

Indolent systemic mastocytosis in a patient with ileocolitis

Georgios Chrysakopoulos^a, Maria Demonakou^b, Stelios Papasavvas^a, Andreas Koutsoumpas^a,
Georgios Mylonas^a, Vassilios Tzias^a

1st I.K.A. Hospital; Sismanoglion General Hospital, Athens, Greece

Abstract

Systemic mastocytosis is a clonal disorder of the mast cell and its progenitor cell. It is a rare disorder with unknown incidence in Greece, with an estimate of 2 cases per year in Great Britain. We present a case of an asymptomatic, 72-year-old man who was found to have ileocolitis on endoscopy. Histology revealed mast cells in lamina propria >15 HPF and biochemistry showed high levels of serum total tryptase. Molecular testing was positive for the mutation Asp816Val in exon 17 of *c-kit* gene. The patient met one major and two minor criteria for the diagnosis of systemic indolent mastocytosis (according to WHO classification). He has been treated prophylactically with H₁- and H₂-histamine receptor antagonists and remains asymptomatic.

Keywords Mastocytosis, indolent, asymptomatic, colitis, ileitis

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Introduction

Systemic mastocytosis (SM) is a heterogeneous clonal disorder of the mast cell and its progenitor cell. It is now classified as a myeloproliferative neoplasm as per the 2008 revision of the WHO classification of myeloid neoplasms [1]. It is characterized by mast cell infiltration of extracutaneous organs. Mast cells typically infiltrate the bone marrow and consequently affect the peripheral blood and coagulation system [2]. The clinical symptoms and signs of SM (systemic mast cell disease) are due to the accumulation of these clonally derived mast cells in different tissues, including bone marrow, skin, the gastrointestinal (GI) tract, the liver and the spleen [3].

Epidemiologic data on the incidence of SM are lacking. Some studies in Great Britain showed 2 cases per year in study population of 300,000. It is more common in adults (median age at diagnosis, 55 years). The somatic *c-kit* mutation D816V is found in the majority of such patients. The natural clinical course in SM is variable. Whereas most patients remain at the indolent stage for many years, some have aggressive SM at diagnosis. Two important diagnostic clues in SM are an

increased serum tryptase level and the presence of abnormal mast cells in the bone marrow [4].

GI symptoms are observed in 65% of patients with SM. Abdominal pain is the most common GI symptom, followed by diarrhea, nausea, and vomiting. Symptoms and signs of gastroesophageal reflux disease and peptic ulcer disease are noted in some patients.

Case report

We hereby present a case of an asymptomatic, 72-year-old man who underwent a colonoscopy in 2011 in our open-access endoscopy unit, after being referred by his General Practitioner (GP). The patient had undergone 3 colonoscopies in the previous 3 years (in other open-access units), the first one for bowel cancer screening in 2007 and the rest for surveillance after endoscopic removal of adenomatous polyps (most of them tubular adenomas with low-grade dysplasia). All of them had shown endoscopically mild colitis and histologically dense infiltration of the lamina propria by eosinophils. The patient had been discharged back to the care of his GP in 2009, without any further investigation, being always asymptomatic. It should be emphasized that he had never had abdominal pain, diarrhea, nausea, vomiting, heartburn or any other GI symptoms. His past medical history included a transurethral prostatectomy in 2010 and right inguinal hernia repair in 2006. He had never smoked and he consumed alcohol only on social occasions. There was no family history of importance and he was not on any medication. Clinical examination was unremarkable.

On endoscopy, patchy erythema, edema and nodularity was seen throughout the colon and terminal ileum (Fig. 1A).

^aGastroenterology Department of 1st I.K.A. Hospital - Present address: Gastroenterology Clinic, General and Oncology Hospital of Kifissia Agioi Anargyroi (Georgios Chrysakopoulos, Stelios Papasavvas, Andreas Koutsoumpas, Georgios Mylonas, Vassilios Tzias); ^bPathology Laboratory of G.H. Sismanoglion (Maria Demonakou), Athens, Greece

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Correspondence to: Georgios Chrysakopoulos, Gastroenterology Department of Kifissia General and Oncology Hospital Agioi Anargyroi, Timiou Stayrou & Noufaron, 14564 Nea Kifissia, Athens, Greece, Tel.: +30 210 3501576, e-mail: chrisakopoulosg@gmail.com

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Few inflammatory polyps were noted in the ascending colon (Fig. 1B). Multiple biopsies were taken, revealing a plethora of eosinophils and mast cells (>15 HPF in aggregates) in lamina propria. Immunohistochemical staining was positive for CD117+ and CD2+ (Fig. 2A, 2B). These findings raised the strong suspicion for SM and further investigations were requested.

