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GRANULOMATOSIS WITH POLYANGIITIS – POSSIBLE ENDOCRINE MANIFESTATIONS

Abstract: Granulomatosis with polyangiitis (GPA), formerly known as Wegener's granulomatosis, is a necrotizing vasculitis of small and medium-sized blood vessels characterized by diffuse inflammation of vascular structures and perivascular and extravascular granulomatosis. In its systemic form, GPA predominantly affects the ear, nose and throat, with lung and kidney involvement with typically rapidly progressive necrotizing glomerulonephritis with extracapillary crescents, while the absence of kidney damage at the time of diagnosis is defined as a limited form of GPA with a more favorable prognosis (1, 2). Antineutrophil cytoplasmic antibodies (c-ANCA) with specificity for proteinase 3 (PR3) represent a biochemical diagnostic criterion. They are detected in 90% of generalized forms and in about 50% of limited forms of granulomatosis with polyangiitis (1, 2). In the absence of treatment, GPA is a disease of progressive evolution. Systemic corticosteroid therapy and immunosuppressive therapy significantly changed the prognostic aspect of the disease. Only a few sporadic observations have been published on endocrine disorders associated with GPA. We present a case of a man, 39 years old, with Wegener's granulomatosis who developed autoimmune thyroiditis 8 years after the initial diagnosis.

Key words: Granulomatosis with polyangiitis, autoimmune thyroiditis, antineutrophil cytoplasmic, antibodies small vessel vasculitis

Introduction

Granulomatosis with polyangiitis (GPA), formerly known as Wegener's granulomatosis, is a necrotizing vasculitis of small and medium-sized blood vessels characterized by diffuse inflammation of vascular structures and perivascular and

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extravascular granulomatosis. In its systemic form, GPA predominantly affects the ear, nose and throat, with lung and kidney involvement with typically rapidly progressive necrotizing glomerulonephritis with extracapillary crescents, while the absence of kidney damage at the time of diagnosis is defined as a limited form of GPA with a more favorable prognosis (1, 2). Antineutrophil cytoplasmic antibodies (c-ANCA) with specificity for proteinase 3 (PR3) represent a biochemical diagnostic criterion. They are detected in 90% of generalized forms and in about 50% of limited forms of granulomatosis with polyangiitis (1, 2). In the absence of treatment, GPA is a disease of progressive evolution. Systemic corticosteroid therapy and immunosuppressive therapy significantly changed the prognostic aspect of the disease. Only a few sporadic observations have been published on endocrine disorders associated with GPA.

Case presentation

MN, 39 years old, was hospitalized for the first time in the University Clinic of Pulmonology 8 years ago, after radiographic changes in the lungs on both sides. Complaints occurred in the form of nosebleeds, migrating pain in the joints, weakness, difficulty in swallowing solid food. An ENT examination diagnosed erosive rhinitis, and Staphylococcus aureus was detected in a nasal swab. Microhematuria present in urine sediment. MDCT of the chest showed multiple focal changes up to 30 mm in diameter, in the right basal zone of parenchymal condensation according to the type of subsegmental atelectasis. Performed immunological analyzes that confirmed Wegener's granulomatosis, c ANCA 1:320, antiPR3At 100. Angiotensin converting enzyme, tumor markers, serological viral markers were within reference values. Therapy with pulse doses of cyclophosphamide and glucocorticoids was introduced, he received 6 cycles, after which oral therapy was started. Control visualization of the lungs showed a progressive course, after which the patient received two cycles of immunoglobulin therapy, and further treatment continued with oral Methotrexate, folic acid and oral glucocorticoid therapy with gradual dose reduction. Due to the increase in PR3At, ANCA c and CRP, along with a stationary NMR lung finding and the absence of complaints, a whole-body positron emission tomography (FDG PET/CT) was performed, which showed increased FDG binding in the thyroid gland, diffuse and moderate (SUV max 4.7 in the right , SUV max 3.3 in the left lobe, discrete binding at the level of multiple changes in the lungs bilaterally (SUV max up to 1.9, in the surrounding lung tissue SUV max 1.1). In the family history, the mother had a thyroidectomy due to goiter. ECHO of the thyroid gland: properly laid thyroid, normal size, pseudonodular, heterogeneous, changed according to the type of chronic thyroiditis, without identifying cystic or solid changes. Biochemical analyzes were normal, as was the assessment of renal function. Hormonal analyses: thyrotropin hormones (TSH) 4.4 m IU/L, free thyroxine (FT4) 9.9 ng/l, antithyroid peroxidase

