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Atypical Presentation of Autoimmune Polyglandular Syndrome Type II: The Tip of the Iceberg at the Interface between Type 2 and Type 3 Multiple Autoimmune Syndrome

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Abstract | **Case Report**

***Background*:** Autoimmune polyglandular syndrome type 2 is a rare condition characterized by at least two induced autoimmune glandular disorders that always includes Addison's disease, as well as type 1 diabetes mellitus and/or autoimmune thyroid diseases. ***Clinical Case*:** A 55-year-old patient with a personal medical history of gout and gastroduodenal ulcer, was admitted to the Internal Medicine department of the University Hospital Center Point G in Bamako for polyarthralgia and long-term fever, in whom the initial diagnosis of seronegative rheumatoid arthritis had been made in the face of an ultrasound scan of the metacarpophalangeal and interphalangeal joints showing signs of synovitis without effusion associated with the ACR/EULAR 2010 criteria; associated with an arthritic disease. During her evolution, she presented with adrenal insufficiency syndrome, after emergency management with hydrocortisone hemisuccinate 100 mg IV, the immunological assessment showed positivity for anti-21-alpha hydroxylase autoantibodies and anti-TSH receptor autoantibodies; leading us to a final diagnosis of autoimmune polyglandular syndrome type II made up of Addison's disease - rheumatoid arthritis and thyroid autoimmunity; in a context of very probable multiple autoimmune syndrome. His evolution was favorable after adequate management with methotrexate associated with folic acid and hydrocortisone; and therapeutic education. ***Conclusion*:** Autoimmune polyglandular syndrome should be considered in all patients with systemic and glandular autoimmune disease, particularly adrenal and thyroid; this in a context of polyautoimmunity.

Keywords: Autoimmune Polyglandular Syndrome Type II, Immunology, Endocrinology, Internal Medicine.

INTRODUCTION

The autoimmune polyglandular syndrome (APS) or polyglandular autoimmune (PGA) syndromes should be considered when immune dysfunction affects two or more endocrine glands and other non endocrine immune disorders are present [1]. The PGA syndromes are classified as two main types : the type I syndrome starts in childhood, the type II or is more likely to present in adults and most commonly and the others [1]. PGA are syndromic groups that are of obvious medical interest both theoretically and clinically [1-3]. In addition, they

require the clinician to develop screening strategies and specific management of patients who suffer from them. The PGA II is characterized by two or more endocrinopathies including primary adrenal insufficiency, Graves' disease or autoimmune hypothyroidism, type 1 diabetes mellitus, or primary hypogonadism. Because adrenal insufficiency is relatively rare, it is frequently used to define the presence of the syndrome [1, 2]. Other associated conditions include hypophysitis, celiac disease (2-3%), atrophic gastritis, and pernicious anemia (13%). Vitiligo and alopecia are less common than in type I syndrome; up to 25% of patients with myasthenia gravis, and an even higher percentage of patients with myasthenia and thymoma [1]. Some authors have attempted to subdivide PGA II on the basis of association with some autoimmune disorders but not others (i.e., type II and type III); type II, Addison with type 1A diabetes or autoimmune thyroiditis; type III, thyroid plus other autoimmune disease (not Addison or diabetes); and type IV, two or more other organ-specific autoimmune diseases [2]. Rheumatoid arthritis is very rarely associated with autoimmune endocrinopathies, especially in its seronegative form [2-4]. Very few reported cases of this atypical presentation of an autoimmune endocrinopathy have been published. Thus, we describe one of the rare cases of a patient with a type II polyglandular autoimmune syndrome associating seronegative rheumatoid arthritis - Addison's disease and and thyroid autoimmunity.

OBSERVATION

We report the case of a 55-year-old female patient of Malian nationality, a teacher. She was admitted on December 4, 2023 to the Internal Medicine department of the Point G University Hospital Center in Bamako for polyarthralgia and long-term fever.

