ASTHMA ALLERGY IMMUNOLOGY
ASTIM ALLERJİ İMMÜNOLOJİ

doi: 10.21911/aai.447
Asthma Allergy Immunol 2019;17:169-171

CASE REPORT

Received: 19/09/2018 • Accepted: 15/03/2019
Online Published: 01/10/2019

An Indolent Cause of Recurrent Anaphylaxis with NSAIDs: Systemic Mastocytosis

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ABSTRACT

Systemic Mastocytosis (SM) is one of the subtypes of mast cell disorders. Patients with SM suffer from flushing, abdominal cramps and hypotension. It may also cause unexplained and recurrent anaphylactic episodes sometimes. The secretion of mediators can be triggered by various factors.

Non-steroidal anti-inflammatory drugs (NSAIDs) are extensively used for their analgesic, antipyretic and anti-inflammatory properties, and they are one of the most commonly prescribed drugs in the world. On the other hand, they may cause a group of adverse reactions, ranging from mild reactions like gastritis to life-threatening allergic reactions like anaphylaxis.

In this paper, we report a patient who had multiple severe adverse reactions against NSAIDs and was referred to our clinic to find a safe alternative NSAID. She was eventually diagnosed with Indolent SM (ISM) when she was evaluated with all of her systemic complaints and symptoms.

Keywords: Systemic mastocytosis, Anaphylaxis, NSAIDs

INTRODUCTION

Mast cell disorders (MCDs) refers to a group of diseases characterized by activation and/or abnormal proliferation and accumulation of mast cells (MCs) in various organs. Signs and symptoms vary depending on the infiltrated tissue and organs. Systemic Mastocytosis (SM) is one of the subtypes of MCDs. In SM, abnormal MCs accumulate in the skin, bone marrow or other tissues. Patients with SM suffer from flushing, abdominal cramps and hypotension. These symptoms last for minutes to several hours. It may also cause unexplained and recurrent anaphylactic episodes sometimes (1,2).

The secretion of mediators can be triggered by various factors in SM. Insect venom and Hymenoptera stings are prominent triggers. Certain medicines like codeine, morphine, radiocontrast media, aspirin, non-steroidal anti-inflammatory drugs, etc may cause MC degranulation. Alcohol ingestion and spices are also important triggers. In addition, physical factors such as cold or heat exposure, massage, sports or surgical interventions may initiate the mediator release from MCs. In some patients, emotional changes alone may be the causative factor for MC activation (3,4).

Non-steroidal anti-inflammatory drugs (NSAIDs) are one of the most commonly prescribed drugs in the world (5), and adverse reactions with this group of drugs are also quite prevalent (6). Risk factors for the development of drug allergy must be kept in mind to understand the underlying mechanism. It is essential to prevent subsequent adverse events (7).

In this paper, we report a patient who had multiple severe adverse reactions against NSAIDs and was referred

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to our clinic to find a safe alternative NSAID. She was eventually diagnosed with Indolent SM (ISM) when she was evaluated with all of her systemic complaints and symptoms.

CASE

A 46-year-old female patient, who had multiple severe adverse reactions against NSAIDs, was referred to our Allergy Immunology Clinic to find a safe alternative NSAID.

Her first reaction was against salicylic acid about 20 years ago, and she experienced flushing, dyspnea, loss of consciousness and hypotension within half an hour after orally taking a 100 mg aspirin tablet. She was successfully treated in the emergency service with intramuscular epinephrine. She described multiple similar occasions with paracetamol and naproxen sodium (different brands) in the subsequent years, all of which required going to the emergency service.

So far, the medical history was consistent with the "usual drug reactions history". She was asked for additional illnesses and systemic symptoms that she might have. She had hypothyroidism but was in euthyroid state with levothyroxine replacement. She also had lower back pain due to a herniated disk. In addition, she described an important detail that provided a clue for the diagnosis. She defined occasional flushing episodes, with and without itching, especially with emotional stress. This information changed the direction of the evaluation of the patient and we decided to investigate for mast cell diseases.

She had no typical skin lesions, Darier sign or gastrointestinal symptoms. As a first step, serum total tryptase was measured (UniCAP-Tryptase fluoroimmunoassay-Pharmacia & Upjohn, Uppsala, Sweden). The result revealed a high level of tryptase at 95.5 ng/ml (<11.4 ng/ml). The patient was asymptomatic at the time the blood sample was drawn. When she was retested by the same method after 1 month, a higher level of serum tryptase was obtained at 124 ng/ml.

A hematology specialist was consulted and bone marrow aspiration and biopsy were performed. In addition, two other diagnostic tests for aberrant expression of CD25 or CD2 on flow cytometry and KIT gene mutation analysis were also planned.

