

Mastocytosis Colitis in 54 year old woman: A rare case report

Colite Mastocitose em mulher de 54 anos: Um relato de caso raro

Mastocitosis Colitis en mujer de 54 años: Informe de un caso raro

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Abstract

Introduction: Mastocytosis is a rare disorder occurring due to neoplastic clonal proliferation of mast cells accumulating in one or more organ systems. Systemic mastocytosis is generally diagnosed after the second decade of life, reported male-to-female ratios range from 1:1 to 1:1.5. **Case description :** A 54-year-old woman came complaining weakness and diarrhea for the last 2 months. Symptoms are watery stools for 2-4 times a day and nausea. Physical examination found that the body temperature was 37.6⁰C, tachycardia, increased bowel sounds, and tenderness on stomach. An endoscopic examination was performed with results: transverse colon appears with polyps with a size of 3 mm, with a mosaic pattern of mucosa. The mucosa of the ascending colon and caecum also appears to be a mosaic pattern. Biopsy was sent for histopathological examination. Morphological features show significant increase of eosinophils & mast cells, differentially diagnosed with Mastocytosis colitis, Eosinophilic colitis, systemic mastocytosis with GI involvement. **Methodology :** Descriptive study of the case report type, data were obtained from the patient's record. **Discussion and Conclusion :** To rule out the differential diagnosis, an immunohistochemical examination and clinical correlation were performed. On histopathological examination, microscopic features showed the proliferation of mast cells in the aggregate only in the colon, without any other systemic manifestations, an increase in the number of mast cells >20/HPF was found in the colonic mucosa. The staining of CD117 on cells in the superficial (1/3 top) of the lamina propria suspected of being a mastocyte, supporting mastocytosis colitis.

Keyword: Mastocytosis systemic; Mastocytosis colitis; Mast cell; Chronic diarrhea.

Resumo

Introdução: A mastocitose é uma doença rara que ocorre devido à proliferação clonal neoplásica de mastócitos que se acumulam em um ou mais sistemas orgânicos. A mastocitose sistêmica é geralmente diagnosticada após a segunda década de vida, as relações entre homens e mulheres relatadas variam de 1:1 a 1:1,5. **Descrição do caso:** Uma mulher de 54 anos veio queixando-se de fraqueza e diarreia nos últimos 2 meses. Os sintomas são fezes aquosas por 2-4 vezes ao dia e náuseas. O exame físico constatou que a temperatura corporal era de 37,60C, taquicardia, sons intestinais aumentados e sensibilidade no estômago. Um exame endoscópico foi realizado com resultados: cólon transverso aparece com pólipos com tamanho de 3 mm, com padrão de mosaico da mucosa. A mucosa do cólon ascendente e do ceco também parece ser um padrão de mosaico. A biópsia foi encaminhada para exame histopatológico. As características morfológicas mostram aumento significativo de eosinófilos e mastócitos, diagnosticados diferencialmente com colite mastocitose, colite eosinofílica, mastocitose sistêmica com envolvimento GI. **Metodologia:** Estudo descritivo do tipo relato de caso, os dados foram obtidos do prontuário do paciente. **Discussão e Conclusão:** Para afastar o diagnóstico diferencial, foi realizado exame imuno-histoquímico e correlação clínica. No exame histopatológico, as características microscópicas mostraram a proliferação de mastócitos no agregado apenas

no cólon, sem outras manifestações sistêmicas, um aumento no número de mastócitos >20/HPF foi encontrado na mucosa colônica. A coloração de CD117 em células na superfície (1/3 superior) da lâmina própria suspeita de ser um mastócito, suportando a colite mastocitose.

Keyword: Mastocitose sistêmica; Colite de mastocitose; Mastócitos; Diarréia crônica.

