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IS IT CORONA VIRUS?

EDITORIAL

IS IT CORONA VÍRUS? NO, IT IS NOT FOR US LIVING IN CHAOS, A WORLD OF FANTASY, A MOMENT OF PEACE, MEMORIES OF CHILDHOOD...

Amanita muscaria, is a fungus basidiomycete with psychoactive and hallucinogenic properties. It is known as *agaric-of-flies fly*. This mushroom is native in coniferous and deciduous forests in the northern hemisphere from regions with cold climate.

Amanita muscaria, a red mushroom with white dots, appears in *Alice in Wonderland* book and picture, from Lewis Caroll. In the movie, Alice is talking with caterpillar that is lying on *Amanita muscaria*, smoking a hookah in a hallucinogenic trance.

Since 1256 this mushroom is cited as insecticide against flies when diluted in milk.

The poisining by *Amanita muscaria* is most often accidental ingestion by children and domestic animals,. *Amanita muscaria* contains chemical compounds with psychoactive properties. The toxic dose in adults is approximately 6 mg of muscimol or 30 to 60 mg of ibotenic acid found in only a single fruiting from the mushroom body. There is a different toxin during the seasons being ten times more poisonous in spring and summer than in autumn. The psychoactive and hallucinogenic properties are due to the presence of two active componentes: ibotenic acid and muscimol. The effects of this fungus begin after fifteen minutes of its ingestion, with symptoms of vertigo, mental confusion, nausea, mouth dryness and restless sleep.

Fifteen mushrooms correspond to a fatal dose, but since the 20th century there are not fatal poisoning after eating these mushrooms.

The active components are soluble in water, and they could be detoxified when boiled but when the mushroom is dried its potency are increased. There is not an antidote or specific treatment. Gastric lavage can be used up to 1 hour after ingesting the mushroom and sometimes the use of activated charcoal is indicated. Atropine or physostigmine as an antidote is not recommended. If a patient is agitated, with seizure, diazepam or lorazepam, can be used, with small doses because they can aggravate the respiratory depressant effects of muscimol. The patient is treated with venous hydration or electrolyte replacement when recurrent vomits are present. Severe and rare cases require intubation, artificial ventilation and hemodialysis to remove the toxins. Currently the prognosis is generally good.

The red mushroom with white spots is a common image in many aspects of popular culture and in our lives. It is present in books, in movies like *Fantasia* from Disney in the forties and in cartoons as Smurfs it is shown as elfs houses. *Amanita muscaria* has been present in fairy paintings themes during the renaissence. Nowadays it is also present in a video game of the Super Mario.

The memory of the popular story of Alice in Wonderland , published in 1865, with the caterpillar resting on top of the mushroom innocently enjoying its effects is unforgettable. In contrast with Coronavirus, although its resemblance with *Amanita muscaria*, humanity will not have good memories and is willing to move on to a promising and healthy year.

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Contents

Our Cover: *Amanita muscaria*
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CASE REPORT AND LITERATURE REVIEW
MYXEDEMA COMA: CASE REPORT AND LITERATURE REVIEW
COMA MIXEDEMATOSO: RELATO DE CASO E REVISÃO DA LITERATURA

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Keywords: Hypothyroidism, Coma, Myxedema.
Descritores: Hipotireoidismo, Coma, Mixedema.

Abstract

Myxedema coma is a rare endocrine emergency that settles in the chronic absence of adequate treatment for hypothyroidism. The clinical condition is severe and occurs as a result to loss of organic homeostasis, affecting all physiological systems. Through an observational study, we present a female patient, 60 years old, with a previous history of thyroidectomy, who was admitted to the University Hospital Evangelical Mackenzie, with signs and symptoms compatible with the presented condition. The homeostatic imbalance caused by comatose myxedema evolves with severe involvement of multiple organs, it is a condition with high mortality rates, therefore, it requires an agile and accurate diagnosis in order to enable a favorable outcome of the condition to the patient. **Endocrinol diabetes clin exp 2020 / 2178 - 2182.**

Resumo

O coma mixedematoso consiste em uma emergência endocrinológica rara e grave, que acomete pacientes em negligência crônica com o tratamento para hipotireoidismo. A escassez constante de hormônios tireoidianos afeta a homeostase do organismo e o quadro clínico de mixedema comatoso pode ser caracterizado por hipotermia, hipercapnia, redução do débito cardíaco e redução do nível de consciência. Através de um estudo observacional, apresentamos uma paciente feminina, de 60 anos, com história prévia de tireoidectomia, que foi internada no Hospital Universitário Evangélico Mackenzie do Paraná, com sinais e sintomas compatíveis com a afecção apresentada. A desequilíbrio homeostático causado pelo mixedema comatoso evolui com acometimento severo a múltiplos órgãos, é um quadro, com elevadas taxas de mortalidade, por isso, requer diagnóstico ágil e preciso, a fim de possibilitar um desfecho favorável do quadro ao paciente. **Endocrinol diabetes clin exp 2020 / 2178 - 2182.**

INTRODUCTION

Myxedematous coma is a rare endocrine emergency that settles in the absence of appropriate treatment for hypothyroidism for a long period. In this situation, the severe and chronic reduction of serum thyroid hormones culminate in the insufficiency of compensatory mechanisms that maintain physiological homeostasis of the organism, potentially affecting all body systems. This balance is even frailer in the presence of stress factors such as cold exposure, infection, trauma and drugs, reason why the myxedema occurs especially in these situations. The clinical condition is severe, commonly associated with hypoxemia, hypercapnia, hypothermia, reduced cardiac output and altered mental status, simulating a situation of coma, as suggested by the name of the condition (myxedematous coma). Therefore, early diagnosis and immediate treatment of the case, are the main to enable a favorable evolution.

METHOD

This is a case report of a patient admitted for Coma Myxedematous to enable knowledge of the medical and academic community about the case, which is a rare entity. This is an observational study, single-arm, transversal and descriptive approach accomplished in Curitiba (PR). The studied population consists of a single patient who was admitted to University Hospital Evangelical Mackenzie. The data reported were obtained through the medical records analysis. Approved by the Ethic Committee of Universitary Hospital Evangelico Mackenzie

CASE REPORT

Patient LM, 60, female, found at home by family members, with drawdown of consciousness, hypothermic and hyporesponsive. An emergency medical care service (SAMU) was activated, which performed the first patient care, who required orotracheal intubation (OTI) and stabilization, and then referred to the emergency care unit.

Patient has a previous history of total thyroidectomy, with an unclear etiology, in use of levothyroxine 25 mcg every two days. No other known comorbidities, use of chronic medications, allergies and other surgeries.

On the same day, the patient was referred from primary care service to the University Hospital Evangelico Mackenzie. On admission, patient was on invasive ventilation, intubated, hemodynamically unstable with vasoactive drugs (VAD), bradycardia, hypothermia, sedated with midazolam 10 mL/hr and fentanyl 10 mL/hr, RASS scale – 2 (Richmond Agitation Sedation Score), isofotoreagents and miotic pupils. Blood pressure (BP) 115x80mmHg with noradrenaline 10 mL/hr, heart rate (HR) 52 bpm and oxygen saturation (SpO2) 94% on mechanical ventilation (MV). Lung auscultation with bilateral vesicular murmur and diffuse snoring, reduced in both lung bases. Auscultation heart sounds with hypophonesis in two stages. The abdomen was distended with air-fluid noises present. Generalized myxedema. Scar on anterior cervical region, without signs of inflammation.

Due to high suspicion of myxedematous coma, was adminis-

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tered attack dose of levothyroxine (500mcg/day) via nasogastric probe in the first three days with hydrocortisone 100mg every 8 hours. The levothyroxine dose was maintained at 250mcg/day by nasogastric probe, and hydrocortisone 50 mg intravenous every 8 hours.

General laboratory tests were requested, in which showed little high amylase(160UI/L) and lipase (250UI/L), TSH 26 (0.3 and 4,0mU/L) and free T4 <0.017 (0.9 to 1.8 ng / dl)

A chest tomography (Figure 1 and 2) was performed, which presented massive pericardial and pleural effusion, as well as parenchymal opacities in the outstanding portions and septal thickening inferring pulmonary edema. The chest X-ray (Figure 3) shows a significant increase cardiothoracic ratio caused by pericardial effusion. Finally, on abdominal computerized tomography (Figure 4) is noted ascites, more evident in the upper abdominal (peri-hepatic) and liquid infiltration of intra and extraperitoneal fat by generalized anasarca. Thoracostomy was performed with closed drain with an outflow of citrus content (1200 mL), uneventful.