The onset of symptoms dates back to about 5 months ago, marked by the gradual onset of cramp-like joint pain in both ankles, knees, elbows, and hand joints, symmetrical, of high intensity estimated at 7/10 according to the visual analog scale without irradiation or fleeting migration; without triggering factors, calmed by taking paracetamol, insomnia, intermittent, without deformities; without notions of repeated angina; aggravated by mobilization; associated with swelling of the above-mentioned joints with morning stiffness ranging from a few minutes to a few hours, an intermittent fever since gradually setting in a few days after the pain. Given this symptomatology, she would have consulted a health center in the city where she would have been diagnosed with gout and for which she would have received treatment based on Opacalcium. All this occurs in a context of global asthenia (physical, psychological) rated at 9/10 according to the global numerical scale increased in the morning upon waking; non-selective anorexia and significant weight loss not quantified for 7 months. In addition to her anamnesis, she reports hyperpigmentation of the inner side of the cheeks of progressive appearance. Given the persistence of the above-mentioned symptoms, she decides to consult us for management. Medical history of gout under Opacalcium and gastroduodenal ulcer under lanzoprazole ; her diabetic mother and the notion of taking opacalcium, metronidazole, paracetamol, propranolol and acetylcysteine; the indications and dosages of which have not been specified.

General examination showed a conscious, emaciated patient with conjunctival pallor; afebrile to touch; her Karnofsky index was 80%. Sitting blood pressure in the left arm was 90/60 mmHg; heart rate 106 bpm; respiratory rate 13 cycles per minute; left axillary temperature 39°C; capillary blood glucose on admission 0.97g/L. Her measurements on admission were weight 70 kg, height 175 cm for a body mass index (BMI) of 22.86 kg/m²; SpO2 89%. Physical examination revealed on inspection a slight ulnar deviation of the fingers in a "wind blow" shape, predominantly on the left hand; a "swan neck" deformity of the 2nd and 3rd fingers with a slight swelling of the middle interphalangeal joints of the same fingers and a slight buttonhole deformity of the little finger of the right hand (**Image1)** on palpation we had a symmetrical painful sensitivity of the metacarpophalangeal and proximal interphalangeal joints of both hands. Swelling of both knees associated with pain on mobilization of the knees. The measurements of the left knee at 14cm and that of the right knee at 13cm. The remainder of the physical examination revealed palmar-plantar conjunctival pallor and melanoderma on the inner side of both cheeks.

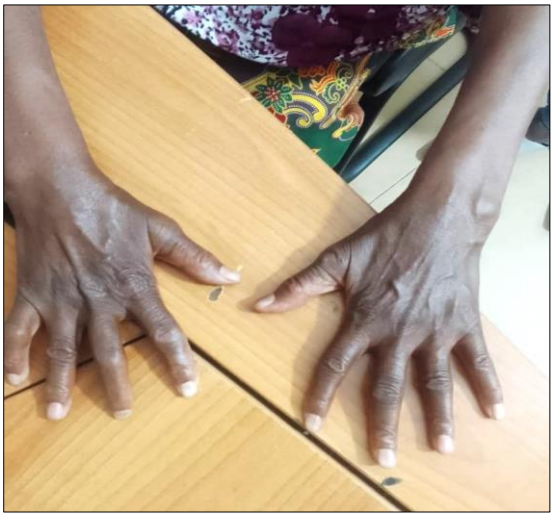

Image 1: Pictures of the patient's hands (Dr Ibrahima Amadou Dembélé)

The initial paraclinical assessment showed :

- Microcytic hypochromic anemia with a hemoglobin level of 6 g/dL, mean corpuscular volume of 70.7 fL, MCHC of 31.4 g/dL. Inflammatory syndrome with CRP of 152.15 mg/L, Hyperferritinemia at 2246 ng/mL and

mild thrombocytosis of 572,000/mm3. White blood cells of 4180/mm3.