Resumen

Introducción: La mastocitosis es un trastorno raro que ocurre debido a la proliferación clonal neoplásica de mastocitos que se acumulan en uno o más sistemas de órganos. La mastocitosis sistémica generalmente se diagnostica después de la segunda década de vida, las proporciones informadas de hombre a mujer varían de 1: 1 a 1: 1.5. Descripción del caso: una mujer de 54 años acude con debilidad y diarrea desde hace 2 meses. Los síntomas son heces acuosas de 2 a 4 veces al día y náuseas. El examen físico encontró que la temperatura corporal era de 37,60C, taquicardia, aumento de los ruidos intestinales y dolor a la palpación en el estómago. Se realiza examen endoscópico con resultado: colon transverso aparece con pólipos de 3 mm de tamaño, con patrón de mucosa en mosaico. La mucosa del colon ascendente y ciego también parece tener un patrón de mosaico. Se envió biopsia para estudio histopatológico. Las características morfológicas muestran un aumento significativo de eosinófilos y mastocitos, diagnosticados diferencialmente con mastocitosis colitis, colitis eosinofílica, mastocitosis sistémica con afectación gastrointestinal. **Metodología:** Estudio descriptivo del tipo reporte de caso, los datos se obtuvieron de la historia clínica del paciente. **Discusión y Conclusión:** Para descartar el diagnóstico diferencial, se realizó un examen inmunohistoquímico y correlación clínica. En el examen histopatológico, las características microscópicas mostraron la proliferación de mastocitos en el agregado solo en el colon, sin otras manifestaciones sistémicas, se encontró un aumento en el número de mastocitos > 20/HPF en la mucosa colónica. La tinción de CD117 en células en la superficie (1/3 superior) de la lámina propia sospechosa de ser un mastocitos, apoyando colitis por mastocitosis.

Palabra clave: Mastocitosis sistémica; Colitis por mastocitosis; Mastocitos; Diarrea crónica.

1. Introduction

Mastocytosis is a rare disorder with uncertain incidence number and gives a heterogeneous / varied picture, making diagnosis difficult, not solely based on histopathological features, but correlation with clinical and other investigations is needed to determine systemic involvement, which is characterized by accumulation of abnormal mast cells in various tissues. While skin mastocytosis (localized skin form) is a classic presentation occurring in children, and tends to heal spontaneously in pediatric cases. One case study estimates that 1 in 1000 people in America have this condition. Mastocytosis generally affects men and women in equal amounts. This disease may begin in childhood or adulthood. (Cancer.net, 2022; Reggiana, 2015).

During puberty, systemic mastocytosis (SM) frequently occur in adults, marked with: mast cell infiltration to extracutaneous organs (e.g, bone marrow, liver, spleen, digestive tract, lymph nodes); this form of SM is progressive and doesn't have the tendency to regress. These two forms of mastocytosis are considered as myeloproliferative disorders. (Reggiana, 2015).

Mastocytosis occurs due to mast cell clonal neoplastic proliferation which accumulates in one or more organs. This is marked by abnormal mast cell infiltrates, which often contain multifocal clusters or cohesive aggregates. The most common symptoms are abdominal pain (avg 51%) followed by diarrhea (avg 43%) and nausea and vomiting (avg 28%). About 50% of children affected show typical skin lesions before the age of 6 months. Skin mastocytosis is much less common in adults than children. The cause of skin mastocytosis in children might be due to embryogenesis and early mast cell formation. Systemic mastocytosis is generally diagnosed after the second decade of life, and reported men-women ratio of 1:1 to 1:1.5. (Horny, 2017; Lee, 2008).

Based on studies in mice, it has been proposed that mammalian mast cells may originate from at least two different sources during embryonic development and that mast cells present in the skin at birth are gradually replaced by different populations as the individual matures. The presence of defects in the mast cell population that originates in the embryonic yolk

sac and predominates in the neonatal period, but not in the population subsequently produced in the bone marrow, may explain the mechanism of disease resolution in most children. (Castells, 2021).

2. Methodology

This is a descriptive study from a case report. In general, case study research is centered on a phenomenon, which is described as detailed as possible (Yin, 2017; Pereira et al, 2018). The analytic description of the clinical case being presented in chronological order, and literally reviewed using a scientific database. Our research ethics committee did not review any ethical clearance for the case report that was already discussed at the clinicopathological conference and approved by the clinician, patient, and pathologist. Following ethical principles, the patient consent to disseminating the data and displaying images of her case for academic purposes. Informed consent form was signed willingly.

