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Hypothyroidism in Microscopic Polyangiitis

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Abstract:

Microscopic polyangiitis (MPA) is a systemic necrotizing vasculitis affecting principally the small vessels and characterized by a large clinical polymorphism with multiple and varied visceral involvement. Theoretically a preferred target because of its vascular wealth, the thyroid gland is still poorly studied during this vasculitis. Thyroid disorders, and particularly hypothyroidism, associated to MPA was only reported as sporadic cases, thus their exact mechanisms, signification, and eventually prognostic implications are not well known.

The aim of this paper is to review thyroid dysfunctions, particularly hypothyroidism, associated with MPA with focus on their epidemiological, therapeutic and evolutionary characteristics, their possible pathogenic mechanisms as well as their prognostic implications.

Keywords: Hypothyroidism, Microscopic polyangeiitis, MPA, Vasculitis,Thyroid disorders, Thyroid gland, Autoimmunity.

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Introduction:

Microscopic polyangiitis (MPA) or micropolyangeitis is a necrotizing vasculitis, with little or no immune deposition, affecting small vessels (capillaries, venules, and arterioles). It has often been confused with polyarteritis nodosa (PAN) or described as a particular form of polyarteritis as evidenced by the classification established by the ACR in 1990 [1.][2.]. It was only in 1993 at the Consensus Conference of Chapel Hill for the nomenclature of systemic vasculitis, that MAP was recognized as a separate entity. His clinic is characterized by a large polymorphism, and remains dominated by glomerulonephritis and pulmonary capillaritis [3.]

This distinction was facilitated by the discovery of antineutrophil cytoplasmic antibodies (ANCA) since, unlike classical PAN, PAM is characterized by the presence of these autoantibodies. They are usually of the perinuclear type (p-ANCA) directed against myeloperoxidase (anti-MPO).

The association between thyroid dysfunction and systemic vasculitis is rarely studied and reported, and Hashimoto's thyroiditis remains the most common form found in systemic angiitis [4.][5.]The exact mechanism of thyropathy in these vasculitis is not well known, and the most common clinical presentation is hypothyroidism [6-18].

Apart from Behçet's disease, giant cell arteritis (GCA), polymyalgia rheumatica (PMR), and to a lesser extent granulomatosis with polyangiitis (GPA) and Henoch-Schönlein syndrome (HSS) where thyroid dysfunction was studied with ±wide series, and even sometimes searched systematically [6-8,11,14-18], those in the others Vasculitis remains poorly studied and known; observations are reported as sporadic cases.

Thus, and despite the apparent rarity, the relationship thyropathies, and in particular hypothyroidism, with systemic angiitis seems far from a mere chance [6-18]. This is also true for MPA, since when it is systematically screened, the involvement of the thyroid gland during MPA can be found in 40% of cases [7].

The aim of this paper is to review thyroid dysfunctions, particularly hypothyroidism, associated with MPA with focus on their epidemiological, therapeutic and evolutionary characteristics, their possible pathogenic mechanisms as well as their prognostic implications.

Thyroid gland involvement during MPA

Classically cited among the exceptional and non-habitual manifestations during MPA, thyropathie and particularly hypothyroidism, is far from being a rare complication during this vasculitis [7].

Indeed the study of Tanaka A et al, which consisted in systematically screening for the thyroid abnormalities in patients with a PAM, reported at a frequency of about 40% hypothyroidism, half of which was subclinical [7]. These authors concluded that thyroid damage during MAP is significantly greater than was thought and referred to it as "***concealed hypothyroidism***". They recommended, since, a greater attention to hypothyroidism at MAP course [7].

In the large study of Lionaki S et al, case-control study whose objective was to estimate the frequency of thyroid diseases during ANCA-associated vasculitis proven by renal biopsy in 150 cases compared to a healthy control group of 99 matched subjects (age and sex), thyroid disease was objectified in 20% of ANCA-associated angiitis patients versus only 7% of the group control; the Odds Ratio was 3.7 (95% CI 1.5-9.2, p=0.005). This association was significantly more significant in women: 38% versus 9% with an Odds Ratio of 5.6 and p=0.002 [19].

One of the major limitations of this study was the non-precision of the type of initial thyroid involvement (hypothyroidism? hyperthyroidism? Hashimoto thyroiditis? Grave's disease?) [19].

The immunological study of Afeltrat A et al, which consisted of systematically screening for ANCA antibodies in patients with autoimmune thyropathy (Hashimoto's thyroiditis and Graves' disease), demonstrated their positivity by immunofluorescence in 28.5% of patients with Graves' disease and in 9% of those with Hashimoto's thyroiditis [20].

