20

Thionamides-Related Vasculitis in Autoimmune Thyroid Disorders: Review of Current Literature and Case Reports

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1. Introduction

Hyperthyroidism is the consequence of excessive thyroid hormone action (AACE Thyroid Guidelines, 2002). In many cases, it results from excessive activity of the thyroid gland, with a pathologically increased production of thyroid hormones. The causes of hyperthyroidism include several conditions, that are listed in Table 1.

• Toxic diffuse goiter (Graves' disease)
• Toxic adenoma
• Toxic multinodular goiter (Plummer's disease)
• Painful subacute thyroiditis
• Silent thyroiditis, including lymphocytic and postpartum variations
• Iodine-induced hyperthyroidism (for example, related to amiodarone therapy)
• Excessive pituitary TSH or trophoblastic disease
• Excessive ingestion of thyroid hormone

Table 1. Causes of hyperthyroidism (AACE Thyroid Guidelines,2002*)*

Graves' disease is the most common cause of hyperthyroidism. It is an autoimmune disorder, caused by the presence of autoantibodies directed against the thyroid-stimulating hormone (TSH) receptor (TRAb), chronically stimulating thyroid hormone synthesis and secretion, and resulting in an excessive amount of triiodothyronine (T3) and thyroxine (T4) and gland growth. In iodine sufficient areas, this prototypical autoimmune disease is the most common cause of thyrotoxicosis in young women as well as in children and adolescents, and it is characterized by thyrotoxicosis, goitre and typical manifestations such as ophthalmopathy and pretibial myxedema.
According to the American Association of Clinical Endocrinologists guidelines (AACE, 2002), the diagnosis of hyperthyroidism relates on TSH values. Thus, with the exception of the excess of TSH secretion, hyperthyroidism of any cases results in a lower-than-normal or

suppressed TSH level, together with an increase of free T4 and free T3 in the case of overt disease.

Once hyperthyroidism has been diagnosed, three main therapeutic options are available, including radioactive iodine, surgical intervention (thyroidectomy) and anti-thyroid drug.

In US, radioactive iodine is currently the treatment of choice for adults with Graves' disease, except for pregnant or breast-feeding women, because of its adverse effects on fetal gland and its appearance in the breast milk. Overall, radioactive iodine is a safe and effective therapy, that can be either administered through an ablative or with a smaller doses regimen in order to render the patient euthyroid. In any case, hypothyroidism requiring a lifelong thyroid replacement therapy is an inevitable consequence with radioiodine therapy.

Thyroidectomy was frequently used in the past, but its use is now limited to pregnant women intolerant to antithyroid drugs, or to patients refusing radioactive iodine as a definitive treatment. Possible complications associated with surgical treatment of Graves' disease include laryngeal nerve damage and vocal cord paralysis, hypoparathyroidism and hypothyroidism.

Anti-thyroid drug treatment is still a widely used approach in the treatment of hyperthyroidism. Since the 1940s, thionamides have been used as anti-thyroid drugs in the management of Grave's disease (Laurberg et al., 2006). This class of drugs includes propylthiouracil (PTU), benzylthiouracil, carbimazole and methimazole (MMI), and all of them have been shown to have comparable efficacy in inducing hyperthyroidism remission (Cooper, 2005).

All these compounds act through the inhibition of thyroid peroxidase, the enzyme responsible for the synthesis of thyroid hormones, thus leading to a reduced hormone secretion (Laurberg et al., 2006). Recently, an alternate mechanism of action has been proposed, relating their efficacy in patients with Graves' disease to a direct immunosuppressive effect (Laurberg et al., 2006).

Despite the similar efficacy, the choice of the anti-thyroid drug is conditioned by other drug characteristics and/or by their pharmacokinetics profile. For instance, MMI has a longer half-life than PTU, and thanks to its once-a-day administration, it represents the best choice when addressing patients compliance. On the other hand, PTU is the drug of choice for treating pregnant and breast-feeding women, because of its limited transfer into the placenta and breast milk (Streetman et al., 2003). PTU is often preferred to MMI also for the additional property of inhibiting the peripheral conversion of T4 to T3.