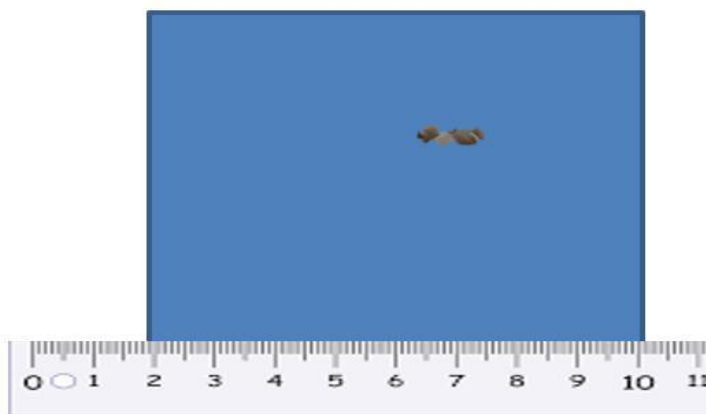
3. Case Description

A 54-year-old woman came to the ER at Sanglah Central General Hospital complaining of weakness and digestive problems for the past 2 months. She suffered an increase in bowel movements frequency approximately 2-4 times a day, her stools are sometimes watery, and sometimes accompanied with nausea. Diarrhea is not accompanied with abdominal pain before or even after stool passing. Patient also complained of weight loss of approximately 8 kg in 2 months. Her previous medical history was only checking herself up to a general medical clinic and received medicines for indigestion and diarrhea. There are no previous chronic illnesses recorded.

On physical examination, the body temperature was sub-febrile with 37.6c, tachycardia, increased bowel movements, and tenderness in the epigastric area. Then, an endoscopic (colonoscopy) exam was done and results were as follows; anus-rectum looks normal, sigmoid colon is normal, descending colon is normal, a 3 mm polyp with mosaic pattern mucosa in transverse colon was identified, whilst terminal ileum looks normal.

On ascending colon, biopsy was performed for histopathological examination. On 24/12/2022, a sample of 3 specimens in 10% NVF solution with patient's identity, Each of the specimens are 1-2 mm long, gray-white color as seen on Figure 1. All of the tissues are processed in 1 cassette. The specimens are then processed for histopathological examination with H&E staining.

Figure 1. Macroscopic Tissue.

