Case report

EJO European Journal of Ophthalmology

European Journal of Ophthalmology
2022, Vol. 32(4) NP52–NP55
© The Author(s) 2021

Article reuse guidelines:
sagepub.com/journals-permissions
DOI: 10.1177/1120672121996637
journals.sagepub.com/home/ejo

Ocular Cicatricial Pemphigoid, Sjögren's Syndrome, and Hashimoto's Thyroiditis as a Multiple Autoimmune Syndrome: A case report

Carlos Cifuentes-González[1], Stefania Amaris-Martínez[1], Juliana Reyes-Guanes[2], Pilar Uribe-Reina[1,2] and Alejandra de-la-Torre[1]

Abstract

Purpose: To present a rare and novel association of Ocular Cicatricial Pemphigoid, Sjögren's Syndrome, and Hashimoto's Thyroiditis as a Multiple Autoimmune Syndrome.

Case report: A 43-year-old Colombian female, presented with corneal ulcers, associated with trichiasis. At the ophthalmological examination forniceal shortening OU and symblepharon OD was found. Conjunctival biopsy was performed, evidencing linear deposition of IgG and IgA antibodies along the basement membrane of the conjunctiva, confirming Ocular Cicatricial Pemphigoid diagnosis. After 12 years, the patient presented constitutional symptoms, xerostomia, and worsening of xerophthalmia. Laboratory tests showed positive Anti-TG, Anti-TPO, Anti-Ro, and Anti-La antibodies, and salivary gland biopsy was consistent with Sjögren's Syndrome. Due to these findings, Hashimoto's Thyroiditis and Sjögren's Syndrome were diagnosed, defining a Multiple Autoimmune Syndrome.

Conclusion: A novel association of Multiple Autoimmune Syndrome is presented in this case. Ophthalmologists and other specialists involved in the evaluation and treatment of patients with autoimmune diseases, should be aware of this clinical presentation. A multidisciplinary approach in this condition is important for optimum treatment instauration and follow-up, in order to prevent complications.

Keywords

Multiple autoimmune syndrome, ocular cicatricial pemphigoid, ophthalmology, rheumatology, autoimmune diseases, novel association

Date received: 26 December 2020; accepted: 31 January 2021

Introduction

The term Multiple Autoimmune Syndrome (MAS) was introduced by Pirofsky and Vaughn.[1] Later, Humbert and Dupond[2] described the entity as the coexistence of three or more autoimmune diseases (AD) in the same patient. Thus, based on their observations, they created the MAS classification, which divided the syndrome into three phenotypes (Table 1).[2] This classification allows to predict the appearance of a third AD, which has been described in 25% of the patients, and to predict the probability of an additional AD.[2]

The pathogenesis of MAS is unknown. However, the autoimmune tautology theory proposes that AD share common immunogenic, physiopathological, and genetic mechanisms. This may lead to a presentation of similar signs and symptoms, demonstrating their common origin.[2,3]

Mucous membrane pemphigoid (MMP) is a chronic autoimmune systemic disease that not only affects ocular

[1]Research Group in Neurosciences NeURos, Escuela de Medicina y Ciencias de la Salud, Universidad del Rosario, Bogotá, Colombia
[2]Escuela Barraquer. Research Group, Escuela Superior de Oftalmología del Instituto Barraquer de América, Bogotá, Colombia

Corresponding author:
Alejandra de-la-Torre, Research Group in Neurosciences NeURos, Escuela de Medicina y Ciencias de la Salud, Universidad del Rosario, Carrera 24 # 63C 69, Bogotá, Cundinamarca 111221, Colombia.
Email: alejadelatorre@yahoo.com

tissue but also oral, nasopharynx, tracheal, and urogenital mucosa. Nevertheless, 65%–80% of the events correspond to ocular manifestations, known as Ocular Cicatricial Pemphigoid (OCP).[4] Some studies have described a clinical association between MMP, vitiligo, and Hashimoto's Thyroiditis (HT).[5] Other related ADs associated to MMP such as Rheumatoid Arthritis and Polymyalgia Rheumatica have been described as well.[6] In the same way, polyautoimmunity has been described in 32% of patients with OCP, being pernicious anemia the most frequently related disease.[6] In addition, genes such as HLA-DQw; HLA-DR4; HLA-DQB1*0301, have been linked to the development of OCP related to MAS.[7]

This study aims to report, to the best of our knowledge, the first case of MAS composed by OCP, Sjögren Syndrome (SS), and HT, providing evidence of a rare presentation of the disease.

