Papel dos Neuropéptidos nas Manifestações Gastrointestinais Associadas à Mastocitose Sistémica e Semelhanças com a Síndrome do Intestino Irritável

Role of Neuropeptides in Gastrointestinal Manifestations of Systemic Mastocytosis and Similarities with Irritable Bowel Syndrome

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Resumo:

A mastocitose sistémica (MS) é uma neoplasia mieloproliferativa rara caracterizada pela proliferação extracutânea de mastócitos clonais na medula óssea ou em outros sítios extramedulares, com ou sem envolvimento cutâneo. As manifestações gastrointestinais (GI), consistindo em dor abdominal, diarreia e má absorção com vários graus de gravidade, são frequentes em pacientes com MS e podem resultar da infiltração direta do trato GI e/ou da libertação de mediadores produzidos por estas células. A síndrome do intestino irritável (SII) é um distúrbio funcional do intestino caraterizado por dor abdominal crónica e recorrente, desconforto associado à defecação e alterações dos hábitos intestinais. A interação entre o sistema imunológico e os neuropéptidos e a intensificação de uma resposta inflamatória da mucosa com um aumento nas células imunológicas é uma característica chave da SII. Evidências anteriores mostram que há um aumento do número de mastócitos na mucosa intestinal e do cólon de doentes com SII. Os mastócitos estão presentes no tracto GI e sua ativação foi associada a alguns neurotransmissores pró-secretores, como a substância P e o peptídeo intestinal vasoativo, na proximidade de nervos entéricos, sugerindo uma via regulatória bidirecional com controlo da ativação dos mastócitos. A investigação sobre o papel dos mastócitos entéricos na MS e na SII ainda é escassa, bem como sua ligação com os neuropéptidos. Da mesma forma, são necessárias mais evidências sobre a interação entre mastócitos e neuropéptidos para compreender melhor a fisiopatologia das manifestações GI associadas à MS e à SII, e as fronteiras entre estas patologias. Nesta revisão, colocamos a hipótese dos sintomas GI em doentes com MS e em doentes com SII terem mecanismos e mediadores semelhantes, com um foco especial no papel do MC da mucosa e neuropéptidos.

Palavras-chave: Diarreia; Mastócitos; Mastocitose Sistémica; Neuropéptidos; Péptido Intestinal Vasoativo; Síndrome do Intestino Irritável; Substância P; Trato Gastrointestinal.

Abstract:

Systemic mastocytosis (SM) is a rare myeloproliferative neoplasm characterized by the extracutaneous proliferation of clonal MC in the bone marrow or other extramedullary sites with or without cutaneous involvement. Gastrointestinal (GI) manifestations, consisting of abdominal pain, diarrhea and malabsorption with various degrees of severity, are frequent in patients with SM and can result from mediator release or direct MC infiltration of the GI tract. Irritable bowel syndrome (IBS) is a functional bowel disorder characterized by chronic and recurrent abdominal pain or discomfort associated with defecation or change in bowel habit. The interaction between immune system and neuropeptides and the enhancement of an inflammatory mucosal response with an increase in immune cells is a key feature of IBS. Previous evidence shows that there is an increased number of MC in the intestinal and colonic mucosa of IBS patients. MC are present in the GI and their activation has been associated to some pro-secretory neurotransmitters such as substance P and vasoactive intestinal peptide in the proximity of enteric nerves suggesting a bidirectional regulatory pathway with neurocrine control of MC activation. Research concerning the role of enteric MC in both SM and IBS is still scarce as well as their link to neuropeptides. Likewise, more evidence is needed regarding MC and neuropeptides interaction in order to further comprehend the pathophysiology of the GI manifestations of SM and IBS, and the boundaries between these pathologies. In this review we hypothesize that GI symptoms SM and in IBS have similar mechanisms and mediators, with a special focus in the role of mucosal MC and neuropeptides.