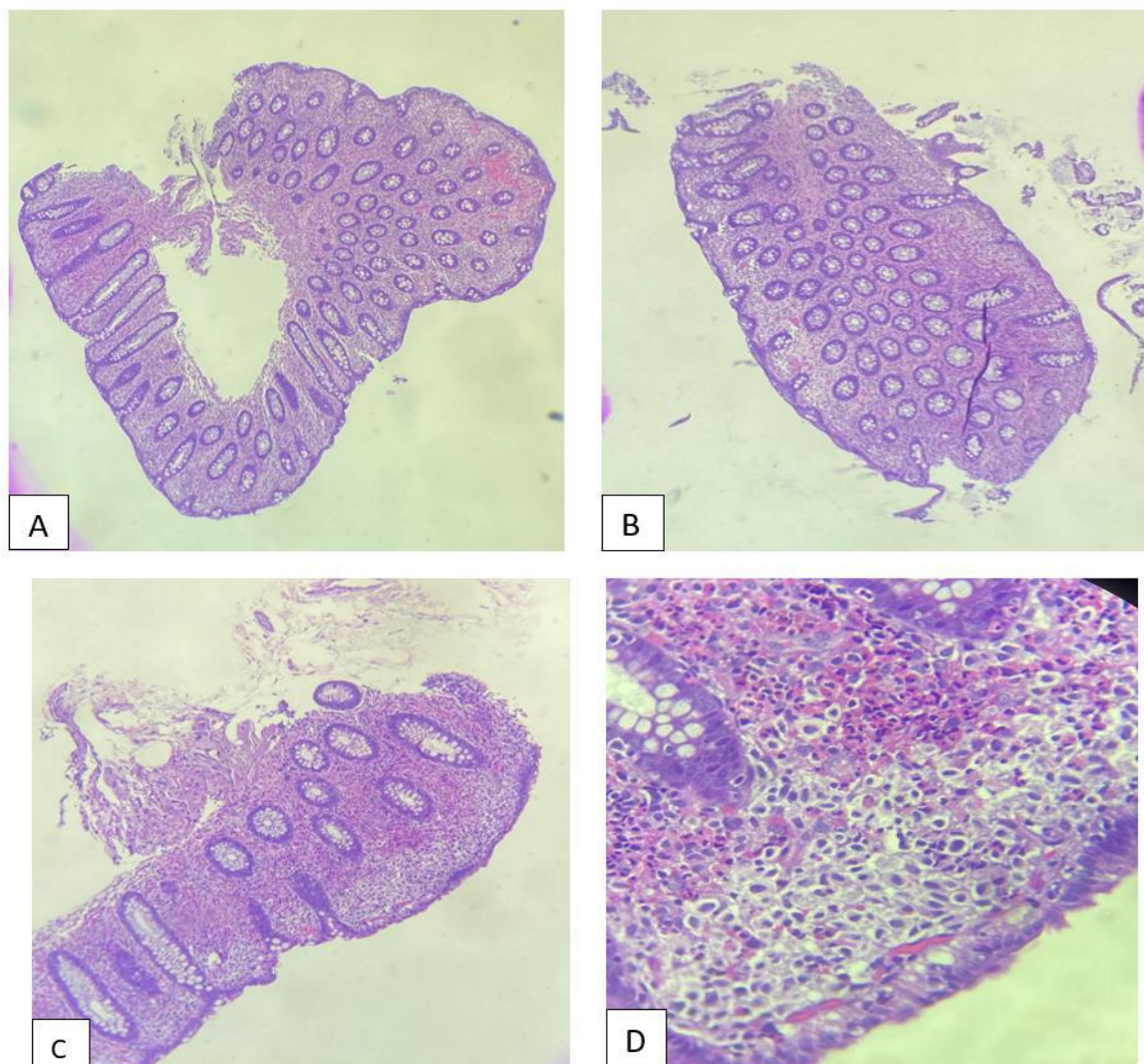


Macroscopic tissue obtained from endoscopy biopsy on ascending colon. Source: Authors.

Microscopic examination on biopsy tissue from ascending colon shows; surface epithelium, crypts, lamina propria & mucosal muscle on one tissue. Crypts generally do not show distortion with *rack of test & daisy flower* pattern. Multiple infiltrative focus of eosinophilic PMN cells to crypt epithelium (in accordance with eosinophilic cryptitis). Lamina propria contains blood vessels with telangiectatic pattern & prominent inflammatory cells. On superficial part (upper $\frac{1}{3}$) shows lamina propria with dense band-like distribution, consisting of cells with morphologically coiled-round nucleus, surrounded by moderate amount of pale-clear cytoplasm, mastocyte cell impression observed under conventional H&E staining, some mixed with mature plasma cells. On lower $\frac{2}{3}$ of lamina propria, abundant eosinophilic PMN distributed along with plasma cells & lymphocytes.

From this microscopic examination on Figure 2, its concluded; Morphology shows lesion of colon mucosa from endoscopic biopsy associated with significantly increased eosinophils and mast cells, maybe diagnostically differentiated with Mastocytosis colitis, Eosinophilic colitis, Systemic mastocytosis with GI involvement. Further histochemical examination is required to ensure the lesion is mastocytosis colitis.

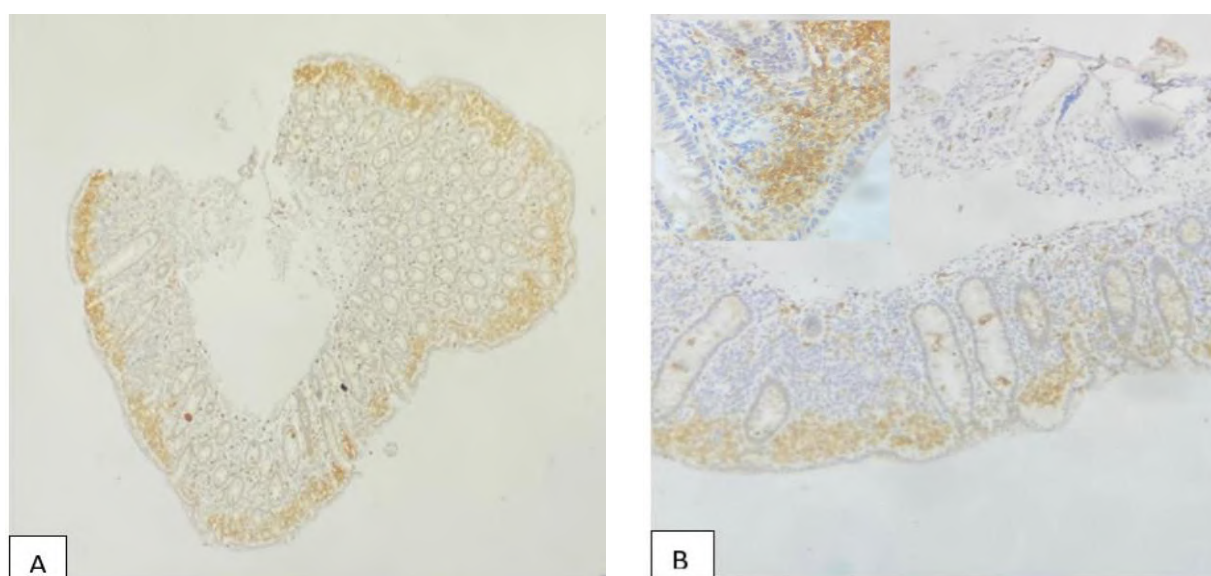
Figure 2. Microscopic Tissue.



