Hyperglycemic hyperosmolar state: A rare adverse effect of prednisolone and cyclophosphamide therapy in Wegener’s Granulomatosis

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Abstract

We describe a clinical case of a 43 year-old-man with a history of recent hospital admittance for community-acquired pneumonia with pleural effusion and irregular nodules in the Computed Tomography (CT) scan, visiting the Emergency Service once again due to persistent arthralgias. In the analytical study, renal insufficiency was identified once again, for which reason the patient was admitted. Following the study of renal failure, pauci-immune necrotizing nephropathy was revealed, with positive anti-proteinase 3 ANCA (PR3-ANCAs), and a diagnosis of Wegener’s Granulomatosis was established. Patient began treatment with prednisolone and cyclophosphamide (CFA), and was discharged from hospital with clinical improvement. Ten days after being discharged, he was readmitted to hospital in a hyperglycemic hyperosmolar state. Even with a reduction in steroid and CFA doses, long term therapy with insulin was required to achieve glycemic control.

The appearance of diabetes mellitus in the form of a hyperglycemic, hyperosmolar state in a previously normoglycemic patient and within a few days of starting steroid therapy, is rare. We believe that the CFA played an important role in this patient, who had a propensity to autoimmunity phenomena. Similar to what happens in rats, and has also been shown also in humans, the CFA may have selected an auto-reactive T-cell clone that promoted the auto-immune destruction of the β-pancreatic cells.

Key words: Wegener’s Granulomatosis, Diabetes mellitus, hyperglycemic, hyperosmolar state, corticosteroids, cyclophosphamide, vasculitis.

Case report

A 43 year-old White male, born and residing in Rio...
Tinto, employed in the civil construction industry, smoker (45 units/pack.year for the last 30 years), with no other relevant pathological history, asymptomatic until the middle of February 2006, when he gradually began to experience polyarthralgias of slight to moderate intensity, in the elbows, shoulders, knees, ankles and lumbar column. The symptoms were persistent, with symmetrical distribution, and without migration or morning stiffness. The symptoms improved slightly with rest. About 5-6 days after the onset of symptoms, a cough appeared, with yellow exudate expectoration, sometimes hemoptysis, with purulent rhinorrhea, migraine, asthenia, anorexia and weight loss. Patient denied fever, dyspnea, thoracic pain, or genitourinary or gastrointestinal complains.

On 17 March 2006, due to persistence of symptoms for more than 15 days, patient visited the Emergency Service of the Hospital de São João (HSJ). Based on the analysis, he did not present significant alterations, except for increased C - reactive protein (CRP) (50 mg/L). Chest x-ray (Fig. 1, left side) showed, besides bilateral hilar reinforcement, right pleural effusion of medium volume. A diagnostic thoracentesis was carried out and it was decided to admit the patient to the Pneumology Service for better clarification of his condition.

Study of the pleural liquid revealed that it was an exudate, and due to suspicion of pneumonia with parapneumonic effusion, treatment with imipenem and ibuprofen was initiated. The bacilloscopy, cultures and CRP for Mycobacterium tuberculosis were negative, as was the serology for HIV, hepatitis B and C. Computed tomography (CT) of the chest was carried out, revealing, besides a small consolidation in the middle lobe, which could later turn into pneumonia, and pleural effusion, various infracentimetric pulmonary nodules in the upper lobe of the same lung, and a nodule in the same position, but more anterior and central, measuring about 19 mm, not well-defined and with irregular outline (Fig. 1, right side). To clarify this nodule, a bronchofibroscopy was carried out, which did not show any suspicious alteration other than a few inflammatory alterations to the bronchial mucosa. Cytology of the bronchial lavage was negative for malignant cells, and in the culture, one Staphylococcus aureus strain was isolated. Despite improvement with the treatment, the complaints of migraines and asthenia continued.

The patient was discharged on the 11th day after admittance, with a diagnosis of pneumonia with parapneumonic pleural effusion. He was referred to an external Pneumology clinic and medicated with ibuprophen 400 mg three times a day.

A few days after discharge, polyarthralgias of increasing intensity reappeared, which were temporarily alleviated with ibuprofen. Associated with this condition, besides the systemic symptoms, pain, redness, photophobia and reduction of visual acuity in the right eye were also present. At that time, patient denied respiratory, urinary, gastrointestinal symptoms, hearing alterations or odynophagia.