- A serum creatinine of 7.5 mg/L with a clearance of 94.7 mL/min. Azotemia of 0.12 g/L, uricemia of 41.33 mg/L and HbA1c of 5,8%. Total proteins of 54.4 g/L. ALAT of 16.1 IU/L and ASAT of 27,3 IU/L. Serum protein electrophoresis revealed hypoalbuminemia (20.56 g/L), hyper-alpha1globulinemia (6.09 g/L), hyper-alpha2globulinemia (9.47 g/L) and hypobeta-1-globulinemia (2.12 g/L); normal gamma-globulins (12.19 g/L) ; albumin/globulin ratio < 2.
- Immunological assessment: anti-nuclear antibodies (ANA-Screen) at 8.17 IU/mL (negative); anti-SSA antibodies not performed; anti-SSB not performed, anti-Sm 3.50 IU/mL (negative), anti-CCP at 8.05 IU/mL (negative), anti-native DNA at 7.00 IU/mL (negative). The complement assay was requested but was not performed. Rheumatoid factor at 8.0 IU/mL (positive threshold approximately 20 IU/mL). Total anti-HBc antibodies positive, HIV1-2 and HCV serologies negative; HbsAg negative.
- Ultrasound of the metacarpophalangeal and interphalangeal joints showing hypertrophy of the synovium without effusion, indicating grade 2 active synovitis.
- The X-ray shows at the level of the upper limbs an absence of osteoarticular lesions of the hands and wrists; a pinching with osteophytic beaks at the level of the cibital and humeral; and at the level of the knees, a pinching of the bilateral femorotibial interlinear joints with sclerosis of the plateaus and osteophytic beaks, a femoropatellar pinching with sclerosis opposite, a bilateral subquadriceps effusion and a calcification of the left popliteal fossa in favor of bilateral gonarthrosis with subquadriceps effusion and bilateral osteoarthritis of the elbows.
- Cytobacteriological examination of the joint puncture fluid was sterile, with less than 1000 cells/mL and less than 25 grams of proteins/mL
- Anatopathological examination of the joint puncture fluid did not find any abnormalities
- Blood cultures in aerobic and anaerobic media remained sterile

In front of the ACR/EULAR 2010 classification criteria at 7 (excluding psoriatic arthritis - viral polyarthritis - gout - calcium pyrophosphate dehydrated rheumatism - systemic lupus), the patient was classified as having seronegative rheumatoid arthritis associated with an arthritic disease associating a bilateral gonarthrosis with subquadriceps effusion and bilateral osteoarthritis of the elbows. The DAS 28 score was 6.26, i.e. highly active rheumatoid arthritis. The assessment of the functional impact by the HAQ index showed a severe functional impact with an HAQ index of 2.74.

Initially, the patient was put on paracetamol + codeine (500/30mg) 2 tablets per day, saline serum 0.9% at the rate of 500mL every 8 hours enoxaparin 4000 IU subcutaneously per day, prednisone 60 mg per day, adjuvant measures to corticosteroid therapy with calcium tablet 1000 mg per day, potassium tablet 600 mg per day, albendazole tablet 400 mg for 3 days and lanzoprazole 30 mg one capsule in the morning on an empty stomach. Two physiotherapy sessions per day. The evolution was marked 8 days later by a decrease in joint pain to 6/10 according to the numerical scale, a DAS 28 at 4.84, i.e. moderate activity of rheumatoid arthritis, measurements of the left knee at 12cm and of the right at 11cm; the progressive regression of corticosteroid therapy was started with methotrexate at 7.5mg per week associated with folic acid 10mg/week; from 20mg of prednisone per day, then 20 days later, the patient presented intense and global asthenia, diffuse abdominal pain, liquid diarrhea 5 to 6 times per day. Acute adrenal insufficiency was suspected and the patient was started on hydrocortisone hemisuccinate 100 mg IV every 6 hours, immediate plasma cortisol sampling returned 4 hours later to 2.44 µg/dL. 8-hour cortisol performed 2 days later returned to 4.87 µg/dL and after Synacthen test to 14.8 µg/dL; TSHus to 1.02 µIU/mL.