Microscopic photos of ascending colon mucosa lesion from endoscopic biopsy. A&B) biopsy tissue limited to ascending colon mucosa layer (H&E 40x). C) consist of surface epithelium, crypts, lamina propria & mucosa muscle, without image distortion with *rack of test & daisy flower like* pattern (H&E 100x). D) multiple infiltrative eosinophilic PMN cells to crypts epithelium (in accordance to eosinophilic cryptitis), lamina propria contains dense distribution of band like cells indicating mastocyte, and on lower $\frac{2}{3}$ of lamina propria shows rich distribution of eosinophilic PMN mixed with plasma cells and lymphocyte (H&E 400x). Source: Authors.

On May 10th 2021, immunohistochemical examination was done to the biopsy tissue. Figure 3 is showing the results as follows: Immunohistochemical staining for CD117/c-kit on ascending colon tissue biopsy, shows strong positively stained mast cells on cell membrane and cytoplasm. CD117 staining on superficial cell parts (upper 1/3) of lamina propria suspected as mastocyte, therefore supporting the diagnosis of mastocytosis colitis.

Figure 3. Immunohistochemical Staining.



Immunohistochemical staining CD117; A) low power microscopic picture ; shows CD117 expressed. B) middle power microscopic picture ; CD117 immunostaining expressed, and high power in the left upper corner small box picture. Showing immunohistochemical staining for CD117/c-kit strong positively stained mast cell on cell membrane and cytoplasm. Source: Authors.

4. Discussion

Systemic Mastocytosis (SM) is a rare disease, heterogenic and progressive, marked with abnormal proliferation and mast cell infiltration on multiple organs. Mastocytosis variants are identified mainly through pathological examination, disease distribution, and clinical manifestation, including GI tract. GI tract symptoms occur on 14-85% patients with systemic mastocytosis. (Horny et al, 2017; Reggiana et al, 2015).

Around 50% of children affected show typical skin lesions before 6 months old. Skin mastocytosis occur very rarely in adults compared to children. Systemic mastocytosis generally diagnosed after second decade of life with 1:1 to 1:1.5 ratio of men to women. (Horny et al, 2017 ; Cestells et al, 2021).

In the reported case, a 54 year old woman with GI tract manifestation without skin involvement.

In general, the symptoms of systemic mastocytosis is grouped into 4 categories: constitutional symptoms (e.g; fatigue, weight loss, fever, diaphoresis), skin manifestation (e.g; pruritus, urticaria, dermatographism, redness), systemik phenomenon related with mediator (e.g; abdominal pain, GI tract disturbances, syncope, headache, hypotension, tachycardia, pulmonary symptoms) and musculoskeletal symptoms (e.g; bone pain, osteopenia/osteoporosis, bone fracture, arthralgia, myalgia). GI tract symptoms are clinically essential due to the severity and chronicity effect it may cause. GI tract symptoms include abdominal pain, diarrhea, nausea, vomiting, and bloating. (Horny et al, 2017; Hyungil et al, 2016; Reggiana et al, 2015).

In the reported case, the patient complained of fatigue, and GI tract disturbances since around the last 2 months. She experienced increased defecation of 2-4 times a day, stools are sometimes runny and accompanied with stomach ache. Patient also complained about weight loss of around 8kg in the last 2 months.

Endoscopic findings as shown by Figure 4 on patients with mastocytosis affecting GI tract range from subtle abnormalities to severe ulceration. Mucosa erythema, nodularity-polypoid, ulceration, or strictures are commonly found depending on GI tract location involved. (Srivastava, 2016).