Although widely used, anti-thyroid drugs have been reported to be associated with a wide range of adverse effects, such as skin eruptions, liver dysfunction and agranulocytosis; fever, arthralgias and arthritis are other common clinical manifestation, usually occurring within the first few months of administration.

The occurrence of these side-effects can be influenced by several factors, such as drug starting dose or treatment duration (Nakamura et al., 2003).

In addition, over the past 2 decades, several cases of thionamides-associated autoimmune vasculitis have been reported, with variable clinical presentation and severity.

Vasculitis are a heterogeneous group of inflammatory disorders of the blood vessels, that occur as a part of several autoimmune disorders. In many cases they are largely mediated by the deposition of immune complexes that precipitate and become trapped within vessel

walls, stimulating an immune response that ultimately leads to vascular injury. This mechanism usually occurs in secondary vasculitis, frequently associated with infections or systemic autoimmune diseases, whereas in the primary vasculitis, immune deposits are generally absent (Kallenberg & Heeringa, 1998).
Clinical manifestations of vasculitis largely depend on the type of vessels and the specific disctrict involved, resulting in a wide-range of signs and symptoms.
The Chapel Hill Consensus Conference nomenclature is one of the most widely used to distinguish different forms of vasculitis, based on vessel size (large, medium, and small), as shown in Table 2 (Jennette & Falk, 2007).

Large Vessel Vasculitis
• Giant Cell Arteritis • Takayasu Arteritis
Medium-Sized Vessel Vasculitis
• Polyarteritis Nodosa • Kawasaki Disease
Small Vessel Vasculitis
• Wegener's Granulomatosis • Churg-Strauss Syndrome • Microscopic Polyangiitis • Henoch-Schönlein Purpura • Cryoglobulinemic Vasculitis • Cutaneous leukocytoclastic angiitis

Table 2. Classification of vasculitis according to the Chapel Hill Consensus Conference

2. Thionamides-related vasculitis in autoimmune thyroid disorders

2.1 Autoimmune markers of thionamides-related vasculitis

Overall, vasculitis have been mainly reported in patients treated with PTU, and most of PTU-induced vasculitis are associated with an increase of anti-neutrophil cytoplasmic antibody (ANCA) circulating levels.
ANCA are antibodies directed against myeloid lysosomal enzymes, that can be identified by indirect immunofluorescence (IIF) with human neutrophils. These autoantibodies can have a cytoplasmic (cANCA) or a perinuclear (pANCA) distribution pattern, that can be detected by ELISA (Savige et al., 2000). In particular, cANCA are directed against antiproteinase3 (PR3-ANCA), and they are specific for Wegener's granulomatosis (Van der Wonde et al., 1985), whereas pANCA can be directed against several antigens, the most important being myeloperoxidase (MPO-ANCA). pANCA is a serological marker for microscopic polyangiitis, but it can also be detected in patients with systemic lupus erythematosus, rheumatoid arthritis and drug-induced vasculitis (Jennette & Falk, 1997).
Any of these patterns can occur in patients with drug-induced ANCA-positive vasculitis and atypical ANCA against several antigens, like elastase, azurocin, cathepsine G, lactoferrin and lyzozim have been also reported.
Although the pathogenetic role of these autoantibodies in drug-induced vasculitis has not been fully elucidated yet, several hypotheses have been proposed.

Thus, it has been reported that PTU can selectively accumulate into neutrophils where it can bind to myeloperoxidase, changing or inactivating the heme structure of the enzyme (Lee et al., 1988). It has been suggested that, in susceptible individuals, the enzyme altered by PTU could then stimulate the production of anti-myeloperoxidase antibodies, inducing neutrophils degranulation and vascular damage (D'Cruz et al., 1995). In particular, MPO-ANCA seems to play an important role in the development of tissue damage in vasculitis or glomerulonephritis (Ashizawa et al., 2003; Arimura et al., 1993). It has also been suggested that viral infections could trigger the development of the autoimmune chain reaction.