Table 1. Multiple autoimmune syndrome classification.[2]

Phenotypes	Diseases
MAS–1	Polymyositis
	Myasthenia gravis
	Giant cell myocarditis
	Thymoma
	Dermatopolymyositis
	Autoimmune myocarditis
MAS–2	Autoimmune thyroid disease
	Sjögren's syndrome
	Primary biliary cirrhosis
	Rheumatoid arthritis
	Systemic sclerosis
MAS–3	Autoimmune thyroid disease
	MG and/or thymoma
	Sjögren's syndrome
	Pernicious anemia
	Idiopathic thrombocytopenic purpura
	Addison's disease
	Type 1 diabetes
	Vitiligo
	Autoimmune hemolytic anemia
	Systemic lupus erythematosus

Case report

A 43-year-old Colombian female, with a history of pterygium surgery OU and recurrent corneal ulcers treated with topical drops for 4 years, consulted to the ophthalmology service elsewhere for presenting several episodes of foreign body sensation, trichiasis, and distichiasis. Due to this symptomatology, eyelash electrofulguration and blepharoplasty OU were performed without improvement. Two years later, the patient was referred to our service, for a second opinion for presenting corneal ulceration and trichiasis persistence.

At her first ophthalmological examination, positive findings OD were: best-corrected visual acuity (BCVA) of counting fingers (CF), trichiasis and distichiasis, corneal pannus, superficial punctate keratitis, 50% forniceal shortening and symblepharon formation of 10% in the lower temporal lid, graded as IIc and IIIa stages according to Tauber and Foster et al classification[8] (Figure 1(a)). Positive findings OS were: BCVA 20/20, trichiasis and distichiasis at the lower lid, associated subepithelial fibrosis in the nasal region, superficial punctate keratitis, and 25% forniceal shortening classified as a IIa stage.

Based on clinical manifestations and medical history, OCP was suspected. To confirm the diagnosis, OD

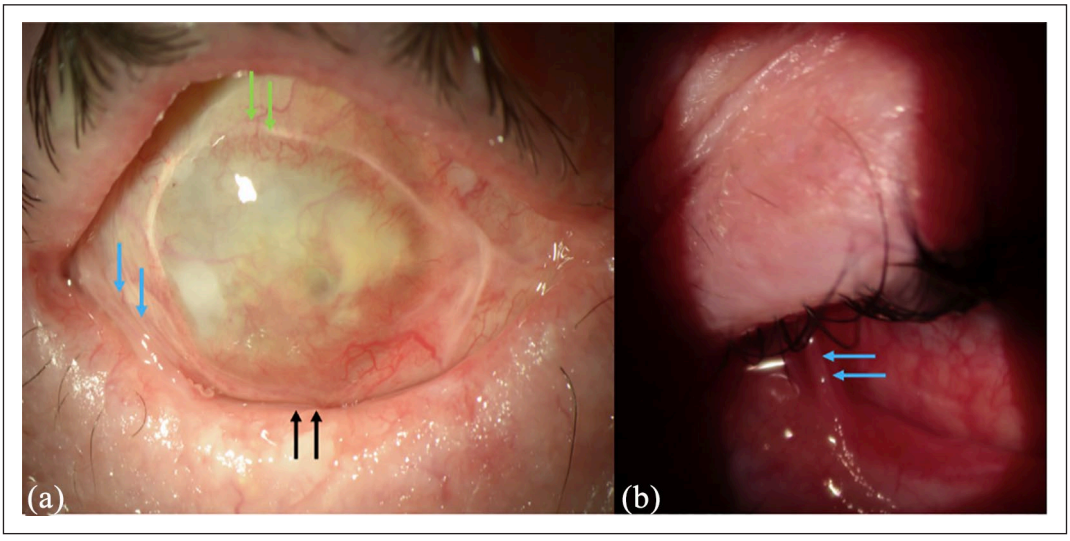

Figure 1. (a) Right eye with trichiasis, distichiasis, madarosis, corneal conjunctivalization, corneal pannus of 360° (green arrows), severe forniceal shortening (black arrows), and symplepharon formation (blue arrows), (b) right eye with trichiasis and symblepharon (blue arrows).

Table 2. Autoinmune panel.

