

Thyroid Involvement in Takayasu's Disease

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Abstract

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 is dominated by subclinical or asymptomatic forms. Autoimmunity plays a crucial role in the majority of cases of dysthyroidism, thus explaining their frequent association with other systemic and/or organ-specific dysimmune diseases, including systemic vasculitis with antibodies. Apart from these "dysimmune" angitis, thyroid involvement is exceptional in other systemic vasculitis, such as Takayasu's disease, and only a few sporadic observations are reported. As a result, the exact significance of thyroid deficiency during this vasculitis is not well known. It can be simply an accidental association but more likely seems to be a specific endocrine involvement of this vasculitis or two conditions sharing the same genetic predisposition. Similarly, the prognostic significance and the physiopathogenic mechanisms of these dysthyroidism associated with systemic vasculitis are not yet well understood.

The purpose of this review is to clarify the thyroid involvement during Takayasu's arteritis and to discuss possible pathogenic mechanisms for these thyropathies.

Keywords: Thyroid; Thyroiditis; Takayasu's arteritis; Takayasu disease; Vasculitis; Autoimmunity

Introduction

Takayasu's disease (TD) or nonspecific aortoarteritis is a primary systemic vasculitis affecting mainly large and medium-sized arteries; especially the aorta and its divisional branches. Its exact etiopathogenesis is still poorly understood and its global incidence varies from 2.6/million/year [1] to 2/10,000 person-year according to countries and ethnic groups [2]. This frequency seems so underestimated since in the autopsy series, the prevalence is 15% in India and 33% in Japan [3]. It is ten times more common among women than men and occurs preferentially before the age of 40 [1,2].

Chronologically, the disease evolves in two successive phases: a first so-called "systemic" or "pre-pulseless" phase with non-specific general inflammatory signs and a second so-called "vascular" or "pulseless" phase where arterial occlusions and stenosis predominate. The clinical presentation of this disease is very variable, ranging from completely asymptomatic forms to severe forms with multi-visceral involvement [4]. It is thus characterized by an important clinical polymorphism which makes its diagnosis a real challenge.

The initial phase is dominated by non-specific symptoms such as fever, asthenia, weight loss and arthromyalgia. Clinical signs such as episcleritis, carotidodynia or erythema nodosum will be of great diagnostic value. The second phase is dominated by peripheral vascular manifestations (vascular claudications, absence of pulse, arterial murmurs, acrosyndome and other vasomotor disorders), ischemic neurological complications, cardiac involvement and renovascular arterial hypertension [1-4].

Medical imaging, in particular arteriography and angio-MR, plays a determining role in the diagnosis of this vasculitis by objectifying the association of stenosing and aneurysmal lesions in the aorta and its main branches [1,2]. Diagnostic criteria were established by the American Colleague of Rheumatology (ACR) in 1990 to facilitate the diagnosis of this vasculitis, with a sensitivity of 91% and a specificity of 98%. The prognosis remains a function of cardiac and cerebrovascular involvement, and arterial hypertension. Treatment combines corticosteroids, immunosuppressive agents, interventional radiology and surgery. The indications are based on the stage of the disease and the nature of the vascular lesions [1-4]. The involvement of the endocrine system, and particularly that of the thyroid gland, remains unusual and very little known during this arteritis.

Endocrine System Involvement in TD

Endocrine gland involvement during TD is exceptionally reported as sporadic cases [5]; we could identify:

- Adrenal gland involvement with primary adrenal insufficiency by autoimmune adrenal disease (Addison's disease) [6],
- Thyroid gland involvement, with particularly autoimmune thyroid diseases such as Graves' disease [2,7] or Hashimoto thyroiditis [8],
- Endocrine pancreas involvement with in type 1 diabetes mellitus [9] or recurrent autoimmune gestational diabetes in two pregnancies two years apart with positive islet cell auto-antibodies [10].
- Ovarian involvement with reduction of ovarian reserves and significantly lower levels of anti-mullerian hormone: 50% during TD versus only 17% of the general population, $p = 0.02$ [11].

- Pituitary involvement with pan-hypopituitarism secondary to granulomatous hypophysitis revealing TD [12],

- Parathyroid involvement with hypoparathyroidism by parathyroid localization of TD [13].

Thyroid Gland Involvement in TD

Concerning the thyroid gland involvement, several isolated observations have been reported, mostly autoimmune thyroid diseases (autoimmune hyperthyroidism, Graves' disease, Hashimoto thyroiditis) and chronic thyroiditis:

- Kettaneh A, et al. reported the association of autoimmune hyperthyroidism with TD in two patients aged 34 and 49; both of them had underlying Crohn's disease [7],

- Ahmed M, et al. reported an autoimmune hyperthyroidism associated with TD in a 52-year-old patient [1],

- Bhattacharya R, et al. reported Graves' disease associated with TD in a 36-year-old woman [14],

- Ben Ghorbel I, et al. reported Graves' disease associated with TD in a 29-year-old woman [15],

- Xu AJ, et al. reported the association of TD with Hashimoto's thyroiditis in a 12-year-old girl [16]. Similarly, Hashimoto's thyroiditis in combination with TD was reported by Adler S, et al. in a 25-year-old woman [17], by Shimokawa H, et al. in a 51-year-old woman [18], by Shih G, et al. in a 54-year-old woman [19] and by Lee ML, et al. in a 16-year-old girl [20].