In this case, the endoscopic findings are normal anus-rectum, normal sigmoid colon, normal descending colon, a polyp of 3mm on transverse colon with mosaic pattern, on mucosa of ascending colon and caecum also show mosaic pattern, meanwhile on terminal ileum no abnormalities were found.

Mast cell plays an important role in immunoregulation, mainly on the mucosal border. Mast cells are preferably located near nerve fibers in gastrointestinal lamina propria. Cel mast can be activated not only by type 1 IgE mediated-hypersensitivity reaction, but also by stress, nerve damage, infection, and other inflammatory processes. Secondary reaction to degranulation of multiple inflammation mediators of activated mast cells may change intestinal motility, visceral sensitivity, intestinal epithelial-mucosal barrier causing hypersecretion and propulsion power, resulting in diarrhea and stomach ache. Therefore, mast cells are triggered as a factor playing an important role in diarrhea-dominant IBS pathogenesis. Mast cell excess can be evaluated through immunohistochemical analysis for CD117, mast cell tryptase, or Giemsa staining. Some research had shown increasing number of mast cells in jejunum, terminal ileum, caecum, and colon gives the presentation of IBS. (Hyungil, 2016; Ramsay, 2010).

SM symptoms arise with mast cell release of mediators or by infiltration of clonal mast cell tissue. According to WHO criteria, diagnosis is based on histological findings of atypical mass cells in tissue, associated with c-kit mutation or coexpression of CD2/CD25 or associated with persistent increment of serum tryptase. In GI involvement, pathological findings can be detected on endoscopic and radiological examination. Macroscopically small intestine involvement of SM including; thickening of intestinal folds, nodular mucosa, edematous or jagged and widening of intestinal loop; these findings are also typical for inflammatory bowel disease. Histological documentation in the small intestine may show the presence of large numbers of atypical mast cells, increased plasma cell and eosinophil content in the lamina propria; Villous fluttering and atrophy may be seen. (Reggiana et al, 2015).

SM is determined by major and minor criteria, a minimum of 1 major and 1 minor criteria, or at least 3 minor criteria met. (Horny et al, 2017; Sristava, 2016).

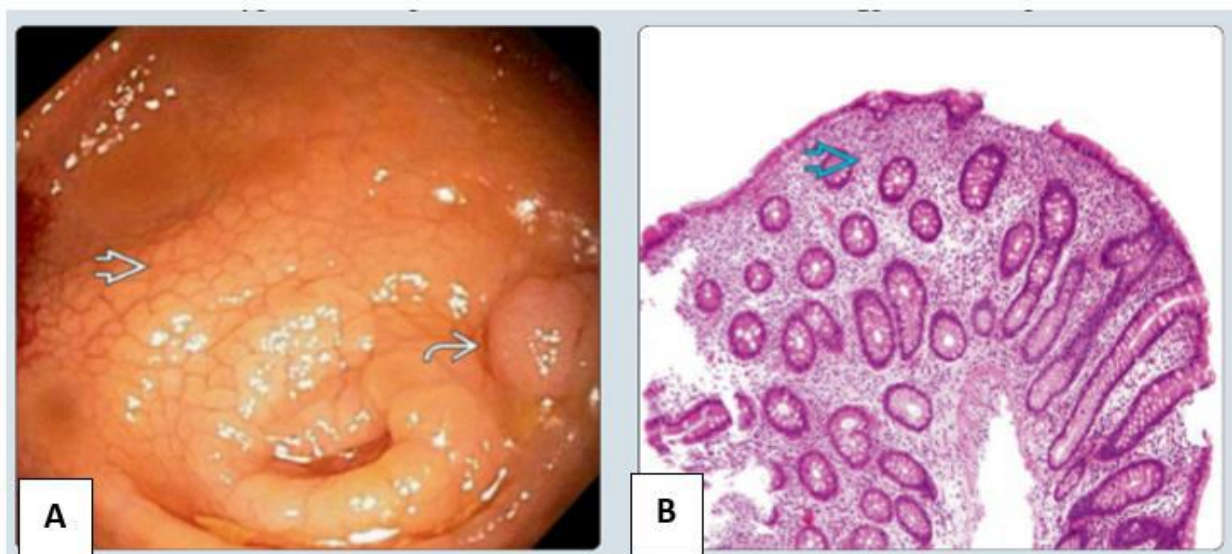
- Major criteria:
 - Dense multifocal mast cell infiltrates (215 mast cells in aggregations) detected in parts of bone marrow and/or other extracutaneous organs.
- Minor criteria:
 - On parts of bone marrow biopsy or other extracutaneous organs, >25% of mast cells in the infiltrate are spindle-shaped or have atypical morphology or >25% of all mast cells in immature or atypical bone marrow aspirate smears.
 - Detection of activating point mutations at codon 816 KIT in bone marrow, blood or other extracutaneous organs
 - Mast cells in bone marrow, blood or other extracutaneous organs express CD25, with or without CD2, in addition to normal mast cell markers.
 - Serum total tryptase persistently > 20 ng/ml, unless an associated myeloid neoplasm is present, in which case this parameter is invalid.

