

Pulmonary Hemorrhage and Renal Involvement in Benzylthiouracil-Induced Vasculitis

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Abstract

Introduction: Vasculitis is a rare complication of antithyroid drugs reported with propylthiouracil, carbimazole, methimazole and Benzylthiouracil. Benzylthiouracil –induced Vasculitis are often severe forms with renal or pulmonary involvement, which can be life-threatening if left untreated. We describe the clinical course and medical management of 2 cases of severe vasculitis with alveolar hemorrhage and renal involvement occurred in 2 patients with Graves' disease treated by Benzylthiouracil.

Cases report: A 36 and 33-year-old women with Graves' disease developed alveolar hemorrhage and acute renal failure after respectively 36 and 144 months of Benzylthiouracil therapy. Kidney biopsy showed pauci-immune crescentic glomerulonephritis in the 2 cases. Anti Neutrophil Cytoplasmic Antibody (ANCA) was positive (P-ANCA in the first patient and c-ANCA in the second patient). The condition of the first patient improved when Benzylthiouracil was withdrawn associated with corticosteroids and immunosuppressive treatment after a follow up of 6 months. However, the second patient died by severe infection after the same treatment.

Conclusion: Benzylthiouracil vasculitis is a serious complication but its prognosis is good if diagnosis and treatment are early. However mortality is related to risk of infection.

Introduction

Vasculitis are common in Grave's disease and are related to antithyroid drugs. We report severe vasculitis with renal and pulmonary involvement in two patients with grave's disease treated by Benzylthiouracil.

Case report 1

A 33 year old woman was admitted with fever and respiratory distress. Her past medical history included a grave's disease treated by Benzylthiouracil for 10 years. Examination revealed a fibril, blood pressure of 120/70 mm Hg, pallor, tachycardia, polypnea, pulmonary, sonorous and vesicular rales, proteinuria and hematuria.

Laboratory investigations showed hemoglobin 7.5 g/dl, serum creatinine 1150 $\mu\text{mol/l}$, hypoxemia hypercapnea, and 24 hour urinary protein 6 g. She was negative for antinuclear and glomerular basement membrane antibodies. Anti Neutrophilic Cytoplasmic Anti body (C-ANCA) were positives for anti proteinase 3. The chest radiograph revealed diffuse bilateral opacities. Ultrasound examination of the abdomen showed normal kidneys. Kidney biopsy revealed pauci immune crescentic glomerulonephritis. The bronchoscopy revealed active alveolar bleeding. Antithyroid drugs have been described in the literature as a possible cause of vasculitis. We suppose that Benzylthiouracil was the most likely cause of vasculitis. The patient discontinued Benzylthiouracil and was started on pulse of methyl prednisolone 15 mg/kg/j for three days followed by oral steroids 1 mg/kg/j. The dose of prednisone has been gradually reduced and maintained at 5 mg/day. She also received 6 pulses of cyclophosphamide 1 g/1, 73 m² body surfaces. After the treatment the general condition of the patient had improved only partially with the latest serum creatinine being 400 $\mu\text{mol/l}$, four month later she died by severe infection.

Case report 2

A 36 year old woman with a history of grave's disease treated by Benzylthiouracil for three years was admitted with asthenia, weight loss, oligo anuria and dyspnea. Clinical examination revealed pallor,

tachycardia, edema of lower limbs, blood pressure of 120/80 mmHg, proteinuria and hematuria. The rest of the systemic examination was unremarkable. Laboratory test showed hemoglobin 5.3 g/dl, ESR 70 mm/1st hr, serum creatinine 304 $\mu\text{mol/l}$ and 24 hour urinary protein 1.4 g. Hormonal exploration showed hyperthyroidism with positive thyroid antibodies. Antinuclear and anti-glomerular basement membrane antibodies were negatives. Screening for Anti Neutrophilic Cytoplasmic Antibody (P-ANCA) was positive for anti Myelo Peroxidase (MPO). Chex –X- ray revealed bilateral alveolar infiltration. The bronchoscopy showed active alveolar bleeding. Ultra sound showed normal kidneys. Kidney biopsy revealed pauci immune crescentic glomerulonephritis. A diagnosis of vasculitis was made and patient was treated by immunosuppression therapy with methyl prednisolone pulses 1 g/day for three days followed by oral steroids 1 mg/kg/day for 1 month with slowly tapering and a monthly pulse of cyclophosphamide 1 g/1.73 m² body surface for 6 months. After a follow up of 6 months, the renal function was normal and alveoli hemorrhage disappeared.

Discussion

Systemic manifestations, such as vasculitis as a consequence of antithyroid drugs have been described with propylthiouracil, methimazole and carbimazole [1-3]. Our literature review yielded few cases of vasculitis associated with Benzylthiouracil. The first case has been described in Tunisian patient [4].

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Received February 28, 2012; Accepted July 17, 2012; Published July 20, 2012

Citation: Kaaroud H, Boubaker K, Khiari K, ben Maiz H, Kheder A (2012) Pulmonary Hemorrhage and Renal Involvement in Benzylthiouracil-Induced Vasculitis. *Thyroid Disorders Ther* 1:114. doi:10.4172/2167-7948.1000114

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The frequency of Vasculitis depends on the molecule used. It's 75% with Propylthiouracil, 6% with Methimazole, 3% with Carbimazol and 2.7% with Benzylthiouracil [5].

The onset of manifestations ranges from weeks to months and up to severe years after the initiation of the treatment.

The average age of patients with this complication is 36 years (8-82 years) and they are adults in 81% of cases.

The high incidence of woman reported is explained by the frequency of thyroiditis in woman.

The rate of ANCA positivity is more important when the duration of the treatment is more prolonged and the dose is high.

The mechanism by which the treatment induces vasculitis is not clear. The main mechanism is thought to be in relation with the thiol radical of antithyroid treatment which is considered as an antigen. Therefore, neutrophils are sensitized and product anti-myeloperoxidase or MPO-ANCA. This results in a degranulation of neutrophils and release of oxygen free radicals [6].

Vasculitis is an immune complex mediated disease predominantly involving small vessels.

Its severity can range from being to life-threatening disease with multiple organ failure. Renal involvement is the most common manifestation observed in 61% of cases with a renal failure in 28%. Skin purpuric rash, arthralgie, fever is also frequent. However pulmonary hemorrhage is rare observed in 1,3% of cases but it's a serious life threatening complication and requires urgent treatment [7].

In our cases, we consider that vasculitis is a drug adverse event, since other possible causes especially autoimmune disease have been excluded after clinical and laboratory examination.

Treatment of vasculitis is based on the discontinuation of the triggering factor.

Non steroidal anti-inflammatory drugs can be used in mild cases, while corticosteroids and immunosuppressive agent are reserved for systemic manifestations [7,8]. Alternative therapies might include plasma exchange as well as azathioprine or mycophenolate mofetil.

Our patient's remission suggests that combination therapy with steroids and cyclophosphamide is effective in this condition.

Mortality is linked mainly to infections complications supported by immunosuppressive treatment. Relapse is possible with high rate ANCA positivity [9].

Conclusion

Vasculitis with pulmonary hemorrhage is rare but potentially serious, possible adverse effect of Benzylthiouracil. Clinical monitoring and screening of urinary abnormalities are necessary to establish an early treatment only guarantee of a favorable outcome.

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