A Rare Case of Aggressive Systemic Mastocytosis Involving the Gastrointestinal System and Review of Literature

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Case report

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Abstract

Background

Systemic mastocytosis is a rare disease and most patients have pigmented urticarial skin lesions. It can be easily missed and misdiagnosed in small biopsies, especially in those patients with nonspecific clinical complaints or untypical skin lesions.

Case presentation

We report a case of 69-year-old man who have presented with 2-year of diarrhea, progressive weight loss of 20kg and abdominal distention for 3 months. Ultrasound and abdominal CT scan showed massive effusions in abdominal and pelvic cavity. Colonoscopy was performed and showed intensive mucosal proliferations forming polypoid appearances. Microscopically, monotonously uniform, small, round tumor cells with slightly rich cytoplasm were concentrated between the residual glands in the colonoscopic biopsy. The tumor cells showed positive expression of CD117 and S-100, and low Ki-67 proliferation index of 2%, while Trypsin, CK, CD68, CD1a, Langerin, Syn, CgA, CD56, SATB2, CD20, CD3, α-inhibin and SMA were all negative. KIT D816V mutation was detected as well. Liver biopsy showed that CD117 positive cells were more than 15 cells in aggregates around the hepatic portal area and less than 15% mast cells were found in bone marrow smears. No multiple or diffuse pattern of mast cells infiltration was seen by repeated skin biopsies of skin lesions. With all these considered, the diagnosis of aggressive systemic mastocytosis was made.

Conclusions

The diagnosis of aggressive systemic mastocytosis is challenging for untypical clinical manifestations and subtle or inconspicuous lesions, especially in endoscopic biopsies, which requires awareness and a close teamwork of pathologists and clinicians.

Background

Mastocytosis (MC) is a heterogeneous group of disorders characterized by abnormal growth, neoplastic proliferation and accumulation of mast cells. Approximately 80% of patients with MC have the evidence of skin involvement, while the rest may involve the gastrointestinal tract, liver, spleen or bone[1]. Three variants of MC are recognized mainly by clinicopathological findings and classified as Cutaneous MC, Systemic mastocytosis (SM) and mast cell leukemia. The diagnosis of MC is made when it meets the World Health Organization diagnostic criteria of neoplastic mast cells infiltration. The diagnosis of SM can be made if the major criterion and at least 1 minor criterion are present, or above 3 minor criteria are satisfied[2]. Aggressive systemic mastocytosis (ASM) is an unusual subtype of SM (12%) and can be diagnosed when the SM patients have more than one “C” finding but do not meet the criteria for mast cell leukemia. When the gastrointestinal system is involved by SM, nonspecific symptoms such as abdominal pain, diarrhea, and vomiting are complained. Overlapping clinical manifestations make the histological
diagnosis extremely difficult. Especially those cases with isolated symptoms and no prior diagnosis can be easily ignored. Here, we report a case of ASM with gastrointestinal manifestations of unusual clinic and pathologic manifestations which is rarely reported.

Case Presentation

The patient was a 69-year-old man with 2-year history of diarrhea, progressive weight loss of 20kg and abdominal distention for 3 months. He complained for 1 to 2 yellow and mushy stools daily at first, and then gradually increased to 4 or 5 times daily. After intermittent anti-Helicobacter pylori treatment, the clinic symptoms were not improved effectively. The symptom of diarrhea still occurred 4 to 5 times a day after stopping drugs. After six months treatment, side effects of nausea and persistent diarrhea with fatigue appeared so the treatments were suspended. Three months later, the patient developed pitting edema and abdominal distension. He was admitted to another local hospital for further treatments. Colonoscopy showed diffuse polypoid hyperplasia in transverse colon, ascending colon and ileocecal region with a pathological diagnosis of tubular adenoma. Ultrasound and abdominal computed tomography (CT) scan showed massive effusions in abdominal and pelvic cavity and multiple cysts in liver and kidney. The bone density was unevenly distributed by three-dimensional rebuilding of abdominal CT (Fig. 1).