	Results	Reference range
Anti-Smith antibodies	Negative	
Anti-Ro/SSA antibodies (AU)	104*	>20
Anti-La/SSB antibodies (AU)	24*	>20
Antinuclear antibodies (ANA)	1/320 speckled pattern*	
Antineutrophil cytoplasmic antibodies IFI (ANCAS)	Negative	
Rheumatoid factor (RF)	7	>30
Thyroglobulin antibody (anti-Tg)	340*	0–115
Thyroid peroxidase antibodies (anti-TPO)	415*	0–35
Thyroid-Stimulating Hormone (TSH)	4.41	0.4–4

*Anti-Ro/SSA, anti-La/SSB, ANA, anti-Tg and anti-TPO antibodies were positive.

direct immunofluorescence in conjunctival biopsy was performed. The results showed the presence of linear deposition of IgG and IgA antibodies along the basement membrane zone of the conjunctival tissue, confirming the diagnosis of OCP. Treatment with azathioprine and prednisolone was started. During the follow-up, ophthalmological examination OD revealed BCVA 20/400, and detention in forniceal shortening. Thus, prednisolone tapering was indicated.

However, the patient presented a new symblepharon at the nasal lower lid region OD, classified as IIc IIIb.[8] For this reason, cyclophosphamide and closer medical controls were indicated. Three months later, the patient was stable with no new pathological findings. So, prednisolone tapering until suspension and 3-month controls were indicated.

A year later, the patient referred suspension of immunosuppressive treatment by a general practice physician, due to the appearance of anemia with iron sulfate supplements requirement. Besides, clinical examination showed an important loss of visual acuity OD, from 20/400 to CF. The patient presented a corneal leukoma secondary to recurrent corneal ulcers OD.

One year later she presented increased foreign body sensation, xerostomia, asthenia, adynamia, skin dryness, and arthralgias. The patient was referred to the rheumatologist, and laboratory tests (Table 2) and a salivary gland biopsy were ordered. She presented positive Anti-TG, Anti-TPO, Anti-Ro and Anti-La antibodies and salivary gland biopsy was consistent with SS. Thus, SS and HT were diagnosed at the same time.

Based on these findings, MAS diagnosis was confirmed. Treatment with hydroxychloroquine, pilocarpine, and levothyroxine was started.

Despite the treatment, 1 year later, although the patient persisted with the same BCVA OU, forniceal shortening progressed to 80% OD and 75% OS. In the next 2 years, the patient suspended the immunosuppressive treatment by her own, presenting OCP reactivation, demonstrated by a progression of the forniceal shortening OD (90%), associated to inferior corneal pannus and corneal opacification OD (Figure 1(b)). For this reason, rheumatology and ocular immunology specialists indicated methotrexate (Mtx) and, according to evolution, cyclophosphamide. With the MTX treatment, the patient has shown VA and clinical stability OU and the absence of progression of OCP has been evident during the last 5 years with no requirement of cyclophosphamide treatment so far.

Discussion

Comorbidity of OCP with other ADs, such as Rheumatoid Arthritis and Pernicious anemia, has been described.[5,6] In the same way, Nayar et al.[6] reported that 11/34 patients of OCP population presented polyautoimmunity. The most common OCP association was pernicious anemia, followed by vitiligo and polymyalgia rheumatica. Similarly, Lee et al.[9] described a polyautoimmunity prevalence of 35%, being autoimmune thyroid disease (AITD) the principal associated AD, followed by rheumatoid arthritis and psoriasis.

In our case, OCP was the patient's first disease, with a posterior appearance of SS and HT. Contrarily, other case reports have described the appearance of OCP as the last manifestation of the syndrome, after vitiligo and AITD.[5] Hence, our patient's disease association and presentation could be considered uncommon.

On the other hand, SS is a systemic AD that frequently presents with other ADs. Rojas-Villarraga et al.[10] described AITD and SS as the ADs with the most frequent coexistence. In this study, 34% of the patients had polyautoimmunity and 3.6% had MAS. These results support the idea that polyautoimmunity is not infrequent, and it follows associated patterns. Likewise, Boelaert et al.[11] reported a polyautoimmunity prevalence of 14% in patients with HT.

Regarding MAS treatment, it remains undetermined and there are no standard guidelines of care. This could be related to factors such as the diversity in the constitution of MAS phenotypes, which may include orphan diseases, and the lack of registration.[12] Similarly, immunogenic factors, such as HLA-DQB1*0301, LRP1/STAT6, AIRE, and physiopathological mechanisms shared by ADS could determine biologic and nonbiologic drugs usefulness in MAS management.[7,12] Butt et al.[13] suggested treating each AD separately, taking into account the clinical condition and individual aspects of each patient.

On account of OCP progression and the risk of visual loss in our patient, treatment was based in a stepladder combined therapy.[12] Considering the reported response and clinical improvement of OCP and SS with MTX, this was the chosen treatment.[14,15] In patients with OCP, MTX has shown to improve disease control, prevention of scarring, and vision loss.[14] Shi et al.[16] demonstrated that MTX can achieve 73% of effectiveness, determined by total control or inhibition of conjunctival inflammation and scarring. In addition, they described a visual acuity improvement in 27.3% of the patients. Besides, MTX in patients with SS ameliorate dry mouth and ocular symptoms, arthralgias, arthritis, parotid gland enlargement, and purpura.[15]

To the best of our knowledge, we present the first MAS description with OCP, SS, and HT comorbidity; thus, establishing regular management was a challenge. It is crucial to consider that a multidisciplinary management is fundamental to achieve control of the disease.