In the other way, the prospective study of Westman KW et al, analyzing anti-thyroid antibodies during ANCA-associated vasculitis, reported positive anti-thyroglobulin (anti-Tg) and/or anti-thyroperoxidase (anti-TPO) in 37.5% of cases [21]. These autoantibodies were at high level, remained positive and at unchanged rates despite immunosuppressive treatment of the underlying disease, and over a three-year surveillance period [21].

Mechanisms of thyropathies/hypothyroidism associated to MPA

1. **An association between two autoimmune diseases**

All of these studies highlight a common immunological mechanism between MPA and thyropathies, leading the majority of authors to consider PAM as an autoimmune systemic vasculitis [22,23].

This hypothesis is reinforced by the sporadic associations of MPA with several other autoimmune affections with auto antibodies; among these associations we note: MPA and autoimmune hepatitis type 1 [24], MPA and primary biliary cirrhosis [8,25], MPA and systemic sclerosis [26-29], MPA and rheumatoid arthritis [23,30-32], MPA and mixed connective tissue [22,33,34], MPA and systemic lupus erythematosus [35], MPA and autoimmune pulmonary alveolar proteinosis [36], MPA and primary Sjögren's syndrome [8], MPA and dermatomyositis [37,38], MPA and autoimmune thyroiditis [7,20,21], MPA and type 1 diabetes [39].

These are true associations of two distinct autoimmune diseases [6,7,40] since the hypothesis of a possible cross-immunological reaction between p-ANCA and anti-TPO autoantibodies evoked by some authors (the myeloperoxidase shares some structural homology with thyroid peroxidase and could therefore produce cross-reactions) [41,42] was totally invalidated by the study of Freire BA et al., which had not shown cross-reactions between these two autoantibodies in both directions and insisted on the difference of the immuno-dominant regions in the spatial configuration of these two autoantibodies preventing any cross-reaction [43].

This hypothesis of dys-immune overlap syndrome (autoimmune thyroiditis/PAM) is comforted by the following findings:

- The associations of the MPA with several dys-immune diseases at the same time in the same patient: , that it is about specific affections of organs or not: MPA + systemic sclerosis + primary Sjögren's syndrome in the observation of Kabota K et al [44], MPA + systemic sclerosis + rheumatoid arthritis in the observation of Anand AS et al [45], MPA + primary biliary cirrhosis + primary Sjögren's syndrome + Hashimoto thyroiditis in the observation of Ben Ghorbel I et al [8], MPA + systemic sclerosis + Hashimoto thyroiditis in the observation of Arenzana CB et al [46].
- The simultaneous positivity of several types of organ-specific or non-organ autoantibodies in several of these observations, including those associating hypothyroidism with autoimmune thyroiditis [8, 44-46].

2. A direct damage of the thyroid gland by MPA vasculitis

Exceptionally, thyroid involvement during MAP may result from a direct vasculitic mechanism (necrotizing vasculitis of the thyroid arteries) due to the systemic character of MPA with preferential involvement of small caliber vessels and the hyper vascularized nature of the thyroid gland. This mechanism remains hypothetical in the absence of histologically proven cases in the world literature. By similarity we can approach to this hypothesis the direct vasculitic damage of the adrenal glands during MPA which has been proven radiologically and histologically in the observation of Ito C et al, of a 67-year-old patient with rapidly progressive glomerulonephritis and intra-alveolar haemorrhage, concomitant with right adrenal gland haemorrhage and necrosis, caused by necrotizing vasculitis of the adrenal arteries proven on histological post mortem examination [47].

3. Iatrogenic association

The association of thyropathy with MPA may be iatrogenic: several cases of ANCA-associated vasculitis, particularly MPA, have been reported in association with hyperthyroidism treated with anti-thyroid drugs type Propythiouracil (PTU) [48,49], Methimazole (MMI) [50] or Carbimazole [51]. This has been reported both in Graves' disease [48,49] and in toxic multinodular goitre [50] and in some observations during pregnancy, once again reinforcing the dys-immune mechanism of this induced vasculitis [52].

Their frequency is variously estimated; Zhao MH et al, in their series of 216 cases of hyperthyroidism treated with anti-thyroid drugs found an overall frequency of 10.2% of ANCA-induced vasculitis. This frequency was significantly more significant among those receiving PTU compared to those receiving MMI or MMI associated with PTU: 22.6% versus 0% and 16.3%, respectively, $p < 0.05$ [49].

The mechanism is dys-immune due to the induction of ANCA autoantibodies by these different treatments [48-50]. Indeed Lee E et al, Demonstrated that the structure of myelo-peroxidase (MPO, target of p-ANCA) can be partially modified by repeated administration of PTU [53], and Jiang X et al, suggested that PTU could serve as a substrate for MPO and the metabolites thus produced could induce autoimmunity by exposing autoreactive lymphocytes to abnormal forms of self-material [54].