Keywords: *Diarrhea; Gastrointestinal Tract; Irritable Bowel Syndrome; Mast Cells; Mastocytosis, Systemic; Neuropeptides; Substance P; Vasoactive Intestinal Peptide.*

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Introduction

Mast cells (MC) are major effector cells of the allergic response and play an important role in immunity by releasing preformed mediators from granules, newly formed mediators or cytokines on activation. These mediators in the gastrointestinal (GI) tract can affect ion secretion, epithelial barrier function and enhance an inflammatory response to local threats such as bacterial and parasitic infections.

Mastocytosis is a heterogeneous group of hematologic neoplasms involving the abnormal growth and accumulation of clonal MC, in one or more organs that are classified in three main categories: cutaneous mastocytosis (CM), systemic mastocytosis (SM) and mast cell sarcoma.[1,2] Although CM is the most common form of presentation of the disease particularly in children and associated with a good prognosis, SM is responsible for various clinical presentations in adult patients.

Systemic mastocytosis is characterized by an abnormal clonal expansion and activation of MC in the tissues, other than skin.[2] Bone marrow is the organ most common infiltrated, followed by the gut. GI manifestations, consisting of abdominal pain, diarrhea and malabsorption with various degrees of severity, are frequent in patients with SM and can result from mediator release or direct MC infiltration of the GI tract. Diagnosis of GI mastocytosis can be a puzzling diagnosis, as symptoms simulate other more common GI diseases, a correct patient´s workup requires a multidisciplinary approach, high index of suspicion to request the appropriated complementary exams.[3]

Irritable bowel syndrome (IBS) is a functional bowel disorder characterized by chronic and recurrent abdominal pain or discomfort associated with change in bowel habit. Although its causative mechanism is not entirely understood, it is accepted that it results from a complex interaction between both host and environmental factors.[4] Clinical manifestations include recurrent diarrhea or constipation and abdominal pain that are a major source of distress for IBS patients. Moreover, they can be similar to those presented by some SM patients with GI involvement. MC have been identified in several studies as a remark cell component of the GI tract of IBS patients, suggesting that they may be part of the pathophysiology of IBS symptoms in a subset of patients. Research concerning the role of enteric MC in both SM and IBS is still scarce as well as their link to neuropeptides.

Mast cell activation can induce release of pre-formed mediators such as histamine and tryptase from MC granules, as well as release of de novo synthesized lipid mediators, cytokines, and chemokines that influences various physiological and pathological responses.[5] In particularly, MC activation has been associated to pro-secretory neurotransmitters such as substance P (SP) and vasoactive intestinal peptide (VIP) in the proximity of enteric nerves suggesting a bidirectional regulatory pathway with neurocrine control of MC activation.

In this review we tried to demonstrate the hypothesis that GI symptoms in SM have a similar mechanisms and mediators as those in IBS with a special focus in the role of mucosal MC and neuropeptides. Moreover, considering the connection between the MC, the GI tract and the nervous system as a remark of the immune-neural interactions,[6] we further suggest that GI regulatory peptides that might be involved in pathways of diarrhea in SM are similar to those in diarrhea-predominant IBS and have MC as a common denominator.

Methods

A literature review was carried out using the platforms PubMed, GoogleScholar and Oxford Academic in July 2021 entering the keywords: systemic mastocytosis, irritable bowel syndrome, neuropeptides, substance P, vasoactive intestinal peptide. The inclusion criteria are original articles, revision articles and clinical cases. Exclusion criteria are non-English articles. The first revision of article names and abstracts identified the articles that fulfilled the criteria. The duplicates were removed, and the full texts of the remaining articles were reviewed.

