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CASE REPORT

Medullary aplasia due to the use of azathioprine in a patient with autoimmune hepatitis Case report

Aplasia medular por uso de azatioprina en paciente con hepatitis autoinmune. Presentación de un caso

Aplasia medular devido ao uso de azatioprina em paciente com hepatite autoimune. Apresentação de um caso

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ABSTRACT

Azathioprine is an immunosuppressive drug derived from 6-mercaptopurine, used in the treatment of various autoimmune conditions. Its metabolism mainly involves xanthine oxidase and thiopurine methyltransferase (TPMT). Adverse effects of azathioprine include allergic reactions and myelotoxicity, such as leukopenia, thrombocytopenia, and anemia, the incidence of which can be as high as 46% in patients with autoimmune hepatitis. The case presented describes a 68-year-old woman with autoimmune hepatitis initially treated with prednisone and continued with azathioprine. He subsequently developed hair loss, asthenia, and weight loss, along with laboratory-confirmed pancytopenia. After the diagnosis of spinal cord aplasia secondary to azathioprine toxicity, the medication was discontinued and treatment with antibiotics, transfusions and corticosteroids was initiated, achieving complete hematological recovery and favorable evolution.

Keywords: azathioprine; immunosuppressant; medullary aplasia; hepatitis; pancytopenia

RESUMEN

La azatioprina es un fármaco inmunosupresor derivado de la 6-mercaptopurina, utilizado en el tratamiento de diversas condiciones autoinmunes. Su metabolismo involucra principalmente la xantina oxidasa y la tiopurinametiltransferasa (TPMT). Los efectos adversos de la azatioprina incluyen reacciones alérgicas y mielotoxicidad, como leucopenia, trombocitopenia y anemia, cuya incidencia puede llegar al 46% en pacientes con hepatitis autoinmune. El caso presentado describe a una mujer de 68 años con hepatitis autoinmune tratada inicialmente con prednisona y se continuó con azatioprina. Posteriormente, presentó caída del cabello, astenia y pérdida de peso, junto con pancitopenia confirmada por laboratorio. Tras el diagnóstico de aplasia medular secundaria a toxicidad por azatioprina se interrumpió el medicamento y se inició tratamiento con antibióticos, transfusiones y corticoides, logrando una recuperación hematológica completa y evolución favorable.

Palabras clave: azatioprina; inmunosupresor; aplasia medular; hepatitis; pancitopenia

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RESUMO

A azatioprina é um medicamento imunossupressor derivado da 6-mercaptopurina, utilizado no tratamento de diversas doenças autoimunes. Seu metabolismo envolve principalmente xantina oxidase e tiopurina metiltransferase (TPMT). Os efeitos adversos da azatioprina incluem reações alérgicas e mielotoxicidade, como leucopenia, trombocitopenia e anemia, cuja incidência pode chegar a 46% em pacientes com hepatite autoimune. O caso apresentado descreve uma mulher de 68 anos com hepatite autoimune tratada inicialmente com prednisona e continuada com azatioprina. Posteriormente, ele desenvolveu queda de cabelo, astenia e perda de peso, juntamente com pancitopenia confirmada em laboratório. Após o diagnóstico de aplasia medular secundária à toxicidade da azatioprina, a medicação foi suspensa e iniciado tratamento com antibióticos, transfusões e corticosteróides, obtendo-se recuperação hematológica completa e evolução favorável.

Palavras-chave: azatioprina; imunossupressor; aplasia medular; hepatite; pancitopenia

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INTRODUCTION

Azathioprine is an imidazole drug that is derived from 6-mercaptopurine (6-MP) and is part of the group of synthetic purine analogues. Its mechanism of action is based on the blockade of nucleotide synthesis, resulting in immunosuppression. Its metabolism is initially by 6-MP, and takes three pathways of metabolism: 1% by hypoxanthine-guanine phosphoribosyltransferase (HGPRT), 84% by xanthine oxidase (XO) and 15% by thiopurine methyltransferase (TPMT).[(1)]

The adverse effects of azathioprine are divided into allergic and non-allergic, within the first group are: skin rash, general malaise and acute pancreatitis. The non-allergic ones are dose-dependent and include: myelotoxicity (leukopenia, thrombocytopenia, anemia or the combination of two or more cell lines known as pancytopenia) which occurs at any time during treatment(1), and can reach up to 46% of incidence in the treatment of autoimmune hepatitis[(2)]; also, hepatotoxicity and tremors occur.[(3)]

This cytotoxicity is due to the fact that the immunosuppressive metabolites of azathioprine, such as 6-thioguanine nucleotides (6-TGN), are incorporated into DNA as false metabolites, which interferes with normal protein synthesis, growth and proliferation of T and B lymphocytes(4), and causes the adverse effects.

