Fever induced by mesalazine☆

Fiebre por mesalazina

Mesalazine (5-aminosalicylic acid) is an effective drug for inducing and maintaining remission in inflammatory bowel disease, especially ulcerative colitis.[1] It is considered a safe drug, with good tolerance and very few adverse effects, which include, due to their potential severity, hypersensitivity reactions with renal, pulmonary or myo-pericardial involvement, sometimes accompanied by fever[2]; however, fever as a predominant symptom in mesalazine-induced hypersensitivity reactions is extremely rare.[3] Moreover, drug-induced fever is considered an uncommon clinical problem, although its actual incidence rate is unknown because symptoms are probably often misdiagnosed.[4] The list of drugs involved is very long, although beta-lactam antibiotics stand out due to the frequency of drug-induced fever with these drugs.[5] The focus of this article is a case of mesalazine-induced fever.

This case involved a 57-year-old female patient with no history of interest, except for Crohn's disease, which was classified as A3L3B1 according to the Montreal classification, together with spondyloarthropathy, spine involvement and bilateral sacroiliitis, with no regular treatment except for celecoxib. She denied any past consumption of alcohol, drugs or herbal products. She visited her doctor due to a mild disease flare-up for which she was prescribed treatment with oral mesalazine at a dose of 3 g/day. After 15 days, she started to experience symptoms of a fever of up to 39 °C, chest pain, difficulty breathing and vomiting. Upon examination, the only significant finding was a blood pressure (BP) of 90/40 mmHg. Significant lab test results included alanine aminotransferase (ALT) 215 U/l, aspartate aminotransferase (AST) 170 U/l, gamma-glutamyl transferase (GGT) 222 U/l, alkaline phosphatase (ALP) 179 U/l and C-reactive protein (CRP) 2.69 mg/dl. Her bilirubin, procalcitonin, myocardial injury markers and haemoglobin levels and her platelet and white blood cell count were normal. She began treatment with fluid therapy, broad-spectrum antibiotics, steroids and noradrenaline infusion and discontinued mesalazine. She had a favourable clinical outcome with the fever disappearing within the first 24 hours. Blood and urine cultures, Epstein–Barr virus (EBV), hepatitis C virus (HCV) and cytomegalovirus (CMV) tests and autoantibody tests were negative. Her hepatitis B virus (HBV) test showed a pattern of immunity. An electrocardiogram, chest X-ray and abdominal CT scan were normal. CT angiography was performed, which ruled out pulmonary thromboembolism, and a transthoracic echocardiogram was done, which showed no ventricular contractility abnormalities, pericardial effusion or other pathologically significant data. After stabilising the patient, a controlled provocation test was performed with 500 mg of oral mesalazine and the patient once again experienced a high fever within a few hours of re-exposure, which improved with symptomatic treatment. During follow-up after discharge, the patient's liver function tests returned to normal; abnormal liver function test results were not observed in tests performed prior to the episode either. The case was reported to the Pharmacovigilance Unit of Osakidetza-Servicio Vasco de Salud [Basque Health Service].

Drug-induced fever is defined as a febrile reaction coinciding with administration of a drug and disappearing after discontinuation of the drug, when no other cause for the fever or other specific associated clinical manifestations are identified.[4,5] The most likely mechanism of drug-induced fever is a hypersensitivity reaction. Early recognition is vital to avoid complications, prolonged hospitalisations, unnecessary diagnostic procedures or treatments, and new exposures to the drug involved.

