ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Review Article

Mast cells and mast cell activation syndrome: what's new?

Mastócitos e síndrome de ativação mastocitária: o que há de novo?

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ABSTRACT

Mast cells are the main effector cells of acute allergic response, also playing an important role in angiogenesis, immune tolerance, regulation of fibrinolysis, neuronal regeneration, and osteoclastogenesis. They are generally located in the skin and mucous membranes of the intestines and lungs, where they perform a "sentinel" function. Mast cell activation syndrome is characterized by recurrent clinical manifestations resulting from the release of mast cell mediators. This complex entity, which involves a spectrum of associated symptoms, is a diagnostic and therapeutic challenge. In this article we overview of the structure and function of mast cells, in addition to the diagnostic criteria and therapeutic approaches to mast cell activation syndrome.

Keywords: Mast cells, mastocytosis, mast cell activation syndrome.

RESUMO

Os mastócitos são as principais células efetoras da resposta alérgica aguda, desempenhando também um papel importante na angiogênese, tolerância imunológica, regulação da fibrinólise, regeneração neuronal e osteoclastogênese. Localizam-se maioritariamente na pele e nas mucosas do intestino e pulmões, onde exercem uma função "sentinela". As síndromes de ativação mastocitária são caracterizadas pela ocorrência de episódios recorrentes de manifestações clínicas resultantes da libertação de mediadores mastocitários. Esta constitui-se como entidade complexa com um espectro de sintomas associados, representando um desafio diagnóstico e terapêutico. Nesta revisão, os autores pretendem apresentar uma visão geral sobre a estrutura e função dos mastócitos e sobre os critérios diagnósticos e abordagem terapêutica da síndrome de ativação mastocitária.

Descritores: Mastócitos, mastocitose, síndrome de ativação mastocitária.

Introduction

Mast cells are connective tissue cells originating from hematopoietic cells located in bone marrow, which may play important roles in host defense to parasitic infections and in allergic reactions. Mast cells are ubiquitously located in the connective tissue, skin, and around blood vessels, but are also located in mucous surfaces of intestine and lungs.[1] Mast cells are very important cells In inflammatory response, since their activation promotes the release a wide variety of pro-inflammatory mediators, of which the following

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stand out: histamine, tryptase, cytokines such as interleukins IL-4 and IL-13, and tumor necrosis factor (TNF)-α, or even lipid mediators, such as leukotrienes, platelet-activating factor, and prostaglandins.[1-3]

In recent years, evidence has emerged that mast cell activation and proliferation may occur in some individuals in a pathological way and can be triggered by several stimuli, such as stress, heat, or cold.[2]

The term mast cell activation syndrome (MCAS) refers to a heterogeneous set of diseases clinically characterized by the occurrence of recurrent episodes of clinical manifestations resulting from the release of mast cell mediators. Given the presence of clonality, MCAS may be classified into clonal MCAS (CMCAS) and non-clonal MCAS (NCMCAS).[1-4]

CMCAS include monoclonal MCAS (MMCAS), cutaneous mastocytosis (CM), and systemic mastocytosis (SM), which present with clinical manifestations resulting from mast cell activation.[5,6] Conversely, NCMCAS may be grouped into secondary (e.g., associated with IgE-mediated hypersensitivity) or idiopathic.[1-3]

Several diagnostic criteria have been suggested so far, often lacking validation.[4] This is an urgent and relevant need, since a growing number of individuals have been misdiagnosed with MCAS, based on unspecific criteria. Therefore, this article aims to critically address currently literature related to MCAS, comparing the criteria presented by two groups of authors more devoted to this area.

Methods

The authors conducted a literature search on the PubMed database covering up to May 31, 2022, and using the following terms: *mast cell*, *mastocytosis*, *anaphylaxis*, combined with the terms *activation syndrome*, *tryptase*, *consensus*. Articles addressing issues related to MCAS published in the last 10 years were used, focusing especially on articles published by authors from reference centers and on consensus publications. Occasionally, we used articles published more than 10 years ago that are still currently relevant.

