Clinical case
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Azathioprine-induced myelosuppression in Sjogren's syndrome.

Mielosupresión inducida por azatioprina en síndrome de Sjögren

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Abstract

BACKGROUND: Sjogren's syndrome is an autoimmune disease, which affects exocrine glands, presenting oral and ocular dryness, moreover, it's considered a rheumatic disease, manifesting pain and swelling in joints. This disease is commonly treated with artificial tears, but can be prescribed some drugs, such as muscarinic agonists, ophthalmic cyclosporine, hydroxychloroquine, azathioprine, and methotrexate (arthralgias and cutaneous manifestations). Azathioprine is associated with several adverse events; myelosuppression, hepatotoxicity and tremors are the most harmful clinical outcomes. These adverse events depend on the duration of treatment, but some genetic conditions lead a faster develop of these events. The measure of thiopurine methyltransferase (TPMT) activity is recommended by Food and Drug Administration (FDA) in patients with azathioprine treatment, although it is poorly accessible in most hospitals.

CLINICAL CASE: A 53-year-old female patient with azathioprine-induced myelosuppression after being treated a short period due to Sjogren's syndrome. This is a common drug prescribed in several rheumatology diseases, and these clinical outcomes need to be taken into consideration.

CONCLUSIONS: Nowadays Sjogren's disease is treated with some different drugs including azathioprine, although cytopenia or myelosuppression are the main severe adverse effects, literature reported a 15.2% of hepatotoxicity, and 9.1% of myelosuppression, of which 17.3% reported pancytopenia.

KEYWORDS: Azathioprine; Pancytopenia; Sjogren's syndrome; Autoimmune disease.

Resumen

ANTECEDENTES: El síndrome de Sjögren es una enfermedad autoinmunitaria que afecta las glándulas exocrinas, causa sequedad oral y ocular, además, se considera una enfermedad reumática, manifestándose dolor e inflamación en las articulaciones. Esta enfermedad se trata comúnmente con lágrimas artificiales, pero pueden prescribirse algunos fármacos, como agonistas muscarínicos, ciclosporina oftálmica, hidroxicloroquina, azatioprina y metotrexato (artralgias y manifestaciones cutáneas). La azatioprina se asocia con varios eventos adversos; la mielosupresión, la hepatotoxicidad y los temblores son los resultados clínicos más dañinos. Estos eventos adversos dependen de la duración del tratamiento, pero algunas afecciones genéticas conducen a una aparición más rápida de estos eventos. La medición de la actividad de la tiopurina metiltransferasa (TPMT) está recomendada por la FDA en pacientes en tratamiento con azatioprina, aunque es poco accesible en la mayor parte de los hospitales.

CASO CLÍNICO: Paciente femenina de 53 años de edad con mielosupresión inducida por azatioprina luego de ser tratada por un corto periodo por síndrome de Sjögren. Éste es un fármaco comúnmente prescrito en varias enfermedades reumatológicas y estos resultados clínicos deben tenerse en cuenta.

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CONCLUSIONES: En la actualidad la enfermedad de Sjögren se trata con diferentes fármacos, entre ellos la azatioprina, aunque la citopenia o la mielosupresión son los principales efectos adversos graves, la bibliografía reporta un 15.2% de hepatotoxicidad y un 9.1% de mielosupresión, de los cuales un 17.3% reporta pancitopenia.

PALABRAS CLAVE: Azatioprina; pancitopenia; síndrome de Sjögren; enfermedad autoinmunitaria.