Overall, ANCA autoantibodies are frequently detected in patients with Graves' disease treated with anti-thyroid drugs, regardless of the presence of clinical manifestations of vasculitis.

Anti-thyroid drugs ANCA-associated vasculitis occurs more frequently in women, consistently with the fact that Graves' disease is more common in female gender.

It has been reported that the prevalence of MPO-ANCA is higher in patients treated with PTU than in those treated with MMI (Wada et al., 2002).

Thus, the prevalence of ANCA positivity has been estimated to average 26% of PTU-treated subjects (Gunton et al., 2000), being even higher in treated children (Hirokazu et al., 2000).

In a study of 117 patients with Graves' disease, Sera et al. reported that MPO-ANCA was negative in all patients treated with MMI as well as in untreated patients, whereas it was detected in 37.5% of patients receiving PTU (Sera et al., 2000). Furthermore, the proportion of patients positive for MPO-ANCA increased with the prolongation of PTU treatment (Sera et al., 2000).

In a retrospective study of 61 patients with Graves' disease, Wada et al. reported that 25% of patients treated with PTU showed positive MPO-ANCA, unlike 3.4% of patients receiving MMI. Moreover, the sole patient MPO-ANCA positive treated with MMI had been taking PTU for six years before starting MMI treatment (Wada et al., 2002).

The annual incidence of MPO-ANCA-associated vasculitis in patients treated with anti-thyroid drugs has been estimated to be between 0.53 and 0.79 patients per 10,000, although several mild cases may not have been reported (Noh et al., 2009).

However, not all ANCA positive patients develop the clinical manifestations of vasculitis, and several factors such as type of drug, ethnicity, timing and dose, treatment duration may concur to the development of overt clinical manifestations.

Overall, the incidence of ANCA positive vasculitis is higher with PTU, being estimated to be 39.2 times the incidence reported with MMI (Noh et al., 2009).

As for ethnicity, the prevalence of ANCA positivity seems to be similar in different ethnical groups, although Gunton et al. suggested that ANCA-positive vasculitis may be more common in patients of Asian origin, being nearly half of the reported cases of PTU-induced ANCA-associated vasculitis from Japan (Gunton et al., 1999).

The timing and doses of thionamides reported in ANCA-associated vasculitis have also been variable. In fact, even if long-term treatment with anti-thyroid drugs seems to have a stronger association with the risk of vasculitis, these complications can also occur within few months after starting the treatment. Furthermore, ANCA-associated vasculitis have been also reported in patients treated with low doses of both MMI and PTU (Noh et al., 2009).

Moreover, it seems that drug dose and duration of anti-thyroid treatment use, together with the titers of antibodies could be related with the clinical course of ANCA-associated vasculitis. Thus, Morita et al. (Morita et al., 2000) reported that anti-thyroid drug-induced ANCA-associated vasculitis was more frequent in patients resistant to drug treatment, who were receiving high doses over a prolonged period of time and with high titers of MPO-ANCA; furthermore, clinical manifestations disappeared according to decreasing values of antibodies. This finding suggests that high titer of MPO-ANCA may be necessary to induce vasculitis.

Beside the role of thionamides in inducing the formation of specific autoantibodies, an alternate hypothesis has to be taken into account.

Thus, given the common autoimmune background, a possible association of ANCA-positivity with the autoimmune disease itself has been suggested.