Adverse effects with mesalazine are uncommon and are similar to those with placebo in clinical trials. The most common are diarrhoea (3%), headache (2%), nausea (2%), skin rash (1%) and thrombocytopenia (<1%).[6] Isolated cases of pulmonary toxicity, myocarditis, pericarditis, pericardial effusion, granulomatous hepatitis, pancreatitis, eosinophilia, interstitial nephritis or nephrotic syndrome have been reported.[2,7] The most likely pathogenic mechanism is a hypersensitivity reaction to the drug that is similar to *Drug Reaction with Eosinophilia and Systemic Symptoms* (DRESS) syndrome,[2] although it is sometimes difficult to determine whether these manifestations are in fact complications of the underlying disease and not associated with exposure to mesalazine.[7] In many of these cases, fever accompanies other clinical findings. However, cases of fever as a predominant symptom associated with mesalazine use are very rare[3,8–10] and have the common factor that clinical suspicion was early and withdrawal of mesalazine was very fast. In our case study, fever was the predominant symptom. Hepatotoxicity was mild and reversible and the ECG, laboratory tests, echocardiogram and CT ruled out the presence of myocarditis or heart or pulmonary involvement. As in similar cases, mesalazine treatment was discontinued at an early stage; it is also likely that continued treatment may have led to more severe symptoms with more significant hepatotoxicity or heart involvement. In previous cases of mesalazine-induced fever, reappearance of fever has been documented after using different mesalazine formulations,[3] and in one additional case, successful desensitisation was achieved after resolving all symptoms.[8]

With regard to determining the causal relationship between fever and mesalazine exposure, our case meets the criteria established by the algorithm of the Spanish Pharmacovigilance System,[11] achieving a score of 9, which allows the adverse reaction to be classified as mesalazine-induced fever. However, in order to confirm this classification, re-exposure to the drug is required, which is not free of risk and should not be performed in severe cases.[4]

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Hepatoblastoma: A success report using a combination therapy with preoperative arterial embolization☆

Hepatoblastoma: éxito de terapia combinada con embolización arterial preoperatoria

Hepatoblastoma is the most common hepatic tumour in children, accounting for 90% of all malignant liver tumours. It is usually diagnosed during the first 3 years of life.[1,2] Signs and symptoms are very subtle, with the main clinical manifestations including abdominal distension and a palpable abdominal mass. For diagnosis, alpha-fetoprotein (AFP) levels, compatible imaging studies and suggestive signs and symptoms are required; however, histological diagnosis of the tumour also plays an important role.[1] Survival rates of these patients have improved significantly over the last 3 decades, currently achieving rates of around 75–80%. This improvement is due to advances in therapy.[2]

Our case study involves a 2-year-old child with no personal or family history of disease, good overall health and no previous symptoms. The child visited the paediatric emergency department with symptoms of bronchiolitis. Upon physical examination, hepatomegaly was detected with no other findings. As a result, an abdominal ultrasound (hepatomegaly) and AFP tests (152,370 ng/ml) were performed. Since a liver tumour was suspected, the child was referred to the paediatric oncology clinic where he underwent imaging studies (Fig. 1: bulky tumour measuring 11 cm long × 6 cm thick, confined to the right lobe of the liver, without exceeding beyond the round ligament, with no portal vein thrombosis, but with compression/encasement of the hepatic hilar vessels) and a liver biopsy, which confirmed the diagnosis of foetal hepatoblastoma. Taking into consideration the *Pretreatment Extent of Disease* (PRETEXT) staging and risk stratification system proposed by the *Société Internationale d'Oncologie Pédiatrique-Epithelial Liver Tumor Study Group* (SIOPEL), the tumour was classified as PRETEXT III, considered inoperable, and therefore treatment was started with cisplatin.[3] The subsequent decision to start more aggressive chemotherapy with cisplatin, carboplatin and doxorubicin was due to suspected encasement of the hepatic hilar vessels. After 3 cycles of chemotherapy, an MR angiogram was performed which revealed overall

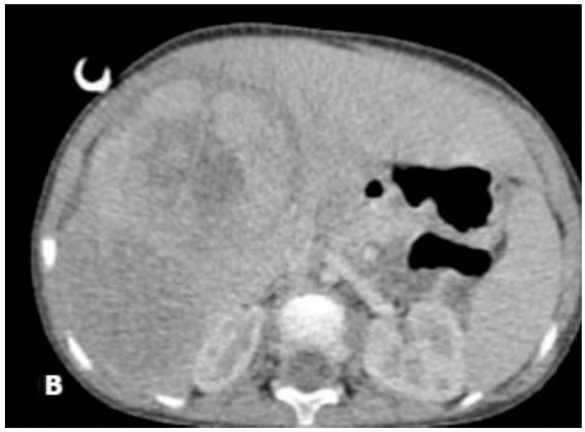

Figure 1 CT image of the abdomen at diagnosis.

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