Since the thiopurine methyltransferase (TPMT) enzyme is of great importance in the production of cytotoxic metabolites,[5] analytical determination of the activity of this enzyme can be performed to avoid the development of adverse effects. If there is a low activity, there is a greater risk of side effects. However, normal activity does not exclude their occurrence in long term. Since the gene encoding the TPMT enzyme can present mutations associated with the deficit of enzymatic activity, producing accumulation of circulating active nucleotides with greater risk of severe medullary toxicity or other lethal adverse effects, even with conventional doses.[6] Therefore, new studies are needed to determine a correct knowledge of the range of therapeutic effectiveness and toxicity.

One of the indications for azathioprine is the maintenance treatment of autoimmune hepatitis, a chronic and progressive disease with fluctuating periods. Its etiopathogenesis is unknown, but there is an immune reaction against hepatocyte antigens that is triggered by external agents.[7] Analytically, it presents an elevation of transaminase levels, IgG and the presence of autoantibodies. The definitive diagnosis is made by liver histology by biopsy, which allows observing periportal punch hepatitis, staging the degree of fibrosis, determining its prognosis, establishing whether it is type 1 or 2 and ruling out other diagnoses. The treatment scheme is based on the use of corticosteroids associated or not with the individualized use of azathioprine.[8]

The following is a case report of an adult female patient with a history of autoimmune hepatitis. She was treated with corticosteroids and azathioprine, after which she presented asthenia, alopecia and weight loss accompanied by paraclinical tests showing pancytopenia and, after a good clinical judgment, it was determined that it was a bone marrow aplasia secondary to toxicity due to the use of azathioprine.

CASE PRESENTATION

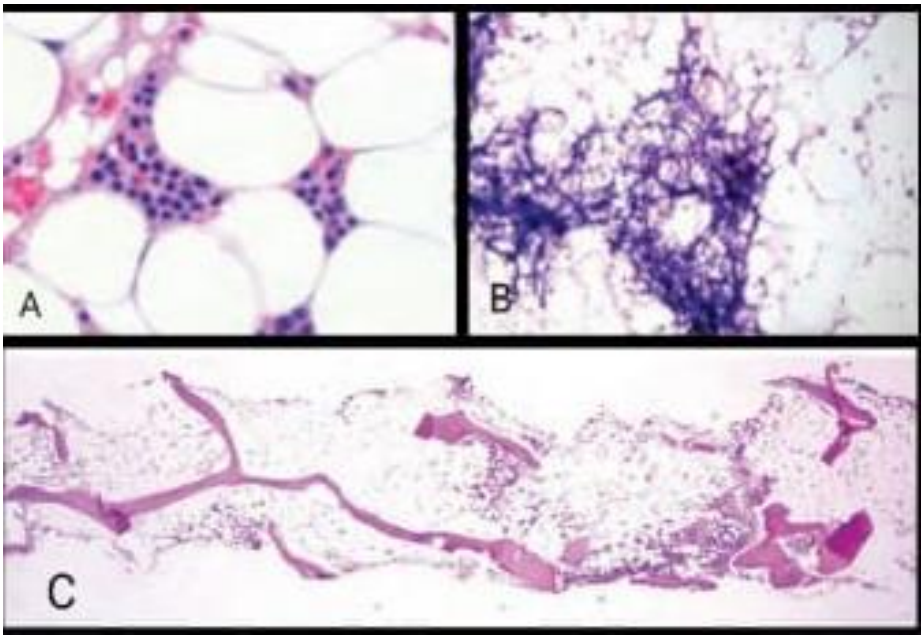
Female patient, 68 years old, with a personal history of hypothyroidism, in treatment with levothyroxine 50 ug/day, long-standing chronic constipation in treatment with fiber and diagnosis of autoimmune hepatitis approximately three months ago, which was treated with prednisone 20 mg/day with gradual decrease for two months until its discontinuation, and later continued with azathioprine 50 mg/day as maintenance. She went to the Immunology service and reported hair loss, asthenia and weight loss for approximately ten days.

