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Case report

Beyond expectations: Concurrent presence of beta thalassemia and Sjögren's syndrome

Más allá de las expectativas: presencia simultánea de beta-talasemia y síndrome de Sjögren

Mateo Aguirre Flórez[a,*], Daniel Toro Restrepo[a], Lina María Saldarriaga Rivera[b], Henry Idrobo Quintero[b], Laura Alejandra Jiménez Osorio[c], Valeria López Pulgarín[c], Daniel Millán Morales[c]

[a] *Critical Medicine and Intensive Care Research Group (GIMCCI), Faculty of Health Sciences, Universidad Tecnológica de Pereira, Pereira, Colombia*
[b] *Internal Medicine Research Group, Faculty of Health Sciences, Universidad Tecnológica de Pereira, Pereira, Colombia*
[c] *Faculty of Health Sciences, Universidad Tecnológica de Pereira, Pereira, Colombia*

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ABSTRACT

Background: Beta thalassaemia and Sjögren's syndrome are rare diseases with distinct aetiologies. Beta thalassaemia is an inherited haemoglobinopathy that causes chronic anemia, while Sjögren's syndrome is an autoimmune disease that affects exocrine glands.
Case report: We present a 45-year-old female with beta-thalassaemia diagnosed by genetic testing who developed Sjögren's syndrome symptoms. The diagnosis was confirmed by clinical, serological, and histopathological criteria. This is the first documented case in a Colombian tertiary institution.
Conclusions: Beta-thalassaemia and Sjögren's syndrome coexistence is extremely rare, highlighting the need for a multidisciplinary diagnostic approach. Further investigation into possible molecular and genetic links is needed.

Palabras clave:
Enfermedades autoinmunes
Beta-talasemia
Colombia
Síndrome de Sjögren

RESUMEN

Introducción: La beta-talasemia y el síndrome de Sjögren son enfermedades raras con etiologías distintas. La beta-talasemia es una hemoglobinopatía hereditaria que causa anemia crónica, mientras que el síndrome de Sjögren es una enfermedad autoinmune que afecta a las glándulas exocrinas.
Reporte de caso: Presentamos el caso de una mujer de 45 años con beta-talasemia, diagnosticada mediante pruebas genéticas que desarrolló síndrome de Sjögren. El diagnóstico se confirmó mediante criterios clínicos, serológicos e histopatológicos. Este es el primer caso documentado en una institución terciaria colombiana.
Conclusiones: La coexistencia de beta-talasemia y síndrome de Sjögren es extremadamente rara, resalta la necesidad de un enfoque diagnóstico multidisciplinario. Se requiere mayor investigación sobre posibles vínculos moleculares y genéticos.

Introduction

Beta thalassemia and Sjögren's syndrome are rare clinical entities with distinctive and complex features. Beta thalassemia is an inherited blood disease resulting from gene mutations encoding hemoglobin, leading to deficient red blood cell production and chronic anemia [1]. Beta-thalassemias are heterogeneous autosomal recessive hereditary anemias characterized by absent or reduced synthesis of the β-globin chain. They are classified into β-thalassemia major, β-thalassemia minor, and β-thalassemia trait. Their diagnosis is usually confirmed by genetic testing that identifies specific mutations [1,2].

Sjögren's, on the other hand, is a chronic autoimmune disease that occurs due to lymphocytic infiltration and inflammation of the exocrine glands, especially the lacrimal and salivary glands. This disease can present clinically with glandular and extra-glandular symptoms, includ-

* *Corresponding author.*
E-mail address: maguirref96@utp.edu.co (M. Aguirre Flórez).

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ing fatigue, musculoskeletal symptoms, and organ involvement such as lung, liver, and kidney [3]. The diagnosis of Sjögren's is based on a combination of clinical, serological, and often histopathological criteria. Its global prevalence is estimated at 60.82 cases per 100,000 population, with variations in symptoms depending on the region; for example, in Colombia, patients appear to have a higher rate of urticaria and dysphagia compared with other Latin American countries [3].

Geographically, beta-thalassemia is more prevalent in regions of the Mediterranean, Middle East, Africa, and South Asia, where malaria was historically endemic, suggesting an evolutionary advantage of carriers of the thalassemic trait against malaria. In contrast, Sjögren's syndrome is diagnosed more frequently in northern European and North American populations, and its prevalence appears to be higher in women, especially in the fifth and sixth decade of life [4]. The association of these diseases with socioeconomic and behavioral factors varies; while beta thalassemia is more closely linked to genetic background and geographic distribution, Sjögren's syndrome may be influenced by environmental and lifestyle factors that modulate the immune response [4].