The control immunological assessment revealed anti-21 alpha hydroxylase antibodies at 0.59 IU/mL, anti-transglutaminase IgG antibodies to 0.00 IU/mL (negative), anti-transglutaminase IgA antibodies to 2.10 IU/mL (negative), anti-TSHus receptor antibodies to 6.12 IU/mL (positive), anti-thyroglobulin antibodies not performed; anti-thyroperoxidase antibodies at 0.55 IU/mL (negative). The adrenal scan shows an atrophic left adrenal gland (arrow) and an infiltrated right adrenal gland **(Image 2).**

The diagnosis of Addison's disease was retained, which associated with seronegative rheumatoid arthritis and the positivity of anti-TSHus receptor antibodies made us suggest a polyglandular autoimmune syndrome type II. The patient had a favorable evolution, corticosteroid therapy was stopped after a very progressive regression and after a significant decrease in polyarthralgia of the hand joints; she received as treatment: therapeutic education, methotrexate 7.5mg/week, folic acid 10mg per week, hydrocortisone 30mg per day (20 mg in the morning at 8 a.m. and 10 mg at 1 p.m.) ; paracetamol + codeine (500/30mg) 2 tablets morning and evening. She is regularly followed in the Internal Medicine department of the Point G University Hospital.

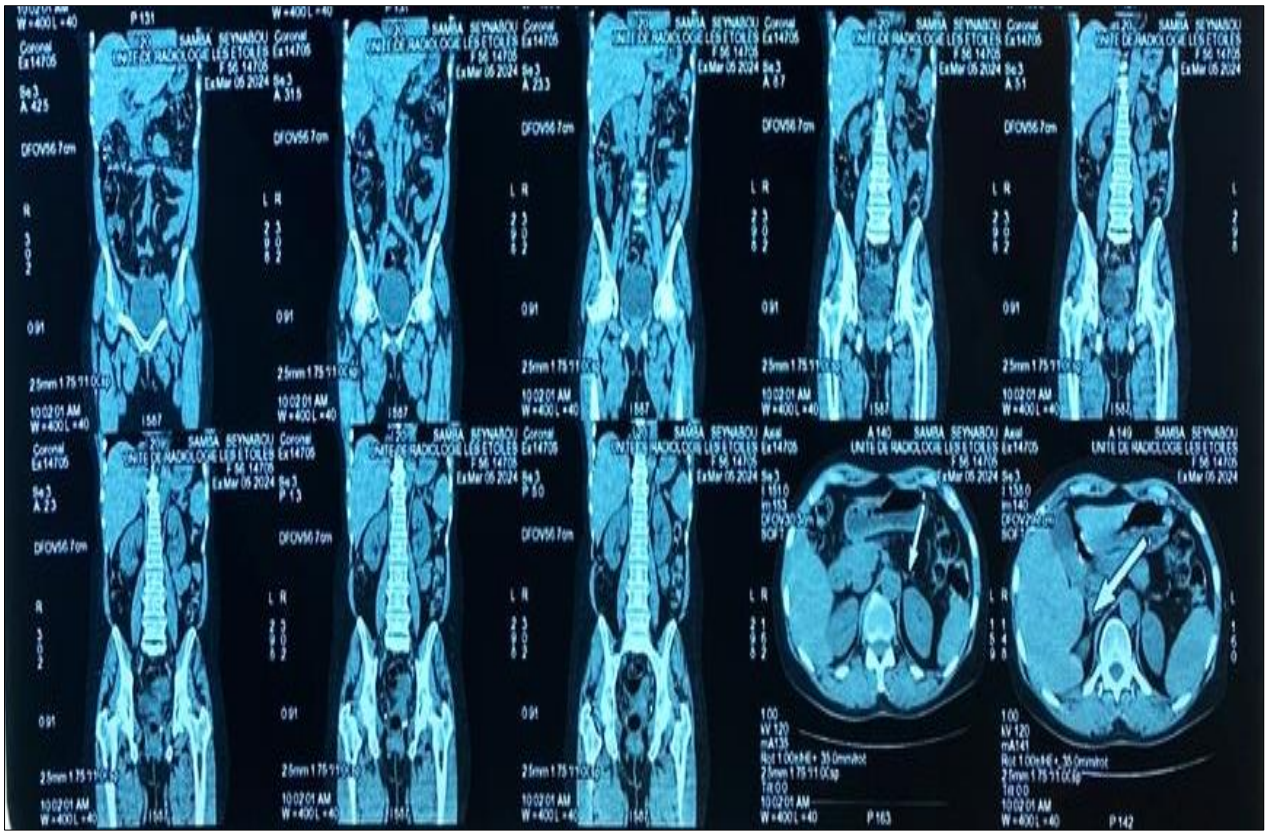

Image 2: Scan of the patient's adrenal glands (Dr Stéphane L Djeugoué – Dr Tientcheu T Dorette)

DISCUSSION

This observation reports a case of type II autoimmune polyendocrine syndrome consisting of seronegative rheumatoid arthritis - Addison's disease - thyroid autoimmunity (the presence of auto-antibodies to the TSHus-stimulating receptor). This is a rare combination of a complex endocrine and autoimmune picture. Indeed, autoimmune polyglandular syndromes correspond to an association of at least 2 endocrine disorders linked to a disruption of the tolerance of the immune system, and often associated with other non-endocrine autoimmune diseases [1]. The concept of polyendocrinopathy is old since it was created by Henri C. J. Claude and Henri Gougerot in 1908 under the term multiglandular endocrine insufficiency [5]. In 1916, Luksh reported a case of Addison's syndrome associated with Hashimoto's thyroiditis and in 1929 Thorpe [5], defined an association of candidates and chronic hypoparathyroidism. Subsequently, publications relating to these polyendocrinopathies have multiplied. To our knowledge, this is one of the rare publications of this autoimmune endocrine picture.

Autoimmune Polyglandular Syndrome [1-9]

The autoimmune polyglandular syndromes are clusters of endocrine abnormalities that occur in discreet patterns in subjects with immune dysregulation and that permit treatment and anticipation of associated systemic or other hormonal deficiencies. Three major entities are recognized, APS1, APS2 and APS3 as well as the extremely rare X-linked syndrome of immunodysregulation, polyendocrinopathy, and enteropathy (IPEX) syndrome. An additional but increasing category occurs in patients treated with checkpoint immunoregulatory agents for cancer, by which the tumor's blockade of immune regulatory checkpoints is inhibited, so that tumor antigens that had evaded recognition can now be targeted, but at the expense of activating autoimmunity against endocrine organs.