On 16 May 06, patient returned to the Emergency Service of the HSJ. Chest X-ray revealed right plural effusion was still present, but smaller than in the previous x-ray. Hemogram showed microcytic normochromic anemia (Hemoglobin [Hb] of 10.8 g/dL; average globular volume [AGV] of 81.7 fl), without leukocytosis and platelets of 324 X 10^9/L. The parameters of renal function, which were within normal values on the date of discharge from the Pneumology Service (40 days previously), were altered, with urea of 0.84 g/L and Creatinine of 23.4 mg/L, and glomerular filtration rate (GFR) estimated by the Cockcroft-Gault formula of about 33.4 mL/min/m^2. In the analysis, patient continued to present hyperalbuminemia (albumin of 32 g/L). Urinary sediment
showed proteinuria and hematuria (not quantified). It was decided to admit the patient to the Internal Medicine Service for study of renal function.

Of personal history, besides the smoking habit, which was abandoned since admission to Pneumology, consumption of equivalent to 50 g/d of alcohol is also reported. Patient denied any previous significant surgical or medical pathology. Of the family history, it is noted that his mother, at that time aged 71, had history of non-insulin dependent diabetes mellitus, but he was unaware of any family history of immunological disease or any other type of disease.

In the physical examination, the patient was conscious, collaborative and oriented. The body mass index (BMI) was 20 (weight: 58 Kg; height: 1.69 m). He presented a slightly increased blood pressure (148/94 mmHg) and reduction in lung sounds in the right lung base. He had no alteration in the cardiac auscultation or in the abdominal exam. The neurological exam was also normal. He had no palpable adenomegalies or fever. He had pain on movement, whether passive or active, in practically all the joints, though none of the joints showed signs of inflammation. Patient still presented sclerosis of the right eye, with signs of inflammation, pain on touch and a reduction of visual acuity in the same eye. Observation by an ophthalmologist was requested, resulting in a diagnosis of anterior uveitis of right eye.

The 24h urine study (1L volume) confirmed acute/rapidly progressive renal insufficiency with creatinine clearance of 30 ml/min/m² and subnephrotic proteinuria of 2.39 g/L. Renal vesicular echography did not show any alterations. Anemia study revealed anemia of chronic disease. Before starting specific treatment, progressive worsening of renal function and increase of CRP were observed. Patient showed no alterations in lipid profile in the supplementary exam either. Immunelectrophoresis showed an increase in immunoglobulin G (1880 mg/dL) and immunoglobulin A (331 mg/dL). Renal biopsy revealed increasing pauci-immune necrotizing nephropathy, with sclerosis of some glomerulus, but without noticeable granulomas. Antibody study was positive for ANCA anti-proteinase 3 (PR3-ANCAs: 86 U/mL) and negative for all other antibodies, including MPO (myeloperoxidase)-ANCAs. A diagnosis of Wegener's Granulomatosis was established and specific treatment with corticoids [methylprednisolone 500 mg ev for 3 days was initiated, followed by oral prednisolone 60 mg/d (1.03 mg/Kg/d)] and CFA 100 mg/d (1.7 mg/Kg/d), as well as prophylactic therapy with cotrimazole, calcium and vitamin D supplements and lisinopril 10 mg/d.

Patient was discharged on the 11th day after admission, 6th day of treatment, with an estimated GFT of 41 ml/min/m², maintaining slight anemia (Hb of 11.9 g/dL). CRP was, at that time, 1.7mg/L (N:<3 mg/L). Throughout the period of hospitalization, fasting glycemic fast remained below 100 mg/dL.

On 07 June 06, approximately 11 days after discharge, the patient was seen by the Internal Medicine external clinic, with complaints of polyuria, polydipsia, marked asthenia and severe myalgias of the lower limbs. He was very dehydrated with high blood pressure (158/94 mmHg) in the physical examination. Analytical study showed marked hyperglycemia (serum glucose of 1044 mg/dL) with osmolarity of 348 mOsms, worsening of renal function (estimated GFT of 31 mL/min/m²) and anemia (Hb of 9.0 g/dL), as well as a rise in the markers of muscular lesion with myoglobin of 478 ng/mL. RCP was maintained within the normal values and did not present ketoacidosis.

Patient was hospitalized on that same day, diagnosed with hyperosmolar, hyperglycemic state. Glycated hemoglobin, requested during this hospitalization, was 12.5%. Treatment with insulin and fluid therapy were initiated, and it was decided to reduce the dose of prednisolone to 30 mg/d (0.5 mg/Kg/d) and of CFA
to 50 mg/d (0.9 mg/Kg/d). The lisipronil dose was also increased to 20 mg/d.

Good clinical evolution was observed during hospitalization with the therapeutic measures taken, and on discharge, 10 days after admission, the patient was clinically asymptomatic and analytically improved, with estimated GFT of about 43 mL/min/m² and Hb de 10.3 g/dL. However, glycemic control required about 40 U/day of insulin.