Before the last admission in June 1st, 2020, gastroscopy and colonoscopy were performed again. Colonoscopy showed intensive mucosal proliferations forming polypoid appearances with a diameter of 0.2cm to 1.2cm from ileocecum to the junction of descending and sigmoid colon (Fig. 2), while gastroscopy showed no obvious abnormalities except for focal mucosa atrophy. Colonoscopic biopsy showed that the mucosal glands of ileocecal valve and hepatic flexure were atrophic, with blunt villous, reduced crypt and uneven distributed glands. Monotonously uniform, small, round tumor cells with slightly rich cytoplasm were concentrated between the residual glands (more than 15 tumor cells in aggregates). The tumor cells had round, oval and spindle nuclei with fine chromatin and no mitoses were detected. Among the tumor cells, a large amount of eosinophils infiltrations were observed (Figs. 3 and 4). The tumor cells showed positive expressions of CD117 and S-100, and low Ki-67 proliferation index of 2%. Trypsin, CK, CD68, CD1a, Langerin, Syn, CgA, CD56, SATB2, CD20, CD3, α-inhibin and SMA were all negative (Fig. 5). Basophilic granules were found in the cytoplasm by Giemsa staining. C-KIT gene detection was further performed to confirm the diagnosis. The results revealed C-KIT gene c.2447A > T (p.d816v) mutation in exon 17 (Fig. 6). Gastroscopic biopsy also showed that there were a few scattered small and round cells of more than 15 tumor cells in aggregates with eosinophils infiltrations between the normal glands. These small clusters of cells were positive for CD117. Thus the diagnosis of SM was confirmed.

As most SM patients were reported to have skin lesions, a close physical examination was done in this case. Brownish red rash and pigmentation was found all over his body with a diameter of 0.5cm to 0.8cm. Most of them were on the trunk or bilateral upper limbs with symmetrical involvement. The skin scratch test was weakly positive and no urticaria was found on both sides of the lower limbs. The patient
complained that he would develop red macules and pruritus on the skin when faced with cold wind or other irritations for 40 years. However, he was treated as eczema in the past years (Fig. 7). To determine whether there was a skin involvement, skin biopsies were repeated twice, while, microscopically, only scattered mast cells in the subcutaneous tissues were outlined by CD117 immunohistochemistry staining.

To explore the findings in the CT scan and evaluate the extent of SM involvement, liver biopsy and bone marrow aspirate was performed. Liver biopsy showed that clusters of CD117 positive cells of more than 15 tumor cells in aggregates were located around the hepatic portal area with focal lobular necrosis or fusion necrosis around the central vein (Fig. 8). Bone marrow smears revealed less than 15% mast cells. The final diagnosis of ASM was confirmed and the patient had the six times neoadjuvant chemotherapy with Cladribine treatment till March 29, 2021. Bone marrow smear was repeated twice and flow cytometric determination was done, while none of those tests results met the criteria for mast cell leukemia. This patient was in remission as less than 1% mast cells were found in the latest bone marrow smear.

**Discussion**

MC was a rare group of disorders of unknown etiology and defined as abnormal proliferation of mast cells. Abnormal mast cells and their mediators could affect many organs and the manifestations might vary differently. Nearly 60–80% of the SM patients had the gastrointestinal system manifestations such as abdominal pain (51%), diarrhea (43%), vomiting (28%), nausea and malabsorption. These symptoms could be a response to the mast cells mediators or direct infiltration [1, 3, 4]. However, gastrointestinal manifestations were not specific and could be easily misdiagnosed. Serum total tryptase levels, as a minor criterion, were helpful if it reached over 20ng/ml. But in this case, the serum tryptase level was not tested before the diagnosis. This patient was misdiagnosed with non-specific gastrointestinal symptoms in the local hospital.