The coexistence of these two diseases in the same patient is extremely rare and presents a significant diagnostic and therapeutic challenge. The combination of an inherited hemoglobinopathy and an autoimmune disease raises questions about the interaction between hematologic disorders and autoimmune diseases [2]. It is suggested that specific mutations and shared molecular pathways could mediate this correlation. One hypothesis proposes that the proximity of genes involved in immune regulation to the β-globin gene locus and the altered concentration of hemorphins could contribute to the immune dysfunction observed in patients with both pathologies [1].

This case report describes a 45-year-old female patient with a confirmed diagnosis of beta thalassemia, who, during her clinical follow-up, developed dry symptoms characteristic of Sjögren's syndrome and who was diagnosed in a tertiary care institution in a city in Colombia. This case highlights the importance of considering dual diagnoses in patients with complex clinical presentations and underlines the need for a multidisciplinary approach to manage such cases. The lack of reported cases underscores the need for further research and additional data collection to improve our understanding and guide treatment in these complex clinical scenarios.

Case report

The patient is a 45-year-old female patient who lives in an urban area of a medium-sized city in Colombia. The patient has worked in various cleaning company occupations for approximately seven years. Her medical history includes a history of migraine with aura and glaucoma with improvement thanks to medical management; in addition, she has bilateral carpal tunnel syndrome that previously required surgical management, as well as an essential family history with her father and sister with chronic anemia. She was in follow-up with internal medicine and hematology since the end of 2023 with a diagnosis of chronic anemia, given constitutional symptoms with asthenia and adynamia as well as myalgias in lower limbs. The case was initially approached with thalassemia trait with microcytic and hypochromic anemia as well as the presence of alterations in the peripheral blood smear, in addition to hemoglobin (HB) electrophoresis: HbA 93.6%, HbF 0.9% HbA2 5.5% compatible with beta-thalassemia and finally individual whole exome sequencing. The related paraclinical reports are shown in Table 1 . For her management, the multidisciplinary team started with general education on her pathology, folic acid and iron supplementation, and periodic follow-ups.

Three months after diagnosis, the patient presented dry keratoconjunctivitis documented by ophthalmology, xerostomia associated with dry and cracked lips, as well as occasional dysphagia, and a favorable immunological profile Anti-Ro: 205.7 U/mL. An ultrasound imaging study of salivary glands confirmed the diagnosis of Sjogren's syndrome. The rheumatology department started treatment with hydroxychloroquine, pilocarpine, and ophthalmic carboxymethylcellulose, with improvement of symptoms.

Table 1
Most relevant paraclinical findings of the patient.

Date	Laboratory test	Result
March 2023	Hemogram	Hb: 11.2 g/dL ACV: 62.8 fl RDW: 16.1%
	ENAs + Anti Ro	198.2/20
April 2024	Anti-DNA	Negative
	Anticardiolipin	3.7 GPL/mL
	IgG	15.5
	Anti Sm	< 3 U/mL
	Anti RNP	< 3.5 U/mL
	Anti Ro	205.7 U/mL
	Anti-La	< 3.3 U/mL
	Lupus anticoagulant	1.6 (positive)
	C3	128 g/L
	C4	33 g/L
	Rheumatoid factor	< 20
	Hemoglobin electrophoresis	Homozygous beta thalassemia
	ANAs	Negative
	Creatinine	0.71 mg/dL
	β-2 glycoprotein 1 IgG antibodies	< 6.4 GLP/mL
	β-2 glycoprotein 1 IgM antibodies	2.6 GLP/mL
	Reticulocytes	2.1%
	Haptoglobin	42 mg/dL
	TSH	2.8 mUI/L
	Ferritin	177 ng/mL
	Vitamin B12	557
	Vitamin D	24.7

Hb: hemoglobin, ACV: average corpuscular volume, RDW: red cell distribution width, ENAs: autoantibodies to extractable nuclear antigens, ANAs: anti nuclear antibodies, TSH: thyroid-stimulating hormone.