INTRODUCTION

The clinical outcomes of azathioprine are associated with several adverse events as myelosuppression, hepatotoxicity, and tremors; but these clinical features are dose dependent, being fever, rash, nausea, and pancreatitis dose-independent manifestations.[1]

Some of these clinical manifestations depends on the durations these adverse effects dependent on the duration of treatment, genetic polymorphism, and mainly the thiopurine methyltransferase (TPMT) activity. A high quantity of 6-thioguanine nucleotide, a metabolite of azathioprine, is related to myelotoxicity.[2]

Some cytopenia are seen as leucopenia, thrombocytopenia or even pancytopenia, but these two lasts are uncommon. These hematological findings are seen in rheumatology ills treatments as lupus nephritis, myasthenia gravis, inflammatory bowel disease, dyshidrotic eczema, psoriatic arthritis, rheumatoid arthritis, and even through organ transplant therapy.[3]

Even some different reports have studied the timing until myelosuppression, a time hasn't yet been accorded, but it was suggested that timing of bone marrow toxicity can be as soon as 2 weeks and delayed up to 11 years, with a median time of onset of 9 months.[2]

According to some reports, it was reported a 15.2% of hepatotoxicity, and 9.1% of myelosuppression, of which 17.3% reported pancytopenia.[1]

High azathioprine levels and low TPMT activity are the main features required to induce pancytopenia. These could be explained because TPMT converts the azathioprine derivative 6-MP to inactive metabolites; because of the lower TPMT activity, 6-MP use an alternate metabolism way, buildup of 6-thioguanine nucleotides, which incorporation into DNA and RNA leads to cytotoxicity and myelosuppression. Some genetical conditions as polymorphisms of TPMT decrease its activity, although pancytopenia is a rare complication, homozygous and heterozygous variant TPMT alleles (TPMT*2, TPMT*3A and TPMT*3C) predispose individuals to greater azathioprine toxicity.[4]

The xanthine dehydrogenase/oxidase is a NAD dependent molybdenum containing hydroxylase which catalyzes the purine degradation, catalyzing the oxidation of 6-mercaptopurine to 6-thioxanthine and 6-thiouric acid.[5]

A low TPMT activity is associated with high quantity of 6-thioguanine nucleotide, increasing myelosuppressive effect, and several clinical outcomes, being a recommendation of Food and Drug Administration (FDA) a genetic

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testing for TPMT before starting azathioprine treatment.[6]

CLINICAL CASE

A 53-year-old female patient with history of subclinical hypothyroidism treated with levothyroxine 25 µg, L5-S1 radiculopathy and osteopenia untreated; Sjogren disease diagnosed with lip biopsy 11 years ago, treated with chloroquine and methotrexate from 2018-2020, stopped due to high blood transaminases, replaced with azathioprine 3 months previous to hospitalization. She was admitted due to upper respiratory tract infection and pancytopenia, without Sjogren's activity (ESSDAI: 0). First days she presented febrile syndrome, treated as a nosocomial infection indicating Meropenem with poor clinical improvement, the fever subsided, adding diarrhea and abdominal pain treated with metronidazole for 3 days; thyroid test, viral panel test, Coombs test, C4, C3, urine analysis, urine culture, blood culture, and abdominal ultrasound were normal, without abnormalities. Hematology department practiced bone marrow examination where hypocellularity was evidenced (**Figure 1**). She was

