Central Nervous System Vasculitis after Starting Methimazole in a Woman with Graves’ Disease

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Background: Graves’ disease (GD), a prototypical autoimmune disorder, is associated with other autoimmune diseases, including vasculitis. Antithyroid drugs, despite their postulated immunosuppressive effects, may cause several autoimmune disorders. Here we describe the first patient with central nervous system (CNS) vasculitis that developed shortly after the start of methimazole (MMI) treatment for GD.

Patient Findings: CNS vasculitis was suspected on the basis of the clinical features and neurologic examination, showing a reinforcement of deep reflexes, especially of the left knee and Achilles reflexes. The diagnosis was confirmed by a brain magnetic resonance imaging (MRI), which showed some hyperintensive spots in the subcortical substantia alba and in the parietal area bilaterally, and by a single-photon emission computed tomography (SPECT) imaging, which showed a nonhomogenous distribution of the blood flow in the brain, with a reduced perfusion on the left side of the frontotemporal and parietal regions, and on the right side of the frontotemporal area. MMI was stopped before total thyroidectomy, and symptoms resolved in the next 5 weeks. Six months after MMI was stopped, the brain MRI and SPECT had become normal.

Summary: To our knowledge, this is the first report of CNS vasculitis related to MMI therapy.

Introduction

Graves’ disease (GD) is the most common cause of thyrotoxicosis in young women living in iodine-sufficient areas. It is induced by autoantibodies directed against the thyroid-stimulating hormone (TSH) receptor (TRAb). Medical treatment of GD is based chiefly on the thionamide antithyroid drugs (1). These exert their antithyroid effect by inhibiting thyroid hormone synthesis (1). They have also been postulated to have an immunosuppressive action that promotes remission of GD (1,2). Methimazole (MMI) and propylthiouracil (PTU) are the most frequently used thionamide drugs for GD. Adverse effects, including skin rash, liver dysfunction, and agranulocytosis, have been associated with both drugs.

There have been multiple patients reported with PTU-associated vasculitis in the past 2 decades, mostly in females, consistent with the fact that GD is more common in this sex than in males (3–6). Almost all patients with PTU-induced vasculitis have detectable antineutrophil cytoplasmic antibody (ANCA) levels, although not all PTU-ANCA-positive patients develop a clinical disease (4–11). The clinical presentation and severity have been variable (3–10). Vasculitis associated with MMI therapy has also been described, but is less common than with PTU.

Interestingly, a patient with central nervous system (CNS) vasculitis caused by PTU therapy has recently been described (12). Here we report the first patient with CNS vasculitis that appears to be related to MMI treatment. The disorder began soon after MMI was started and resolved shortly after it was stopped.

Patient

A 22-year-old woman was seen in our outpatient clinic in December 2002 because of fatigue, palpitations, tremor, insomnia, sweating, and weight loss of 1-month duration. Physical examination was significant for glomerulonephritis at 12 years of age. Physical examination revealed warm, moist skin; tremors of the extremities; hyper-reflexia; and a diffuse goiter. Her heart rate was 100 beats/min, and her mean blood pressure was 150/70 mmHg. Despite complaints of...
photoreceptor cell damage. The funduscopy revealed white disc margins and a dome-shaped macula. *=8 mm in diameter) in the left nasal quadrant, which was consistent with a possible neovascular retinopathy. Funduscopy was normal.

Discussion

Here we describe a young woman with GD who developed CNS vasculitis 3 weeks after starting on MMI. The close proximity of CNS vasculitis to the start of MMI and that CNS vasculitis resolved within 5 weeks of stopping MMI are very consistent with this drug being the cause of her CNS vasculitis and has not been previously reported. Vasculitis is one of the major toxic reactions to antithyroid drugs (13). It is usually associated with PTU therapy (4–11,13), but MMI-related vasculitis has been reported (14–16). Because vasculitis is more often associated with PTU than with MMI, the latter antithyroid drug has been advocated as safer for the management of GD (5,11,13).

Patients with drug-induced vasculitis usually have a good prognosis and a milder course than those with idiopathic vasculitis, in part because the underlying cause can be removed by stopping the drug. In a series of 16 patients (12 receiving PTU and 4 receiving MMI), none manifested CNS effects, but one did have sensory polyneuropathy that regressed upon the drug was stopped (10). The first patient with CNS vasculitis in association with antithyroid drug treatment was reported in 2005 (12). This patient was taking PTU. We are not aware of any reports before this of CNS vasculitis related to MMI therapy. Most of the reported patients with antithyroid drug–induced vasculitis are ANCA positive.

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positive, although not all ANCA-positive patients develop the disease. In our patient, ANCA (as well as other non-organ-specific autoantibodies) was always negative, consistent with the notion that ANCA is not critical for developing drug-induced vasculitis.

GD and Hashimoto’s thyroiditis are both autoimmune disorders. Vasculitis in patients with these two disorders is exceedingly rare and may be based on chance or the presence of other autoimmune disorders when reported (17–19). In the patient reported here, the development of CNS vasculitis was clearly associated with MMI treatment, not the presence of GD. This patient illustrates that the risk of vasculitis cannot be entirely avoided by prescribing MMI instead of PTU.

References


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