- **Etiopathogenesis**

APS1 results from a failure to eliminate T-cells that have acquired receptors with high affinity to auto-antigens, as these T-cells mature and traverse the thymic epithelium during their development. Normally, such T-cells are prevented from entering the periphery because of the ectopic expression of multiple antigens within the thymus that usually are expressed only in discrete tissues, e.g. insulin in pancreatic β-cells. A developing T-cell that acquires and expresses a high affinity receptor for insulin will be bound to the ectopically expressed insulin antigen within the thymus, undergo apoptosis and be excluded from entering the periphery to initiate auto-immunity. This ectopic expression of antigens within the thymus is mediated by the Auto-Immune REgulator gene (AIRE) located on chromosome 21. Discovered in 1997 as the gene whose variable inactivation is responsible for the clinical entity APS1, this gene is now known to be an essential component of the adaptive immune response cascade, and the spectrum of disorders ascribed to

mutations in this gene extend beyond the APS1 syndrome.

APS2 is characterized by the triad of Type 1 Diabetes Mellitus (T1DM), adrenocortical insufficiency, and hypothyroidism as a result of autoimmunity to components of the pancreatic β-cell, adrenal cortex, and thyroid synthesizing machinery. APS3 is essentially identical to APS2 except that adrenocortical insufficiency is absent. This similarity has led some investigators to label the former as APS2a and the latter as APS2b. Whereas APS2a is rare, APS2b is relatively common, as approximately 20% of patients with T1DM harbor circulating antibodies to thyroid synthesis components, namely thyroid peroxidase (TPO) and thyroglobulin (TGB), markers associated with Hashimoto thyroiditis. Note however that the presence of autoantibodies is not necessarily predictive of glandular failure and its clinical manifestations. The genes responsible for the disordered immunity in APS2 and APS3 are in the DQ and DR regions of the HLA complex on the short arm of chromosome 6; specific alleles or mutations facilitate the presentation of antigens co-expressed with the particular HLA complex by antigen presenting cells such as dendritic cells and macrophages. This facilitated presentation of self-antigens, along with other regulatory factors such as lower expression of T-regulatory cells, initiate auto- immunity. Consistent with the generally heightened immune responses in females, these forms of autoimmune endocrine disorders are significantly more prevalent in women, whereas in APS1 the sex distribution is equal.