Discussion

The presence of dual diagnoses in a patient is a clinical challenge, especially when both conditions may have clinical presentations that overlap in some signs and symptoms. Carriers of hemoglobinopathies are usually clinically silent and are the most common monogenic disorders in the world. The genetic causes are variants in the DNA or near globin genes. In the case of DNA variants, this can result in altered synthesis of α- or β-globin and thus produce α- and β-thalassemia syndromes. Approximately 7% of the world's population carries a genetic variant that causes defective hemoglobin synthesis [5].

Sjögren's syndrome is an autoimmune disease that has two forms of presentation, primary and secondary, where in either of them, an involvement of the exocrine glands is observed. This disease can present clinically with glandular and extra glandular symptoms, where within its extra glandular involvement is involved the hematological system, which in 30–60% of cases patients present anemia and thus intermingle with the signs and symptoms given, for example, in a patient with beta thalassemia, especially at the beginning of the presentation or in mild cases where its manifestation is given with nonspecific symptoms [5].

The coexistence of beta-thalassemia and Sjögren's syndrome in the same patient is extremely rare and poses a significant diagnostic challenge due to the overlap of hematologic and systemic symptoms. The current literature on the concurrence of these two diseases is sparse, with no reported cases, which limits our understanding of their man-

agement and prognosis. This rarity may be attributed to several factors, including the low individual prevalence of each disease and the possible underestimation or lack of recognition of the coexistence of both conditions in daily clinical practice. We found only one report, by Castellino et al., examining the concurrence of beta thalassemia and Sjögren's syndrome [2]. However, it is important to clarify that this article does not mention the coexistence of systemic lupus erythematosus (SLE) and Sjögren's syndrome (SS) with steatosis in the presence of thalassemia. Instead, the study highlights a higher frequency of beta thalassemia in patients with SS (71%) compared to those without thalassemia (16%). All cases and non-cases involved a context of polyautoimmunity with SLE, unlike the current case. As the study's authors indicated, further reports and studies are needed to clarify whether this association is not merely coincidental [2].

The case presented of a 45-year-old female patient with a confirmed diagnosis of beta-thalassemia, who, during her clinical follow-up, developed symptoms characteristic of Sjögren's syndrome, underscores the importance of a comprehensive, multidisciplinary clinical approach.

Given that the clinical symptoms of Sjögren's syndrome (SS) became evident three months after the diagnosis of anemia, it is possible that SS had a subclinical course before clearly manifesting. The autoimmune dysregulation characteristic of SS could have started months before the observed clinical presentation. In this context, it is plausible that the presence of beta thalassemia, with its chronic component of oxidative stress and underlying inflammation, may have contributed to triggering or exacerbating a latent autoimmune predisposition, leading to the development of SS. This case raises the hypothesis that the interaction between beta thalassemia and Sjögren's syndrome might not be purely coincidental, but could represent a phenomenon of concurrent onset, where one condition predisposes to or exacerbates the appearance of the other.

The poor characterization of the co-occurrence of these diseases is due, in part, to the lack of extensive and detailed studies examining the interaction between autoimmune conditions and hemoglobinopathies. This highlights the need for further research and the collection of additional case data to improve our understanding and guide treatment.

Diagnostic challenges include differentiating common symptoms, such as anemia, which can be attributable to beta-thalassemia and Sjögren's syndrome [6]. The anemia in Sjögren's syndrome is usually a chronic disorder or autoimmune hemolytic anemia, whereas, in beta-thalassemia, it is a microcytic, hypochromic anemia. However, the coexistence of both conditions can complicate the interpretation of hematologic studies and require a more sophisticated approach to differential diagnosis [6,7].

When facing a case of anemia in the context of autoimmunity such as Sjögren's syndrome (SS), several differential diagnoses should be considered. It is crucial to rule out autoimmune hemolysis through appropriate testing such as the direct Coombs test. For cases of microcytic hypochromic anemia, the diagnostic approach should include serum iron studies, ferritin levels, and, when indicated, hemoglobin electrophoresis. The decision to request hemoglobin electrophoresis is typically based on suggestive findings in the complete blood count, such as microcytosis with normal or elevated red blood cell counts, and specific peripheral blood smear findings, like target cells or basophilic stippling, which may distinguish beta thalassemia from iron deficiency anemia. Genetic studies, such as whole exome sequencing, are not commonly performed as part of routine evaluations due to their high cost and limited availability; they are generally reserved for atypical or complex cases where the diagnosis remains uncertain. Understanding these considerations can help differentiate between the more common causes of anemia in SS, such as iron deficiency or anemia of chronic disease, and the rarer association with conditions like beta-thalassemia [5,6].