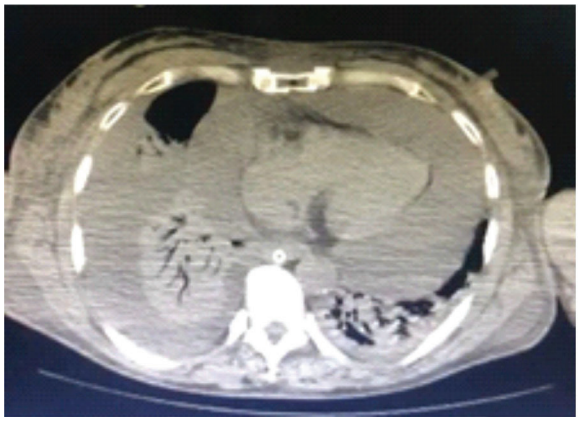
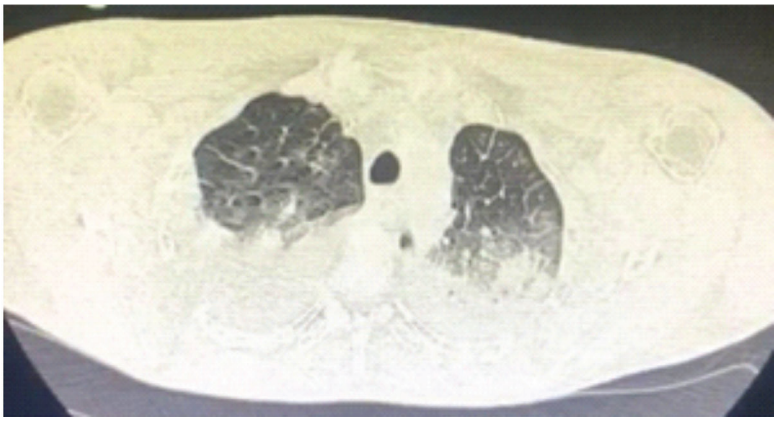


Figure 1



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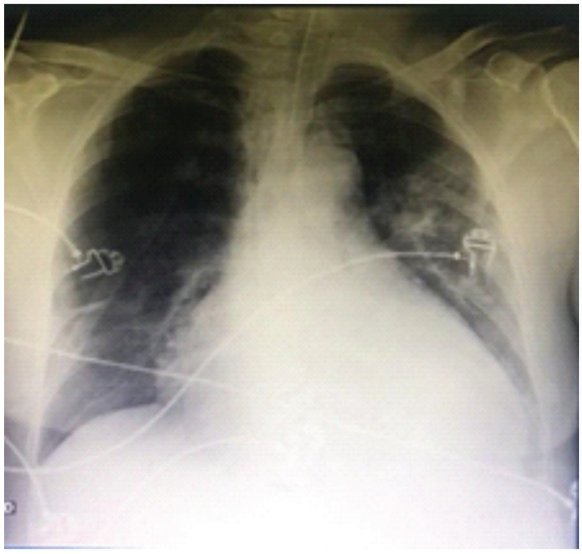

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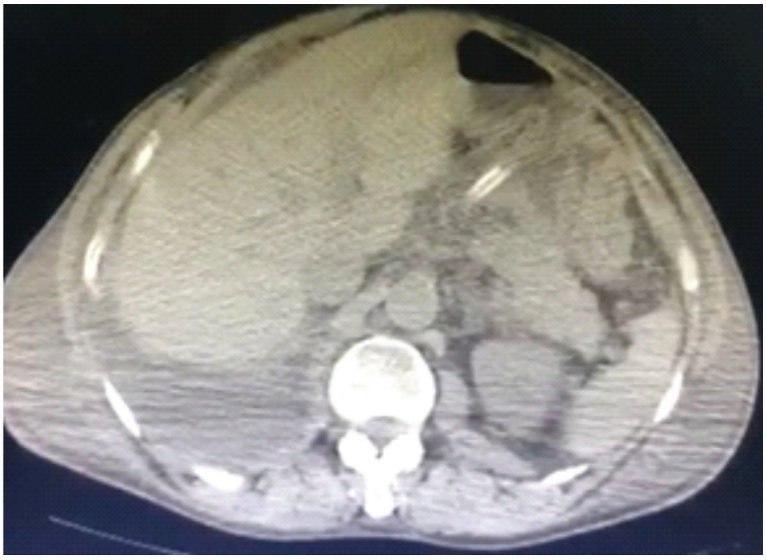

Figure 4

During stay in the emergency room, the patient evolved with cardiorespiratory arrest (CPR), probably due to restrictive shock owing to cardiac tamponade for approximately 7 minutes, with spontaneous circulation returning after emergency pericardiocentesis with removal of 300 mL of serous fluid.

Forwarded to the ICU with OTI/MV, widespread myxedema, mainly in the face, hemodynamically unstable using norepinephrine 24mL/hr, BP 75/59 mmHg, HR 78 bpm, sedation with midazolam 15 mL/hr and fentanyl 15mL/hr, RASS - 5, isophotoreagents and miotic pupils.

On the fourth day was initiated administration of T3 10 mcg, every 12 hours and remained until the eleventh day of hospitalization when the drug was discontinued.

During ICU stay, chest drain on the right continued to have debt, but with progressively reducing volume. A new pericardiocentesis was necessary with removal of 500 ml of sero-hematic liquid.

Patient evolved with hyponatremia (115-125 mmol/L), hypocalcemia (6,9-8,1mg/dL), hypomagnesemia (1.3mg/dL) and hypokalemia (2.7mmol/L), administration triiodothyronine (T3) 10 mcg, calcium gluconate, 10 ampoules with saline 1000 ml in 24 hours until calcium stabilization, calcium carbonate 500 mg, 1 tablet every 8 hours, and 0.25 mcg calcitriol every 12 hours and vitamin D 50.000 IU/week.

From the sixth day, the patient developed progressive awakening, hemodynamic stability, vasoactive drugs weaning and sedation in addition to reducing the dose of Hydrocortisone 25 mg every 8 hours and removal of pericardial catheter.

On the eleventh day of admission, patient was more lucid, obeying commands, and then fulfilled extubation in the morning.

On the twelfth day of hospitalization, the patient had significant improvement in the condition, without sedation and improved level of consciousness, Glasgow Coma Scale (GCS) 14, using norepinephrine use 3mL/hr and hydrocortisone 25mg 8 in 8 hours, with face myxedema reduction, and the presence of ecchymosis in the lower limbs.

However, on the fourteenth day, presented fluctuations in the level of consciousness (GCS 10), isophotomiotic pupils, decreased vesicular murmur globally, hypophonetic heart sounds, globose abdomen with decreased hydro noises, pain on palpation, and absent bowel movements.

On the fifteenth day of hospitalization, worsened level of consciousness (GCS 6), with no eye opening, did not obey commands, was not communicative, with limb movement only at painful stimulus. However, hemodynamically stable, saturating 97% in room air, without the use of vasoactive drugs. On examination, pulmonary auscultation had diminished breath sounds in left hemithorax, and hypophonic heart sounds, ascitic abdomen, decreased hydro-air sounds, pasty evacuation without pathological products.

Intubation was necessary due to the decrease in the level of consciousness - Glasgow Coma Scale (GSC) 3 (eye opening 1 + verbal response 1 + motor response 1), and then restarted with 3 mL / h of noradrenaline.

On imaging exams, computed tomography of the chest, demonstrated moderate bilateral pleural effusion, with compressive atelectasis of the underlying lung parenchyma, inflammatory bronchopathy with perfusion changes, in addition to moderate pericardial effusion.

On the seventeenth day of admission, there was a fever peak of 38°C and hypotension. Was decided to start a sepsis protocol – antibiotic therapy with meropenem and vancomycin, general laboratories collection, peripheral and central blood culture, in addition to replacement of the central venous catheter.

On the eighteenth day of admission, the patient was without sedation, with GSC 8 (eye opening to voice 3, movement of withdraws to pain 4, absent verbal response 1), hemodynamically stable with low dose of norepinephrine and afebrile. Complete weaning from hydrocortisone (300mg/day) and maintained other medications.

Remained stable until the twenty-first day of admission, when he presented progressive hypoxemia and hemodynamic instability. Thus, due to suspicion of pulmonary thromboembolism, in addition to the adjustment of vasoactive drugs, full dose enoxaparin was initiated.

Meantime, due to severe condition of refractory hypotension the measures instituted, the patient progresses to death in his twenty-second day of hospitalization.

DISCUSSION AND LITERATURE REVIEW

The thyroid gland has its operation regulated by thyroid stimulating hormone (TSH), which is synthesized and secreted by the anterior pituitary. Thyroid hormones (TH) provide negative feedback on the hypothalamic-pituitary-thyroid axis, which leads to reduction of TSH secretion when there is excess TH, or increases the secretion of TSH by decreasing the TH. Hypothyroidism is characterized by the deficiency of thyroid hormone with increased TSH. May manifest as a mild, moderate or severe condition (1).

The diagnosis is confirmed by the serum TSH analysis. When this is increased, free-T4 (FT4) should be requested, which may be decreased and it is a primary hypothyroidism, or FT4 at normal levels in a case of subclinical hypothyroidism (2).

The causes are diverse, the most common is the chronic autoimmune thyroiditis (Hashimoto's disease). The treatment of hyperthyroidism can also lead to hypothyroidism, either by radiation with 131-I or post-total thyroidectomy, requiring a larger dose of levothyroxine to replace TH in these situations, the recommended dose is 2 mcg/kg/day (2). We found that the patient in the present report, used a much lower than ideal dose of levothyroxine replacement, since she had undergone total thyroidectomy and the correct dose should be 130 mcg/day (weight 65kg patient).