Importance of mast cells in inflammatory response

Mast cells are the main effector cells of acute allergic response. However, they can also play other roles in angiogenesis, immunomodulation, regulation of fibrinolytic mechanisms, regeneration of nervous fibers, and promotion of osteoclastic differentiation.[7]

These cells originate-from bone marrow, being derived from the hematopoietic lineage (CD34+/CD117+ progenitor cells). After traveling briefly through bloodstream, they differentiate in the connective tissue in general (including mucosae), where they acquire their specific phenotype, in the presence of local growth factors such as IL-9, IL-10, IL-3, IL-4, IL-33, CXCL12, neuronal growth factor (NGF), and transforming growth factor (TGF)-β.[1,3,8] In structural terms, they present with granules containing histamine, tryptase, heparin, chondroitin, sulphates, and other glycosaminoglycans.[8]

These cells may be classified in different ways, based specifically on granular concentration of serine, tryptase and chymase proteases.[3,9] Mast cells whose granules contain mainly tryptase (MCT) are predominantly located in the alveolar septa and in small intestine mucosa, whereas mast cells that contain both proteases (MCTC) may be found in skin, layers of small intestinal submucosa, and also in the connective tissue.[3,9] MCT, which are found mainly in mucosae, interact closely with lymphocytes T, namely Th2 cells.[5] Globally, they are located in tissues, skin, blood vessels, and mucosae.[3]

Mast cell membrane receptors

Mast cells have a diversity of membrane and cytoplasmic receptors, which allows them to be activated by several stimuli, such as anaphylatoxins (C3a and C5a), IgG, medicines, insect venoms, physical stimuli (variations in pressure and temperature), neuropeptides, cytokines (IL-4Rα, IL-5Rα, IFN-γRα, and ST2), and vascular endothelial growth factors (VEGFR1 and VEGFR2).[7] They also express receptors for several ligands, such as toll-like receptors (TLR), which are activated by pathogen-associated molecular patterns (PAMPs), being thus involved in responses to bacteria, parasites, and viruses.[10]

Allergenic activation (mediated by IgE) promotes mast cell degranulation, with release of preformed molecules such as histamine, serotonin, proteases (tryptase, chymase, carboxypeptidase), and tumor necrosis factor (TNF), as well as *de novo* secretion of numerous vasoactive and pro-inflammatory mediators, including leukotrienes, prostaglandins, PAF, cytokines (IL-6, IL-9, IL-13), and chemokines (CXCL8, CCL2, CCL5).[11-13]

In addition to IgE-dependent reactions, in which high-affinity IgE receptors (FCεRI) of mast cells are extremely relevant (non-covalent tetrameric complexes that, together with IgE, will attach to the antigen and trigger mast cell activation), there are also non-IgE-mediated reactions, in which activation of the complement system and respective mast cell degranulation occur.[3] In addition to these two types of reactions, there also are non-immunologic reaction, in which there is the direct mast cell degranulation mediated by MAS-related G Protein-Coupled Receptor-X2 (MRGPRX2).[3]

All mast cells express KIT receptor (CD117), whereas only some types of mast cells (e.g., those located in the skin or in synovial fluid) express MRGPRX2, which is activated by neuropeptides such as substance P.[7]

Maturation and regulation of immunological and non-immunological cells

Mast cells play very different roles in maturation and activation/regulation of several cells, namely dendritic cells or lymphocytes T and B, through the release of numerous mediators (histamine, prostaglandins, leukotrienes, tryptase, chymase, carboxypeptidase, and numerous interleukins) present within mast cells.[14]

Furthermore, mast cells can activate macrophages (through histamine, IL-13, IL-6, PAF and PGD2), dendritic cells (after release of histamine, PGE2, PGD2, VEGF-C and IL-13), and innate lymphoid cells (ILCs), via IL-1β, IL-9, PGD2, and LTD4. Conversely, mast cells stimulate NK cells through the release of histamine and heparin, and also T cells, through the release of histamine, LTC4, LTD4 and TNF-α.[15]

Endothelial cells also undergo mast cell regulation, through the release of mediators such as histamine, LTC4, LTD4, PGD2, PAF, VEGF-A, IL-13, and IL-1β. The regulatory effect is also exerted on bronchial epithelial cells, smooth muscle cells, fibroblasts, or lymphatic endothelial cells, among others, with the release of VEGF-C and VEGF-D to promote angiogenesis thorough endothelial cell proliferation.[15]