Abdominal CT and ultrasound revealed no abnormality. Blood tests showed leukocytosis (total: 13,530/mm³, neutrophils: 10,620/mm³, lymphocytes: 1,530/mm³, monocytes: 780/mm³, eosinophils: 280/mm³), high levels of gamma-globulins (24.90%), β_2 -microglobulin (2.81 mg/L) and immunoglobulin IgE (406 IU/mL). Inflammatory markers (CRP, ESR) were normal. Serum total tryptase was 40 ng/mL.

Myelogram revealed reactive bone marrow with predominance of granular series over erythroids (10:1) and marrow infiltration by eosinophils and mast cells (>15/HPF in aggregates, CD117+). Foreign cells were not found and

mast cells morphology had no neoplastic characteristics. Bone marrow karyotype was negative for chromosomal abnormalities. Molecular testing of colonic mucosa was positive for the mutation Asp816Val in exon 17 of *c-kit gene* (DNA amplification and melting curve analysis).

Esophagogastroduodenoscopy and push enteroscopy were performed with normal endoscopic findings. Duodenal and jejunal biopsies showed small bowel mucosa infiltration with eosinophils and mast cells (>15/HPF in aggregates, CD117+, CD2+).

In summary, histology from duodenum, jejunum, ileum, colon and bone marrow revealed mast cells >15/HPF in aggregates and immunohistochemical staining was positive for CD117 and CD2. In accordance with the WHO criteria, this patient was diagnosed with indolent SM, fulfilling one major and two minor criteria (Table 1).

This patient is currently treated prophylactically with H1 and H2 blockers and remains asymptomatic up to the present

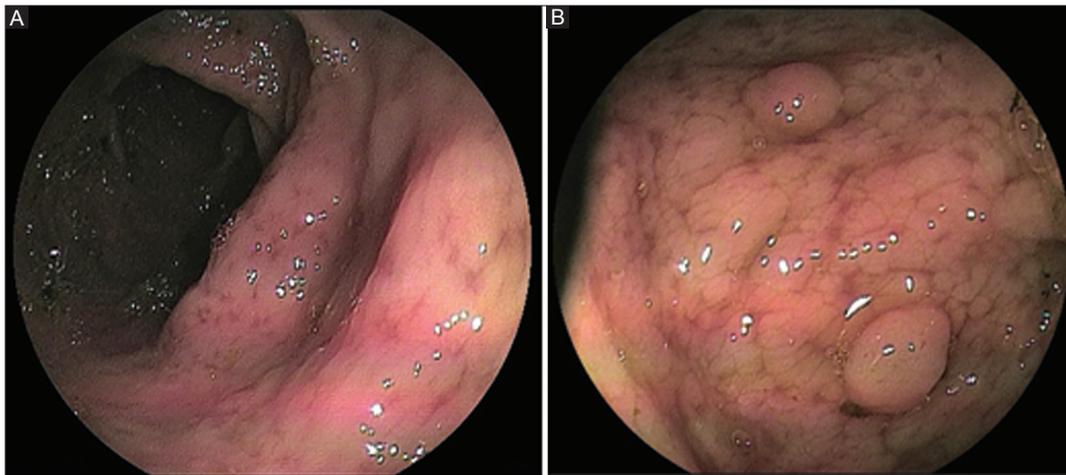


Figure 1 (A) Patchy mucosal erythema, edema and loss of vascular pattern of the descending colon. (B) Granularity of the ascending colon with post-inflammatory polyps