Hypothyroidism is a disease with multiple nonspecific signs and symptoms, which in turn can make diagnosis difficult. Among them, bradycardia, slowed achilles reflex, thick and dry skin, lethargy, edema of the eyelids and face, cold skin, alopecia, hoarse voice, constipation and cold intolerance, among many others.

SYMPTOMS	
Bradycardia	Hypercapnia
Ankle jerk reflex slowed	Hypothermia
Swelling of face and eyelid	Altered level of consciousness
Hypoxemia	Reduction of Cardiac Output

Source: The author.

The treatment is carried out with levothyroxine, which must be taken orally and on an empty stomach. Tablets should not be placed near a heat source or previously removed from the packaging (2). The dose should be staggered, with a progressive increase until TSH standards if it is primary hypothyroidism, or FT4 standards if it is central hypothyroidism (1).

The myxedema coma is a severe form of uncompensated hypothyroidism, with a high risk of life for the patient, associated with a mortality rate between 20 to 50% (3). It is an extremely rare condition with an incidence of 0.22 per one million inhabitants. (4). Myxedema coma is a clinical emergence derived from a long-standing extreme condition of hypothyroidism, untreated or interrupted treatment (5). Despite the name, the patients are not actually in a coma, however, are in a severe physiological imbalance frame, with variable level consciousness.

This condition most commonly affects women (80% of cases) and is more prevalent in the elderly population and in winter (6). The reported case patient was female, 60 years old, and was found unconscious in winter, which is consistent with literature epidemiological data.

Possible triggering factors are exposure to cold, infection, electrolyte disorders, trauma, stroke, heart failure, gastrointestinal tract bleeding, burns and drugs (diuretics, sedatives, analgesics, amiodarone, lithium) (6,2). Furthermore, low adherence to drug treatment is an important precipitating factor for myxedema coma, as occurred with the patient's case report.

Mortality rates are high - approximately 29.5% of affected patients will died (7). The physiological balance of a hypothyroid patient is maintained at the expense of neurovascular adaptions, which include chronic peripheral vasoconstriction, diastolic hypertension and decreased blood volume, in an attempt to preserve normal body temperature (8). Decompensation in myxedematous coma occurs when these homeostatic mechanisms are suspended (6).

The pathophysiology of myxedematous coma is one of the consequences of low levels of intracellular T3, secondary to prolonged hypothyroidism, which leads to reduced metabolic rate and decreased oxygen consumption (3). Thus, there is a

severe involvement in several systems of the human organism, especially: respiratory, cardiovascular, neurological and renal (9). The involvement of the respiratory system is characterized by hypoxemia and hypercapnia due to respiratory drive depression, associated with dysfunction of the respiratory muscles, macroglossia, nasopharynx and larynx edema, as well as pleural effusion and pneumonia, with frequent use of mechanical ventilation in these situations (10).

The cardiovascular function and cardiac contractility are impaired, leading to reduced stroke volume, low cardiac output, bradycardia, hypotension, and peripheral vasoconstriction. In addition, the plasma volume decreases and increases capillary permeability, leading to fluid accumulation in tissues, spaces, pericardial effusions and widespread myxedema (11). In decompensated states, low cardiac output, and hypotension culminate in cardiogenic shock, which, if there is thyroid hormone replacement, may not be responsive to vasopressors (3). Due to the significant reduction in cerebral oxygenation, along with a reduction in the use of glucose there are frequent changes in the level of consciousness (11).

T3 has the important effect of stimulating the sodium pump through the enzyme Na +, K + - ATPase cell membrane (10). Therefore, a reduction in renal tubular sodium reabsorption is observed, leading to hyponatremia, also associated with an increase in serum antidiuretic hormone, decreased water excretion and serum hypoosmolality (12). In general, there is a reduction in renal blood flow and glomerular filtration (3).

Laboratory diagnosis of hypothyroidism is performed by measuring serum thyroid hormones (T3, FT4 and total T4) and TSH. In emergency, in conjunction with the clinical impression, the following tests are used to confirm the diagnosis of myxedematous coma: arterial blood gas analysis demonstrating respiratory acidosis hypoxia, high levels of CPK and LDH, hypoglicemia and decreased levels of sodium and potassium. Pancytopenia due to bone marrow hypoplasia and was hypothesized reported in patients with myxedema coma, but there appears to be uncommon (3, 10). The main mechanism would be by systemic hypoperfusion, leading to reduced perfusion of major organs of hemolymphopoietic system, such as the spleen, liver and kidney. (13). In some cases, leukocytosis is detected after thyroid hormone therapy. The evaluation of cortisol and ACTH (adrenocorticotropic hormone) is required to rule out the presence of primary or secondary adrenal insufficiency (14).

Patients with severe hypothyroidism may experience hemorrhagic manifestations, and investigations reveal prolonged bleeding and clotting time, decreased platelet adhesion, elevated TAP and abnormal factor VIII activity. The acquired von Willebrand disease can be found in a condition of hypothyroidism and possibly is type 1, in most cases, with a normal proportion of the von Willebrand factor antigen in relation to the ristocetin r cofactor. The underlying defect may be a decreased synthesis of von Willebrand factor in absence of suitable levels of thyroxine and thyroxine replacement of T4 corrects these abnormalities (15,16). Erfurth and colleagues demonstrated that desmopressin immediately reduced the bleeding time, increased platelet adhesion, significantly increased plasma concentrations of factor VIII and von Willebrand factor, so it may be appropriate for the treatment of bleeding, or else, in surgical situations in an episode of myxedema crisis or severe hypothyroidism (3).

The electrocardiogram (ECG) when requested demonstrates sinus bradycardia, low voltage complexes and abnormal T waves. Among the imaging exams, chest radiography stands out, presenting with pleural or pericardial effusion (17). In this case report, a similar picture is seen, since the patient had clinical condition, laboratory and image changes consistent with myxedematous coma changes: fluctuating level of consciousness, anasarca, TSH 26 and FT4 <0.017, hyponatremia, ranging 115-125 mmol/L and hypokalemia 2.7 mmol/L. It was visualized right pleural effusion and extensive pericardial effusion in chest computed tomography (CT) scans, and the patient submitted to thoracentesis and then to emergency pericardiocentesis, due to a cardiorespiratory arrest caused by a cardiac tamponade, in addition to MV dependence throughout hospitalization.

Faced with a clinical suspicion of myxedematous coma, treatment should be started immediately, even before laboratory results, due to severity of the condition. MV and hormone replacement with T4 should be prioritized, starting with bolus doses of T4 to quickly restore TSH levels and then maintenance doses should be administered. Given the rarity of the clinical condition, there is a shortage of scientific evidence on the best treatment to be instituted. Thus, there is no consensus referring monotherapy T4 is preferable to the combined form between T3 and T4 or *vice versa* (1).

The guidelines regarding of the initial dose is 300 to 500 ug intravenously (IV) and should not exceed 500 ug, due to the higher risk of mortality, particularly in the elderly. In Brazil, however, it is only available levothyroxine orally, which is the route of administration used in cases of myxedema coma. In this presentation the ideal dose is not known due to the absence of data in the literature, but high doses are recommended since there is less absorption of orally medication, as patients usually have intestinal loops myxedema(18), as a result of all metabolic status. Also, in this context, it is possible to invest in the use of T3 concurrently, as a way to enhance the treatment, if there is no response within 24 hours. After clinical improvement, the T3 is stopped and a daily dose of oral T4 replacement is maintained.

The pituitary-adrenal function is impaired in severe hypothyroidism. The restoration of the normal metabolic rate with exogenous thyroid hormones may precipitate adrenal insufficiency. Therefore, it is prudent to administer doses of glucocorticoids in stress (e.g., hydrocortisone 100 mg intravenously every 8 hours) (16).

Furthermore, volume replacement, monitoring body temperature, maintenance of warm environment, correcting possible hypoglycemia are indicated. (19).

The report patient was promptly treated with thyroid hormone therapy at high doses associated with T3 in the evolution, with a good response, and recovering the mental status, with weaning of VAD and MC.

Among the factors contributing to the poor prognosis of this patient, listed advanced age, hypotension and bradycardia at admission. Other factors are, the coma depth, degree of hypothermia, CO2 retention and delay in the onset of treatment (20). The main causes of death are related respiratory failure, cardiocirculatory failure and hemorrhagic stroke, secondary to loss mechanisms responsible for organic homeostasis (21).

The main factors associated with a worse prognosis for myxedematous coma are hypotension, bradycardia on admission with need for MV, hypothermia unresponsive to treatment measures, sepsis, intake of sedative drugs, lower GCS and high APACHE II (22), as well as high values of the score for the assessment of sequential organic insufficiency (SOFA) at admission, with an increase during the first 96 hours. The use of the SOFA index is reported to be more reliable than other models proposed. The SOFA index is calculated using a sum of scores that assess: PaO2 level, platelet count, bilirubins, level of consciousness (GCS), mean arterial pressure (MAP) and serum creatinine level. Studies still point to advanced age and cardiovascular diseases may be associated with higher mortality, in addition to the use of high doses of T3, with a better prognosis when using low doses of T3 and T4(3).

CONCLUSION

The present study presented the case of a female patient, 60 years old, hospitalized for myxedema coma. This condition is considered a rare endocrine emergency, tends to develop in face of chronic neglect in the treatment of hypothyroidism, as was the case of the patient in question.