SYSTEMIC MASTOCYTOSIS: A BRIEF REVIEW

Systemic mastocytosis is a rare myeloproliferative neoplasm characterized by the extracutaneous proliferation of MC in the bone marrow (BM) or other extramedullary sites with or without cutaneous involvement. Is occurs more frequently in adults and marginally more in men than women.[2] It can be further classified in five groups comprising indolent systemic mastocytosis (ISM), smoldering systemic mastocytosis (SSM), systemic mastocytosis with an associated hematological neoplasm (SM-AHN), aggressive systemic mastocytosis (ASM) and mast cell leukemia (MCL).[2]

The diagnosis of SM according to the World Health Organization 2016 classification criteria requires that 1 major criterion and 1 minor criterion or 3 minor criteria need to be fulfilled. The major criteria are multifocal dense infiltration of MC (15 or more cells) detected in BM and/or other extracutaneous organ, usually identified by the expression of CD117 (c-kit) and/or tryptase; minor criteria include serum tryptase concentration persistently above 20 ng/mL, more than 25% of the MC with abnormal morphological features (e.g., fusiform), aberrant CD2 or/and CD25 expression on MC, and detection of an activation *KIT* point mutation (more often D816V) (Table 1).[2]

The clinical manifestations of SM are diverse, and they may be caused by the infiltration of organs and tissues with the abnormal MC and/or depend on the effects of the mediators released by MC (Table 2).

GASTROINTESTINAL MANIFESTATIONS IN SYSTEMIC MASTOCYTOSIS

Gastrointestinal symptoms are common in SM and are estimated to be present in 60% up to 80% of patients.[7] They most commonly include abdominal pain, diarrhea, nausea, weight loss, bloating, vomiting or reflux.[8-11] These clinical

Table 1: World Health Organization 2016 criteria for diagnosis of systemic mastocytosis

Major	Multifocal dense infiltrates of MC (> 15 MC aggregating) detected in section of bone marrow and/or of other extracutaneous organ(s) by tryptase-immunohistochemistry or other stains
Minor	In MC infiltrates detected in sections of bone marrow or other extracutaneous organs, >25% of MC are spindle-shaped or: in bone marrow smears, atypical MC (type I plus type II) comprise >25% of all MC;Detection of a c-kit point mutation at codon 816 in bone marrow or blood or other extracutaneous organ(s);
If one major and one minor or three minor criteria are fulfilled then the diagnosis is SM	

MC, mast cells; SM, systemic mastocytosis * In case of SM associated hematopoietic clonal non-MC lineage disease (SM-AHNMD), this criterion is not valid.

Table 2: Mast cells mediators

Histamine	
Proteoglycans	Heparin, chondroitin sulfate E
Neutral proteases	Tryptase, chymase, carboxypeptidase A
Lipid-derived mediators	Prostaglandins (e.g. PGD2), thromboxanes, leukotrienes, HETEs, HPETEs.
Cytokines and chemokines	TNF-α. IL-4, IL-5, IL-6, IL-8, I-309, MCP-1, MIP-1α, MIP-1β

HETE, hydroxyeicosatetraenoic acid; HPETE, hydroperoxyeicosatetraenoic acid; IL, interleukin; MCP-1, monocyte chemoattractant protein-1; MIP-1, macrophage inflammatory protein-1; PGD2. prostaglandin D2, TNF, tumor necrosis factor.

manifestations are frequently chronic and a major source of morbidity and may be precipitated by exposure of MC degranulating agents, drugs, temperature, trauma, stress, and ingestions of certain foods.

The exact mechanisms and mediators that take part in the pathophysiology of GI symptoms are not entirely understood, however they may result from systemic and local release of MC mediators (e.g., histamine, leukotrienes, heparin, and proteases) or direct infiltration of GI mucosa by MC that results in local effects of mediators and malabsorption. Furthermore, GI involvement is not necessarily correlated to symptomatic mastocytosis, including in the form of aggressive disease, and studies have shown no relation between MC counts and GI symptoms.[12,13]

Diarrhea, which is present in about 40% of mastocytosis patients,[7] has been suggested to result from a combination of mechanisms. One mechanism is small bowel, colonic or rectal involvement. Another is the hypersecretion of gastric acid which can cause the precipitation of bile acids, inactivation of the pancreatic enzymes and has a direct effect on the small intestinal villi. Changes in GI transit can be another mechanism while diarrhea due to abnormal motility without altered transit could be considered. Malabsorption is less frequently reported in patients with SM as a result of the dysfunction of the small intestine but can also play a role in some patients who report diarrhea.