antibodies 37.09 IU/ml, antithyroglobulin antibodies 124.2 IU/ml, follicle stimulating hormone (FSH) 2.6 IU/L, luteotropic hormone (LH) 3.2 IU/L, testosterone (T) 13.39 nmol/l, PRL 314 m IU/L, dehydroepiandrosterone (DHEA-S) 5.7 mmol/l, vitamin D 95 nmol/l, PTH 50 ng/l. Therapy with inositol preparations was introduced, with monitoring of thyroid function in 3 months.

Discussion

Granulomatosis with polyangiitis (GPA, Wegener's granulomatosis) is an idiopathic systemic disease that classically manifests as a triad of upper and lower respiratory tract involvement with glomerulonephritis (3). The most common symptoms are nonspecific and include fever, malaise, cough, weight loss, chest pain, and hemoptysis. The prevalence of WG was estimated at 23.7–156.5: 1000000 (4, 5), with an annual incidence of 3.0–14.4: 1000000 (6, 7).

Antineutrophil cytoplasmic autoantibodies (ANCA) are a serological determinant of GPA. ANCA are mainly directed against proteinase 3 (PR3-ANCA). Sinusitis is the most common initial presentation in about half to two thirds of patients with VG (3). Lung and kidney involvement are classic manifestations of WG, and ocular manifestations occur in 28% to 58% of patients with WG. Other rather uncommon presentations of WG include salivary gland, skin, gastrointestinal, and cardiac involvement. The disease can occur at any age, but the peak incidence is in early middle age. It occurs somewhat more often in men. Untreated, the disease is associated with a very poor prognosis. Although ANCAs are found in most patients with WG, histopathological analysis still provides the most reliable basis for diagnosis.

Disease activity is assessed based on the Birmingham Vasculitis Activity Scale from 2008, version 3 (8), and the chosen treatment modality depends on the assessment of the severity of vasculitis according to the European Vasculitis Study Guide (9). For more severe forms of the disease, a regimen consisting of glucocorticoids in combination with cyclophosphamide or rituximab is recommended. Rituximab (anti CD20 monoclonal antibody) is as effective as cyclophosphamide in achieving remission in patients with newly diagnosed or relapsed GPA (10, 11). The rates of serious adverse events are similar with both drugs and there is currently no generalizable conclusion about the initial immunosuppressive regimen.

Endocrine dysfunctions during GPA are considered uncommon, with central diabetes insipidus (DI) prominent, with about 10 published cases in the literature (12–15). Central DI occurs secondary to granulomatous infiltration of the hypophysis and/or pituitary stalk. Central diabetes insipidus may be the first clinical manifestation of GPA as illustrated by the observations of Al-Fakhouri A et al. (16), and some authors estimate the frequency of involvement of the pituitary gland during GPA from 1% (17) to 1.3% (18). Testicular involvement can be present in both adult and pediatric

forms of GPA (19–21). Also, the clinical picture includes primary hyperparathyroidism or, more often, a clinical picture similar to hyperparathyroidism as a consequence of hypercalcemia caused by ectopic activation due to hyperactivity of macrophages in GPA granulomas (22, 23). A Swedish study, based on a Swedish "multigenerational" registry, showed that type 1 diabetes mellitus in offspring was significantly associated with 13 different parental autoimmune diseases including GPA with a standardized incidence ratio (SIR) of 2.12 (24). Damage to the adrenal parenchyma by granulomatous vasculitis was first reported by Thomas GO and Lewis RJ in 1979 during the autopsy of a man who died after hemorrhagic adrenal infarction (25). It is important to note specific cases of granulomatous polyangiitis during the treatment of Graves-Basedow disease with thyrosupressive therapy (propylthiouracil (PTU) and methimazole (MMI)) (26). It is estimated that ≈25% of patients with Graves' disease treated with PTUs will develop ANCA antibodies, and some patients will develop true ANCA-associated systemic vasculitis including GPA (27, 28).