Laboratory tests showed: leukopenia (leukocytes: 1.40 10^3/uL), mild anemia (hemoglobin 11.3 g/dL, hematocrit 32.8%), increased inflammatory reactants (CRP 63.52 mg/L).

Immunological examinations showed: increased complement C3: 216.0 mg/dl; increased complement C4: 55.0 mg/dl; negative anti-DNA, negative lupus anticoagulant, negative anti-endomysial IgA and IgG, negative anti-gliadin IgA and IgG, negative tissue transglutaminase IgA and IgG, negative total IgE: 99.58 IU/ml, ANA positive 1/160, anti Ro/SS-A negative, Anti-LA/SS-B negative; after which methylprednisolone 125 mg IV in single dose and prednisone 20 mg daily were indicated.

After a week of evolution the patient presented significant asthenia, universal alopecia and fever of 40°C, so she went to the Emergency Department where blood tests were performed, which showed: pancytopenia due to leukopenia (leukocytes: 0.5 10^3/uL), severe neutropenia (neutrophils: 0.0 10^3/uL), lymphocytosis (lymphocytes: 90.0 %; 0.5 10^3/uL), decreased red blood cells (3.0 10^6/Ul), hemoglobin: 9.6 g/dL, hematocrit: 27.3 % and thrombocytopenia (platelets 12.0 10^3/Ul; manual platelet count: 81,000/mm3).

On the other hand, there was an alteration of the inflammatory response: increased Westergreen erythrocyte sedimentation rate: 40 mm/h, increased LDH 140 U/l, C-reactive protein 99.8 mg/l. Hepatic, lipid and electrolytes profile within normal parameters, serology: TORCH negative. Bone marrow aspirate was performed, that showed a decreased cellularity for age at the expense of all cell lines (Figure 1). No blasts or metastasis cells were observed, presence of megakaryocytes, erythroid series: erythropoiesis very hypoplastic; myeloid series: myelopoiesis hypoplastic, keys and segmented 2%, hypoplastic marrow with few clumps of stromal cells such as mast cells, and residual lymphocytes with presence of lymphocytosis.



Bone marrow morphology in bone marrow aplasia, Bone marrow aspirate (A,B) with bone spicules in whose interstitium yellow bone marrow with hypocellularity and residual stroma is observed. The bone marrow sample (C) shows marked hypocellularity.

Taken from: Hematology Basic Principles and Practice. Hoffman R, Benz E, Silberstein L, Heslop H, Weitz J, Salama M, et al.[15]

She was hospitalized with a diagnosis of bone marrow aplasia and febrile neutropenia. Patient was oriented in her three spheres, Glasgow 15/15, temperature 38°C, other vital signs within normal, generalized pallor, pale sclera, with no other abnormality in the physical examination.

IV antibiotic therapy was started with piperacillin-tazobactam 4.5 grams every 8 hours. Suspension of azathioprine was indicated. For hematology, it was indicated transfusion of one red blood cell concentrate (day 1) and six platelet concentrates (day 1 and 3), as well as prednisone 60 mg/day PO and leukocyte colony stimulating factor one subcutaneous ampoule daily for five days. On the third day of hospitalization, blood cultures showed Pseudomona aeruginosa sensitive to all antibiotics. Thiopurine methyltransferase (TPMT) was also requested, which was found to be within the normal range with a value of: 19 U/mL, so antibiotic therapy was continued.

After completing eight days of hospitalization, the patient was discharged, with significant improvement of her blood test: leukocytosis (leukocytes: 23.1 10^3/uL), lymphocytosis (lymphocytes: 7.9%; 1.8 10^3/uL), neutrophilia (neutrophils 84.6%; 19.5 10^3/uL), mild anemia (hemoglobin 11.2 g/dL; hematocrit 32.0 %), thrombocytopenia (platelets 98.0 10^3/uL, manual platelet count 152,000/mm3), in peripheral blood smear was observed in the red series: normochromic normocytosis without changes in the erythrocyte form and in the white series: leukocytosis with predominance of mature neutrophils with reinforcement of toxic granulation + keys 5 %, and slight increase of monocytes of normal characteristic.