Colon and ileum are the most commonly sites involved, followed by duodenum, and stomach. Although the number of mucosal MC is not consistent between studies,[14] MC are usually present in the *lamina propria* and underneath epithelium in focal aggregates of MC.[9,10,15-19] Nonetheless, histopathologic features of GI involvement are variable among patients, and a high index of suspicion is required to reach the diagnosis. The endoscopic findings are frequently unremarkable or nonspecific and GI infiltration by MC can be focal and subtle, requiring multiple biopsies. In addition, special stains should be performed in order to observe the MC infiltrate. Therefore, diagnosis requires a multidisciplinary approach including gastroenterologists, hematologists, and pathologists.[3]

In GI tract, MC are preferentially located close to nerves in the *lamina propria*[20] where they can be activated by substances such as IgE, interferons, complement factors, hormones, and neuropeptides. When stimulated they release mediators, such as serotonin, proteases and proinflammatory cytokines, that can stimulate ion secretion and decrease epithelial barrier function which results in increased intestinal permeability and increase contraction of smooth muscle causing painful contractions of the gut.[21] Additionally, intestinal MC play an important role of immunoregulation in the interface between intestinal mucosa and the environment. They have a crucial role in fighting bacterial and parasitic infections while actors in innate immunity. Through the release of cytokines and chemokines, MC can increase the recruitment of inflammatory cells which may contribute to the burden of GI manifestations.[22]

EVIDENCE FOR THE INVOLVEMENT OF THE MAST CELLS IN GASTROINTESTINAL MANIFESTATIONS OF PATIENTS WITH SYSTEMIC MASTOCYTOSIS

A study published by Sokol *et al* in 2013, involving 83 patients with mastocytosis, showed that the mean absolute number of MC in GI tract was higher when compared to the control group, but no correlation was found between MC infiltration and GI symptoms.[23] This further supports the hypothesis that GI symptoms are more due to MC mediators than MC local infiltration. One year later, Doyle *et al* reported on 24 patients with SM, demonstrating that the histologic findings highlighted the various presentations of MC as focal and multifocal aggregates and variable MC density.[9] Regarding the role of MC in inducing anorectal symptoms, in Libel *et al* study,[24] done over two decades ago and including patients with increased MC consistent with SM, the results suggested that

MC may decrease rectal compliance or over-reactive rectal contractility. One limitation to detect gastrointestinal MC infiltrates are difficulties in identifying these cells in GI biopsies.[25] Patients with unexplained symptoms such as chronic diarrhea and abdominal pain with initial findings of inflammatory infiltrates in biopsy of GI tract specimens might benefit from a further immunohistochemical analysis that targets MC, such as CD117 and tryptase, and to detect abnormal MC, such CD25, but these studies are not usually easy to interpret.[26,27] Likewise, a high index of suspicion may be required in cases where GI manifestations are present without previous established diagnosis of SM in order to overcome the challenges of MC identification in mucosal biopsy specimens.[28]

In Johncilla *et al* study,[29] the authors further suggested that MC aggregates can be found in biopsies from GI tract in asymptomatic individuals without previous or suspected diagnosis of SM. This additionally propose that even when MC aggregates are observed in symptomatic patients, the causative mechanism of GI symptoms cannot be solely reduced to MC infiltration and the number of tissue MC but also depending on the extent and type of MC mediators released.[30]