On histopathological examination, a microscopic picture of mastocytosis will show mast cell infiltration in the lamina propria with round or spindle cell nucleus morphology and moderate pale to clear cytoplasm. As explained on **Figure 5**, mast

cell infiltration density varies, fine infiltrates usually show a band-like appearance under the surface epithelium in the mucosal layer. A biopsy of the nodular lesion shows a denser confluent infiltrate and clearly resemble a lymphoproliferative disorder.

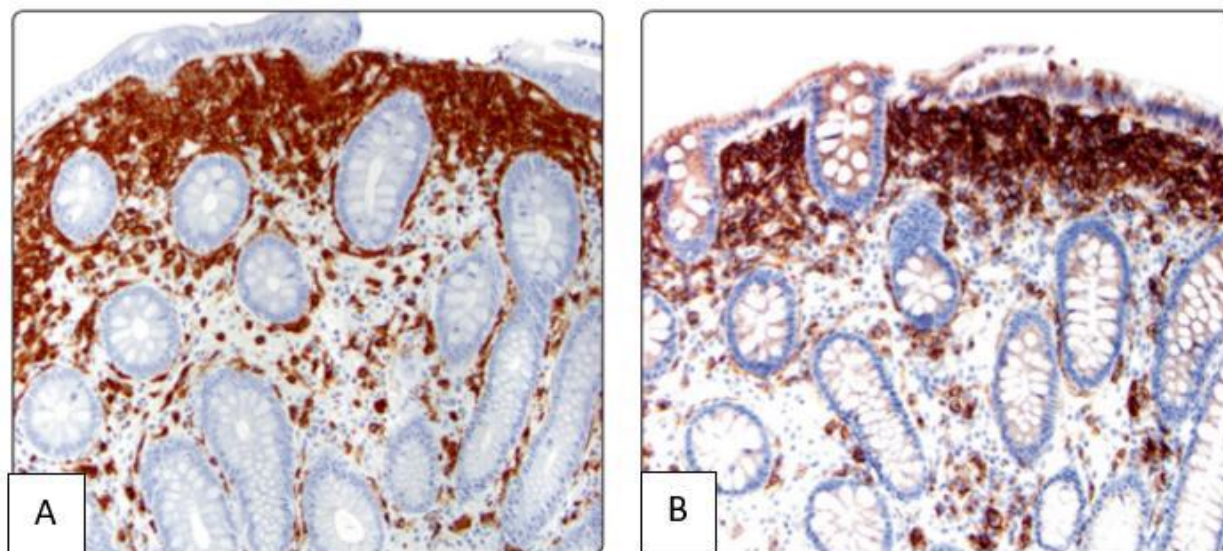
In the reported case, Mast cell proliferation abnormalities were found in aggregates only in the colon, without any clinical skin manifestations such as urticaria pigmentosa or other systemic signs such as hematological abnormalities. Histopathological examination found an increase in the number of mast cells $>20/HPF$ in the colonic mucosa, accompanied by symptoms of chronic diarrhea. Therefore, this case is more suitable to be diagnosed as mastocytosis colitis.

Figure 4. Endoscopic Findings.



A) Endoscopic findings in patients with systemic mastocytosis involving the GI tract range from subtle abnormalities to marked ulceration. This image shows a multinodular mucosa with multiple polypoid lesions. B) Mast cell infiltrate on mucosal biopsy can be easily missed. This biopsy is from the same patient and a band-like infiltrate is seen beneath the surface epithelium. (Sristava, 2016).

Figure 5. Mucosal Biopsy.