Mechanisms of Thyroid Involvement in Takayasu Arteritis

These associations let us think about the causality: they are considered fortuitous by some, [15] whereas the majority of authors consider them as "far from being a simple coincidence" [2,7,17-20] and evoke a common genetic predisposition, a common autoimmune mechanism or more rarely a direct causal link by inflammatory vasculitic mechanism. Arguments in favor of this "unfortunate association" between thyroid injury and TD are epidemiologic concordance [2,21], temporal concordance [2,18,19], evolutionary concordance (synchronous recurrence) [17,20], and similar histological features [18] noted by most authors between thyroid gland injury and Takayasu arteritis. Schematically two major mechanisms can be advanced to explain the thyropathy observed during Takayasu arteritis: indirect: the association of two dysimmune/autoimmune diseases and direct: the specific thyroid localization of Takayasu vasculitis.

Indirect mechanism of thyroid involvement during TD

For the majority of authors reporting these associations, an autoimmune mechanism and a common genetic predisposition are strongly incriminated in the pathogenesis of these two diseases [2,7] based on the following arguments:

- The association of TD with several alleles of human leukocyte antigens (HLA) is reported by several authors without individualizing a particularly dominant association (different associations according to populations) [2]. The HLA DP seems to be a preferred marker of this disease according to the study of Dong RP, et al. [22], HLA B* 52: 01 and HLA B67: 01 and the HLA B39 haplotype are also strongly

associated with TD, particularly in the Japanese population [14,23,24]. In addition, recent genetic studies have revealed the marked association of TD with multiple other non-HLA susceptibility genes; in particular the IL12B region, which seems to play a crucial role in the development and progression of TD [23]. Similarly, the association of autoimmune thyroid diseases with HLA alleles is as well known for either Hashimoto's thyroiditis or Graves' disease [25,26].

Thus, the association of hyperthyroidism by autoimmune thyroiditis with TD and Crohn's disease in both observations of Kettaneh A, et al. could be explained by the predisposing genetic factors and the iodine deficiency that characterize these diseases [7]; these two factors alter the nuclear Kappa B pathway (Nuclear Factor Kappa B pathway). This alteration may represent the common denominator favoring this association [2,7].

- The autoimmune hypothesis of TD is strongly evoked by several authors and is based on:

The association of TD with several other auto-immune/dys-immune disorders such as autoimmune hepatitis [8,27,28], chronic autoimmune thyroiditis [8,28,29], chronic sialadenitis/primary Sjögren's syndrome [28], systemic lupus erythematosus [30], rheumatoid arthritis [31,32], primary anti-phospholipids antibodies syndrome [33-35], cryptogenic inflammatory bowel diseases (Crohn's disease and ulcerative colitis) [29,36-38], pustular dermatosis of the scalp, celiac disease [39,40], autoimmune thrombocytopenic purpura [41], type 1 diabetes mellitus [9] and ANCA-associated angiitis, particularly granulomatosis with polyangiitis (former Wegener's disease) [42,43]. This hypothesis is reinforced by the association of TD with several autoimmune/dys-immune disorders at the same time: TD with autoimmune hepatitis, autoimmune thyroiditis, and chronic sialadenitis in the observation of Suzuki H, et al. [28], TD with autoimmune hepatitis, Hashimoto thyroiditis, and pustular dermatitis of the scalp in the observation of Watanabe S, et al. [8], TD with autoimmune thyroiditis and Crohn's disease in the two observations of Kettaneh A, et al. [7], TD with chronic autoimmune thyroiditis and type 1 diabetes mellitus in the observation of Bulum J, et al. [9], TD with autoimmune thyroiditis and celiac disease in the observation of Korinek J, et al. [39], TD with autoimmune thyroiditis, autoimmune thrombocytopenic purpura, and seropositive polyarthritis in the observation of Saab F, et al. [41]. Indeed, in the Ohta Y, et al. series of 36 patients with TD, eleven (30.5%) had at least one associated chronic inflammatory disease such as autoimmune hepatitis, chronic autoimmune thyroiditis, subacute thyroiditis, Crohn's disease, ulcerative colitis, erythema nodosum, pyoderma-gangrenosum or chronic sialadenitis) [29]. The observation of several immunological abnormalities concerning both innate and acquired immunity [44,45] and so humoral and cellular immunity [44,46,47]:

- Tamura N, et al. reported significantly higher levels of TNF- α and interleukin-6 (IL-6) during TD compared to the general population with a positive correlation with the disease activity [45],

- The presence of a large polyclonal hypergammaglobulinemia in both the active and inactive forms of TD [47],

- A significantly higher rate of Th17-type T-cells compared to the general population: odds ratio at 2.1 versus 0.75 ($p < 0.0001$) [44],

- Interleukin 17 (IL-17) and interleukin-23 (IL-23) levels significantly higher than the general population: odds ratio at 6.2 versus 3.9 and 15 versus an undetectable level respectively, $p < 0.001$ [44].