Based on the above, a diagnosis was made: toxicity secondary to medication (azathioprine). Outpatient treatment was indicated: prednisone 20 mg every 12 hours, gradually decreasing its dose during six months until its suspension.

The control performed three months later showed a complete hematological recovery without alteration of the hepatic profile. Currently, the patient does not need medication, is stable and has a good evolution.

DISCUSSION OF THE CASE

Medullary aplasia is an entity characterized by a significant decrease of progenitor cells of the three hematopoietic series in the bone marrow, presenting as pancytopenia in peripheral blood. There are hereditary forms (20%) of the disease, however, the vast majority of cases are acquired (80%) and mediated by immunity, with environmental triggers being drugs (25%), viruses and toxins (5%), but mainly the cases are idiopathic (70%).[9]

The patient in the present case debuted with pancytopenia confirmed by bone marrow biopsy and was diagnosed with bone marrow aplasia secondary to the use of azathioprine. This drug is widely used as an immunosuppressant in diseases such as inflammatory bowel disease or autoimmune hepatitis, and its adverse effects include pancytopenia, which is known to be 17.3%.[3]

The first known reported case of pure red cell aplasia was reported in two patients by McGrath, et al. in 1975.[10] In a 1993 study of 739 adult patients with inflammatory bowel disease who used azathioprine, 5% had myelotoxicity(11); in the study by Present, et al. of 396 patients with inflammatory disease, 2% had leukopenia.[12]

It has been established that the incidence of patients presenting with azathioprine-induced myelotoxicity is approximately 6.5%.[13] It is believed that the toxic activity of azathioprine is due to a genetic polymorphism that can be demonstrated by determining the TPMT and thus being able to calculate the correct dose of thiopurine to avoid adverse effects. In the case of our patient, the study was performed late; however, it was within normal ranges, which indicated that apparently myelotoxicity would not occur. Such succession is very common as it happens in the clinical case presentation of Martinez,et al. of 2016, where both patients had a TPMT activity within the normal range[13], in the same way the clinical case of a patient with renal transplant in maintenance with azathioprine the TPMT level was normal.[10] So it is thought that there are other factors or metabolites that interfere in the activity of the enzyme.

Kennedy, et al. in 2013, in their study of patients with Crohn's disease to whom azathioprine produced myelotoxicity and who were subsequently administered mercaptopurine, tolerated it in 74%. This confirms that the appearance of myelotoxicity is multifactorial and not only due to the use of thiopurines.[5] Although its use is controversial, TPMT allows knowing the enzyme activity status for drug administration safety and therapeutic strategy design, however it does not replace clinical follow-up, hematological and liver enzyme monitoring.[6] TPMT determination may not be cost-effective, but avoiding a case of bone marrow aplasia makes it ethically available.

New research is looking for other methods for the detection of intraerythrocyte metabolites of AZA by HPLC-UV, which are specific and sensitive for the monitoring of Crohn's disease treatment[4], however many studies still need to be performed to arrive at a more specific determination.

Subsequent to severe neutropenia, the patient presented positive cultures for Pseudomona aeruginosa, which was considered a highly prevalent opportunistic pathogen in febrile neutropenia and has caused approximately 30% mortality in patients with underlying hematologic/oncologic disorders in the 2000s.[14] Fortunately, in our patient it was a multisensitive strain, so she presented a good response to the antibiotic management administered.

FINAL CONSIDERATIONS

In conclusion, azathioprine is an effective immunomodulator in the treatment of autoimmune diseases; myelotoxicity is an adverse effect present in some cases. According to the literature, it could be avoided by monitoring TPMT activity; however, its use is still controversial due to the existence of adverse effects, even with normal TPMT values, as occurred in this case; likewise, it does not replace continuous monitoring by means of hemograms.

Autoimmune hepatitis is a chronic and progressive disease that is diagnosed by hepatogram and antibodies, however, the definitive diagnosis is made with a liver biopsy, a test that was not performed in the patient and its correct diagnosis remains in doubt.

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