This hypothesis has been tested in a prospective study, where a group of patients with newly diagnosed Graves' disease were followed up before and during therapy with PTU, and compared to a cross-sectional group of previously diagnosed Graves' patients who had already been treated with PTU, of patients with Hashimoto thyroiditis and those with toxic nodular goiter, as well as to healthy controls. As a result, all untreated newly diagnosed Graves' patients were ANCA negative, but 32.1% became ANCA positive after initiating PTU administration. On the other hand, patients with Hashimoto disease, untreated toxic nodular goiter and euthyroid subjects did not show ANCA positivity. This study suggested that it is PTU treatment, and not hyperthyroidism or autoimmunity, which induces ANCA production (Ozduman Cin et al., 2009). In agreement with this, ANCA prevalence is increased in Graves' disease, but not in patients with other autoimmune thyroid disease, such as Hashimoto thyroiditis (Harper et al., 2004). Furthermore, it has also been demonstrated that PTU administration is associated with ANCA positivity at a similar rate in both patient with Graves' disease and those with toxic multinodular goiter, suggesting that PTU but not Graves' disease itself is the most important factor for ANCA development (Yazisiz et al., 2008).

2.2 Clinical manifestations of thionamides-related vasculitis

Clinical presentation and severity of anti-thyroid drug-induced vasculitis are variable, and largely related to the type of vessels and to the anatomical district involved.

Thus, although not all ANCA positive patients develop a clinical disease, a wide-range of clinical symptoms have been reported in patients with thionamides-related vasculitis.

ANCA-associated vasculitis is usually characterized by small vessel inflammation and necrosis, that may involve any system and organ, being arthralgia and fever the most commonly reported clinical manifestations (Morita et al., 2000).

An ANCA-positive vasculitis in association with anti-thyroid drugs was first reported in 1992 by Stankus and Johnson, who described a patient treated with PTU who developed respiratory failure and MPO-ANCA positive test (Stankus & Johnson, 1992).

Since then, several cases of ANCA-associated vasculitis in patients with Graves' disease treated with anti-thyroid drugs have been described, although ANCA-positive vasculitis have also been reported in patients with toxic multi-nodular goiter treated with PTU. Thus, in 1999 a case report of a PTU-induced vasculitis was described in an elderly women with

toxic multi-nodular goiter, presenting with haemoptysis and acute renal failure (Gunton et al., 1999).

Overall, drug-induced vasculitis presenting symptoms may include renal involvement (67%), arthralgia (48%), fever (37%), skin manifestations (30%), respiratory tract involvement (27%), myalgia (22%), scleritis (15%) as well as other manifestations (18%) (Gunton et al., 1999).

As for skin manifestations, leukocytoclastic vasculitis, principally affecting the lower limbs, is the most common cutaneous manifestation (Gunton et al., 1999; Day et al., 2003).

In addition, several cases of pulmonary involvement have been reported, including pulmonary infiltrates associated with respiratory failure, eosinophilic pleuritis, interstitial pneumonitis or respiratory distress syndrome and pulmonary harmorrhage (Stankus & Johnson, 1992; Chevrolet et al., 1991).

Renal involvement in drug-induced vasculitis is also common. In 1995, D'Cruz et al. published the first report of renal biopsy-proven vasculitis in two patients treated with anti-thyroid drugs. Both patients developed a crescentic glomerulonephritis and responded to immunosuppressive therapy and dismission of anti-thyroid drugs (D'Cruz et al., 1995).

Recently, Chen YX et al. published a retrospective study of 19 patients with ANCA-positive vasculitis associated with PTU treatment. In this study, renal injury was the most common manifestation, occurring in 94.74% of cases. At renal biopsy, focal proliferative glomerulonephritis and necrotizing glomerulonephritis with crescent formation, minor glomerular abnormalities, IgA nephropathy, membranous nephropathy, focal proliferative glomerulonephritis, granulomatous interstitial nephritis and focal segmental glomerular sclerosis were all described (Chen YX et al., 2007).

Rare fatalities have been also reported in patients with anti-thyroid drugs-associated vasculitis. Batchelor et al. described the case of a 60-year-old man with a history of Graves' disease, treated with PTU, and presenting with rash, pancytopenia, and lymphadenopathy and subsequently developing acute renal failure and diffuse alveolar hemorrhage, who died despite the discontinuation of PTU and an aggressive therapy including immunosuppressive drugs and plasmapheresis (Batchelor & Holley, 2006).