The presence of several types of organ-specific or non-organ-specific autoantibodies in the same patient with an underlying TD testifies again for the dys-immune nature of this condition; this situation is well illustrated in the observation of Mauricio D, et al. where in a 29-year-old woman with TD associated with recurrent autoimmune gestational diabetes, besides the anti-islet autoantibodies specific to diabetes, the positivity of anti-gastric parietal cell antibodies and anti-thyroid-peroxydase antibodies (anti TPO) [10] and the observation of Saab F, et al., reporting TD associated with hypothyroidism by autoimmune thyroiditis and autoimmune thrombocytopenic purpura, where we also noted the positivity of rheumatoid factor and anti-nuclear antibodies [41].

Thus, these so-called "unusual" associations of Takayasu's arteritis with autoimmune thyroiditis, in particular that of Hashimoto, reasonably suggest the possibility of a physiopathological association between them [2,7]; Cell-mediated immunological mechanisms play an important role in both diseases. Proinflammatory cytokines such as tumor necrosis factor (TNF- α), interleukins 6, 8, 12 and 18 are common to both conditions amplifying the inflammatory process and causing disease in genetically predisposed subjects [16]. Moreover, for many authors, TD is currently considered as an "autoimmune arteritis" [41,45].

Direct mechanism of thyroid involvement in TD

More rarely, thyroid involvement during TD could result (at least theoretically) from a direct vasculitic mechanism (thyroid specific location of Takayasu arteritis), especially that the thyroid gland is richly vascularized and the involvement of small vessels has been objectified during TD [48]. This hypothesis could explain the cases in which the thyroid dysfunction is not immunological (negative anti-thyroid antibodies) and where the thyroid imaging shows an enlarged thyroid with local vascular abnormalities suggestive of granulomatous thyroid vasculitis specific for TD. However, no case has been histologically proven in the world literature. Finally, TD may be discovered by chance on the morphological examinations requested as part of the diagnostic assessment of thyrotoxicosis; indeed Pickering M, et al. reported a case of TD discovered on a cervical CT scan in a patient with autoimmune hypothyroidism, showing stenosis of the internal carotid arteries [49] and Nam SJ, et al. reported a case of TD discovered on a Doppler ultrasound performed as part of the etiological review of a thyroid nodule in a 52-year-old woman, showing prominent collateral thyroid arteries and stenoses of common carotid arteries [50]. It should also be noted that goiter and thyroid nodules were exceptionally reported during Takayasu arteritis [2,18,50].

Is there a Prognostic Significance of Thyroid Involvement in Takayasu Arteritis?

Although thyrotoxicosis seems to be benign in all cases and does not directly interfere with the functional or vital prognosis of patients with TD, it has been noted that thyroid involvement is often associated with severe forms, hyperactive and complicated TD; indeed:

- In the observation of Uhm JS, et al. hyperthyroidism was associated with pulmonary localization of TD with multiple thromboembolic complications [51],

- In the case of Achraf M, et al. autoimmune hyperthyroidism was associated with TD with severe cardiac involvement, renovascular

arterial hypertension, and multiple arterial stenoses: renal, gastrointestinal, and supra-aortic trunks [2],

- In the case of Shimokawa H, et al. Hashimoto's thyroiditis was associated with TD complicated of severe annulo-aortic ectasia [18],

- In the case of Saab F, et al. hypothyroidism was associated with highly active TD with severe and relapsing episodes, resistant to corticosteroid and immunosuppressive therapy, and complicated with multiple vascular involvement and myocardial infarction [41].

Although thyroid involvement has no direct impact on the prognosis of TD, its diagnosis and its early and effective treatment can improve the quality of life of patients, and therefore their overall prognosis.

Conclusion

To sum up, and concerning thyroid involvement during TD, we can conclude that thyroid involvement associated with TD is mainly dominated by autoimmune thyroid diseases (Basedow disease and Hashimoto thyroiditis), fewer goiter and thyroid nodules. This association (thyrotoxicosis/TD) results according to the majority of authors of an underlying autoimmune mechanism common to both conditions, whereas direct thyroid involvement caused by granulomatous vasculitis of the thyroid arteries specific to Takayasu arteritis is much rarer.

It is thus necessary, at least because of the particular frequency of dysthyroidism, to screen for thyroid function in any patient with Takayasu's disease.

Conflicts of Interest

No conflicts

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