Bone marrow aspirate showed a hypercellular bone marrow, The MC ratio was 5 percent. Bone marrow biopsy material was evaluated using CD117, CD68, CD3, CD20, CD41, CD34 and reticulin stains. CD117 (+) MC aggregates were detected at a ratio of 25%. In addition, myelofibrosis with increased reticulin fibers and normal myeloid and erythroid maturation were detected. We could not apply CD2 and CD25 because there was no kit in our department (Figure 1A-C).

Flowcytometric and genetic investigations could not be performed because of the temporary technical problems of the related laboratories. All other tests revealed normal results, including no hepatomegaly and/or splenomegaly, no extramedullary involvement, and no bone loss (osteopenia and/or osteoporosis).

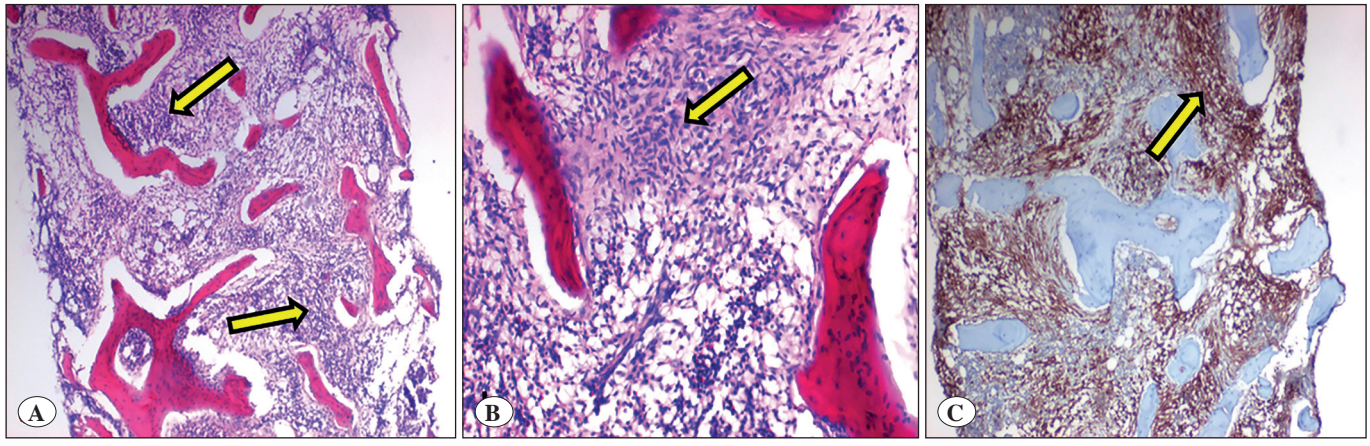

Figure 1. A) x40 H&E Hypercellular bone barrow, **B)** x100 H&E The aggregates of spindle-shaped mast cells (yellow arrow), **C)** x40 Immunohistochemical CD-117 expression in mast cells (yellow arrow).

The results were interpreted according to the WHO Diagnostic Criteria for Systemic Mastocytosis (4), and the diagnosis of Indolent Systemic Mastocytosis (ISM) was made.

DISCUSSION

Drug reactions present a very large clinical spectrum from ordinary urticaria to anaphylaxis. Determination of the responsible drug is essential to prevent possible reactions in the future, particularly in patients with recurrent anaphylaxis. However, finding the responsible drug is not enough on its own. Facilitating factors and/or worsening factors of anaphylaxis should also be investigated, including beta blocker or ACE inhibitor use and coexisting obstructive airway disease or heart disease.

The prevalence of anaphylaxis among patients with MCDs is higher than in the general population, and the cumulative incidence of anaphylaxis in adults with mastocytosis is 49% (8). The presence of mastocytosis makes the patient susceptible to anaphylaxis through the release of histamine from the abundant mast cells. Investigation for MCDs in patients with a history of recurrent anaphylaxis is therefore essential (1,9,10).

A high serum tryptase level is the most valuable evidence of mast cell activation in patients clinically suspected of suffering from MCDs. However, a high serum tryptase level is not specific to mastocytosis and a decision should not be made with a single measurement.

In patients clinically suspected of suffering from mastocytosis, basal serum tryptase levels higher than 20 ng/ml on two occasions support the diagnosis. In case of a normal basal level of tryptase, a second measurement obtained immediately after the symptoms may be useful. Increases greater than 1.2 x baseline value + 2 ng/mL are suggestive for mast cell activation (2).

In conclusion, MCDs are rare disorders. It is therefore always possible to overlook patients with MCDs. To be able to diagnose MCDs, abnormal mast cell activation must be kept in mind in every case of recurrent anaphylaxis, idiopathic anaphylaxis or drug-induced anaphylaxis.

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