BIOLOGY IN LOWER GASTROINTESTINAL SYMPTOMS AND PEPTIDES

The connection between the GI tract and the nervous system is an essential remark of the immune-neural interactions and the interface between the body and the outside world. This connection encompasses the role of the central nervous system, the hypothalamic pituitary axis and sympathetic, parasympathetic, and enteric nerves that can function independently or in conjunction to alter GI function. The consequences of such connections are a coordinated mucosal secretion and enteric motor propulsion with side effects of abdominal pain, diarrhea and fecal urgency.[31] Some of the neurotransmitters release from terminal endings of enteric nerves are SP, VIP, serotonin, neuropeptide Y, somatostatin and motilin. While mucosal MC in the GI tract occur particularly in the intestinal *lamina propria*, its distribution in GI tract varies between individuals and disorders. Though MC are frequently present in the proximities of enteric nerves in pathological and non-pathological conditions, the number of MC and nerve density might differ depending on the disorder. Stress neuropeptides have been associated with MC activation in GI tract and changes in ion secretion and permeability.[32,33] Furthermore, MC activation has been associated to some pro-secretory neurotransmitters such as SP and VIP[34] in the proximity of enteric nerves suggesting a bidirectional regulatory pathway with neurocrine control of MC activation. Therefore, MC mediators act as stimuli for neurotransmitters release from nerve endings and these substances activate directly and indirectly mucosal MC to induce changes in ion secretion.[35]

SUBSTANCE P

Unmyelinated nerves in colonic mucosa contain neuropeptides such as SP, one of the major neurotransmitters of the innervation of human intestine. Substance P is a peptide member of the tachykinin family localized in the central nervous system and several peripheral tissues. The immunomodulatory properties of SP have been studied using the GI tract as a model.[36] It is proposed that SP can regulate gut motility and secretion and modulate gut sensitivity in humans. Although not the primarily activation pathway, MC can be activated by non-immune stimuli that include neuropeptides, stress and bacterial toxins. The neuropeptide SP has shown to cause higher rates of release of histamine in inflammatory bowel disease patients,[37] suggesting the potential of the functional interactions between enteric MC and the nervous system. In Wang et al study,[38] intestinal MC were involved in changes in intestinal ion secretion mediated by SP. It suggested that SP caused the release of histamine from MC.

Besides the capacity of SP to cause MC degranulation, it has been demonstrated that it can lower stimulation threshold to a second stimuli resulting in responsiveness of MC without degranulation in particular physiologic conditions.[39] Overall, whether MC activation might result from expression of neurokinin receptors for SP or local environment, SP can influence intestinal MC triggering.[40]

VASOACTIVE INTESTINAL PEPTIDE

Vasoactive intestinal peptide is a neurotransmitter and neuroendocrine releasing factor produced in neurons and widely distributed in the digestive system in the myenteric and submucosal neurons and nerve terminals.[41] VIP is also produced by immune cells including MC and it has shown to increase degranulation of MC in *in vitro* experiments.[42] While VIP receptors are well distributed along human intestine, the highest levels were found in colon sigmoid.[43] VIP role in the GI tract encompasses outcomes on secretion, intestinal barrier and mucosal immunology. The effects of VIP in the digestive system include relaxation of smooth muscle, vasodilatation and decrease water transport in the small intestine as well as increase water, ion and mucus secretion, and delay muscle contraction in the colon.[44,45] Hypersecretion induced by VIP leads to watery diarrhea, while VIP-induced vasodilatation in gut mucosa as well as its role in epithelial paracellular permeability is associated with edema.[46] VIP has been associated with GI disorders including IBS[47,48] and inflammatory bowel diseases (IBD). In Duffy *et al* study,[49] VIP levels in patients with IBD were positively associated with activity of the disease during the period of study, suggesting a potential role of VIP measurement in the follow up of IBD patients. Furthermore, increased VIP levels and MC expressing VIP receptors were found in IBD patients.[42]

SIMILARITIES BETWEEN SYSTEMIC MASTOCYTOSIS AND IRRITABLE BOWEL SYNDROME

Irritable bowel syndrome is a functional bowel disorder characterized by chronic and recurrent abdominal pain or

discomfort associated with defecation or change in bowel habit that affects adolescents and adults and predominantly females.[50] The main symptoms that form the basis of IBS classification according to Rome II criteria are diarrhea and constipation, so much so they are also used to distinguish two main presentations of this disorder, diarrhea-predominant IBS and constipation-predominant IBS. Although the clinical manifestations of IBS are present in many degrees of severity, IBS patients have an impaired quality of life, and the disease is associated with high health care costs.

