Unprecedented complexity of six coexisting autoimmune diseases: A case report

Coexistence de six maladies auto-immunes simultanées: Cas clinique

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Abstract

Introduction: Autoimmune disorders often exhibit interconnectedness, although encountering multiple autoimmune conditions in a single patient is uncommon. Multiple autoimmune syndrome is characterized by the presence of at least three distinct autoimmune diseases in an individual. This report outlines the case of a middle-aged woman diagnosed with autoimmune thyroiditis, Sjögren's syndrome, scleroderma, autoimmune hepatitis, primary biliary cirrhosis, and antisynthetase syndrome. Additionally, it includes a literature review encompassing multiple autoimmune syndromes involving five or more autoimmune diseases.

Observation: A 57-year-old woman, with no previous medical history, presented with fever, extensive muscle weakness, progressive exertional dyspnea, inflammatory polyarthralgia, dysphagia, and dry mouth. Clinical examination revealed muscular deficit in the scapular and pelvic girdles, distal muscular deficit, synovitis in the wrists, and features indicative of "mechanic's hand". Laboratory examinations showed cytolysis, cholestasis, elevated muscle enzymes, hypergammaglobulinemia and elevated thyroid stimulating hormone. Immunoassays showed positive results for antinuclear antibodies, anti-histidyl-t-RNA synthetase, anti–Sjögren's-syndrome-related antigen A, anti-ribonucleic-acid-polymerase-III-RP155, anti-fibrillarin, anti-mitochondrial, anti-liver/kidney microsomal type 1, anti-glycoprotein 210, and anti-thyroid peroxidase antibodies. Further investigations led to the diagnosis of a multiple autoimmune syndrome involving autoimmune thyroiditis, Sjögren's syndrome, scleroderma, autoimmune hepatitis, primary biliary cirrhosis, and antisynthetase syndrome. The patient received treatment with intravenous immunoglobulins, corticosteroids, azathioprine, and ursodeoxycholic acid, which resulted in favorable clinical and biological outcomes.

Conclusion: This patient presented with six concurrent distinct autoimmune disorders, categorizing this case as a type two multiple autoimmune syndrome. The identification of antisynthetase syndrome notably distinguishes this case.

Key words: Autoimmune hepatitis, Autoimmune thyroiditis, Myositis, primary biliary cirrhosis, Sjogren's syndrome

Résumé

Introduction: Les troubles auto-immuns sont fréquemment interconnectés, bien qu'il soit rare de trouver plusieurs affections auto-immunes chez un seul patient. Le syndrome auto-immun multiple est défini par la présence d'au moins trois maladies auto-immunes distinctes chez un même patient. L'objectif de ce cas clinique était de rapporter le cas d'une patiente d'âge moyen présentant une thyroïdite auto-immune, un syndrome de Sjögren, une sclérodermie, une hépatite auto-immune, une cirrhose biliaire primitive et un syndrome des anti-synthétases, et de faire une revue de la littérature sur les syndromes auto-immuns multiples impliquant cinq maladies auto-immunes ou plus.

Observation: Une femme de 57 ans sans antécédents médicaux, a présenté des symptômes comprenant de la fièvre, une faiblesse musculaire diffuse, une dyspnée d'effort progressive, des polyarthralgies inflammatoires, une dysphagie et une sécheresse buccale. L'examen a révélé un déficit musculaire des ceintures scapulaire et pelvienne, ainsi qu'un déficit musculaire distal, une synovite des poignets et un aspect de "main de mécanicien". Le bilan biologique a mis en évidence une cytolyse, une cholestase, des enzymes musculaires élevées, une hypergammaglobulinémie et un taux élevé d'hormone thyréostimulante. Le bilan immunologique a montré la positivité des anticorps antinucléaires, anti-histidyl-ARNt-synthetase, anti-antigène A lié au syndrome de Sjögren, anti-acide-ribonucléique-polymérase-III-RP-155, anti-fibrillarine, anti-mitochondriaux, anti-liver/kidney-microsomal-type 1, anti-glycoprotéine 210 et anti-thyroperoxydase. Des investigations complémentaires ont conduit au diagnostic d'un syndrome auto-immun multiple, englobant une thyroïdite auto-immune, un syndrome de Sjögren, une sclérodermie, une hépatite auto-immune, une cirrhose biliaire primitive et un syndrome des anti-synthétases. La patiente était traitée par des immunoglobulines intra-veineuses, des corticoïdes, de l'azathioprine et de l'acide ursodeoxycholique avec une bonne évolution clinique et biologique.

Conclusion: Cette patiente présentait six affections auto-immunes distinctes concomitantes, classifiant ce cas comme un syndrome auto-immun multiple de type 2. L'incorporation du syndrome des antisynthétases dans ce cas le distingue de manière significative.