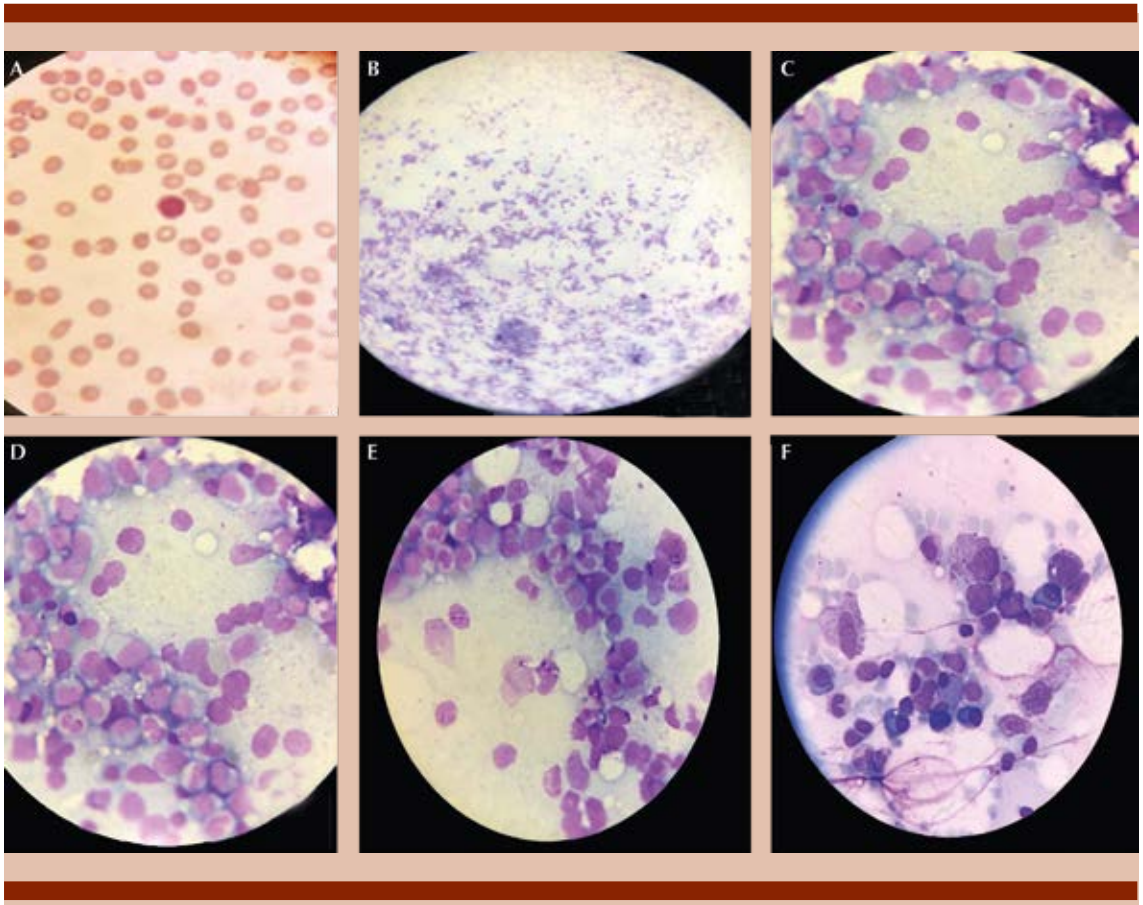

Figure 1. A. Peripheral blood smear, the red cells are microcytic, hypochromic, and a small lymphocyte is shown. **B.** Bone marrow examination, 10x, decreased cellularity and megakaryoblasts present. **C-E.** Bone marrow 100x, with Wright's stain, loss of erythroid myeloid relationship is observed, dysplastic young granules, as well as some adults, decreased normoblasts, no blasts are observed. **F.** Some non-clonal plasma cells of reactive origin are observed.

treated for severe neutropenia with filgrastim and methylprednisolone, dexamethasone 6mg regimen; once platelets were normal, prophylactic enoxaparin was started. Patient remained hospitalized until she recovered from pancytopenia, being discharged with steroid treatment, and sent to third level rheumatology service.

DISCUSSION

Nowadays Sjogren's disease is treated with some different drugs including azathioprine, although cytopenia or myelosuppression are the main severe adverse effects, literature reported a 15.2% of hepatotoxicity, and 9.1% of myelosuppression, of which 17.3% reported pancytopenia,[1] delaying up to 11 years, with a median time of onset of 9 months;[2] however, our patient developed these adverse events in a short lapse of time, remarking that any other myelosuppressive treatment was taken. The higher azathioprine doses and low TPMT activity levels are the two main features needs to produce myelosuppression the buildup of 6-thioguanine nucleotides and its incorporation into DNA and RNA leads to cytotoxicity and myelosuppression,[4] reason why the FDA recommends the TPMT genotype or phenotype testing in all patients before initiating treatment with azathioprine.[6] A key step in the treatment of these events, is the replace of azathioprine to another non suppressive drug, to raise blood cells, or even the use of granulocyte colony stimulating factor (G-CSF) to avoid cytopenia complications.

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