Patient was kept under strict observation by the Internal Medicine external clinic, and approximately 9 months after diagnosis of WG, he was asymptomatic, with an estimated GFT of about 68 mL/min/m², no anemia, negative PR3-ANCAs, and with CRP always within the normal values (Table II). The patient is currently being treated with prednisolone 10 mg/d, CFA has been now replaced by azathioprine [50 mg/d (0.8 mg/Kg/d)], and the rest of above-mentioned treatment has been maintained. In terms of diabetes control, a need for 40 U daily of insulin to achieve good glycemic control was observed (Table II), with no reduction in this requirement, despite the marked reduction in prednisolone dose.

**Discussion**

Up until the end of the 20th Century, diagnosis of WG was essentially clinical. Before the availability of laboratorial exams for neutrophil anticytoplasm antibodies (ANCA), the criteria proposed by the American College of Rheumatology had some diagnostic importance. With the emergence of laboratory determination of ANCAs, particularly PR3-ANCA, diagnosis of the disease became more accurate, as when the clinical development is suggestive, and in the active phase of the disease, the sensitivity (>90%) and specificity (>95%) of these tests in the diagnosis of WG are high.1, 2, 15-20

In the case presented here, the initial respiratory complaints, the most common form of presentation of WG,1, 2, 18, 21 were interpreted as pneumonia, isolating a strain of Staphylococcus aureus which, curiously, is the most commonly identified agent in cultures of patients with respiratory infections secondary to WG.8 A diagnosis of auto-immune disease, specifically WG, was considered in the second hospitalization, due to the persistence of polyarthralgias, a recent history of respiratory manifestations, uveitis, and repeated alterations in renal function parameters. The diagnosis of WG was confirmed by the positivity of PR3-ANCAs and compatible renal biopsy, although there was no histological identification of granulomas, which is not essential for diagnosis, besides which the presence of granulomas in renal biopsy is rare (<3%).1, 18, 22

This case report also highlights the importance of strict observation during follow-up visits, of patients with this type of pathology, observing the potential side effects of drugs used for its treatment.

Finally, due to the rare nature of the event, the onset, within just a few days, of a hyperglycemic, hyperosmolar state in a patient who was previously normoglycemic, is of extreme relevance in the case reported here.

The effects of corticoids on the glycemic metabolism are well known, promoting a variety of actions (increased substrate for hepatic gluconeogenesis,
inhibition of glucose uptake and use by the peripheral tissues, increased resistance to insulin) which lead to hyperglycemia.23,24 This frequently leads to difficulty achieving glycemic control in patients with diagnosed diabetes, and sometimes, repeat hyperglycemia or in rarer cases, a non-ketonic hyperosmolar state in patients with glucose intolerance or subclinical diabetes.10,11,23,24 By contrast, the development of repeat diabetes in a patient with normal glucose tolerance is uncommon, and when it occurs, generally it is easily controlled with oral antidiabetic drugs, improves with the reduction of dose, and can be totally reverted after suspending corticoid treatment.10,11 In the majority of studies that use similar doses of corticoids in the treatment of auto-immune pathologies, repeat development of diabetes was lower than 10%,1,5-8 and acute presentation in the form of a hyperglycemic, hyperosmolar state is rare.25-28

CFA, on the other hand, does not appear to have direct toxic effects on the pancreatic cells, or to directly alter the glycidic metabolism.25,26 However, the effect of CFA on accelerating the appearance of autoimmune diabetes in NOD (non obese diabetic – animal model for type 1 diabetes) rats, apparently by a process of a reduction in suppressor T-cells and selection of auto-reactive T-cells is also well-known, and is widely used in the laboratory.9,25-28

Although the emergence of diabetes in patients submitted to therapeutic regimes which include both drugs is almost always associated with corticoids, and not CFA, Gepner et al demonstrate that CFA can also induce auto-immune diabetes in humans.9

In this specific case, although we cannot exclude the importance of corticoids in the emergence of diabetes, we believe that CFA plays an essential role for several reasons. First, due to the emergence of a hyperglycemic, hyperosmolar state with extremely high serum glucose values in a previously normoglycemic patient. Second, due to the constant need for insulin, despite the progressive reduction of corticoids, suggesting pancreatic-β cell failure. The CFA may have selected, in this patient with propensity to auto-immune phenomena, an auto-reactive T-cell clone, which could have promoted the destruction of the pancreatic β cells, similar to what happens in rats25-28 and has been already observed in humans.9 For this reason, we decided to reduce, in the second acute phase of diabetes, not only the corticoid dose but also the CFA dose.

Finally, the case presented here is one in which the form presentation of diabetes mellitus was a non-ketonic hyperosmolar state in which CFA may have had a decisive role.

References

<table>
<thead>
<tr>
<th>Table II</th>
<th>Analytical evolution from discharge after first admittance in Medicine to second admittance (hyperglycemia observed once again) and subsequent follow-up in the external clinic.</th>
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<tr>
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<td>Hb (g/dL)</td>
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<td>VCM (fl)</td>
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<td>Creatinine (mg/L)</td>
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