Mots clés: Cirrhose biliaire primitive, Hépatite auto-immune, myosite, Syndrome de Sjogren, Thyroïdite auto-immune

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Introduction

Autoimmune diseases (AD) are characterized by an aberrant immune response resulting in tissue damage and organ dysfunction [1]. Despite ongoing research, the pathogenesis of multiple ADs remains incompletely understood. It is generally believed that environmental triggers in genetically predisposed individuals lead to immune dysregulation [2]. Approximately a quarter of patients diagnosed with an AD eventually develop additional ADs [3]. While the co-occurrence of two or three ADs within a single patient has been documented [3], the concept of multiple autoimmune syndrome (MAS) was introduced by Humbert and Dupond [4] in 1988, defining it as the presence of three or more ADs in one patient. MAS categorizes different ADs into three distinct groups based on their co-occurrence frequency and shared underlying mechanisms [4].

In this context, we report for the first time, the occurrence of six simultaneous ADs encompassing autoimmune thyroiditis, Sjögren's syndrome (SS), systemic scleroderma, autoimmune hepatitis, primary biliary cirrhosis (PBC), and antisynthetase syndrome (ASS) in the same patient. To comprehensively investigate the existence of cases presenting with five or more ADs, we employed on December 2023 an extensive search strategy using PubMed and Google Scholar databases. The Keywords and Medical Subject Headings used were the following: "multiple autoimmune disease", "multiple autoimmune syndrome", "polyautoimmunity", "connective tissue diseases", "lupus", "myositis", "sjogren syndrome", "autoimmune thyroiditis", "autoimmune hepatitis", "scleroderma", "primary biliary cirrhosis", "overlap syndrome", as well as terms like "coexistence", "simultaneous" and "concurrent".

Case report

The patient was a 57 years old female with no significant medical history except for a cholecystectomy. She was admitted to the hospital for the investigation of diffuse muscle weakness, predominantly in the limbs. This weakness had been present for two months and was accompanied by progressive exertional dyspnea, fever, and a moderate decline in the general condition. On examination, the patient complained of severe dysphagia to solid foods, dry mouth, and inflammatory polyarthralgia. She presented with a performance status (PS) of 4, indicating significant impairment [5]. Muscular deficit was noted in both the scapular and pelvic girdles, along with a pronounced distal muscular deficit, particularly in the lower limbs. Skin examination showed a conical nose with thinned lips without reduction in the mouth opening, suggestive of scleroderma as well as sulky fingers with a fissured digital palmar hyperkeratosis, reminiscent of the appearance of "Mechanic's hands". Synovitis of the wrists and metacarpophalangeal joints was observed during joint examination.

Table 1 exposes the results of the laboratory examinations. Its main conclusions were the following: i) Biological inflammatory syndrome (high erythrocyte sedimentation rate and C-reactive protein levels); ii) Hyperleukocytosis and lymphopenia; iii) Normal renal function; iv) Liver cytolysis (ie.; high aspartate aminotransferase and alanine aminotransferase levels), associated with cholestasis (ie.; high alkaline phosphatase and glutamyl transpeptidase gamma levels); and v) Muscle lysis (ie.; high creatine phosphokinase and lactate dehydrogenase levels).

Table 1. Biochemical data before and one month after the initiation of treatment.

Laboratory parameters	Unit	Normal value	On admission	One month after the initiation of treatment
Alanine aminotransferase	UI/L	[10-35]	262	37
Aspartate aminotransferase	UI/L	[10-35]	378	28
Gamma-glutamyl transferase	UI/L	[5-36]	112	31
Alkaline phosphatase	UI/L	[25-90]	160	76
Creatine phosphokinase	UI/L	[25-175]	5293	161
Lactate dehydrogenase	UI/L	[60–160]	750	153
White blood cells	g/L	[4-10]	21	8.1
Lymphocytes	g/L	[1.5-4]	700	1500
Hemoglobin	g/dl	>12g	13	12.2
C-reactive protein	mg/L	[0–8]	89	6
Erythrocyte sedimentation rate	mm/h	[0–15]	120	40
Thyroid-stimulating hormone	mU/L	[0.3-5]	10	-
Gamma globulin	g/l	[6–12]	19.8	-