In view of the severity of the clinical condition, through systemic changes due to malfunction of the thyroid gland, the pathology has a high rate of lethality even when early treatment is instituted. Among the factors that contribute to the poor prognosis are: advanced age, hypotension, bradycardia at admission, similar to the state in which the patient arrived at the University Hospital Evangelico Mackenzie.

However, despite the fact that myxedematous coma has an arduous prognosis, there are still gaps regarding the best medication management. It is emphasizes the need for studies for the development of scientific basis that standardizes the most appropriate pharmacological treatment to be instituted. Since there is no consensus on the best form of monotherapy - T4 or in combination with T3. Furthermore, there is a lack of data in the literature to corroborate the effective dose of levothyroxine orally in myxedematous coma in places where there is no IV medication, such as the situation of this clinical case.

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CASE REPORT AND LITERATURE REVIEW THIONAMIDES-INDUCED AGRANULOCYTOSIS IN A PATIENT WITH PREVIOUS HEMATOLOGICAL DISEASE

AGRANULOCITOSE INDUZIDA POR TIONAMIDAS EM PACIENTE COM DOENÇA HEMATOLÓGICA PRÉVIA

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Abstract

The treatment of thyroid diseases with thionamides can cause agranulocytosis a potentially fatal side effect. The manifestations resulting from such a condition include, in most cases, infections that, if not treated immediately, have a high risk of septicemia. We report the case of a patient who had Chronic Myeloid Leukemia without follow-up and treatment. She developed severe neutropenia induced by thionamide used to control hyperthyroidism. The absence of evidence of transformation into accelerated and blastic phases of Chronic Myeloid Leukemia, positive clinical response, resolution of neutropenia 8 days after the suspension of thionamides and the presence of a 5/1 Myeloid:Erythroid ratio in bone marrow biopsy, suggested previous destruction of neutrophils, with recovery after drug discontinuation. This clinical scenario evidenced the differential diagnosis between thionamide-induced agranulocytosis and blood disease recurrence. After resolution of the condition, which occurred 8 days after drug discontinuation, a definitive treatment for hyperthyroidism was considered with radioactive iodine or surgery. **Endocrinol diabetes clin exp 2020 / 2183 - 2186.**

Resumo

O tratamento de doenças tireoidianas com tionamidas pode provocar um efeito colateral potencialmente fatal, a agranulocitose. As manifestações decorrentes de tal condição incluem, na maioria dos casos, infecções que, se não abordadas de imediato, possuem elevado risco de evolução para septicemia. Relatamos o caso de uma paciente que apresentava Leucemia Mieloide Crônica sem acompanhamento e tratamento, que evoluiu com neutropenia grave induzida por tionamidas utilizada para controle do hipertireoidismo. A ausência de evidências de transformação para as fases acelerada e blástica da Leucemia Mielóide Crônica, resposta clínica positiva, resolução da neutropenia 8 dias após a suspensão das tionamidas e a presença da relação mielóide/eritróide de 5/1 em biópsia de medula óssea, sugeriu destruição prévia dos neutrófilos, com recuperação após a interrupção da droga e evidenciou o diagnóstico diferencial de agranulocitose induzida por tionamidas sobrejacente à doença hematológica de base. Após a resolução do quadro, que se deu em 8 dias após a suspensão da droga, foi considerado um tratamento definitivo para o hipertireoidismo, com iodo radioativo ou com cirurgia. **Endocrinol diabetes clin exp 2020 / 2183 - 2186.**

INTRODUCTION

Hyperthyroidism is a thyroid gland dysfunction characterized by hyperfunction and hypersecretion of hormones T3 and T4 in the body. The most common causes are Graves disease, toxic multinodular goiter and toxic thyroid adenoma. The main symptoms are fatigue, nervousness, heat intolerance, weight loss with hyperphagia, among others. It preferably affects elderly population, caucasians and residents in areas with iodine deficiency (1).

The diagnosis of hyperthyroidism is based on thyroid function tests: TSH supressed, higher Free T3 (FT3), T3, Free T4 (FT4) and TSHR antibody titres (TRab).

The treatment of Graves disease can be done with drugs as thionamides (metimazole or propiltiouracil), radioiodine therapy or surgical treatment (2) (3). Pharmacotherapy, for 18 to 24 months, is the main treatment for Graves disease. These drugs act interfering thyroperoxidase action, whose main function is to mediate the iodination of tyrosine residues in thyroglobulin and consequently, inhibits the thyroid hormone synthesis (4). Another effect in thyroid hormones of thionamides is the immunosuppressive state, resulting directly from the action of the drug or indirectly through the decrease in hormonal secretion (5).

Adverse events can occur within the first 90 days of treatment. Mild events occur in 1 to 5% of patients and include skin rash, itching, hives or arthralgia. If there is no spontaneous symptomatic remission, one thionamide can be replaced by another, although there is cross-reaction in 50% of cases (5). Serious side events occur in 1% of patients and include severe polyarthritis, agranulocytosis and toxic hepatites or cholangitis. The occurrence of a serious reaction is an indication of immediate suspension and contraindicates the reintroduction of thionamides (6).

Agranulocytosis or severe neutropenia is a potentially fatal hematological condition characterized by a circulating neutrophil count of less than 500 per mm3 of blood (7). When associated with the use of thionamides to treat Graves disease, this complication has a prevalence of 0.1 to 0.5% (8). Both direct toxicity and immune-mediated responses have been described as possible mechanisms of drug-induced agranulocytosis (9). The normalization of the neutrophils counting occurs approximately 8 days after antithyroid drug suspension (10).

In the literature, severe neutropenia (absolute neutrophil count < 0.5 x 10 9 /L) has been shown to be attributable to drugs in 70 to 90% of cases. Thus, the differential diagnosis of this acute and severe neutropenia in adults includes a certain number of conditions. In fact, the main differential diagnoses

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include myelodysplastic syndromes and acute leukemia (11).

Patients with agranulocytosis have a significant increase in the risk of bacterial infections and sepsis (7). Therefore, clinical presentation include fever of unknown origin and infections such as pneumonia, tonsillitis and abscesses. Most patients who do not receive immediate medical intervention progress to septicemia, a fact which shows the relevance of early diagnosis and adequate management. (12).

We report the case of a patient who had hematological disease without follow-up and treatment, that evolved with thionamide-induced agranulocytosis used to treat hyperthyroidism.

CASE REPORT

The report of this case was approved by the Ethic Committee of Universitary Hospital Evangelico Mackenzie.

A 38-year-old female patient was referred from the 24-hour Emergency Care Unit (UPA) in the city of Curitiba-PR to the Hospital Universitário Evangélico Mackenzie (HUEM) due to low back pain, 40 °C fever, odynophagia, weight loss of 10 kg in 30 days and jaundice. She was hospitalized for 6 days at the Basic Health Unity, where she received treatment with ceftriaxone + clindamycin. Patient reports onset of symptoms15 days after starting treatment with methimazole. Exams results on the last day of UPA admission showed pancytopenia (Hb 8.2 g/dL; leukocytes 1100/mm3; platelets 95,000/mm3) and increased bilirubins (TB 6.6 mg/dL; DB 5.6 mg/dL).

The patient reported a diagnosis of hyperthyroidism 4 years ago, without follow-up for 2 years, using propranolol 40 mg twice daily and propylthiuracil 100 mg once a day, when a doctor at the Basic Health Unit replaced propylthiuracil for methimazole starting 20mg/day in combination with propylthiuracil 100 mg, because this drug, was not interrupted by the patient. The patient started with the symptoms and was hospitalized on the 15th day after using drug combination by herself. The patient reported use of methimazole 2 years ago and reported having the same symptoms that also led her to hospitalization. She has history of hypertension using Enalapril 10mg/day and of Chronic Myeloid Leukemia treated with Imatinib Mesylate (Glivec), but this treatment was unattended 2 years ago. The patient is also a smoker of 25 packs a year and has been a drug addict for a year.

On physical examination, the patient was in regular general condition, jaundiced, dehydrated, feverish, with trismus, herpetic lip lesion, diffuse oral moniliasis, goiter and pain at abdominal palpation. Laboratory tests performed on admission to the HUEM showed Hb 8.6 g/dL, pancytopenia with worsening leucopenia: leukocytes 720/mm3, absolute segmented count 9 /mm3, 0/mm3 (zero) basophils, 0 /mm3 (zero) blasts, and 670/mm3 lymphocytes, TSH 0.029mU/L (normal 0.4-4.5mU/L) and free T4 4.93ng/dl (normal 0.7-1.8ng/dl). Autoantibodies against TSH receptor (TRAb) were negative. On thyroid ultrasound, performed on the first day of admission at the HUEM, the patient presented an increase on thyroid volume, a finely heterogeneous texture and multiple nodular images that were confluent and isoeogenic to the parenchyma, suggesting a diagnosis of multinodular goiter. Ultrasonography of the total abdomen showed a diffuse heterogeneous liver parenchyma, choledochus with caliber at the upper limit of normality without obstructive factors.

