Immunological studies in a case of Hydrochlorothiazide-induced pulmonary edema

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Summary. A case of acute onset non-cardiogenic pulmonary edema induced by hydrochlorothiazide (HCT) is presented. Rapid recovery was obtained with supportive therapy. Leukopenia was evident during the acute phase, with rapid recovery parallel to the clinical improvement, suggesting pulmonary sequestration of granulocytes. Immunological studies including lymphocyte stimulation test with HCT and measurement of specific IgG and IgE to HCT elicited negative results. The pathogenesis of this type of reaction remains to be elucidated.

Key words: Hydrochlorothiazide (HCT), pulmonary edema, adverse drug reaction, idiosyncratic reaction.

Introduction

The use of HCT for treating hypertension is widespread. A case of acute onset non-cardiogenic pulmonary edema induced by hydrochlorothiazide (HCT) is presented. Rapid recovery was obtained with supportive therapy. Leukopenia was evident during the acute phase, with rapid recovery parallel to the clinical improvement, suggesting pulmonary sequestration of granulocytes. Immunological studies including lymphocyte stimulation test with HCT and measurement of specific IgG and IgE to HCT elicited negative results. The pathogenesis of this type of reaction remains to be elucidated.

Case report

We report the case of a 49 year-old female patient, with no significant medical history, who worked as a hospital nurse. She decided on her own to take one pill of Ameride® (5 mg of amiloride + 50 mg of Hct) for a mild ankle edema. She had taken the same product for identical purpose, one year ago, without any adverse reaction.

Forty minutes after intaking Ameride, she felt dizziness, epigastric pain, chills, nausea, and intense dyspnea. At the emergency room, her skin was cold and clammy, with peripheral cyanosis. No neck vein distention could be appreciated. Chest auscultation revealed bilateral rales, without wheezing. Heart sounds were normal. Her blood pressure was 105/50 mm Hg, her heart rate 44 beats/min and regular, 37.5°C axillary temp, SaO 58% when breathing room air.

Initial chest X-ray showed bilateral intersticial infiltrates without cardiomegaly. EKG revealed sinus bradycardia. Blood gases showed pH 7.25 with metabolic acidosis. White blood cell (WBC) count was 1000/ mm^3 (31.8% segmental, 64% lymphocytes, monocites 2.6% and eosinophils 1%); normal red blood cell count, blood chemistries were normal, including cardiac enzymes. Once at the Intensive Care Unit, blood tests were repeated, which showed WBC count of 500/ mm^3, confirmed by a peripheral blood smear.

Improvement was evident under supportive treatment (oxygen therapy, furosemide 10 mg/12h and methylprednisolone 10 mg/8h IV, and dopamine) within 24 hrs, WBC count reaching 3780/ mm^3. Central venous pressure (measured by femoral catheter) was always normal. Echocardiogram was normal.

The patient was discharged with a slight right pleural effusion that disappeared in four days.

One month after the reaction a lymphocyte

proliferation test was carried out in peripheral blood from the patient and two healthy control subjects, with increasing dosis of HCT and phytohemagglutinin (PHA). Proliferation was evaluated after a five-day culture by quantifying the incorporation of tritiated thymidine into newly synthesized DNA. No significant lymphocyte stimulation was found with HCT. Additionally, an enzyme-linked immunosorbent assay (ELISA) using HCT conjugated to human serum albumin as solid phase was performed to detect specific IgG and IgE. Results were negative again.

Discussion

Since the first case report by Steinberg in 1968, more than 50 cases of acute non-cardiogenic pulmonary edema caused by HCT have been reported [1]. Patients are mainly women, aged 45-60, and the reaction developed either upon taking HCT for the first time, or after having taken it previously without any reaction. Most of the cases have an acute onset of symptoms and rapid improvement with supportive treatment, although death and need of mechanical ventilation have been described. In most cases, they have a positive challenge test with HCT and they tolerate furosemide [1].

Informations obtained by clinical examination, radiological and laboratory tests are typical of acute non-cardiogenic pulmonary edema. Some cases reveal transient leukopenia [2] and/or thrombopenia, possibly by pulmonary sequestration of neutrophils. Blood eosinophils and total IgE are within normal values.

In all the cases reported, immunological studies have been rarely performed. Two studies reported contradictory results related to lymphocyte stimulation by HCT [3,4]. One study reported a positive patch test with HCT in one single patient, one hour reading, but without control patients [5]. Another study showed an increase of serum IgG, IgG1, and IgG4; and a decrease of IgM and C3 with normal phenotypic distribution of lymphocytes [6].

Conclusion

On the basis of the evidence available, pulmonary edema caused by HCT seems to be due to an idiosyncratic reaction rather than to a specific immune response to the drug. Leukopenia during the acute phase is consistent with the hypothesis of intrapulmonary sequestration of granulocytes causing pulmonary edema.

Because HCT-induced pulmonary edema may be underestimated or underreported, it should be considered in the differential diagnosis in any case of pulmonary edema. Although it is an uncommon reaction, it may be potentially life threatening.

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