The presence of cytolysis and cholestasis, along with negative viral serologies and normal radiological investigations (ultrasound and abdominal computed tomography scan), led to the consideration of screening for anti-hepatic antibodies. The screening yielded positive outcomes for antibodies against anti-mitochondrial, anti-glycoprotein 210, and anti-liver/kidney-microsomal-type1. These findings, in combination with hypergammaglobulinemia observed in protein electrophoresis, led to the diagnosis of primary biliary cirrhosis-autoimmune hepatitis overlap syndrome, following the exclusion of drug-induced causes. Although a liver biopsy could not be performed, the diagnostic score for autoimmune hepatitis was 6, suggesting a probable diagnosis [6]. A depressed mood and a high thyroid-stimulating-hormone level warranted an anti-thyroid peroxidase antibodies test, which was positive, confirming the diagnosis of autoimmune thyroiditis. A thoracic computed tomography scan was conducted in response to worsening dyspnea, desaturation on room air, and a normal cardiac ultrasound with a left ventricular ejection fraction of 60%, excluding interstitial lung disease and pulmonary embolism. Electromyography showed diffuse and severe myogenic damage. The remaining immunological evaluation indicated a high positivity for antinuclear antibodies and the presence of anti-histidyl-t-RNA synthetase, anti-ribonucleic-acid polymerase III-RP155, anti-fibrillarin, and anti-Sjögren's syndrome-related antigen A antibodies. All anti-phospholipid antibodies were negative. The diagnosis

of ASS was retained, given the clinical presentation of polymyositis and anti-histidyl-t-RNA synthetase antibodies, according to the 2017 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) criteria [7]. Labial biopsy showed chronic Chisholm stage 3 sialadenitis, confirming the diagnosis of associated SS according to the 2016 ACR/EULAR criteria [8]. Scleroderma was also considered due to cutaneous signs present, hypotonia of the lower esophageal sphincter observed during esophageal manometry, and positivity of anti-RNA polymerase-III-RP155 and anti-fibrillarin antibodies. Treatment included administering a 2g/kg immunoglobulin bolus over two days considering the severity of the condition and the potential damage to the respiratory muscles. This was followed by high-dose corticosteroid therapy (1 mg/kg per day of prednisone) for six weeks. Immunosuppressants (azathioprine) and ursodeoxycholic acid were also prescribed. In addition, the treatment was enhanced through physiotherapy sessions that focused on building up the muscles.

The initial course was marked by the occurrence of cerebral thrombophlebitis, which was manifested by a status epilepticus requiring a stay in intensive care. One month after the start of treatment, the patient showed a favorable evolution: she was no longer febrile, her thymia had improved, joint pain had disappeared, and her autonomy had improved (ie; PS of 2), and her liver and muscle enzymes had returned to normal (Table 1).

Discussion

We report the case of a patient with autoimmune thyroiditis, SS, autoimmune hepatitis, PBC, ASS and scleroderma. The association of at least three ADs defines MAS [4,9]. MAS is a rare clinical entity classified into three types [4]: type 1 MAS includes myasthenia gravis, thymoma, polymyositis and giant cell myocarditis; type 2 MAS includes SS, rheumatoid arthritis, PBC, scleroderma, and autoimmune thyroid disease; type 3 MAS includes together autoimmune thyroid disease, myasthenia gravis and/or thymoma, SS, pernicious anemia, idiopathic thrombopenic purpura, Addison's disease, type 1 diabetes mellitus, vitiligo, autoimmune hemolytic anemia, systemic lupus erythematosus, and dermatitis.

The occurrence of multiple ADs is likely not a coincidence but rather a result of possible genetic predisposition [9,10]. For instance, the human leukocyte antigen-D-related 3 or human leukocyte antigen-D-related 4 haplotype may significantly contribute to the association between ADs. In addition to genetics, environmental factors play a crucial role [2]. Patients with one AD often exhibit a tendency to develop others [3]. Specific autoantibodies can be identified in diseases that affect multiple organs.

The ASS is a rare group of inflammatory myositis diseases that is not fully understood. It is characterized by the presence of anti-aminoacyl-tRNA synthetase antibodies, with the most common being anti-histidyl-t-RNA synthetase. It was first described in 1990 by Marguerie et al. [11] as a primary inflammatory myositis often associated with diffuse interstitial pneumonia [10]. In our case, the patient did not develop diffuse interstitial pneumonia but had the typical mechanic's hand involvement. This reinforces existing data in the literature highlighting the variation in target organ involvement from patient to patient, possibly related to the specific subtype of anti-tRNA synthetase antibodies [11]. There are eight different types of anti-synthetase antibodies (histidyl-t-RNA synthetase; threonyl-tRNA synthetase; alanyl-tRNA synthetase; glycyl-tRNA synthetase; isoleucyl-tRNA synthetase; phénylalanyl-tRNA synthetase; asparaginyl-tRNA synthetase; tyrosyl-tRNA synthetase), each of which is associated with a different clinical manifestation [11]. It is not uncommon for this syndrome to be associated with other AD, as documented in the literature, illustrated by its association with conditions such as SS and scleroderma [12].