Based on data from the literature, involvement of the thyroid gland by WG is an extremely rare event. A large study of 158 patients by Hoffman et al found no evidence of thyroid involvement (29). Cordier et al recorded one case of hypothyroidism in a sample of 77 patients, but the thyroid gland was not evaluated histologically (30). To our knowledge, to date there is only one well-documented case of WG in the thyroid gland, which was recently reported by Schuerweg et al (31). Their research emphasizes that WG should be considered in the differential diagnosis of inflammatory thyroid lesions. WG, with the appearance of well-formed granulomas, should be distinguished from other forms of granulomatous thyroiditis. Granulomatous lesions, including well-formed granulomas, can be seen in cases of subacute granulomatous thyroiditis, so-called painful thyroiditis, infection (tuberculosis), sarcoidosis, histiocytic reactions near hemorrhage in hyperplastic nodules or tumors, foreign body reactions, and vasculitis. In contrast to subacute granulomatous thyroiditis and painful thyroiditis, infectious granulomas and granulomatous vasculitis are very rarely seen. The thyroid gland can be a target organ in any form of systemic vasculitis. Cases caused by systemic are described vasculitis of hypersensitivity to pharmacological agents (phenytoin and phenylhydantoin) (32, 33). The early stage of De Quervain's thyroiditis can present with microabscesses, which can also be part of the presentation of WG. For the purpose of differential diagnosis, careful processing of the pathological sample is necessary, especially in the periphery of necrotizing granulomatous inflammation.

Coexistence of autoimmune thyroid disease and ANCA small vessel vasculitis (SVV) has been described in a small case series of 10 patients with MPO-ANCA SVV (34) and in several case studies (35,36). Cases of patients with ANCA SVV diagnosed concurrently or sequentially with other autoimmune diseases have been described, including rheumatoid arthritis (37), systemic lupus (38), Sjogren's syndrome (39), and myasthenia gravis (40). The fact that several different autoimmune diseases can occur

in family members supports the existence of a common genetic determinant. Cytotoxic T lymphocyte antigen-4 (CTLA-4) polymorphism has been associated with autoimmune thyroiditis (41, 42) as well as Wegener's granulomatosis, suggesting a potential genetic predisposition to autoimmunity. In a cohort of 218 patients with autoimmune thyroid disease, 14% were found to have systemic autoimmune disease (42). In a study of patients with Hashimoto's thyroiditis or Graves' disease, 30% had another form of autoimmune disease; 51% among those with chronic thyroiditis and 16% among those with Graves' disease (43). The relationship between AIT and ANCA vasculitis was shown in the works of Lionaki et al. (44). It has been shown that when ANCA vasculitis was diagnosed, as many as 40% of women had thyroid disease. Among men, the prevalence of thyroid disease was significantly lower. Patients with a positive history of thyroid disease are more likely to have myeloperoxidase (MPO)-ANCA (86%) than proteinase 3-ANCA (14%) (53). Both genetic predisposition and cross--reactivity between antigens have been postulated as potential mechanisms. A functional polymorphism in the tyrosine phosphatase gene, the PTPN22 620V allele, has been recognized as a predisposing factor for several autoimmune diseases including Graves' disease and chronic thyroiditis (45), and more recently Wegener's granulomatosis and ANCA positivity (46). PTPN22 is located on chromosome 1p13.3–13.1.10 and encodes a protein of 807 amino acids that interacts with a tyrosine kinase involved in an intracellular signaling cascade following T-cell activation. A missense variation in an allele that predisposes to autoimmunity leads to a gain of function that raises the threshold for T-cell receptor signaling (47).

Even in genetically predisposed individuals, it is likely that environmental factors, including occupational and infectious exposures, play a role in the autoimmune phenotype. Exposure to a number of environmental factors such as silicon (48), and infectious agents such as Staphylococcus aureus (49) has a role in the development of ANCA SVV, while exposure to Yersinia enterocolitica or retroviruses are thought to play a role in pathogenesis of autoimmune diseases of the thyroid gland (50). However, large studies that would draw conclusions about gene-environment interaction and pathogenetic mechanisms within specific autoimmune diseases are lacking.

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