

## References

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## Response to celecoxib in a patient with indolent systemic mastocytosis presenting with intractable diarrhea



Systemic mastocytosis (SM) comprises a group of disorders characterized by an abnormal proliferation and accumulation of mast cells (MCs) in different organs and tissues, such as bone marrow and skin and gastrointestinal tract. Diarrhea due to MC mediator release is a common symptom in SM, usually well controlled with adequate therapy, such as the MC stabilizer oral disodium cromolyn. Celecoxib is a sulfa nonsteroidal anti-inflammatory drug (NSAID) and selective cyclooxygenase 2 (COX-2) inhibitor used in the treatment of acute pain and reduction of polyps in familial adenomatous polyposis and solid tumors<sup>1</sup>

A 52-year-old woman with a 32-year history of maculopapular skin lesions was referred to our center for pruritus, flushing, nausea, and diarrhea. A complete bone marrow study<sup>2</sup> revealed the presence of morphologic abnormal MCs, forming aggregates that aberrantly expressed CD25<sup>bright+</sup> and comprised 0.3% of the bone marrow cellularity as assessed by flow cytometry. Applying a peptide nucleic acid-mediated polymerase chain reaction method to highly purified fractions of bone marrow populations,<sup>3</sup> the D816V *KIT* mutation was identified in MCs and other myeloid lineages. The patient presented with a serum tryptase level of 99 ng/mL (ImmunoCAP Tryptase System; ThermoFisher Scientific Inc, Waltham, Massachusetts) at basal conditions, and a diagnosis of indolent SM was established based on the World Health Organization criteria for SM. The patient began antimediation therapy with oral disodium cromolyn and histamine<sub>1</sub> and histamine<sub>2</sub> antihistamines, causing control of her symptoms.

One year after referral, the patient developed an invasive ductal carcinoma stage I breast cancer, and she required a lumpectomy plus axillary lymph node removal followed by radiation therapy for 2 months and hormone therapy with tamoxifen during 5 years. When tamoxifen treatment was stopped, the patient experienced a marked increase in the severity and frequency of diarrhea (>9 diarrheic stools per day).

Despite the mastocytosis history of the patient, we performed a complete gastroenterologic study consisting of a routine peripheral blood cell count and differential diagnosis; routine biochemical analysis; stool analysis with microscopic examination; chemical, biological, and fecal occult blood tests; bacteriological culture; abdominal ultrasonography; and gastrointestinal pan-endoscopy with biopsies to rule out other causes of the diarrhea. All these test results were negative, and the underlying mastocytosis was assumed to be the most probable origin of her symptoms. On the basis of that belief, the antimediation therapy was increased by adding montelukast and oral corticosteroids to the previous treatment; the corticoid therapy initially consisted of prednisone (0.3 mg/kg daily) and was later replaced by budesonide (9 mg/d with progressively decreasing doses). This approach, however, did not improve the symptoms, and the diarrhea remained out of control.

For this reason, a treatment with scheduled celecoxib was proposed; however, the patient referred not to have taken NSAIDs or cyclooxygenase inhibitors since the onset of her indolent SM, and, for this reason, the tolerance to celecoxib was unknown. To address this issue, an open oral challenge with celecoxib was performed, reaching a total dose of 350 mg, which was well tolerated by the patient. On the basis of these findings, 200 mg/d of celecoxib was added to the treatment, leading to a complete response of the diarrhea in 4 days. Serum prostaglandin E<sub>2</sub> metabolites were determined before celecoxib therapy by radioimmunoassay, with a resulting level greater than 750 pg/mL. One month after initiation of treatment, there was a significant reduction in prostaglandin E<sub>2</sub> production (583 pg/mL). The patient was then prescribed celecoxib at demand, and a complete resolution of the gastrointestinal symptoms was reached during a 2-year follow-up.

Activation of MCs can be triggered in allergic and nonallergic diseases by several immunologic pathways, such as cross-linking of IgE with FcεRI, Fcε receptors, complement proteins, IgG and C3a aggregates, Toll-like receptors 4 and 2, CD48, complement receptor, and other nonimmunologic signaling. When MCs are activated, they release mediators, including arachidonic acid metabolites, such as leukotrienes and prostaglandins, among others. These mediators can elicit MC-related symptoms (pruritus, hives, flushing, tachycardia, abdominal pain, diarrhea, and/or syncopal or presyncopal episodes). Although NSAIDs can evoke MC-related symptoms, their therapeutic utility was described in a subset of patients with mastocytosis who experienced symptoms due to the release of prostaglandins<sup>4</sup>; these beneficial effects were associated with a reduction in prostaglandin synthesis due to the NSAIDs' capacity to block COX activity and therefore prevent the enzymatic conversion of arachidonic acid into its aforementioned mediators. Prostaglandins appeared to play an important role in modulating colonic epithelial secretion and were closely associated with acute inflammatory conditions, contributing to edema formation through their vasodilator effects, generating hyperalgesia, and regulating the contractile activities of digestive smooth muscle.<sup>5</sup> In addition, the potential COX-2 contribution to the colonic barrier dysfunction has also been described.<sup>5</sup>

There are 2 isoforms of COX enzymes: COX-1 and COX-2. COX-1 was considered to be the constitutive isoform and was expressed in almost all tissues. It was found in abundance in the gastrointestinal tract and produced prostaglandins with cytoprotective and physiologic functions, such as control of mucosal blood flow and electrolyte secretion; on the other hand, COX-2 was considered inducible by inflammatory cytokines, so its derived prostaglandins were considered deleterious. Unlike COX-1, COX-2 was only found at sites of inflammation and was able to exacerbate the inflammatory response; in this regard, a constitutive expression of COX-2 in several tissues (including colon) was also reported, changing the classic conception of the physiologic role of the COX enzymes.<sup>6</sup> In addition, it was reported

that in a variety of cultured cells the induction of COX-2 is regulated by different mitogen-activated protein kinases in each cell type.<sup>7</sup> It is well known that selective COX-2 inhibitors can attenuate the bowel smooth muscle contractility and can be beneficial in inflammatory bowel disease.<sup>8</sup> Moreover, this case presents a patient with clinical worsening due to a marked increase in MC mediator–related symptoms after tamoxifen treatment discontinuation. The case illustrates that tamoxifen might inhibit MC mediator release in vivo because it was previously reported that tamoxifen had the ability to block in vitro the high-affinity estrogen receptors expressed in MCs and subsequently to inhibit MC mediator release due to down-regulation of protein kinase C activity.<sup>9</sup>

On the basis of these observations, we hypothesize that in this case the intractable diarrhea could be secondary to an increase in COX-2 activity due to the underlying SM; this notion was also supported by the excellent response to the selective COX-2 inhibitor celecoxib. Because this drug used in short cycles has exceptional adverse effects when it is compared with other nonselective NSAIDs, we propose it as a candidate to treat the acute episodes of gastrointestinal MC-related symptoms in mastocytosis. Moreover, the measurement of mediators that can act as proinflammatory markers, such as prostaglandin E<sub>2</sub>, may be useful in these patients as a potential biomarker that correlates with clinical response.

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