Due to their distribution, versatility response to multiple stimuli, and variety of molecules they release, mast cells play the role not only of "sentinel" of the immune system but also of maintaining homeostasis. Moreover, they are involved in several physiological and pathological processes, in the context of innate immunity, autoimmunity, neuroinflammation, immunomodulation, and antimicrobial activity.[10,11,16-20]

Types of mast cell activation

Mast cells are located in tissues that interact continuously with exterior. Additionally, they are stimulated by a vast number of different triggers, including bacteria, medicines, foods, and physical agents that promote the secretion of mediators.[21] It is possible to observe that there are two main modes of mast cell degranulation: the first one, named anaphylactic degranulation, is a rapid and immediate event that occurs after IgE activation, whereas the second one, piecemeal degranulation, is slower.[22] Some examples of mast cell degranulation triggers include acetylcholine, complement factors, medicines (some antibiotics and anesthetics), peptides such as endorphin, endothelin, and somatostatin, and physical stimuli such as heat, cold, pressure, stress, and vibration. Mast cells also respond to non-allergic activators through mediators that can be released without degranulation. Finally, corticotropin-releasing hormone (CRH), cytokines, and some microorganisms have been identified as mast cell triggers without degranulation.[21,22]

Mast cell activation syndrome

MCAS is a complex entity characterized by the occurrence of acute severe recurrent episodes whose heterogeneous symptoms involve at least two organ systems and present multiple triggering agents, posing important diagnostic and therapeutic challenges. There are two types of MCAS to consider. Clonal (or primary) MCAS is characterized by the presence of clonal markers, such as *KIT*^{D816V} mutation, abnormal expression of CD25 or CD2 by mast cells in bone marrow, or atypical morphology (e.g., fusiform, binucleated).[1,2] Non-clonal MCAS is subdivided into two types, the first of which is caused by a known stimulus (secondary MCAS), whereas in the second type mast cell degranulation is caused by an unknown stimulus (idiopathic MCAS).[23]

MCAS is a disease of complex etiology whose diagnosis is usually late and challenging.[1,2,21] Patients may present with signs and symptoms that mimics cardiovascular, gastrointestinal, respiratory, or cutaneous diseases, or compatible with allergic reactions and recurrent anaphylaxis episodes, which may be IgE-mediated or not.[21]

Triggering factors and symptoms

Several stimuli can trigger mast cell degranulation, including allergens (similar in frequency to the general population), bacteria, viruses, toxoids, food, alcohol, medicines (non-steroidal anti-inflammatory drugs [NSAIDs], opiates, and contrast media, among others), or even physical agents such as pressure, friction, cold, or heat.[21] Stress also seems to play an important role, as well as hormone changes.[24-26]

Typical manifestations of MCAS can include acute urticaria, flushing, pruritus, abdominal pain, diarrhea, shortness of breath, and hypotension. None of these manifestations are absolutely specific, but the simultaneous development of a set of recurrent signs and symptoms related to at least two organs or body systems are highly suggestive for MCAS.[4,27]

The main clinical manifestations of the syndrome are described in Table 1.

In addition to the aforementioned clinical manifestations, objective laboratory evidence of mast cell involvement, confirming a substantial transient increase in mast cell mediators and control of symptoms with drug therapy is required for the diagnosis of MCAS to be established.[4]

There is another myriad of non-specific symptoms/diseases that are not specific for this disease (Table 2).

Differential diagnoses

These same symptoms may be present in other clinical entities, including some cardiovascular, endocrine, cutaneous, gastrointestinal, and neuropsychiatric diseases.

In general, MCAS is a syndrome defined by a severe, recurrent systemic reaction (often in the form of anaphylaxis), resulting from a clinically significant release of vasoactive and pro-inflammatory mast cell mediators.[1,4] When there are no signs of anaphylaxis, MCAS is much less likely to be the correct diagnosis. For less severe or localized forms of mast cell activation (e.g., limited to skin or respiratory tract) not meeting MCAS criteria, further research is needed to evaluate these patients.

