

Thyroid Disorders in Systemic Angiitis: Myth or Reality?

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Thyroid disorders are among the most common endocrine pathologies and are often primary due to damage to the thyroid gland itself. Their overall prevalence is estimated at 10% and are largely dominated by subclinical or asymptomatic forms. This frequency is particularly high in certain groups such as elderly people, pregnant women, people living in iodine deficient areas and those with a family history of thyroid diseases [1].

Vasculitis or angiitis is an inflammation of the vascular wall that may be primitive defining primary vasculitis, or secondary to several factors/conditions (infections, toxic, solid neoplasia or malignant hemopathies, drug intake, connectivitis..) defining secondary vasculitis. The most appropriate nosological/nomenclature classification for vasculitis is that of the Chapel Hill consensus of 1994 revised in 2012 (International Chapel Hill Consensus Conference on the Nomenclature of Systemic Vasculitides (CHCC)) [2] based primarily on the caliber and type of affected vessels. This classification distinguishes:

- Vasculitis of large vessels: represented mainly by giant cell arteritis (GCA) or Horton's disease and Takayasu's disease (TD),
- Vasculitis of medium-sized vessels: mainly represented by polyarteritis nodosa (PAN) and Kawasaki disease,
- Vasculitis of small vessels: grouping vasculitis with antineutrophil cytoplasmic antibodies (ANCA), namely granulomatosis with polyangiitis (GPA), eosinophilic granulomatosis with polyangiitis (GEPA) and microscopic polyangiitis (PAM), with cryoglobulinemic vasculitis, leukocytoclastic vasculitis and Henoch-Schonlein syndrome (HSS).

The 2012 revision of this consensus conference, recognized two new systemic diseases as vasculitis namely Behçet's disease (BD) and Cogan's syndrome. Both vasculitis affect all vessels independently of the type (artery or vein) and caliber (large, medium or small) [2].

Autoimmunity plays a crucial role in the majority of thyroid dysfunctions (Hashimoto's thyroiditis, postpartum lymphocyte thyroiditis, Graves' disease, granulomatous thyroiditis, Riedel's thyroiditis, and sub-acute DeQuervain thyroiditis). Frequent association of these dysthyroidism with other systemic and/or organ-specific dys-immune diseases are noted, among others systemic vasculitis with autoantibodies such as GPA, GEPA, and MAP, cryoglobulinemia, and vasculitis of connective tissue diseases. The common dysimmune signature is at the base of the pathogenesis of the two affections.

In addition to these "dysimmune angiitis", endocrine and especially thyroid disorders remain exceptional during systemic vasculitis. They are mostly reported in association with small vessel angiitis suggesting a direct attack of the glandular parenchyma by the inflammatory vasculitic process. Thyroid involvement during other systemic primary vasculitis (vasculitis of medium and large vessels) remains unusual and only few sporadic observations were reported.

As a result, the exact meaning of thyroid dysfunction during systemic vasculitis is not well known: is it just a simple coincidence? A specific endocrine involvement of this vasculitis? Or an association of two different diseases with a same predisposing terrain? Likewise, the epidemiological and clinical features, the prognostic significance, and the physiopathogenic mechanisms of these systemic vasculitis-associated dysthyroidism are not yet well defined. Hashimoto's thyroiditis remains the most common form found in systemic angiitis and the most frequent clinical presentation is overt hypothyroidism.

Excluding BD and polymyalgia rheumatica (a more general term including GCA and rhizomelic pseudo-polyarthritits) [3,4], and to a lesser extent cryoglobulinémie, GPA and HSS where thyroid dysfunctions were studied with \pm wide series and sometimes even systematically screened [5], those during other vasculitis remain poorly studied and known; observations are reported as sporadic cases, and Takayasu's disease (TD) [6] and hypocomplementemic urticarial vasculitis are the most commonly reported.

Thus, and despite the apparent rarity, thyroid dysfunctions, and in particular hypothyroidism, during systemic angiitis, seems far from a simple coincidence. In favor of this causal link we retain:

- The extreme rarity of the two diseases makes the possibility of having them simultaneously in the same subject far from being a mere coincidence,
- The simultaneous/synchronous occurrence of both conditions in most patients,
- The autoimmune signature common to the majority of cases: autoimmune thyroiditis and dys-immune vasculitis such as PAM, GPA, BD and TD...,
- The association, in the same patients with both conditions, with other organ specific or non-specific dys-immune diseases,
- The existence of a genetic predisposition common to autoimmune thyroiditis and several systemic vasculitis; in particular susceptibility associations to some HLA haplotypes,
- The notion, in some cases, of concomitant and synchronous evolution of the two affections: relapses and recurrences of thyroiditis concordant temporally with the flares of the underlying vasculitis,
- The existence of several cases of direct and histologically proven specific involvement of the thyroid parenchyma by the underlying vasculitis,
- The notion, in some cases, of dramatic improvement in thyropathy with normalization of disturbances of thyroid status under specific treatment of underlying vasculitis, without the need for hormone replacement therapy,
- The richness of the arterial vascularization of the thyroid gland making it a preferred theoretical target for vascular inflammation during systemic vasculitis.

The possible mechanisms of these thyropathies associated with systemic vasculitis could be: an underlying autoimmune mechanism common to both conditions, a common genetic predisposition, or a specific glandular localization of systemic vasculitis. More rarely, systemic vasculitis may be a complication of antithyroid drug therapy, particularly Graves' disease (antithyroid drug-induced ANCA-associated vasculitis).

The treatment of these dysthyroidism is not specific compared to that of thyroid disorders 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 vasculitis. This would be explained by the share of systemic vasculitis in the genesis of thyroid hormone deficiency. Hormone therapy may be unnecessary or will be discontinued after remission of vasculitis. These disorders can be reversible if the thyroid glandular disease is diagnosed early; On the other hand, the destruction of the thyroid parenchyma by the vasculitis can be definitive and irretrievable if late diagnosis or unsuitable treatment of the vasculitis making the deficiency in thyroid hormones definitive.

Usually there are no direct prognostic implications of thyroid dysfunction on the course of underlying systemic vasculitis; It should be noted, however, that thyroid involvement is often reported in the severe and very active forms of vasculitis with multi-visceral involvement. Similarly, an anecdotal case of carcinomatous degeneration of GPA-specific granulomatous thyroiditis was reported, prompting good clinical and biological monitoring and long-term follow-up in these patients.

Taking into account these findings, several authors recommend a systematic screening of thyroid hormones (TSH, fT4 and t3) as well as thyroid autoimmunity (anti-thyroglobulin and anti-TPO autoantibodies) in any patient with systemic vasculitis, even in the absence of clinical signs and/or symptoms suggestive of dysthyroidism.

This early diagnosis will allow appropriate and early management of both thyropathy and underlying vasculitis. This early and adapted management makes it possible to improve the prognosis of this combination in the forms where there is an association between vasculitis and autoimmune thyroiditis by improving the specific prognosis of thyroiditis; in the rarer cases where thyropathy results from a specific thyroid localization of vasculitis (thyroid vasculitis), this early and adapted management is the only guarantee of a subsequent recovery of normal thyroid function.

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