Thus, even if in the majority of cases vasculitis usually resolve after the discontinuation of anti-thyroid drugs, patients can present with more severe or life-threatening manifestations. In a study evaluating cutaneous and systemic manifestations following thionamides administration, death occurred in 10% of all published cases, with a predominance in patients with involvement of multiple organ systems (ten Holder et al., 2002).

Until 2005, the main case reports of thionamides induced-vasculitis described above all renal, musculoskeletal and cutaneous manifestations. In that period, the first case of thionamides-induced central nervous system (CNS) vasculitis has been also reported (Vanek et al., 2005): a PTU-treated patients presenting with generalized muscle spasms, amnesia and confusion, who showed a complete resolution of CNS symptoms after cessation of drug administration.

Since most of thionamides-related vasculitis have been associated with PTU, MMI treatment has been advocated as safer for the treatment of Graves' disease; however, several cases of vasculitis following MMI administration have been reported.

In 1995, Kawaki et al. reported the first case of ANCA-associated vasculitis caused by MMI: a 24-year-old woman with Graves' disease treated with MMI for 4 years, who developed

recalcitrant ulcers on the lower legs and ANCA positivity, improved after MMI was withdrawn (Kawaki et al., 1995).
Besides skin manifestations, also renal involvement, such as crescentic glomerulonephritis (D'Cruz et al., 1995), and pulmonary involvement, with hemoptysis and hypoxic respiratory failure (Tsai et al., 2001) have been reported in MMI-treated patients.
Furthermore, we recently reported the first case of MMI induced CNS vasculitis in a young woman with Graves' disease, completely recovered after the discontinuation of treatment (Tripodi et al., 2008). CNS vasculitis was suspected on the basis of the clinical features and neurological examination, and confirmed by brain magnetic resonance imaging (RMN) and single-photon emission computed tomography (SPECT). In our patient, ANCA test was negative, supporting the concept that ANCA are not critical for the development of drug-induced vasculitis.
Thus, although less common than with PTU, vasculitis associated with other thionamides-drugs therapy have been also described.
Although more infrequently, carbimazole-associated vasculitis have been reported. Carbimazole has been associated with leukocytoclastic vasculitis and acute renal failure secondary to interstitial nephritis, without any evidence of ANCA positivity (Day et al., 2003), and to ANCA-positive vasculitis with crescentic glomerulonephritis (D'Cruz et al., 1995). Respiratory involvement in carbimazole-treated patients appears to be less common, although a case of MPO-ANCA vasculitis with massive pulmonary hemorrhage and necrotizing glomerulonephritis has been described (Calanas-Continente et al., 2005). Also a case of polyneuropathy, with evidence of microvasculitis in nerve biopsy, was reported as associated to this drug administration (Leger et al., 1984).
In a large cross-sectional study of 407 patients with Graves' disease, Harper et al. reported that both PTU and carbimazole therapy were associated with an increases rate of ANCA-positivity, although the risk in carbimazole-treated patients was smaller than in PTU-treated ones (15.9% and 33.3% respectively vs 4,6% of controls) (Harper et al., 2004). Its administration has also been related to the development of rare side effects, such as those described by Sève et al., who reported the first case of eosinophilic granulomatous vasculitis localized to the stomach in a patient with Graves' disease treated for five months with carbimazole, with complete resolution of clinical manifestations after drug dismission (Sève et al., 2005).
Since there are no evidence that carbimazole can accumulate in neutrophils or to act as a hapten as PTU, the underlying mechanism associated to the development of vasculitis related with other thionamides-drugs has not been yet elucidated.