In recent years, a specific type of NCMCAS has been described, named hereditary alpha-tryptasemia (HaT), which is an autosomal dominant inherited disease with still unknown penetrance, caused by increased number of *TPSAB1* gene copies.[4] With a prevalence ranging from 5% to 6% of the general population, HaT results in elevated baseline tryptase, often greater than 10 ng/mL.[4] Up to two thirds of patients with this condition may have mild symptoms or being completely asymptomatic.[4] The other patients may present with dysautonomia with postural orthostatic hypotension, joint hypermobility, vibratory urticaria, irritable bowel syndrome, chronic musculoskeletal pain, and a myriad of manifestations compatible with respiratory and/or cutaneous allergic disease, such as shortness of breath, cough, wheezing, anterior/posterior rhinorrhea, or sneezing.[4]

Some authors recommend evaluating the presence of the gene *TPSAB1* gene to determine the presence of concomitant HaT in these patients. However, investigation for the presence of HaT is mandatory in individuals with mastocytosis or allergic to hymenoptera venom.[4,21,25] The exact percentage of patients with clonal and idiopathic MCAS who currently have HaT is unknown.[4]

Table 1
Mains organ systems involved in MCAS and main clinical manifestations of the disease

Skin	Flushing, urticaria, pruritus, angioedema
Cardiovascular	Syncope/presyncope, hypotension
Gastrointestinal	Diarrhea, vomiting, abdominal pain, gastroesophageal reflux
Respiratory	Nasal/conjunctival congestion and pruritus, sneezing, wheezing, shortness of breath, laryngeal edema, hypoxia

MCAS = mast cell activation syndrome.
Adapted from Gülen T et al. (4)

Table 2
Symptoms and diseases not diagnostic for MCAS

NOT diagnostic symptoms/ diseases of MCAS	Fatigue, fibromyalgia-like pain, chronic back pain, edema, dermatographism, alopecia, warts, tinnitus, adenopathy, weight changes, hypo/hyperthyroidism, metabolic syndrome, electrolytic changes, type 2 diabetes mellitus, gastroenterology disease (constipation, gastroesophageal reflux, irritable bowel syndrome, inflammatory bowel disease, celiac disease), neuropsychiatric disease (headache, attention deficit /hyperactivity disorder, anxiety, depression, posttraumatic syndrome, mood disturbances, restless leg syndrome, schizophrenia), essential hypertension, pulmonary hypertension, atherosclerosis, dysautonomia syndrome (POTS), joint hypermobility (hEDS), chronic kidney disease, prostatitis, endometriosis, polycystic ovary syndrome, autoimmune diseases, multiple food/chemical sensitivity syndrome, malignancies, anemia, polycythemia, quantitative changes in antibodies, nonspecific peripheral blood mutations

MCAS = mast cell activation syndrome.
Adapted from Gülen T et al.[4].

Diagnostic criteria

Diagnostic criteria for MCAS have been proposed by the European Competence Network on Mastocytosis (ECNM)[4,25,28] and by Molderings et al.[2,29]

According to the ECNM, there are three diagnostic criteria for suspected cases of MCAS: recurrent severe episodes with typical systemic symptoms of mast cell activation involving two or more organs; increase of 20% in serum tryptase level above individual's baseline plus 2 ng/mL within 4 hours after a symptomatic crisis (e.g., an increase of 10 ng/mL for values above 14 ng/mL, or of 30 ng/mL for values above 38 ng/mL); favorable therapeutic response to antimediator therapy (e.g., antihistamine H1 and H2, mast cell membrane stabilizing agents, antileukotrienes) (Table 3).[4,25]

MCAS can be classified into 3 subtypes: 1) primary (or monoclonal) MCAS with *KIT*^{D816V} mutation, with or without diagnosis of mastocytosis; 2) MCAS secondary to IgE-dependent allergy, hypersensitivity reaction, or immunological disease likely to induce mast cell activation (e. g., Hashimoto thyroiditis); 3) idiopathic MCAS, in which no KIT mutation or other underlying condition could be detected.[4,25] Patients who simultaneously have IgE-dependent hypersensitivity and mast cell clonality can be classified as presenting with mixed MCAS.[4]

Molderings et al. proposed that the diagnosis of MCAS involves major and minor criteria (Table 4). Diagnosis can be established up demonstration of both major criteria, or alternatively, the second major criterion combined with at least one minor criterion.[29]