Our patient's case is remarkable in that the occurrence of the six ADs was simultaneous. For instance, autoimmune thyroid disease, which consistently occurs in MAS [13], typically precedes other ADs [3]. However, in this patient's case, thyroiditis was confirmed at the same time as the other ADs, contrary to what is classically reported in the literature. Approximately 10 to 15% of individuals diagnosed with autoimmune thyroiditis are also affected by PBC [14], as observed in our patient. PBC is frequently accompanied by other ADs like thyroid disease, SS, and systemic sclerosis, with the latter being the most common autoimmune comorbidity and often identified approximately nine years following the onset of PBC [15]. However, this chronological sequence does not correspond with our patient's scenario.

MASs are rare and intriguing entities in medicine, particularly those associating five or more ADs, as evidenced by the limited number of cases reported in medical literature. In adults, to the best of the authors' knowledge, six cases have been reported (Table 2) [16-21]. Within these cases, some combinations of ADs are particularly noteworthy, including PBC, systemic lupus, SS and autoimmune thyroiditis, which appear to occur frequently [15,16]. Additionally, in MAS, patients often present with at least one dermatological condition, typically vitiligo or alopecia [20]. This was also evident in four out of the six MAS cases examined in this literature review [16,19-21]. Santos and Sousa [20] reported a case of MAS involving four autoimmune dermatoses associated with Crohn's disease. Wielosz et al. [16] reported a case involving three connective tissue diseases, including systemic lupus with secondary antiphospholipid syndrome, SS, and scleroderma, associated with PBC and psoriasis. This case is intriguing because the patient initially presented with mixed connective tissue disease, which was subsequently differentiated into three distinct connective tissue diseases. Additionally, antiphospholipid syndrome could have been considered as a sixth AD. This reinforces the hypothesis of the intricacy of such syndromes and the various ways distinct components of the immune system can target diverse organs and tissues of the body.

Table 2. Literature review of cases of multiple autoimmune syndromes including five autoimmune diseases or more.

Authors	Age (years)	Sex	Particularities	Number of AD	Types of AD	Type of MAS
Ewa Wielosz et al. [16]	36	F	Initial presentation as mixed connective tissue disease, which was subsequently differentiated into 3 distinct connective tissue diseases associated with psoriasis and PBC. Antiphospholipid syndrome could have been considered as a sixth AD.	5	- Psoriasis - SLE with secondary antiphospholipid syndrome - SSc - SS - PBC	Type 2
Turkcapar et al. [17]	45	F	-	5	- Rheumatoid Arthritis - SLE - SSc - SS - Hashimoto disease	Type 2
Salzano et al. [18]	29	F	1st publication of 4 AD associated with Down's syndrome arthropathy (with positive rheumatoid factor)	5	- Down's syndrome arthropathy - T1DM - Celiac Disease - Hashimoto's Thyroiditis - Graves' disease	-
Masood et al. [19]	42	F	-	5	- T1DM - Autoimmune hemolytic anemia - SLE - Vitiligo - Psoriasis	Type 3
Santos and Sousa [20]	31	M	Coexistence of 4 autoimmune dermatoses in association with Crohn's disease	5	- Vitiligo - Alopecia areata - Crohn's disease - Psoriasis vulgaris - Oral lichen planus	
Müller et al. [21]	62	F	The diagnosis of PBC was established based solely on immunological criteria. The positivity of anti-thyroperoxydase antibodies could suggest consideration for Hashimoto's thyroiditis, but it was not considered as a sixth AD.	5	- SS - PBC - Crest syndrome - SLE - Lichen planus	Type 2

AD: Autoimmune disease. **ASS**: Antisynthetase syndrome. **F**: Female. **M**: Male. **MAS**: Multiple auto-immune syndrome. **PBC**: Primary biliary cirrhosis. **SLE**: Systemic Lupus Erythematosus. **SS**: Sjogren's syndrome. **SSc**: Systemic sclerosis. **T1DM**: Type 1 diabetes mellitus.

Our study has some limitations. The absence of histopathological evidence hinders the formal confirmation of autoimmune hepatitis. Additionally, confirming respiratory muscle involvement in myositis is challenging without specific tests.

Conclusion

To the best of the authors' knowledge, this is the first accurately documented case of coexisting ASS, PBC, systemic scleroderma, SS, Hashimoto's thyroiditis, and autoimmune hepatitis in a single patient. The presence of this array of ADs should be considered in the evaluation of patients presenting with symptoms and clinical indicators associated with each disorder. Such awareness is essential to enable timely diagnosis and effective management strategies for these patients.

Ethic statement

The patient has been informed of the purpose of the case writing and has willingly given consent in the presence of a witness.

Declaration

In order to correct and improve the academic writing of our paper, we have used the language model CHATGPT 3.5 [22].

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