The diagnostic hypotheses initially included agranulocytosis due to thionamides, leukemia, febrile neutropenia and thyrotoxic crisis. Antibiotic therapy was started with piperacycline-tazobactam and associated on the second day of hospitalization with vancomycin, oral nystatin and acyclovir.

An evaluation was requested to the Endocrinology team. A thyrotoxic crisis was ruled out and the suspension of thionamides and a beta-blocker prescription were proposed, maintaining broad-spectrum antibiotic therapy. The possibility of hepatotoxicity accompanied by cholestasis due to thionamide was raised as jaundice, nausea and abdominal pain were present. In addition, an evaluation was requested to the Hematology team who performed bone marrow biopsy on the eighth day of hospitalization.

After 8 days of medication interruption and maintenance of antibiotic therapy, neutropenia resolved: leukocytes 3400/ mm3: absolute segmented count :1836mm3 (54%), (zero) basophils, blasts zero and platelets (286,000/mm3) besides improvement in bilirubin levels (BT: 1.6 mg/dl, BD 1.3 mg/dl). Jaundice, nausea and abdominal pain resolved and the patient was stable and in good general condition and was discharged with propranolol 40 mg twice a day. In order to have a better therapeutic approach, the Endocrinology team requested scintigraphy with 131I for differential diagnosis of Graves disease and multinodular goiter, T3 dosage and requested the patient not to continue with metimazole. The patient did not return for follow-up. Through the electronic medical record it was possible to access the result of the bone marrow biopsy, which showed bone marrow with 60% cellularity, myeloid:erythroid ratio - 5/1 with little maturation until segmented, being a histological picture suggestive of myeloproliferative disease that needed correlation with clinical data . So far, the patient did not return for evaluation with the Hematology team.

DISCUSSION

Hyperthyroidism is a thyroid dysfunction that results in increased T3 and free T4. Its symptoms are varied, including fatigue, nervousness, anxiety, low concentration, insomnia and weight loss with hyperphagia (13) . Some individuals have a genetic predisposition to develop this problem, including women and smokers (1).

About 60 to 80% of all cases of hyperthyroidism are due to Graves' disease (14). It occurs due to lymphocyte infiltration of the thyroid by immunological activation with an increase in T lymphocytes in the body, with the consequent appearance of autoantibodies that bind to the TSH receptor (TRAb), culminating in increased synthesis and secretion of thyroid hormones (15). It mainly affects women and the elderly, its cause is still uncertain, but the association between genetic, constitutional and environmental factors is reported in the medical literature. Treatment consists in administration of antithyroid drugs, radioactive iodine or surgery (2).

Toxic multinodular goiter, which is also a possible etiology for this patient, results from the presence of 2 or more thyroid nodules that release excess thyroid hormones, generating signs and symptoms of hyperthyroidism. Compressive symptoms resulting from the swelling of the gland may also occur, such as dysphagia, dysphonia or pressure on the neck. Its cause is still unknown, but individual cell mutations are believed to generate a clonal expansion of nodules. The diagnosis is performed measuring thyroid function tests and requesting scintigraphy with 131I which demonstrates high uptake in various areas of the gland. The treatment can be carried out with administration of antithyroid drugs, radioactive iodine or thyroidectomy (15).

The reported patient is a woman, a smoker and complained of weight loss. In addition, it had a TSH of 0.029 mU/L and a free T4 of 4.93ng/dl, in agreement with the literature regarding the symptoms, epidemiology and laboratory alterations of hyperthyroidism. However, the patient is young, coming into conflict with the age with the highest incidence of the disease. TRab, total T3 and scintigraphy were requested for differential diagnosis of Graves disease and multinodular goiter, for a better therapeutic approach.

It is known that the presence of infection could cause cholestasis induced by inflammatory cytokines (16). In addition, hyperthyroidism itself and the use of thionamides class antithyroid drugs have been associated with toxic hepatitis and cholestatic jaundice in rare cases (17). In drug-induced hepatitis, resolution usually occurs within 2 to 3 weeks after drug withdrawal. However, methimazole-induced hepatitis takes 2 to 3 months to resolve, after drug withdrawal (18). Thionamide-induced cholestasis was suspected because the patient had

jaundice, elevated bilirubins (BT 6.6 mg/dl; BD 5.6 mg/dL at basic health unit and BT 3.70 mg/dl, BD 3 mg / dl on the second day of HUEM hospitalization) and high alkaline phosphatase (153 U/L) . However, the improvement in liver tests in 8 days as well as the improvement in clinical symptoms suggested that cholestasis was induced by infection and hyperthyroidism itself (BT: 1.6 mg/dL, BD 1.3 mg/dl and BI 0.3 mg/dl).

Agranulocytosis is a rare and potentially fatal hematologic disorder characterized by neutropenia less than 500/mm3 (7). It has several possible etiologies, among them, congenital, associated with viral infections and drug-induced (19). These symptoms include fever, pneumonia, acute tonsillitis, skin infections, deep abdominal or thoracic abscess and pyelonephritis (8).

The World Health Organization defined a pattern for the drug-causing effect for onset and disappearance of symptoms and improvement of laboratory tests for the drug adverse events. The causality between drug ingestion and agranulocytosis was assessed as "right", when the time relationship to drug ingestion was plausible, a clinically reasonable response to drug withdrawal ("positive disapproval") was observed and agranulocytosis was observed in re-exposure to the same drug ("positive re--challenge") (20). All of these criteria are observed in our case. In addition, causality was assessed as "probable" when agranulocytosis was unlikely to be attributed to other causes (20). Although the patient has a previous hematological disorder, we believe that agranulocytosis was due to the use of thionamides.

According to the literature, the state of severe neutropenia has been shown to be attributable to drugs in 70 to 90% of cases. All other conditions induce moderate neutropenia, with an absolute neutrophil count between 1.5 and 0.5 x 109/L, mainly neutropenia secondary to sepsis and neutropenia associated with hypersplenism. The patient was admitted with 720 leukocytes / mm3 and an absolute segmented count of 9 (1.3%), consistent with agranulocytosis due to medication. The differential diagnosis of acute and severe neutropenia in adults includes a limited number of conditions as myelodysplastic syndromes and acute leukemia the main differential diagnoses (11).

The patient reported previous treatment for Chronic Myeloid Leukemia (CML) with Imatinib Mesylate, however, she did not currently use the medication. It is known that 50% of patients diagnosed with CML are asymptomatic and are usually diagnosed during a physical exam or routine blood tests. The diagnosis of typical CML consists in persistent unexplained leukocytosis with left shift (or occasionally thrombocytosis), the presence of chromosome Philadelphia abnormality (Ph) at (9; 22q34; q11), or the molecular abnormalities related to Ph BCR - ABL1 (21). We are unaware of a previous important leukocytosis status in the case of our patient because we did not have access to previous exams, since the follow-up was performed in another hospital and there was a loss of follow-up. However, in cases when accelerated and blastic phases of chronic myeloid leucemia are present, there is the appearance of blasts in peripheral blood or bone marrow (22). This was not observed in our patient exams favoring our diagnosis of agranulocytosis due to combined use of propiltiouracil and methimazole by the patient.

In addition, patients with drug-induced agranulocytosis, the bone marrow usually shows a lack of mature myeloid cells (11), compatible with the histopathological analysis of the patient's bone marrow. This appearance is described as "stopping myeloid maturation", which can be a consequence of a drug / antibody reaction specifically directed against mature cells or an early stage of the recovery process (11), which is also consistent with the case, since bone marrow biopsy was performed on the eighth day of hospitalization when the patient was already recovering the blood count. Likewise, the 5/1 Myeloid:Erythroid ratio suggests previous destruction of neutrophils with recovery - after drug interruption which do not occur in cases of myeloproliferative disease when bone marrow infiltration impairs the production of neutrophils.

The severe neutropenia induced by drugs occurs mainly by administering antithyroids with the propylthiouracil and methimazole (23). Some studies have shown that agranulocytosis is more likely to occur with propylthiuracil (1), which was used without clinical repercussions for 4 years by the patient, until it was synergistically associated with methimazole. Among patients treated with these drugs, 3 out of 10,000 are at risk of developing this dysfunction and the majority are women between approximately 29 and 59 years old. Our patient is within the age group and sex. In most cases, the symptoms begin to manifest about 3 months after use of the drug in question (12,24). In the case reported, the patient had symptoms of neutropenia 15 days after starting tapazol and it may be suspected that the synergistic action of thionamides has led to the early appearance of this condition.

In cases of drug-induced agranulocytosis, the number of neutrophils regularizes in a median of 8 days, with a possible interval between 3 and 14 days (10). At the time of admission, the patient had 9 segmented by mm3 and 8 days after discontinuing the medication, this number rose to 1836/mm3 , which reinforces the possibility that the patient had an agranulocytosis induced by medication.

The first step to be taken after diagnosis is to suspend the medication used. Hospitalization is necessary in cases where there is a high risk of infection, so that intravenous antibiotics are administered and blood, urine and other samples are taken for culture, in addition to changing the therapeutic option for hyperthyroidism treatment (7,9).

Currently, with modern medicine, only about 4% of patients progress to death (12). The factors that most influence the prognosis are age over 65 years, neutrophil count at diagnosis, severe infection clinical status and the presence of comorbidities (24). After resolution of the condition, patients will need definitive treatment for hyperthyroidism, usually with radioactive iodine or surgery (9).