A) Mast cells infiltrate in tissue mucosal biopsy positive for CD117 (C-kit). Note the characteristic band-like distribution pattern. B) Neoplastic mast cells in systemic mastocytosis show abnormal expression of CD25 (and CD2) in C-kit-positive mast cells. (Horny et al, 2017).

Differential diagnosis:

1. **Eosinophilic Colitis (EC)**; very rare, only a few cases have been reported since 1979. The diagnosis of EC depends on histopathology identifying an excess of eosinophils. Clinical presentations include abdominal pain, diarrhea (bloody or bloodless), and/or weight loss. EC in primary cases may be associated with other atopic conditions. Colonic eosinophilia may also occur secondary to helminthic infections (eg pinworm / helminthic, hookworm), inflammatory bowel disease, autoimmune diseases (eg scleroderma, Churg-Strauss syndrome), celiac disease, and drug reactions. Normal eosinophil counts vary based on the anatomic location of the GI tract. **In the duodenum**, it is defined as <10 eosinophils per 1 large visual field (HPF) in pediatric patients and <19 eosinophils/HPF in adults. Therefore, microscopic examination showing >10 eosinophils/HPF in children and >20 eosinophils/HPF in adults has been established as the threshold for meeting both diagnostic criteria for mucosal eosinophilic gastroenteritis. However, **in the caecum**, the threshold should be set at a higher value, up to 40 eosinophils/HPF has been suggested as a normal value at this location. While the **colon** is up to 16/HPF in pediatric patients, up to 50/HPF in adults. Furthermore, when evaluating eosinophil counts, environmental factors need to be observed and considered: eosinophil counts will be higher during peak allergy seasons and among populations living in the southern regions of the US. (Sunkara et al, 2019).
2. **Systemic mastocytosis with GI involvement**; Based on the diagnostic criteria described above, SM can be determined by major and minor criteria, there must be at least 1 major and 1 minor criteria, or at least 3 minor criteria are met to establish the diagnosis of SM. Consensus criteria for the diagnosis of systemic mastocytosis have been established and five variants are recognized: indolent systemic mastocytosis, smoldering systemic mastocytosis, systemic mastocytosis associated with hematological neoplasms, aggressive systemic mastocytosis and mast cell leukemia.

Because the criteria for systemic mastocytosis and its variants are not met according our references, the reported case is more suitable for mastocytosis colitis. Clinical correlation and multidisciplinary approach also needed (Zanelli M, 2021).

5. Prognosis

In this case report, it is important for diagnosis accuracy especially on conditions with unresolved chronic diarrhea. This mastocytic colitis has no specific therapy, symptomatic treatment is necessary. Treatment with H1 and H2 histamine antagonists may be considered with varied results. Prognosis can be poor if aggressive clinical manifestations occur. (Sristava, 2016).

6. Conclusion

Mastocytosis is a rare disorder and may occur due to neoplastic clonal proliferation of mast cells that accumulate in one or more organ systems. One of the most common is gastrointestinal (GI) manifestations that can occur in up to 85% of patients with systemic or focal mastocytosis, with manifestations such as; abdominal pain, diarrhea, nausea, vomiting, and bloating. It is generally diagnosed after the second decade of life, and reported male-to-female ratios range from 1:1 to 1:1.5. Mastocytosis with skin manifestations is much less common in adults than in children. Endoscopic findings in patients with mastocytosis involving the GI tract macroscopically generally reveal mucosal erythema, nodularity-polypoid, ulceration, or stricture. On histopathological examination, the microscopic picture shows proliferation of mast cells in the aggregates only in the colon, without any other systemic manifestations, an increase in the number of mast cells >20/HPF was found in the colonic mucosa. The staining of CD117 on cells in the superficial (upper 1/3) lamina propria suspected mastocyte, then may

support the diagnosis of mastocytosis colitis. Management and prognosis in this case are closely related to the accuracy of diagnosis, therapy with H1 and H2 histamine antagonists can be considered with varied results. Prognosis can be poor if aggressive clinical manifestations occur.

We hope this article will provide better insight for this special disease and we suggest routine GI checkup such as GI tract endoscopy on systemic or focal mastocytosis patients, mainly with GI symptoms. Suspicions to this disease should yield more aggressive diagnostic techniques since early detection would improve the outcome. More reports should be brought to light further improving our understanding to the disease.

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