2.3 Anti-thyroid-induced ANCA-associated vasculitis and idiophatic ANCA vasculitis: Comparison of clinical manifestations and outcomes

Clinical and serological characteristics of drug-induced and idiophatic systemic vasculitis are similar; however, the appropriate diagnosis is of great importance since they may have a different treatment and prognosis.
Thus, the removal of anti-thyroid drugs is usually associated with the resolution of the clinical symptoms of vasculitis, whereas patients with idiophatic vasculitis always need to be treated more aggressively with immunosuppressive and anti-inflammatory drugs, or plasmapheresis.

Clinical and serological data from idiophatic and anti-thyroid drug-induced ANCA positive vasculitis were compared in a 11-year retrospective study. In this cohort (Bonaci-Nikolic et al., 2005), both groups of patients showed a similar high frequency of arthralgia and myalgia, whereas skin involvement, especially represented by urticaria and urticaria-like vasculitis, was more common in patients treated with anti-thyroid drugs, with histological evidence of leucocytoclastic vasculitis. Furthermore, patients with idiophatic systemic vasculitis showed more frequently fever, weight loss, renal and respiratory manifestations, pulmonary-renal syndrome, ear/nose and nervous system manifestations.

As for serological profile, patients with drug-induced vasculitis, showed positivity for ANAs and antihistone antibodies, and had high levels of IgM anticardiolipin antibodies cryoglobulinemia and low C4 values (Wiik et al., 2005; Bonaci-Nikolic et al., 2005).

Hence, drug-induced vasculitis seem to have a milder course and a better long-term prognosis, since the withdrawal of anti-thyroid drugs usually leads to the resolution of clinical manifestations in the vast majority of cases.

Thus, the prognosis of anti-thyroid-induced ANCA-associated vasculitis is usually good as long as the drug is discontinued. However, early recognition of clinical symptoms is very important because of the potential risk of life-threatening injury, such as pulmonary-renal syndrome, with pulmonary hemorrhage and renal failure. In these patients, additional treatment with steroids and/or immunosuppressive agents should be recommended.

In a retrospective study of fifteen patients with PTU-induced ANCA-associated vasculitis, Gao et al. investigated treatment protocols and outcomes of patients, suggesting that immunosuppressive therapy should be administrated only in those patients with vital organ involvement, such as lung and kidney vasculitis, in order to prevent progression to irreversible disease.

Interestingly, unlike what is normally found in patients with primary ANCA-associated vasculitis (Hogan et al., 2005), none of the patients with drug-induced vasculitis experienced relapse after the discontinuation of immunosuppressive therapy at follow-up (Gao et al.,2008).

Moreover, immunosuppressive therapy may be administered only for a shorter period of time, usually 6-12 months, than in primary ANCA-associated vasculitis, without any further maintenance therapy (Gao et al., 2008).

3. Conclusion

Anti-thyroid drugs are a common and widespread treatment for Graves' disease and the other forms of hyperthyroidism. It is a safe and efficacy treatment, and it is the treatment of choice in patients refusing radioactive iodine as definitive treatment or during pregnancy and breast-feeding.

However, this treatment has been associated with several side effects and among them, vasculitis, with a wide-range of severity and clinical presentations.

Vasculitis are more commonly reported in PTU-treated patients, with a long duration of treatment, and with positivity for ANCA autoantibodies.

Thionamides-related vasculitis usually recover after discontinuation of therapy, although rare cases of fatalities have been also reported.

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Autoimmune disorders are caused due to break down of the immune system, which consequently fails in its ability to differentiate "self" from "non-self" in the context of immunology. The diseases are intriguing, both clinically and immunologically, for their diversified clinical phenotypes and complex underlying immunological mechanisms. This book offers cutting-edge information on some of the specific autoimmune disease phenotypes, respective diagnostic and prognostic measures, classical and new therapeutic options currently available, pathogenesis and underlying mechanisms potentially involved, and beyond. In the form of Open Access, such information is made freely available to clinicians, basic scientists and many others who will be interested regarding current advances in the areas. Its potential readers will find many of the chapters containing in-depth analysis, interesting discussions and various thought-provoking novel ideas.

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