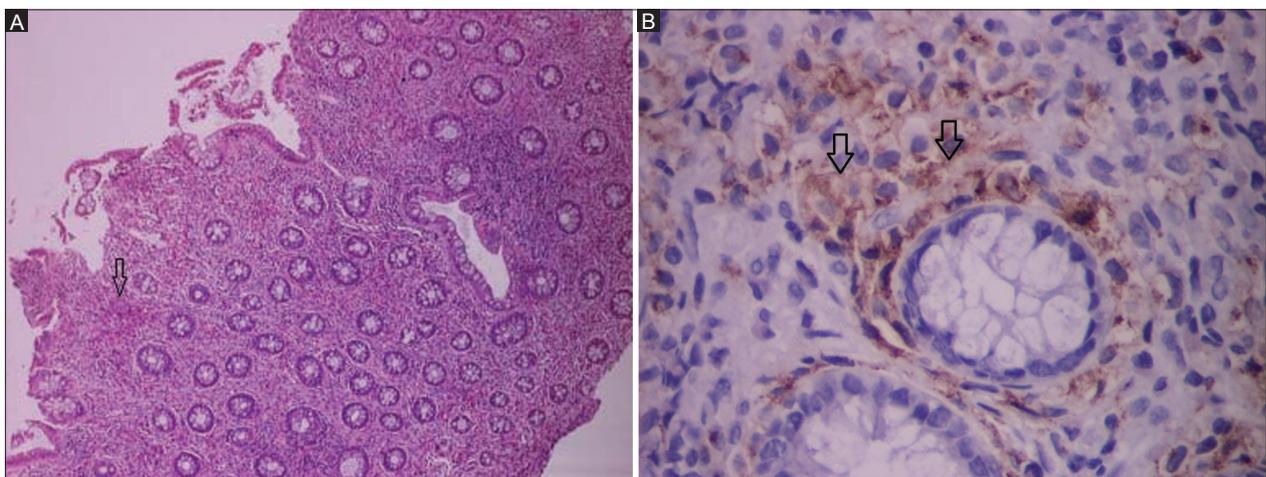


Figure 2 (A) HE X 25. Colonic biopsies. Dense inflammation of lamina propria with aggregation of eosinophils. (B) CD117 X 400. (Envision / DAKO 1:250). Dense infiltration of mast cells >15 HPF

Table 1 Diagnostic criteria for systemic mastocytosis [3,5]

Major criteria	Multifocal dense infiltrates of mast cells in bone marrow or other extracutaneous organ(s) (>15 mast cells in aggregate)
Minor criteria	<ul style="list-style-type: none"> a. Mast cells in bone marrow or other extracutaneous organ(s) show an abnormal morphology (>25%) b. <i>C-kit</i> mutation at codon 816 in extracutaneous organ(s) (activating mutations at codon 816; in most cases, <i>c-kit D816V</i>) c. Mast cells in bone marrow express CD2 and/or CD25 d. Serum total tryptase >20 ng/mL (does not count in patients who have associated hematologic clonal non-mast cell lineage disease-type disease)

If at least 1 major and 1 minor, or at least 3 minor criteria are met, the diagnosis of systemic mastocytosis can be established

time. He knows that he should avoid triggers of mast cell degranulation, such as alcohol and venoms. He has regular follow-up appointments in our outpatient clinic.

Discussion

To our knowledge and after a thorough search of the literature, this is the first report of a completely asymptomatic patient diagnosed with indolent SM, based on incidental non-specific ileocolitis at colonoscopy. This case study illustrates the importance of considering SM in the differential diagnosis of patients with endoscopic findings of ileitis and/or colitis with eosinophilic infiltrates in histology, even in the absence of typical symptoms, such as diarrhea and abdominal pain. It is very important to assess the presence of dense infiltration of eosinophils in lamina propria in colonic biopsies and to further investigate it accordingly. Eosinophilic infiltration can occur commonly secondary to parasitic and helminthic infections, such as *Strongyloides stercoralis*, *Enterobius vermicularis*, and *Trichuris trichiura* (whipworm) as well as secondary to drugs such as clozapine, carbamazepine, rifampicin, gold and naproxen. Liver transplant recipients on tacrolimus as an immunosuppressant agent are at risk of developing colonic eosinophilia. A dense eosinophilic infiltrate may initially be present in ulcerative colitis, mimicking eosinophilic colitis (EC) and implicating a pathogenetic role for eosinophils in inflammatory bowel disease. Other less common causes of colonic eosinophilia include vasculitides (e.g. Churg-Strauss syndrome) and Tolosa-Hunt syndrome, a rare neurological disorder with high serum IgE level (>1300 U/mL). Primary

EC remains a diagnosis of exclusion [6]. In our patient, dense infiltration of lamina propria with eosinophils encrypted actually dense infiltration of mast cells.

SM treatment is generally palliative. Patients with indolent SM have a normal life expectancy. However, if symptoms do appear, symptom-directed therapy is indicated; infrequently, cytoreductive therapy may be indicated for refractory symptoms [7]. In our patient's case, although he was asymptomatic, we preferred to treat him prophylactically with H1 and H2-histamine receptor antagonists, in order to avoid a sudden mast cell degranulation, which could lead to life-threatening complications.

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