Hypothyroidism during MPA

Hypothyroidism during MPA was reported nine times by six authors [6-8, 40, 46, and 55] and was overt in seven cases:

- Four cases reported by Tanaka A et al, in 1999 in a small series of ten cases of MPA, two of which were overt and two subclinical hypothyroidism, and all screened systematically. The etiologies as well as the underlying mechanisms of hypothyroidism have not been specified in this study [7],

- A case of hypothyroidism secondary to Hashimoto's thyroiditis reported by Ben Ghorbel I et al, in 2015 in association with MPA, primary biliary cirrhosis and primary Gougerot-Sjögren's syndrome in a 62-year-old patient [8],

- A case of hypothyroidism of Hashimoto's thyroiditis associated with a MPA in a 54-year-old woman reported by Martinez-Gabarron N et al, in 2011. The diagnosis was made simultaneously [55],

- A case of hypothyroidism due to Hashimoto thyroiditis reported by Lai JY et al, in 2014 in a 60-year-old man [40],

- A case of hypothyroidism of Hashimoto thyroiditis reported by Rothe HM et al, 2008, in a 58-year-old woman with severe MPA. The diagnosis of Hashimoto's thyroiditis was made two months before the outbreak of MPA and was characterized by the joint positivity of anti-TPO and blocking type anti-TSH receptor autoantibodies [6],

- A case of hypothyroidism of Hashimoto thyroiditis reported in 2014 by Arenzana CB et al, in a 53-year-old woman with systemic sclerosis, who developed a severe form of MPA [46].

This involvement most often reveals an autoimmune mechanism common to both conditions (MPA and autoimmune thyroiditis) defining overlap syndromes [23]. These two conditions share the production of autoantibodies, lymphocytes B and T abnormalities, as well as a favoring genetic predisposition: the genetic study of Lyons PA el al, showed a significant association between p-ANCA-associated vasculitis (PAM) with the HLA-DQ haplotype [56]; Similarly, the implication of HLA alleles in the genesis of autoimmune thyroiditis is now well known (both the favoring role of certain alleles and the protective role of others) [57].

The clinico-biological characteristics of hypothyroidism associated with systemic vasculitis, including MAP, do not differ from that of the general population in the same age groups, particularly with female predominance and ages around 40 and over [6-8,11,14-17].

Screening and prognostic implications of thyropathie/hypothyroidism in MPA

Even in the absence of formal recommendations or consensus, some authors strongly recommend the evaluation of thyroid function as well as the screening of anti-TPO autoantibodies in patients with ANCA-associated angiitis and similarly to search for ANCA-associated vasculitis (with or without renal impairment) in subjects having autoimmune thyroiditis [6,7,19,55].

The treatment of these dysthyroidisms has nothing specific compared to that of hypothyroidism/dysthyroidism not associated with systemic vasculitis; however, it should be kept in mind that the dose of thyroxine needed to correct the hormonal deficiency after specific treatment and thrust of the underlying systemic vasculitis may be reduced in case of direct thyroidopathy secondary to thyroid localization of the vasculitis. This would be explained by the share of systemic vasculitis in the genesis of thyroid hormone deficiency, which after specific treatment of active vasculitis will be able to be recovered at least partially.

The diagnosis of thyropathy, and especially hypothyroidism, during MPA does not seem to have a particular impact on the prognosis of the disease. Indeed, in the study of Tanaka A et al, the activity of the disease evaluated according to the Birmingham Vasculitis Activity Score (BVAS) showed a lower activity in the group with hypothyroidism: score at 18.5±9 versus 24.2 ± 16.16, $p < 0.05$ [7].

It should be noted, however, that even if the treated hypothyroidism does not influence either the activity or the prognosis of the MPA [7], the majority of cases of association found in the world literature were characterized by severe presentations of the angiitis, multi-visceral attacks and often an important comorbidity [6-8,55].

Conclusion:

Involvement of the thyroid gland during MPA seems far from a mere coincidence. It is mainly primary hypothyroidism due to Hashimoto's thyroiditis, which signifies the common autoimmune nature of these two diseases. In addition, it seems that both diseases share the same predisposing genetic background and similar immunological disturbances of B and T lymphocytes. The direct involvement of the thyroid parenchyma by MPA-specific vasculitis remains rarer.

Finally, the combination of thyropathy/hypothyroidism and MPA can simply result from an adverse effect of anti-thyroid medications (antithyroid drug-induced ANCA-positive vasculitis).

A better understanding of MPA-associated thyroid disorders is useful for clinicians and several authors recommend systematic screening for thyroid hormones and anti-thyroid autoantibodies in any patient followed for MPA. An early diagnosis of this thyroid dysfunctions, and their appropriate management can improve the overall prognosis of both diseases.

Conflicts of Interest: No conflicts.

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