Nearly half of the SM had skin lesions and skin symptoms were more common in indolent SM than ASM [1]. Although 61% of those SM had gastrointestinal manifestations, few had mast cells aggregates under endoscopic biopsies[5]. This patient was diagnosed by close pathological examinations before skin symptoms were noticed. Although this patient had brownish red rash and pigmentation all over the body and he would develop red macules and pruritus when faced with cold wind or other irritations in the past 40 years, the skin scratch test was just weakly positive. Microscopically, only scattered mast cells were seen by repeated skin biopsies instead of clusters or diffuse patterns of mast cells infiltrations. Further studies were still needed to investigate the possible disease progression from cutaneous MC to ASM.

Endoscopy with biopsies was the most common procedures performed on patients of SM with nonspecific gastrointestinal complaints. In 60% of the cases, the most frequently observed lesions were small nodules, mucosal edema and polypoid lesions in the intestinal tract, while the other might appear endoscopically unremarkable[6, 7]. In some cases, ulcerations had been reported and could result to a
wrong impression of inflammatory bowel diseases[8]. No special disorders were observed in esophagus and stomach except gastric ulcers, esophageal reflux, inflammations and nodular mucosa. Therefore, multiple serial biopsies was needed when the patient had continuous gastrointestinal complaints[9]. The main endoscopic features were polypoid appearances formed by intensive mucosal proliferations, which had no visible abnormalities. Thus biopsies remained a critical step to further diagnosis[10].

Pathologically, mast cells were usually scattered in healthy individuals, without any clinical implications. Only a few subtle and multifocal clusters of mast cells infiltrations could be seen in nearly 23.5–74.3% of MC patients, and could be easily missed and mistaken for histocytes in random endoscopic biopsies, not to mention those dispersed mast cells in the background of inflammation [9]. It was notable only in a diffuse infiltration pattern or multifocal clusters. The major criterion of SM was clusters of more than 15 mast cells in any extracutaneous tissues. Mast cells were most commonly seen under the crypts or at the top of the villi [7]. Mast cells were uniform, small, round cells with slightly rich cytoplasm accompanied by prominent eosinophilic infiltrations. Sometimes, mast cells could be atypical with spindle morphology or reduced granularity. Few mitoses could be seen.

CD117 was expressed in both normal and neoplastic mast cells. CD25, CD2 or both were reliable markers to distinguish neoplastic from normal mast cells [11, 12]. CD25 staining was particularly effective in the bone marrow rather than in extramedullary tissues, because there was a few CD25 positive lymphatic cells in the background[13]. High expression of CD25 had a close relationship with C-KIT gene D816V mutation, which was related with poor prognosis in SM patients, while wild type C-KIT status was correlated to the absence of CD25 in most cases[7]. Unfortunately, we did not have CD25 antibody and CD2 was not positive in the endoscopy or liver biopsies. KIT D816V mutation, as a minor criterion of SM, was found up to nearly 85% in the bone marrow, blood or another extracutaneous organ of all patients with SM[14]. However, diagnosis of SM could not be completely excluded by false-negative results of KIT D816V mutation due to insufficient samples when tested in endoscopic biopsies. KIT D816V mutation was not only presented in MC but also could be seen in other lymphomas or soft tissue tumors. Besides, other oncogenes in variants of KIT mutation, somatic mutations of TET2, SRSF2, ASXL1, RUNX1, JAK2, NRAS and KRAS and pro-oncogenic key mutants of CALR, PDGFRA, PDGFRB mutations were also identified[15].