Current evidence supports the awareness that IBS develops in a brain-gut unbalance influenced by environmental and intrinsic factors to the host that can help explain the variation in symptoms presented by patients. The interaction between immune system and neuropeptides and the enhancement of an inflammatory mucosal response with an increase in immune cells is a key feature of IBS. Stress, psychiatric disorders, history of physical abuse and psychosocial factors, as well as diet choices, are some of the features associated to the clinical expression of IBS.[51,52]

The potential role of MC in the pathophysiology of IBS symptoms has been questioned before[53,54] and it regards not only the common increase in intestinal mucosal MC, the close proximity of MC to enteric nerves but also the variety of mediators release by MC with potential to cause GI symptoms. MC participate in allergic and parasite inflammation, as well as, regulation of epithelial barrier, mucosal immune function, motility and gut visceral sensitivity.[35,54,55] Previous evidence shows that there is an increased number of MC in the intestinal and colonic mucosa of IBS patients,[56-60] particularly in the ileum-caecum region and rectum.[61-63] In Katinios *et al* study, the results show an increase in intestinal permeability and MC counts in IBS patients.[60] In Piche *et al* research, MC infiltrates in the *lamina propria* of caecum specimens were associated with the severity of fatigue and depression in both IBS subtypes patients.[59] The attempt of Libel *et al* study to associate MC with anorectal symptoms also suggests a plausible explanation for these symptoms in both IBS and SM patients.[24] Considering the pathologic features, the mast cell/inflammatory cell ratio has been shown to favor MC in patients with mastocytosis. In other GI diseases with an increase in histologic inflammation, the ratio was in favor of inflammation.[23] The interaction between MC and enteric nerves provides a base for stress-activation and in addition to behavioral factors and the inflammatory response impact gut physiology. There is an association between the proximity of MC to enteric nerves, and specifically SP-positive enteric nerves,[64] and severity and frequency in symptoms.[65] There is a possibility that jejune MC may contribute to functional disorders and symptoms of diarrhea-predominant IBS.[56] Substance P and VIP levels were found higher in IBS patients as well as MC with VIP-receptors[47,66,67] which is consistent with the suspected role of these cells and peptides in the genesis of GI symptoms in diarrhea-predominant IBS patients. In parallel, MC and the levels of VIP and SP may as well be influenced by gender as they were found to be correlated in women and not in men.[67] The immune therapeutic targets that have been studied in IBS patients with focus in the neuro-immune activation have the potential to be an important asset in the treatment of other GI dysfunctional and inflammatory disorders.[68]

Conclusion

This present review takes a general approach to SM and IBS focused on the similarities in GI manifestations and the role of MC and neuropeptides.

Neuron-mast cells interactions play an important role in GI manifestations of SM and IBS. Several studies have tried to identify a link between MC and neuropeptides in the intestinal tract that might help to explain the GI manifestations common both in SM and IBS. The close proximity of MC to neurons in the digestive tract does not seem accidental, so much so that a bidirectional communication line has been implied in order to explain the complexity of the enteric nervous system and the predisposition to GI symptoms.

So far, SM and IBS are likely to share a common denominator in the pathogenesis of GI symptoms, the mast cells. Both disorders can have a similar clinical expression of symptoms such as abdominal pain and diarrhea that cause great morbidity and affect quality of life. Considering that MC histological identification can be a challenge, in patients with recurrent and chronic GI symptoms without previous diagnosis, the identification of MC in biopsy specimens may require an additional grade of suspicion to use additional techniques particularly in the presence of an inflammatory cells. This limitation can partially explain the lack of understanding of the role of MC in many GI disorders.

Nevertheless, more evidence is needed regarding MC and neuropeptides interaction in order to better understand the pathophysiology of SM and IBS. Additional studies that can contribute to the knowledge of the active role of MC as local or systemic mediators in GI symptoms common to many gut disorders are required. ■

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