Methimazole-Induced Diffuse Alveolar Hemorrhage: A Rare but Severe Adverse Drug Reaction and Clinical Case Analysis

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Abstract

Diffuse alveolar hemorrhage (DAH) is a rare & catastrophic complication of methimazole therapy. The author reports a 44-year old female with a history of hyperthyroidism & poor compliance to methimazole therapy, presented to the emergency department with complaints of massive hemoptysis & respiratory failure. Further investigation lead to the diagnosis of thyroid storm & she was started on methimazole, steroids & beta blockers. Despite appropriate treatment, the patient's condition worsened. Further workup revealed that the patient had DAH. After ruling out other etiologies, methimazole induced DAH was postulated & the patient was switched to propylthiouracil & steroids. Repeat bronchoscopy did not reveal any additional signs of DAH & the patient made a good recovery.

Introduction

Thyroid storm is an endocrinological emergency, which can be challenging to diagnose. The possibility of methimazole causing DAH in a thyroid storm patient is quite rare. Presence of drug-induced ANCA-vasculitis in patients on anti-thyroid therapy was first presented in 1993 by Doleman et all. (1). Albeit rare, methimazole induced DAH in the setting of thyroid storm is presumed to occur due to anti-neutrophilic cytoplasmic antibody (ANCA) associated vasculitis. This complication is more frequently seen in propylthiouracil therapy with 15-37% patients developing complications, while only 0-3% patients develop the complication on methimazole therapy. (2)(3). Our patient presented with a rare case of ANCA-negative DAH due to treatment with methimazole for thyroid storm.

Case presentation

1. Presenting illness

A 44-year old presented complaining of vomiting & massive hemoptysis. She had a history of hyperthyroidism & poor compliance with methimazole therapy at home. She did not show any signs of preceding illness, respiratory infections, dyspnea, fever or trauma. She was not taking any anticoagulants or antiplatelet therapy.

2. Investigations

On admission, the patient was intubated for respiratory failure. Blood analysis revealed hemoglobin of 7.7, RBC level of 3.17, lactic acid of 3.5, T3 of 18.8, free T4 of 8 & undetectable TSH, elevated CRP of 103 & normal ESR levels. Her urine drug screen was positive for cannabinoids & benzodiazepines. Her chest x-ray revealed bilateral infiltrates & CT scan demonstrated diffuse ground glass opacities. Pulmonary embolism was ruled out however an abnormally large multinodular thyroid gland was noticed.

An emergency bronchoscopy was performed which revealed a significant amount of diffuse bleeding without clearing on sequential aliquots. Bronchoalveolar lavage analysis also revealed hemosiderin-laden macrophages confirming the diagnosis of diffuse alveolar hemorrhage.

3. Differential diagnosis

The common known etiologies of DAH includes immunologic diseases, infections & certain drug toxicities. Our patient presented with severe lymphopenia of 3300 & although the initial screening test for HIV was positive, the confirmatory Western blot test ruled it out. Serological markers for vasculitic diseases were essentially unremarkable. Initial blood cultures & other infectious disease work-up including respiratory viral panel & Pneumocystis jiroveci were also negative. Her echocardiogram was also not significant for any valvular lesions, structural or functional abnormalities. Coagulation studies were within normal limits as well. Urine drug screen was positive only for cannabinoids & no other drugs.

4. Treatment

Meanwhile, the patient was started on pulse dose of methylprednisolone for management of DAH while awaiting serological results. Propranolol & methimazole were also given for management of thyroid storm. Her condition gradually improved & she was eventually extubated. However, within 24 hours of that, she was re-intubated for acute respiratory failure. Follow-up chest x-ray revealed worsening bilateral infiltrates raising the suspicion of recurrent DAH & methimazole was thought to be responsible for the same after ruling out all other potential known causes to the best of our ability. Methimazole was then switched to propylthiouracil with dramatic improvement within a few days. Repeat bronchoscopy did not reveal any more signs of DAH prior to extubation. Steroids were then tapered down & free T3 levels improved significantly.

Results and discussion

Results

Switching to propylthiouracil from methimazole resulted in significant improvement of symptoms & the patient eventually had a good outcome. Later during the hospital course, patient was found to have bacteremia with blood cultures positive for Fusobacterium species. She was empirically started on broad spectrum antibiotics & later switched to amoxicillin-clavulanate on discharge. Repeat CT of chest revealed resolution of the pulmonary infiltrates & no sign of septic emboli.

Discussion

Methimazole is a common therapy used for the treatment of hyperthyroidism. DAH presents with a cluster of symptoms including hemoptysis, anemia, respiratory failure & diffuse pulmonary infiltrates. To the best of our knowledge, there have been only a few reported cases of ANCA-negative vasculitis due to methimazole therapy. (4) (5). Another rare complication of ANCA-negative nephritis from methimazole therapy has also been reported in the literature. (6). The pathogenesis of such vasculitis is unknown & requires further studies. It is postulated to be caused by the destruction of pulmonary microcirculation, a condition also known as pulmonary capillaritis. (4). The diagnosis of ANCA-negative vasculitis due to anti-thyroid drug is made by clinical evidence of vasculitis after starting an offending drug & excluding other causes of vasculitis. (7). Due to a limited number of reported cases, a definitive treatment for such life-threatening complications is not clear & empiric treatment with high dose steroids in addition to withholding the offending medication seems to be effective with a good prognosis.

Conclusion

1. DAH is not a known complication of methimazole therapy but it can be life-threatening & should be considered when other known causes have been ruled out.
2. Majority of reported cases presented with ANCA positivity however, our patient was unique as her serological workup was essentially unremarkable.
3. The concomitant presentation of DAH with thyroid storm, is in itself a rare presentation & requires treatment of both entities at the same time.
4. Definitive treatment for such a rare scenario is not known however, the offending medication should be withheld & high dose steroids should be initiated.

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