Liver involvement was common in ASM and might lead to abnormal liver laboratory examinations, ascites and/or portal hypertension. This patient had the characteristic features of SM and progressive weight loss of 20kg with ascites and liver biopsy confirmed the diagnosis of ASM. Bone marrow smears of less than 20% mast cells did not meet the diagnosis of the mast cell leukemia. ASM diagnosis was made due to the major criterion and one minor criterion of SM and had at less two “C” findings of ascites with impairment of liver function and malabsorption with significant weight loss, while the bone marrow smears of less than 20% mast cells did not reach the mast cell leukaemia diagnosis. ASM was further divided into untransformed form and transformed form. ASM in transformed form had 5%–19% MCs in bone marrow smears and could frequently progress to MCL of poor prognosis[16].
ASM was a rare disease which needed to be ruled out from other tumors when it showed a diffuse pattern between the residual glands with rare tumor formations. The differential diagnoses included reactive hyperplasia of histiocytes, neuroendocrine tumors, langerhans cell histiocytosis, poorly differentiated adenocarcinoma, soft tissue tumors and lymphomas. They had partially similar histopathological characteristics but could be easily distinguished by a group of immunohistochemical markers. Another important feature was that a large amount of eosinophilic granulocytes among the mast cells could be seen, whereas only a few eosinophilic granulocytes could be present in nonspecific inflammations or inflammatory bowel diseases in the intestine. To date, there was no generally accepted first-line treatment for patients with ASM of abdominal symptoms of pain and/or diarrhea, treatment was intended to avoid mast cell deregulations and inhibit the actions of the constitutive mediators released by mast cells including H1/H2 antihistamines, proton pump inhibitors and antileukotrienes. For severe cases, cytoreductive agents of interferon alpha, Glucocorticoids (especially with severe malabsorption or ascites) and Cladribine, Tyrosine kinase inhibitors and hematopoietic stem cell transplant were optional[17]. Recently, emerging treatment concepts against KIT mutations and other relevant targets in neoplastic mast cells would receive recognition hopefully in the recent years[15, 18].

Conclusions

In summary, ASM diagnosis with first impressions of gastrointestinal symptoms requires a serious awareness and close teamwork between pathologists and clinicians. Although immunohistochemistry of CD117 and KIT D816V gene mutation may be helpful in the diagnosis, the diagnosis of endoscopic biopsy specimens is challenging because the lesions could be subtle or inconspicuous.

Abbreviations

MC: Mastocytosis; SM: Systemic mastocytosis; ASM : Aggressive systemic mastocytosis; Kg: kilogram; CT: computed tomography; CD117: Cluster of differentiation 117; CK: Cytokerotin; CD68: Cluster of differentiation 68; Syn: Synaptophysin; CgA: Chromogranin A; CD1a: Cluster of differentiation 1a; CD56: Cluster of differentiation 56; SATB2: special AT-rich sequence binding protein 2; CD20: Cluster of differentiation 20; CD3: Cluster of differentiation 3; SMA: Smooth muscle actin

Declarations

Author information

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Contributions

All authors contributed to the study conception and design. JJW, ZZ, FNN, TW, and BZ made contributions to analysis and interpretation of data. JJW were involved in drafting the manuscript and revising it critically for important intellectual content. XSF and HPY performed the histological analysis, and HPY gave final approval of the version to be published and agreed to be accountable for all aspects of the work. All authors read and approved the final manuscript.

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Ethics approval and consent to participate

Not applicable.

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Consent for publication

Written informed consent for the publication of patient clinical details and clinical images was obtained from the patient.

Competing interests

The authors declare that they have no competing interests.

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**Figures**
Figure 1

Abdominal CT scan revealed that multiple cysts in liver and kidney and massive effusions in abdominal and pelvic cavity. The bone density was unevenly distributed in the scanning field by three-dimensional rebuilding.
Figure 2

Colonoscopy showed intensive mucosal proliferations forming polypoid appearances with a diameter of 0.2cm to 1.2cm from ileocecum to the junction of descending and sigmoid colon.
Figure 3

Between the residual glands, monotonously uniform, small, round tumor cells with slightly rich cytoplasm were seen.
Figure 4

The tumor cells had round, oval and spindle nuclei with fine chromatin and no mitoses were detected.
Figure 5

The tumor cells showed positive expressions of CD117 and more than 15 tumor cells in aggregates were seen.
c.2447a > t (p.d816v) mutation was found in KIT exon 17.

Figure 7

The patient had brownish red rash and pigmentation all over the body with a diameter of 0.5cm–0.8cm, mostly on the trunk or bilateral upper limbs with symmetrical involvement.
Figure 8

Clusters of CD117 positive cells were found around the hepatic portal area with focal lobular necrosis or fusion necrosis around the central vein. More than 15 tumor cells in aggregates were seen.