In addition, the extra glandular manifestations of Sjögren's syndrome can affect several organ systems, including the hematologic system, which can further complicate the clinical picture of a patient with an underlying hemoglobinopathy [6]. Hematologic involvement in Sjögren's syndrome can include leukopenia, thrombocytopenia, and, more rarely, lymphomas, which adds a layer of complexity to the clinical management of these patients [7]. It is also important to consider the physiological and etiological roles of hemorphins in this case; which are peptides derived from the proteolysis of hemoglobin, have been suggested to have immunomodulatory effects that could potentially contribute to the development of autoimmune diseases [8].

This case highlights the need for ongoing clinical surveillance and periodic reassessment of symptoms in patients with complex chronic diseases. Healthcare professionals should be alert to the possibility of dual diagnoses and consider interdisciplinary collaboration to address the multiple facets of these conditions adequately.

Limitations and strengths

The present case report has several limitations that affect the generalization and interpretation of the findings. A major limitation is the scarcity of previous scientific literature documenting the coexistence of beta-thalassemia and Sjögren's syndrome in a single patient, making it challenging to compare and validate our results. Additionally, the absence of a minor salivary gland biopsy in this case could be considered a diagnostic limitation, as it might have provided valuable information regarding the presence or absence of hemosiderin deposits, especially in patients who have already begun transfusions without a clear diagnosis of thalassemia. As this is a single case report, the generalization of findings to a broader population is limited, and the opportunity for a comprehensive longitudinal evaluation to explore potential interactions and complications over time between the two diseases is also restricted. The rarity of this coexistence further implies that some diagnostic aspects might not have been fully explored, potentially influencing the interpretation of the results [9].

Despite the limitations above, this case report presents several significant strengths. The most outstanding is that, to our knowledge, this is the first documented case in the world describing the coexistence of beta-thalassemia and Sjögren's syndrome in the same patient. This uniqueness brings novel and valuable information to the medical field, opening up new areas of research and study. In addition, the diagnosis of beta thalassemia was confirmed by genetic testing, which added precision and robustness to the diagnosis. The comprehensive management of the case in a tertiary institution with a multidisciplinary approach ensures a thorough evaluation and appropriate treatment. Also, the detailed clinical description provides a solid basis for future studies and comparisons and can serve as a reference for other health professionals facing similar cases. In summary, this case report contributes to medical knowledge and highlights the importance of considering dual diagnoses in patients with complex clinical presentations.

Conclusion

The coexistence of beta-thalassemia and Sjögren's syndrome is rare, presenting significant diagnostic and therapeutic challenges. This first documented case highlights the need for a comprehensive, multidisciplinary approach for patients with complex conditions. The interaction between hematologic and autoimmune disorders suggests possible molecular and genetic links needing further research. Healthcare professionals should consider dual diagnoses in atypical cases and encourage collaboration across specialties. This case underscores the importance of documenting unique cases to enhance understanding and improve management of rare disease interactions.

Authors' contributions

Aguirre-Flórez: Study concept and design, acquisition, analysis, interpretation of data, manuscript drafting, critical revision of the

manuscript for important intellectual content, original material, and construction of figures.

Toro-Restrepo: Study concept and design, acquisition, analysis, and interpretation of data.

Saldarriaga-Rivera: Study concept and design, acquisition, analysis, and interpretation of data.

Idrobo Quintero: Critical manuscript revision for important intellectual content and study supervision.

Jiménez-Osorio: Critical manuscript revision for important intellectual content and study supervision.

López-Pulgarín: Critical manuscript revision for important intellectual content and study supervision.

Millán-Morales: Critical manuscript revision for important intellectual content and study supervision.

Ethics approval and consent to participate

This report was written following Helsinki's declaration and accepted by the institutional bioethics committee.

Ethical considerations

Informed written permission was obtained from the patient when he moved to the general guard.

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Conflict interests

None of the authors declare conflicts of interest.

Availability of data and materials

All data and materials relevant to the presentation of this case are included in this manuscript.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found in the online version available at https://doi.org/10.1016/j.rcreu.2024.12.002.

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