According to Molderings et al., this disease may affect up to 17% of the general population[2], which the authors of this article believe to represent an overdiagnosis of the disease, since the suggested diagnostic markers show low sensitivity. Conversely, according to the ECNM, when including an elevation of mediators relatively specific for mast cells, it would also be important to define their respective thresholds. The ECNM believes that patients with typical symptoms of MCAS without confirmed acute elevation of any validated biomarker of mast cell activation should not be given a diagnosis of MCAS. An argument against using such markers is the limited access to these tests. Furthermore, MCAS patients may experience certain symptoms almost chronically, so that a truly asymptomatic serum baseline tryptase that allow for comparison between episodes is difficult to obtain.[4]

However, many reactive inflammatory states and neoplasms, as well as individuals with no specific symptoms, may present with an increase in local

Table 3
Proposed diagnostic criteria for MCAS according to the European Competence Network on Mastocytosis (ECNM)[4,25,27]

Typical MCAS-related clinical symptoms (see Table 1)
Event-related increase > 20% in baseline serum tryptase plus 2 ng/mL within 4 hours after a symptomatic crisis
Improvement of symptoms with the use of H1 antihistamine, other stabilizing agents, or drugs directed to mast cell mediators

MCAS = mast cell activation syndrome.

mast cells without MCAS and without filling criteria for this disease.[4]

General approach

The approach of MCAS involves the implementation of prophylactic and therapeutic measures for its control. After ruling out other diseases that can mimic MCAS, it is essential for patients to known and avoid agents likely to trigger their episodes of MCAS. However, similar that what occurs with mastocytosis, generalized avoidance of these potential stimuli is not recommended.[30]

Nonetheless, there is a considerable variety of stimuli, such as exposure to extreme temperatures or temperature variations, excessive solar exposure, emotional stress, sleep deprivation, physical stimuli, alcohol, and susceptive medicines. NSAIDs, opioids, anesthetic agents, and iodide contrast media may also trigger episodes of MCAS.[31,24]

Table 4
Proposed diagnostic criteria for MCAS according to Molderings et al. [2,29]

Major criteria	Minor criteria
Presence of multifocal mast cell aggregates in bone marrow (BM) or extracutaneous organs (ECO)	Abnormal morphology in > 25% of mast cells in BM of ECO
Clinical history compatible with recurrent/chronic release of mediators due to increased mast cell activity	Mast cell expression of CD2 and/or CD25.
	Presence of mast cell genetic mutations (*KIT*^{D816V} mutation)
	Values above normal for mast cell mediators (serum tryptase, chromogranin A, plasma heparin, plasma histamine, urinary N –methyl-histamine, leukotrienes B4, C4, D4, and E4, PGD2, 11-beta-PGF2α)
	Symptomatic response to mast cell activation inhibitors

MCAS = mast cell activation syndrome.

Premedication protocols are usually recommended for the treatment of mastocytosis. Despite the lack of similar protocols for MCAS, in clinical practice patients with this disease follow premedication protocols in certain conditions, such as before invasive procedures (both surgical and diagnostic), radiological tests with contrast, dental procedures, and vaccination. The protocols usually include H1 and H2 antihistamines, leukotriene antagonists, benzodiazepines, and prednisolone, depending on the case.[1,30]

It is worth mentioning that the level of evidence of these protocols is low and based on the opinion of some specialists; moreover, any therapeutic protocol should be carefully adapted to the patient and reviewed by the medical team before administration.[30]

Pharmacological treatment

Pharmacological control depends on the use of different agents, either isolated or combined, according to the intensity, severity, and type of symptoms of each patient. Second generation antihistamine (anti-H1) are the main pharmacological agents to be used in these situations. When necessary, their usual dose can be quadrupled, with no significant secondary effects. There are reports of patients who need to take them on a chronic basis.[1,25]

There are few studies to support the choice and the dose of H1 antihistamines. Desloratadine and ketotifen showed mast cell stabilization properties.[35] Rupatadine has an antagonist effect of PAF receptor, a mediator involved in episodic hypotension and flushing, and was associated with improved quality of life and symptoms in patients with mastocytosis and symptoms of MCAS.[32,33] Both rupatadine and levocetirizine, at a lower extent, show the inhibiting effect of PAF in mast cell degranulation, which is not observed with desloratadine.[31-35]