Telephone contact with the patient was attempted to return to follow-up with Endocrinology team for definitive therapy , but without success. The hematology team also remains out of contact with the patient.

CONCLUSION

The state of severe neutropenia has been shown to be attributable to drugs in 70 to 90% of cases. The absence of evidence of transformation for the accelerated and blast phases of Chronic Myeloid Leukemia, positive clinical response associated with resolution of neutropenia after thionamide withdrawal and the presence of a 5/1 Myeloid:Erythroid ratio in bone marrow biopsy, suggesting previous destruction of neutrophils, with recovery after discontinuation of the drug evidences the differential diagnosis of thionamide-induced agranolocytosis overlying the underlying diagnosis of hematological disease. The manifestations resulting from such a condition include, in most cases, infections that have a high risk of progressing to septicemia. After resolution of the condition, which occurs between 3-14 days after the drug is discontinued, a definitive treatment for hyperthyroidism should be considered, usually with radioactive iodine or surgery.

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TOPICS IN MEDICAL CLINIC

ORIGINAL ARTICLES

ASSOCIATION OF SERUM BILIRUBIN AND URIC ACID LEVELS WITH INFLAMMATORY ACTIVITY IN RHEUMATOID ARTHRITIS

ASSOCIAÇÃO ENTRE NÍVEIS DE BILIRRUBINAS SÉRICAS E ÁCIDO ÚRICO E ATIVIDADE INFLAMATÓRIA EM ARTRITE REUMATOIDE.

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Keywords: Rheumatoid Arthritis, Serum Uric acid, Bilirubin, Inflammatory activity.
Descritores: Artrite Reumatoide, Ácido úrico sérico, Bilirrubina. Atividade inflamatória.

Abstract

Introduction: Rheumatoid Arthritis (RA) is a chronic inflammatory disease that affects mostly women, around 45 years old and impacts approximately 1% of the Brazilian population. The disease activity can be evaluated by laboratory markers such as C-Reactive Protein (CRP) and Erythrocyte Sedimentation Rate (ESR), and functional markers such as Disease Activity Score (DAS)-28 CRP, DAS-28 ESR, and Clinical Disease Activity Index (CDAI).
It is believed that uric acid (UA), a final product of purine degradation, is related and increased in systemic inflammatory response. On the other hand, serum bilirubin (SB) can be a substance correlated to antioxidant activities, with possible anti-inflammatory properties. Therefore, it becomes relevant to study their actions in the disease and correlate their index and inflammatory actions in RA. **Objective:** To evaluate the association between SB and UA levels with inflammatory activity in RA. **Methods:** This work is a cross-sectional observational study of 119 medical records of rheumatoid arthritis' patients. Data on SB, UA and inflammatory markers (ESR, CRP, DAS-28-CRP, DAS28 ESR and CDAI) were collected simultaneously. Results: In this sample of 99 females and 20 males,the median ESR was 33 mm, the median CRP was 6 mg/dL;the mean DAS-28 ESR was 4.33±1.51, the median DAS28 CRP of 3.37 and the median CDAI of 8.0. No correlations were found of these three inflammatory composite indexes with bilirubin (for total billerrubin with p =0.78, 0.74 and 0.20 respectivelly) nor with UA (p==0.36, 0.79 e 0.28 respectivelly). **Conclusion:** It was not possible to correlate the UA or SB levels with the disease activity in RA. **Endocrinol diabetes clin exp 2020 / 2187 - 2191.**

Resumo

Introdução: A Artrite Reumatoide (RA) é uma doença inflamatória crônica, que afeta principalmente mulheres, por volta dos 45 anos e impacta aproximadamente 1% da população brasileira. A atividade da doença pode ser avaliada por marcadores laboratoriais como Proteina C reativa (PCR) e Velocidade de hemossedimentação (VHS) além de indices funcionais como Escore de Atividade da Doença (DAS)-28 PCR, DAS-28 VHS e Índice de Atividade de Doença Clínica (CDAI).
Acredita-se que o ácido úrico (AU), produto final da degradação das purinas, esteja relacionado e aumentado na resposta inflamatória sistêmica. Por outro lado, a bilirrubina sérica (BS) pode ser uma substância correlacionada a atividades antioxidantes, com possíveis propriedades anti-inflamatórias. Portanto, torna-se relevante estudar suas ações na doença e correlacionar seu índice e ações inflamatórias em AR. **Objetivos:** Avaliar a associação entre os níveis de BS e AU com atividade inflamatória em pacientes da AR. **Métodos:** Este trabalho é um estudo observacional transversal de 119 prontuários médicos de pacientes com artrite reumatoide. Os dados sobre BS, AU e marcadores inflamatórios (VHS, PCR, DAS-28-CRP, DAS28 ESR e CDAI) foram coletados simultaneamente. **Resultados:** Nesta amostra de 99 mulheres e 20 homens, a mediana da VHS foi de 33 mm, a mediana de PCR foi de 6 mg/dL; a média do DAS-28 VHS foi de 4,33±1,51; a mediana do DAS-28 PCR foi de 3,37 e mediana do CDAI foi de 8,0 . Não foram encontradas correlações desses três índices compostos com bilirrubina (para bilirrubina total com p=0,78, 0,74 e 0,2 respectivamente) ou com AU (p=0,36, 0,79 e 0,28 respectivamente). **Conclusão:** Não foi possível correlacionar os níveis de UA ou SB com a atividade da doença em AR. **Endocrinol diabetes clin exp 2020 / 2187 - 2191.**

INTRODUCTION

Rheumatoid arthritis (RA) is an autoimmune pathology whose evolution is chronic and progressive, manifesting through infiltration of inflammatory cells and fibroblasts in the joints. It affects mainly diarthrodial joints, symmetrically, distressing approximately 1% of the world population, with an estimated prevalence between 0.2 to 1% in the Brazilian population. It has a peak of incidence between 40-55 years, most often affecting females (2.5 / 1). The manifestations initially are insidious in 2/3 of the cases. It has a multisystemic character due to intense inflammatory activity (1,2,3).

During the inflammatory period, joint synovium activates the release of a large number of reactive oxygen species (ROS) through the NADPH oxidase system. Excess of these species generates concomitant pro-inflammatory tissue responses and damage to lipids, proteins, and DNA. Excessive ROS were detected in RA patients in both synovium and blood and their levels correlated with disease activity (1).

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Bilirubin (SB) is a potent antioxidant and is also considered an immunomodulatory substance. Its antioxidant effect may be attributed to its inhibitory activity in relation to the oxidative damage of ROS,hindering the production of autoantibodies. Moreover, it induces apoptosis of immune cells, down-regulates the expression of MHC-II molecules and promotes Treg expansion. Thus, it is believed that this antioxidant substances may bring benefits to patients with RA (1) .

Uric acid (UA) is an end product of purine metabolism and it is involved in the physiopathology of RA. There is some evidence that show that UA is a potent inflammatory inducer and is involved in redox imbalance. Also, it is a stimulator of the production of pro-inflammatory cytokines such as IL-6, IL-1β, TNF-α. Some studies suggest the correlation between UA and situations of systemic inflammation, such as RA. In addition, UA elevation has been shown to be an independent predictor of cardiovascular disease, other causes of mortality, and the development of the metabolic syndrome. Several components of metabolic syndrome, such as abdominal diameter, hypertension, and insulin resistance are associated with hyperuricemia, while HDL-cholesterol is inversely proportional to high serum UA levels (4,5).

This study aims to evaluate the association of SB and UA with the inflammatory activity of rheumatoid arthritis.

METHODS

This is a retrospective study that included 119 patients from the Rheumatology Outpatient Clinic of the Mackenzie Evangelical University Hospital (HUEM) who met the classification criteria for Rheumatoid Arthritis of 2010 - ACR / EULAR (6). This is a retrospective study that was approved by the Ethics Committee of the Evangelical Society of Curitiba under protocol number 3.155.050.

We included adult patients, of both sexes, over 18 years of age, who filled at least 4 of the classification criteria of the 2010 ACR for RA (6). Patients with disease onset before 16 years of age were excluded. Those with gout; taking medications that may influence the measurement of serum uric acid (allopurinol, narcaricin, probenecid, sulfinpyrazone, benzobromarone, leflunomide, diuretics, angiotensin II antagonists, cyclosporine, tacrolimus and low-dose AAS (4), individuals with creatinine above 1.8 mg / dL , with other associated chronic inflammatory diseases, Gilbert's disease or liver dysfunction were also excluded.

The medical records were reviewed for: (a)- Epidemiological data: sex, race, age, smoking, age at disease onset of disease; (b) Clinical and laboratory data: nodules, rheumatoid factor; used treatment; bilirubin and uric acid, glycemia and lipid profile; (c) Disease activity: by ESR (erythrocyte sedimentation rate), CRP (C reactive protein), DAS (disease activity score)-28 ESR, DAS-28 PCR and CDAI (Clinical disease activity index).