Autoimmune Polyglandular Syndrome type II [3-10]

APS-2 is diagnosed by occurrence in the same patient of at least 2 out of 3 manifestations including primary adrenal insufficiency (Addison disease), autoimmune thyroid disease-causing Grave disease or hypothyroidism and T1DM. Other endocrine and non-endocrine manifestations of PAS-2 are primary hypogonadism, myasthenia gravis and celiac disease, alopecia, vitiligo, pernicious anemia, idiopathic heart block, Stiff-man syndrome, Parkinson disease, IgA deficiency, serositis, dermatitis herpetiformis, idiopathic thrombocytopenia, and hypophysitis. Our patient presented as a non-endocrine autoimmune manifestation a seronegative rheumatoid polyarthritis, which is very rarely associated with it.

Diagnosis of Addison disease or primary adrenal insufficiency is based on a morning serum cortisol level less than 5.0 mcg/dl or a serum cortisol less than 18 mcg/dl at 60 minutes after ACTH stimulation test using 250-mcg intravenous or intramuscular bolus of cosyntropin. The presence of 21-hydroxylase or 17-hydroxylase autoantibodies can confirm autoimmune adrenalitis. Diagnosis of hypothyroidism due to Hashimoto's thyroiditis or hyperthyroidism due to Graves' disease can be made by evaluation of TSH and T4 for the former and TSH, T4, and T3 for the latter. In euthyroid patients, the presence of anti-thyroglobulin antibodies, thyroid microsomal antibodies and thyrotropin receptor antibodies (Graves' disease) can detect patients at risk of thyroid disease in the future. Our patient was euthyroid and without clinical manifestations of dysthyroidism, but she had anti-TSH receptor autoantibodies present but at a non-high titer, reflecting the onset of Basedowian thyroid autoimmunity to be followed up. Diagnosis of T1DM can be made with classic symptoms of polyuria, polydipsia, and polyphagia associated with elevated serum glucose level (fasting greater than 125 mg/dl and random over 200 mg/dl and or elevated HbA1c, greater than 6.4%). Standard guidelines should be used for the diagnosis of individual organ dysfunction. These patients can be tested for anti-glutamic acid decarboxylase antibodies (GAD), anti-islet cell antigen 2 and anti-Zn transporter 8 antibodies. Also following a challenge with glucagon (1 mg) the plasma C-Peptide is less than 0.6 ng/ml. In our observation, we did not observe any clinical-biochemical signs of diabetes mellitus, anti-GAD antibodies were not requested.

A timely diagnosis of APS-2 requires knowledge of the complete spectrum of this disease. A complete history and thorough physical exam may give important clues. In many cases, the diagnosis of APS-2 may be delayed due to the heterogeneous presentation. It is uncommon for these patients to have dysfunction of all 3 major endocrine organs simultaneously and there is usually a latent phase between the endocrinopathies. Patients with APS-2 and their family members should be monitored long-term due to the risk of development of organ-specific dysfunction over time. Family members who are not affected with APS-2 should watch for symptoms related to adrenal, thyroid and endocrine pancreatic dysfunction. Asymptomatic carriers should be followed on an annual basis. Throughout the care of our patient, individual and collective therapeutic education was provided to the patient and those around her.