H2 receptor antagonists, such as famotidine and cimetidine, are particularly useful in dyspeptic gastrointestinal symptoms, abdominal pain, diarrhea, and severe recurrent episodes.[28]

Leukotriene receptor antagonists, such as montelukast, has proven to be useful in controlling respiratory, cutaneous, and gastrointestinal symptoms.[1,28,36]

Acetylsalicylic acid may help control flushing and hypotension in selected cases with known tolerance to the drug. In the past it was used in the treatment of cases of anaphylaxis in patients with SM, but the doses required to block mast cell activation are high and not always tolerated.[27,36] A study reported that celecoxib could be considered an option for intractable diarrhea in mastocytosis patients.[36] Systemic corticosteroids are a resource reserved for individuals with refractory symptoms.[28]

Therapy with anti-IgE monoclonal antibody, omalizumab, has shown to be effective and with a good safety profile in patients with secondary MCAS who have underlying IgE-dependent allergy, especially anaphylaxis refractory to conventional therapy, as well as in those with primary and idiopathic MCAS.[37] A French study including 55 patients diagnosed with MCAS and persisting symptoms treated with omalizumab for 3 years showed an overall best response rate of 78% of patients (maintained for at least 3 months in 77% of them), and a final overall response rate of 58% in the last follow-up.[37]

Patients with reactions compatible with anaphylaxis should use self-injectable adrenaline devices, two of them if necessary. These patients are prone to develop the most severe, potentially fatal, forms of anaphylaxis, especially those with allergy to insect (hymenoptera) venom.[30,38]

With regard to hymenoptera venom-induced (IgE-dependent) anaphylaxis, i.e., secondary MCAS in this case, it is recommended to initiate venom immunotherapy (VIT) specific to the concerned venom, which should be maintained throughout life, since severe reactions persist if treatment is interrupted.[39]

VIT has proved to be effective in SM patients who have an IgE-mediated reaction, although there is a known higher risk of adverse reactions in patients with SM undergoing treatment with VIT compared to the general population.[39] Therefore, omalizumab may be useful in reducing associated adverse effects and facilitates building up to the VIT maintenance dose.[39]

In general, vaccination against COVID-19 is recommended in individuals with MCAS, as well as in individuals with mastocytosis. The only exception to consider is when there is suspected or known allergy to a one of the vaccine components. Patients will need to receive premedication according to their individual risk and undergo a postvaccination observation period, similarly to the general population.[40]

Final considerations

MCAS is a complex entity with unknown prevalence[41] characterized by the occurrence of acute

severe recurrent episodes whose heterogeneous symptoms involve at least two organ systems, presenting multiple triggering agents and posing important diagnostic and therapeutic challenges.

Several differential diagnoses should be carefully evaluated before diagnosing MCAS, such as HaT. An incorrect diagnosis of MCAS may affect patients, delaying appropriate treatment and thus compromising their quality of life and prognosis. In most cases, elevation of serum tryptase during the events confirms mast cell involvement.

Currently two models have been proposed for the diagnosis of MCAS. The first one, established by the ECNM, presents more robust and specific criteria. The other model, proposed by Molderings et al., presents more comprehensive criteria that have not been validated in the specific context of MCAS, leading to a serious risk of overdiagnosing the disease. Nowadays, it has been observed that many patients diagnosed with MCAS do not present confirmed involvement of mast cell activation.

Recent findings have suggested this disease had been identified in a significant number of COVID-19 patients. The scientific community is concerned these patients are actually delaying their true diagnosis, according to the criteria established in the Vienna consensus by the ECNM.

The therapeutic approach of MCAS involves the use of second generation H1 antihistamines, H2 receptor antagonists, montelukast, corticoids, omalizumab (anti-IgE), and mast-cell targeted therapies. Symptomatic control also depends on the identification and cautious avoidance of triggers.

Initial therapy may be implemented before definite diagnosis of MCAS, with response being a useful factor to support diagnosis. According to the type and severity of the syndrome, it may be necessary to combine therapies, including anti-IgE therapy and targeted therapy.

The diagnosis of MCAS is still complex, multidisciplinary, and demanding. In the future, it will be important to discover new biomarkers that allow for physicians to clearly distinguish MCAS from other mimicking diseases.

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