The obtained results were collected in frequency tables. Data comparisons (bilirubin and uric acid according to clinical, serological and epidemiological variables) were done by Mann Whitney and unpaired t-tests. Correlation of inflammatory activity levels (ESR, CRP, DAS-28 and CDAI) with bilirubin and serum uric acid values were performed by Spearman or Pearson tests. The adopted significance was 5%.

RESULTS

a) Description of the studied sample

In the studied sample there was 119 RA patients: 99 women and 20 men. The other characteristics are on **Table 1**.

TABLE 1: Description of the studied data:119 rheumatoid arthritis patients.

Data		Number	Mean±SD/Median(IQR)
Age (years)		25 – 81	55.9 ± 9.9
Age of disease onset (years)		17.0 - 77.0	45.5 ± 11.9
Tabacco exposure		Current- 18/100 – 18%	
		No - 52/100 – 52%	
		Ex- 30/100 – 30%	
Duration of illness (years)		1 – 34	9.0 (6.0-15.0)
Ethnic Background		Caucasian-75/107 – 70.0%	
		Afrodesc -31/107 – 28.9%	
		Asian 1/107 – 0.8%	
Positive rheumatoid fator		73/119 – 61.3%	
Treatment			
	Methotrexate	78/119 – 65.5%	
	Leflunomide (*)	73/119 – 61.3%	
	Antimalarics	27/119 – 22.6%	
	Anti-TNF α	21/119 – 17.6%	
	Tocilizumabe	6/119 – 5.0%	
	Tofacitinibe	2/119 – 1.6%	
	Rituximabe	2/119 – 1.6%	
	Abatacept	3/119 – 2.5%	
	Glucocorticoid	74/119 – 62.1%	

(*)- These patients were excluded in the study of uric acid.

SD= standard deviation; IQR= interquartile range.

Data on the inflammatory activity of the disease, bilerrubin and uric acid levels can be seen in **Table 2**, that shows that most of the patients had mild to moderate inflammatory activity.

TABLE 2: Inflammatory disease activity data and laboratory data in the sample of 119 rheumatoid arthritis patients

	Median (IQR)/Mean±SD
Erythrocyte sedimentation rate (mm)	33 (15.5-61.5)
C Reactive protein (mg/dL)	6.0 (2.0-12.6)
DAS-28 ESR	4.33 ± 1.51
DAS-28 CRP	3.37 (2.30-4.71)
CDAI	8.0 (4.0-21.0)
Indirect bilerrubin (mg/L)	0.30 (0.22-0.47)
Direct bilerrubin (mg/L)	0.20 (0.15-0.28)
Total bilerrubin (mg/L)	0.52 (0.40-0.70)
Uric Acid (mg/dL)	3.8 ± 1.2

ESR= Red Blood Cell Sedimentation Value; CRP= C-Reactive Protein; DAS= disease activity score

SD= standard deviation; IQR= interquartile range; CDAI= Clinical Disease Activity Index

b) Study of bilirubin and inflammatory activity

Bilirubin data were obtained from 84 patients. The correlation of total bilerrubin and its fractions with inflammatory markers can be seen in **Table 3**.

TABLE 3: Correlation studies of bilirubin levels with inflammatory variables

	Spearman Rho	95% Confidence Interval	P
Indirect bilirrubina			
Uric Acid	0.04	-0.22 to 0.29	0.75
ESR	-0.14	-0.35 to 0.08	0.21
CRP	0.02	-0.25 to 0.21	0.86
DAS 28- ESR	-0.14	-0.37 to 0.10	0.24
DAS 28- CRP	0.02	-0.25 to 0.28	0.88
CDAI	-0.16	-0.43 to 0.11	0.23
Direct bilirrubina			
Uric Acid	0.19	-0.06 a 0.42	0.13
ESR	0.01	-0.24 a 0.20	0.85
CRP	0.09	-0.32 a 0.14	0.40
DAS 28- ESR	0.12	-0.12 a 0.35	0.31
DAS 28- CRP	0.02	-0.24 a 0.28	0.87
CDAI	-0.13	-0.40 a 0.15	0.25
Total bilirrubina			
Uric Acid	0.15	-0.10 a 0.39	0.21
ESR	-0.11	-0.33 a 0.10	0.29
CRP	- 0.03	-0.25 a 0.20	0.79
DAS 28- ESR	-0.03	-0.26 a 0.20	0.78
DAS 28- CRP	0.04	-0.22 a 0.30	0.74
CDAI	-0.17	-0.43 a 0.10	0.20

ESR= Red Blood Cell Sedimentation Value; CRP= C-Reactive Protein; DAS= disease activity score; CDAI=clinical Disease assessment index.

c) Study of uric acid

The considered number of patients with uric acid data was 29 as most of the patients were using leflunomide and were excluded. The results are on **Table 4**.

TABLE 4: Correlation studies of uric acid values with inflammatory variables

	Spearman Rho	95% Confidence Interval	P
ESR	-0.19	-0.55 to 0.21	0.32
CRP	-0.35	-0.67 to 0.08	0.10
DAS 28- ESR	-0.21	-0.60 to 0.26	0.36
DAS 28- CRP	0.07	-0.48 to 0.59	0.79
CDAI	0.32	-0.29 a 0.74	0.28

ESR= Red Blood Cell Sedimentation Value; CRP= C-Reactive Protein; DAS= disease activity score; CDAI=clinical Disease assessment index.

DISCUSSION

Our findings did not corroborate previous studies that serum bilirubin and uric acid levels are altered with rheumatoid arthritis activity (4). Unfortunately, the study sample of uric acid values was very small given the intense use of leflunomide in the studied population. In the retrospective study by Choe and Kim (4), it was established that leflunomide therapy could decrease serum UA concentrations by increasing its urinary excretion. Furthermore, they showed that decreased levels of UA during leflunomide treatment were not associated with changes in predictors of acute-phase disease such as CRP (4). Our findings suggest that UA is not a potent predictor of inflammatory activity, opposing to what has been shown in some clinical and experimental studies, which stated that UA would be associated with inflammatory responses. However, our sample was small and this could blurred our findings.

It was also not possible to associate bilirubins with inflammatory activity. Our findings do not confirm those of Peng, Wang and Pan (7), where bilirubin concentrations were significantly lower in RA patients than in control patients, and negatively correlated with DAS-28, ESR and CRP. Another study, not confirmed by our findings, was that of Fischman et al. (8), whose findings were similar to those of Peng, Wang and Pan (7). However their patient inclusion criteria were not based on the diagnosis defined by the 2010 - ACR / EULAR criteria, but based on subjective answers to the questions: “has any doctor ever told you that you had arthritis?”. “What type of arthritis?”. Another difference with our study was the fact that only total bilirubin was evaluated.

Laboratory markers (CRP and ESR), although inflammatory activity markers are not very accurate and should be associated with clinical reasoning and other complementary tests(9). Both ESR and CRP are unespecific and may suffer unfluence of non-inflammatory parameters. ESR depends of size, shape and number of erythrocytes, gender and age of the patient, as well as other plasma constituents such as immunoglobulins, other than fibrinogen. CRP, on the other hand, is not influenced by these factors but may reflect any other inflammatory state, other than RA. This may lead to inaccurate and incorrect results (10,12). Also, depending on the circumstances, the ESR and PCR results may differ from each other. This may be due to factors related to the inflammatory process including differences between each acute phase reagent and its sensitivity to change as a result of differences in specific cytokines or modulators in various diseases. Distinctions may also result from factors that may increase or decrease ESR values related to others acute or chronic causes of inflammation (such as comorbidities). In addition, as the patient's condition worsens or improves, ESR changes slowly while CRP changes rapidly. According to Medeiros et al. (1). the use of CRP still requires further studies, as some RA patients have tended to have higher ESR and lower CRP values (10,11).

So, judging disease activity in RA is quite difficult. If levels of uric acid and bilirubin had shown any association, they could help bridge this gap. Unluckely, this could not be proved in the present work.

This study has some limitations. One is its retrospective design. Another is the small number of patients in the sample mainly in the analysis of uric acid caused mainly by the very restrictive exclusion criteria. Further studies with larger samples are needed to judge the true value of bilirubin and uric acid levels in the context of rheumatoid arthritis.

CONCLUSION

In this study, it was not possible to associate uric acid levels or serum bilirubin or their fractions with the inflammatory activity of RA.

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TOPICS IN MEDICAL CLINIC

ORIGINAL ARTICLES

ANTIMALARIALS AND ELECTROCARDIOGRAPHIC ALTERATIONS: A CROSS SECTIONAL STUDY IN 100 LUPUS PATIENTS

INFLUÊNCIA DOS ANTIMALÁRICOS EM ALTERAÇÕES ELETROCARDIOGRÁFICAS: ESTUDO TRANSVERSAL EM 100 PACIENTES COM LÚPUS.

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Keywords: Antimalarials, Hhydroxychloroquine, Systemic Lupus Erythematosus..
Descritores: Antimaláricos, Hidroxicloroquina, Lúpus Eritematoso Sistêmico.