Conclusions

A novel association of MAS, where OCP was the first AD, followed by SS and HT is presented in this case. Therefore, ophthalmologist and other specialists involved in the evaluation and treatment of patients with autoimmune diseases, should be aware of this association since these three ADs can co-exist. We emphasize the importance of a multidisciplinary approach, as it assures an optimum disease and treatment instauration and follow-up.

Acknowledgements

We thank Universidad del Rosario for financing the publication of this article.

Authors' note

All authors attest that they meet the current ICMJE criteria for Authorship.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical considerations

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given her consent for images and the clinical information to be reported in the journal. The patient understands that her name and initials will not be published, and due effort will be made to conceal her identity, but anonymity cannot be guaranteed.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

ORCID iDs

Carlos Cifuentes-González https://orcid.org/0000-0002-2703-0977

Juliana Reyes-Guanes https://orcid.org/0000-0002-2326-7213

Alejandra de-la-Torre https://orcid.org/0000-0003-0684-1989

Supplemental material

Supplemental material for this article is available online.

References

1. Pirofsky B and Vaughn M. Addisonian pernicious anemia with positive antiglobulin tests: a multiple autoimmune disease syndrome. *Am J Clin Pathol* 1968; 50: 459–466.
2. Humbert P and Dupond JL. Multiple autoimmune syndromes. *Ann Med Interne (Paris)* 1988; 139: 159–168.
3. Anaya J-M. The autoimmune tautology. *Arthritis Res Ther* 2010; 12: 147.
4. Ong HS, Setterfield JF, Minassian DC, et al. Mucous membrane pemphigoid with ocular involvement. *Ophthalmology* 2018; 125: 496–504.
5. Niknezhad N, Ghalamkarpour F, Niknejad N, et al. Coexistence of mucous membrane pemphigoid, vitiligo, and hypothyroidism: a second report of a new multiple autoimmune syndrome. *Dermatol Ther* 2018; 31: e12717.
6. Nayar M, Wojnarowska F, Venning V, et al. Association of autoimmunity and cicatricial pemphigoid: is there an immunogenetic basis? *J Am Acad Dermatol* 1991; 25: 1011–1015.
7. Ahmed AR, Foster S, Zaltas M, et al. Association of DQw7 (DQB1*0301) with ocular cicatricial pemphigoid. *PNAS* 1991; 88: 11579–11582.
8. Tauber J, Jabbur N and Foster CS. Improved detection of disease progression in ocular cicatricial pemphigoid. *Cornea* 1992; 11: 446–451.
9. Lee J, Seiffert-Sinha K, Attwood K, et al. A Retrospective study of patient-reported data of bullous pemphigoid and mucous membrane pemphigoid from a US-based registry. *Front Immunol* 2019; 10: 2219.
10. Rojas-Villarraga A, Amaya-Amaya J, Rodriguez-Rodriguez A, et al. Introducing polyautoimmunity: secondary autoimmune diseases no longer exist. *Autoimmune Dis* 2012; 2012: 254319.
11. Boelaert K, Newby PR, Simmonds MJ, et al. Prevalence and relative risk of other autoimmune diseases in subjects with autoimmune thyroid disease. *Am J Med* 2010; 123: 183.e1–183.e9.
12. Saw VPJ, Dart JKG, Rauz S, et al. Immunosuppressive therapy for ocular mucous membrane pemphigoid: strategies and outcomes. *Ophthalmology* 2008; 115: 253–261.e1.
13. Butt N, Khan MA, Abid Z, et al. A case of polyautoimmunity: celiac hepatitis, Grave's disease and autoimmune hemolytic anemia. *J Coll Physicians Surg Pak* 2019; 29: S106–S108.
14. McCluskey P, Chang JH, Singh R, et al. Methotrexate therapy for ocular cicatricial pemphigoid. *Ophthalmology* 2004; 111: 796–801.
15. Skopouli FN, Jagiello P, Tsifetaki N, et al. Methotrexate in primary Sjögren's syndrome. *Clin Exp Rheumatol* 1996; 14: 555–558.
16. Shi Y, Xie C, He Y, et al. Efficacy and adverse reactions of methotrexate in the treatment of ocular cicatricial pemphigoid: a case series study. *Medicine* 2018; 97s38): e12338.