, Oztürk MA, Sancak B, et al. Serum interleukin 17 and interleukin 18 levels in familial Mediterranean fever. *Clin Exp Rheumatol*. 2005;23:S77–S80.

ՇԵԳՐԵՆԻ ՀԱՄԱԽՏԱՆԻՇԻ և ՊԱՐԲԵՐԱԿԱՆ ՀԻՎԱՆԴՈՒԹՅԱՆ ՀԱԶՎԱԴԵՊ ՀԱՄԱԿՑՈՒՄ

Գինոսյան Քնարիկ,[1] Իրինա Ղազինյան,[2] Էդուարդ Նազարեթյան,[3] Եղիազարյան Նիկոլայ,[4] Էֆրեմիդու Մարիցա,[5] Սևոյան Լիլիթ,[4] Օսիպյան Մագդա[5]

[1] Երևանի Մ.Հերացու անվան Պետական Բժշկական Համալսարանի ռևմատոլոգիայի ամբիոնի վարիչ,դոցենտ, Հերացի համալսարանական հիվանդանոց, Երևան, Հայաստան
[2] Երևանի Մ.Հերացու անվան Պետական Բժշկական Համալսարանի Ներքին հիվանդությունների պրոպեդևտիկայի ամբիոնի դասախոս, Երևան, Հայաստան
[3] Երևանի Մ.Հերացու անվան Պետական Բժշկական Համալսարանի Ներքին հիվանդությունների պրոպեդևտիկայի ամբիոնի պրոֆեսոր, Երևան, Հայաստան
[4] Երևանի Մ.Հերացու անվան Պետական Բժշկական Համալսարանի ռևմատոլոգիայի ամբիոնի դասախոս, «Հերացի» համալսարանական հիվանդանոց, Երևան, Հայաստան
[5] Երևանի Մ.Հերացու անվան Պետական Բժշկական Համալսարանի ռևմատոլոգիայի ամբիոնի ասիստենտ, Հերացու անվան համալսարանական հիվանդանոց, Երևան, Հայաստան

Ամփոփում

Շեգրենի համախտանիշը քրոնիկական աուտոիմուն հիվանդություն է, որը բնութագրվում է աչքերի և բերանի լորձաթաղանթների չորությամբ, ինչպես նաև հենաշարժիչ համակարգի ախտահարմամբ: Միջերկրածովյան ընտանեկան տենդը կամ նույն ինքը՝ Պարբերական հիվանդությունը (ՊՀ) աուտոսոմ-ռեցեսիվ աուտոբորբոքային հիվանդություն է, որը բնութագրվում է պարբերաբար կրկնվող տենդով, որովայնամզի բորբոքումով, սինովիտով, պլևրիտով և մաշկի էրիզիպելոիդ տիպի ախտահարումներով: ՊՀ- ի ժամանակ դիտվում է համակարգային աուտոիմուն հիվանդությունների հանդիպման հաճախականության բարձրացում: Նկարագրված են պարբերական հիվանդության և աուտոիմուն հիվանդությունների զուգակցման բազմաթիվ կլինիկական դեպքեր, որտեղ ՊՀ-ն համակցված է անկիլոզացնող սպոնդիլոարթրիտի, վասկուլիտների, Բեխչետի հիվանդության հետ: Սույն հոդվածում ներկայացված է ՊՀ-ի և Շեգրենի համախտանիշի հազվադեպ զուգակցման կլինիկական դեպք:

РЕДКАЯ КОМБИНАЦИЯ СИНДРОМА ШЕГРЕНА И ПЕРИОДИЧЕСКОЙ БОЛЕЗНИ

Гиносян Кнарик,[1] Ирина Газинян,[2] Эдуард Назаретян,[3] Егиазарян Николай,[4] Ефремиду Марица,[5] Севоян Лилит,[4] Осипян Магда[5]

[1] Доцент, заведующий кафедрой ревматологии, Ереванский государственный медицинский университет имени М. Гераци, Университетская больница «Гераци», Ереван, Армения
[2] Преподаватель кафедры пропедевтики внутренних болезней, Ереванский государственный медицинский университет им. М. Гераци, Ереван, Армения
[3] Профессор кафедры пропедевтики внутренних болезней, Ереванский государственный медицинский университет им. М. Гераци, Ереван, Армения
[4] Преподаватель кафедры ревматологии, Ереванский государственный медицинский университет имени М. Гераци, Университетская больница «Гераци», Ереван, Армения
[5] Ассистент кафедры ревматологии, Ереванский государственный медицинский университет имени М. Гераци, Университетская больница «Гераци», Ереван, Армения

Резюме

Синдром Шегрена - хроническое аутоимунное заболевание, характеризующееся сухостью глаз и полости рта, а также поражением опорно-двигательного аппарата. Периодическая болезнь (ПБ) - аутосомно-рецессивное аутовоспалительное заболевание, характеризующееся периодически повторяющимися приступами лихорадки и серозитов: перитонитом, плевритом, синовитом и эризипелоид-подобной сыпью. При ПБ наблюдается увеличение частоты развития системных аутоиммунных заболеваний. Описано достаточно много сочетаний ПБ с анкилозирующим спондилоартритом, васкулитом, болезнью Бехчета и рядом других аутоиммунных заболеваний. В данной статье нами описан клинический случай редкого сочетания ПБ и синдрома Шегрена.

Ginosyan K, Ghazinyan I, Nazaretyan E, et al. Coexistence Of Sjogren's Syndrome And Familial Mediterranean Fever: A Rare Combination. *Bulletin of Stomatology and Maxillofacial Surgery*. 2023;19(4):31-35. doi: 10.58240/1829006X-2023.19.4-31