Abstract

Background: Antimalarials are considered very important drugs in the treatment of systemic lupus erythematosus (SLE). The study of the influence of antimalarials in electrocardiogram parameters has yield controversial results. **Aim:** To study the influence of the cumulative dose of antimalarials in electrocardiogram of SLE patients. **Methods:** One hundred SLE patients were included: 82% using antimalarials and 18% not. Cumulative antimalarial doses were calculated through chart review. All patients were submitted to a 12-lead surface electrocardiogram (EKG) with device of 25mm/sec speed and 10mm/MV (gain) calibration. The EKGs of patients receiving and not receiving ATM were compared. **Results:** No electrocardiographic alterations were associated with the use of antimalarials (cardiac frequency with p=0.77; PR interval with p= 0.21; QTc interval with p=0.62). Neither the ATM cumulative dose, nor the duration of use correlated with values of PR or QTc intervals (p=ns). **Conclusions:** According to our results, antimalarials are safe drugs from electrocardiographic point of view. **Endocrinol diabetes clin exp 2020 / 2192 - 2194.**

Resumo

Justificativa: Antimaláricos são drogas importantes no manejo do paciente com lúpus eritematoso sistêmico (LES). O estudo da influência dos antimaláricos em alterações eletrocardiográficas tem fornecido resultados controversos. **Objetivo:** Estudar a influência da dose cumulativa de ATM em eletrocardiograma de pacientes com LES. **Métodos:** Cem pacientes com LES foram incluídos: 82% usando e 18% não usando ATM. A dose cumulativa de antimaláricos foi calculada por revisão de prontuários. Todos os pacientes foram submetidos a eletrocardiograma (ECG) de superfície de 12 derivações com dispositivo de velocidade de 25mm / seg. e calibração de 10mm / MV (ganho). Os ECGs dos pacientes recebendo e não recebendo ATM foram comparados. **Resultados:** Não foi observado diferenças entre usuários e não usuários de ATM (frequência cardíaca com p=0.77;intervalo PR com p=0.21; intervalo QTc com p=0.62. A dose cumulativa e tempo de uso de ATM não se se correlacionaram com valores de intervalos PR ou do QTc (p=ns). **Conclusão:** De acordo com os resultados presentes, antimaláricos são drogas seguras do ponto de vista eletrocardiográfico. **Endocrinol diabetes clin exp 2020 / 2192 - 2194.**

INTRODUCTION

Antimalarials (ATM) are drugs widely used in the treatment of rheumatic diseases, mainly in systemic lupus erythematosus (SLE) (1). In lupus these drugs are considered to have properties that inhibits the disease flare (1). Otherwise its effects on lipid and glycemic profiles and action as anti-platelets are beneficial from the vascular point of view (2). In pregnant lupus patients, ATM avoids the transport of anti-Ro through placental barrier and protects the baby from neonatal lupus (3). Lupus patients using antimalarials have lower mortality rates due to any cause than those who did not and their survival benefit could be augmented by a good drug adherence (4).

However, these drugs have also side effects; the most recognized are retinal deposition with potential to impaired the vision irreversibly (5). The heart may also be affected by this drug. Cardiomyopathy is a well-recognized complication although considered rare (6,7). Electrocardiographic alterations have also been ascribed to these medications. (8,9) Cairoli et al. (8) noted that patients using hydroxychloroquine had a decrease in heart rate that was proportional do the cumulative dose. Alterations of QTc interval have also been observed (11). Nevertheless Costedoat-Chalumeau et al. (9) could not identified electrocardiographic changes in ATM users and McGhie et al. (11) found that these drugs have a protective effect in this context.

Presently, we studied the electrocardiogram of 100 lupus patients aiming to know if there is difference between ATM users and non-users.

MATERIAL AND METHODS

This study was approved by the local Committee of Ethics and Research and all participants signed consent. One hundred systemic lupus erythematosus patients from a single Rheumatology Outpatient Clinic were invited to participate. This is a convenience sample that included all patients that come for regular consultation and that agree to participate in the study for the period of six months. All included patients were asymptomatic from cardiac point of view and filled at least four of classification criteria from SLICC Classification Criteria for Systemic Lupus erythematosus (12). Patients that started receiving ATM in other service (that precludes cumulative dose calculation) were excluded.

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Charts were reviewed for demographic and treatment profile. All patients were submitted to a 12-lead surface electrocardiogram with device of 25mm/sec speed and 10mm/MV (gain) calibration. All the electrocardiograms analyzed were performed by a single individual, and were performed after resting for 15 minutes. The QT interval was corrected by heart rate according to Bazett's formula (13). All readings were made by a single researcher who was blinded to the other clinical data. Limits of normality of the QTc interval of 0.46s (460ms) for males and 0.47s (470ms) for females were considered; normal heart rate ranged between 50 and 100 beats per minute (bpm).

Cumulative dose and the period of ATM use for each patient were calculated. Patients were divided in ATM users and non-users and compared between themselves. Antimalarials users were further divided in those using high and low cumulative dose. The cut-off between high and low cumulative dose was of 365g of hydroxychloroquine (8). The high dose users were compared with non-users.

All obtained data was collected in frequency and contingency tables. The Shapiro Wilks test was used to judge data distribution. Comparison of nominal data was done through Fisher and chi squared test, of numeric data by Mann Whitney and unpaired t test. Correlation of cumulative dose and ATM use duration with electrocardiographic intervals were made by the Spearman test. The adopted significance was of 5%.

RESULTS

The studied sample of 100 SLE patients had 83% females, 77% Caucasians, with a median disease duration of 72 months (range 6 to 301 months).

In this sample, 82% were using antimalarials and 18% did not use them. The cumulative hydroxychloroquine dose in those using ranged from 72 to 2.222 g (median 683 g). ATM were used for the period of 6 to 232 months (median of 76.5 months).

The comparison of electrocardiographic findings in patients using and not using antimalarials is on **Table 1**.

Table 1- Comparison of electrocardiographic findings in antimalarials (ATM) users (n=78) and non-users (N=22).

	ATM non-users N=22	ATM users n=78	P
Cardiac frequency (p/minute	55-98 Mean 69.6±10.9	49.0-103 Mean 68.8±11.2	0.77
PR interval (mm)	108-220	112-202	0.21
(IQR)	Median 148 (137-167.5)	Median 144 (132-158.0)	
PR anormal (n)	1/22 – 4,5%	1/78 – 1,2 %	0.9
QT interval (mm)	360-438 Mean 393±20.6	324-416 Mean 397.1±30.2	0.55
QTc- (mm)	380-463 Mean 418.9±23.1	345,0-495.0 Mean 422.1±28.3	0.62
Prolonged QTc (n)	0/22 -	3/78- 3.8%	1.00

IQR= Interquartile range; n=number.

Only one patient had atrial extrasystoles (4/min) and another one had ventricular extrasystoles (10/min). Both were in the ATM users' group.

Among ATM users, 58/89 (72.5%) were in the group of high cumulative dose. When high cumulative ATM users were compared with non-users, the results on **Table 2** were found.

Table 2- Comparison of electrocardiogram findings between antimalarial (ATM) non-users and high cumulative ATM users.

	ATM non-users N=22	**ATM users with high cumulative dose N=78**	**p**
Cardiac frequency (/min)	55-98 Mean 69.6±10.9	49 - 103 68.6 ± 11.8	0.73
PR interval (mm)	108-220 Mean 152.6±24.5	112-202 Mean 145.9±18.3	0.18
PR anormal- (n)	1/22 – 4,5%	1/58 -1,7%	0.47
QT interval (mm)	360-438 Mean 393±20.6	324-464 Mean 398.5±30.1	0.43
QTc interval (mm)	380-463 Mean 418.9±23.1	345-495 Mean 422.3±28.07	0.61
Abnormal QTc (n)	0/22 -	3/58 – 5.17%	0.55

Correlation studies of PR interval with cumulative ATM dose showed p=0.55 and with time of use showed p=0.66. Correlation studies of QTc interval with cumulative ATM dose showed p=0.39 and with time of use showed p=0.74.

DISCUSSION

Our data failed to show electrocardiographic alterations associated with the use of antimalarials even when the cumulative dose was high. No changes were observed in heart rate contradicting the findings of Cairoli et al. (8) that found that hydroxychloroquine had a bradycardic effect. However, these authors studied, in vitro, the beating rate of sinoatrial node cells of animal models and this data may not be transferred to humans. Others (14) have found that chloroquine seems to play a protective role in high rate of cardiac arrhythmias and conduction disturbances. However, they could say if this effect was due to the drug itself or to control of SLE activity. (14) Lupus itself may cause arrhythmias. Tachyarrhythmias were found in 6% of SLE patients, with the most common being atrial fibrillation (3%). QT prolongation was present in 17% of patients upon direct ECG review (15).

We could not find differences in the effects on QTc interval between antimalarial users and non-users but three patients had prolonged QTc interval and were on the antimalarial user group. Although not significant statically, this data may be clinically significant as this abnormality is associated with higher risk of *torsade point* (16), an arrythmia that can lead to ventricular fibrillation (17). All three patients were in the group of ATM users. This medication was suspended in these patients and the electrocardiogram was repeated in six months; one of them return to normal but not the other two. Nevertheless, it is possible to image that the antimalarial impregnation will not resolve with drug suspension for this period. By other side, the lupus itself could be the origin of the problem.

CONCLUSION

Concluding, we can say that the present data points to the fact that antimalarial are safe drugs from electrocardiographic point of view.

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