Delay in diagnosis can cause significant morbidity and mortality in these patients due to the risk of severe hypothyroidism, adrenal crisis, and diabetic ketoacidosis. Thyroid ultrasound is an excellent noninvasive tool to evaluate thyroid disease. The diffuse or multifocal hypoechoic pattern is commonly seen in autoimmune thyroid disease. CT scan and MRI of the adrenal gland is often normal, but sometimes there is a decrease in the volume of the gland suggestive of atrophy. Unfortunately, there is no reliable imaging technique which can indicate endocrine pancreatic disease.

These patients are at risk of adrenal crisis, hypoglycemia, diabetic ketoacidosis, among others. The treating physician should be proactive to diagnose these conditions and possible manifestations expected to occur over time without delay to avoid complications. Care should be taken to treat patients with thyroxine as this

can precipitate life-threatening Addisonian crisis if the patient has undiagnosed adrenal insufficiency. In these patients, testing for adrenal insufficiency should be done before treating hypothyroidism with levothyroxine. Hydrocortisone replacement should precede thyroxine therapy by about a week. Our patient received adequate treatment with a favorable outcome; she is regularly followed in outpatient consultation in the Internal Medicine department of the Point G University Hospital Center in Bamako.

Autoimmune Polyglandular Syndrome and Multiple Autoimmune Syndromes [11, 12]

Multiple autoimmune syndrome (MAS), MAS is the coexistence of three or more autoimmune diseases. In this unusual condition, dermatological autoimmune diseases and especially vitiligo have an important place. Disorders of autoimmune pathogenesis occur with increased frequency in patients with a history of another autoimmune disease. Familial or genetic, infectious, immunologic and psychological factors have been implicated in the development of MAS. Certain auto antibodies are found in disorders affecting mul tiple organs. Disorders of an autoimmune nature are known to occur with increased fre quency in patients with another autoimmune disease. About 25 percent of patients with au toimmune diseases have a tendency to develop additional autoimmune disorders. The pathogenesis of multiple autoimmune disorders is not known. Environmental triggers in a genetically susceptible individual are be lieved to cause disorders of immune regula tion. Multiple autoantibodies can be found in a patient and some of the specific mono- or poly clonal autoantibodies may be multiple organ reactive.

Multiple autoimmne syndrome can be clas sified into three groups that correspond with the prevalence of their being associated with one another in patients with two autoimmune diseases, this classification is helpful when signs of a third disorder emerge :

- **Type 1 MAS:** includes myasthenia gravis, thymoma, polymyositis and giant cell myocar ditis
- **Type 2 MAS:** includes Sjögren's syndrome, rheumatoid arthritis (RA), primary biliary cholangitis (PBC), scleroderma, and autoimmune thyroid disease
- **Type 3 MAS :** groups together autoimmune thyroid disease, myasthenia gravis and/or thymoma, Sjögren's syndrome, pernicious anemia, idiopathic thrombopenic purpura (ITP), Addison's disease, type 1 diabetes mellitus, vitiligo, autoimmune hemolytic anemia (AIHA), systemic lupus (SL), and dermatitis herpetiformis.

This classification helps to detect a new condition liable to appear in a patient who has had two previous autoimmune diseases. It provides a basis for analysis of the pathophysiological mechanisms of autoimmunity. Multiple autoimmune syndromes occur with increased frequency in patients with a history of another autoimmune disease. When more than one autoimmune disease coexists, this is defined as polyautoimmunity. When three or more autoimmune diseases coexist, this is known as multiple autoimmune syndrome (MAS). The presence of one autoimmune disease should alert patients to the need to monitor for another in predisposed patients. In many cases, the presence of one autoimmune disorder contributes to the discovery of other autoimmune diseases, including autoimmune endocrinopathies. Individuals with an autoimmune disease or a family history of autoimmune diseases should be aware of their tendency to develop other autoimmune disorders.

CONCLUSION

Autoimmune polyglandular syndrome is not so rare but underdiagnosed, it should be considered and actively sought in all patients with systemic and glandular autoimmune diseases, especially adrenal and thyroid; and integrated into an overall picture of multiple autoimmunity. In perspective, efforts must be made in terms of research on the different entities of autoimmune polyglandular syndrome in the sub-Saharan region.

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