Case Report

Gastrointestinal Exaggeration of Mast Cells in Pediatric Patients: A Localized Process without a Worrisome Concern? A Report of 3 cases and a Review of the Literature

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Abstract

Non-cutaneous pediatric systemic mastocytosis is exceedingly rare. In selected circumstances an isolated elevation of gastrointestinal mast cells is discovered. I report three cases with exaggerated gastrointestinal mast cells determined during the histological assessment of tissue obtained during the diagnostic evaluation of abdominal concerns. Each child had a different clinical presentation; including chronic protein intolerance, mast cell activation symptoms with abdominal pain, and eosinophilic esophagitis. This literature review will help to determine the steps necessary for the evaluation of this occurrence.

Keywords: mastocytosis, pediatric, gastrointestinal tract, mast cell

Introduction

Mast cells play a pivotal role in the interaction of the mucosal surface and the external environment [1]. Mast cells at the mucosal barrier interact with the innate and adaptive immune system to respond to parasites and other outside microbiological invaders [1]. The exaggerated presence of mast cells occurs in a number of clinically relevant circumstances [2-4]. In children, the presence of excessive mast cells is almost always cutaneous [5]. When extra-cutaneous mast cells are discovered, more concerning forms of mast cell disease is possible [6]. I present three pediatric cases of exaggerated mast cells in gastrointestinal tissue, and that longitudinal observation and additional studies failed to demonstrate additional extra-gastrointestinal concerns.

WHO classification of mastocytosis

The excessive presence of mast cells is termed mastocytosis [2-4]. The World Health Organization (WHO) consensus classification identified seven categories [7]. The basic histopathological presence of >15 multifocal dense aggregates of mast cells in bone marrow and/or other extracutaneous tissue was the histopathological criteria established, coupled with pathological mast cell marker positivity (CD25 and or leucocyte function antigen 2 (CD2+) mast cells), a molecular mutation (D816V kit), and serum tryptase >20 ng/ml. In humans this can be expressed as malignant forms (3 types) and aggressive persistent systemic disease, indolent systemic disease, cutaneous forms
(with or without systemic involvement), or extra-cutaneous mastocytoma. Pediatric patients predominately have the non-systemic cutaneous presentation [5].

**Extra-cutaneous manifestations of WHO supported mastocytosis**

Reviews of mastocytosis outline clinical manifestations in the gastrointestinal tract, musculoskeletal system, bone marrow pathology, and hepatic and splenic organs [2-4]. In interest to this particular report is the significant gastrointestinal presentation of WHO criteria supported mastocytosis, including diarrhea, bloating, abdominal pain, vomiting, and gastroduodenal ulcers [8-12]. Mast cell mediator release from the accumulated mast cells (in one or more tissue sources) can result in acute multi-localized symptoms (primary mast cell activation syndrome) [13].

**Allergic diseases with mast cell exaggeration**

Mast cells, of a non-pathological variety, are modestly elevated and likely genetically constitutive, in all allergic disease, including: allergic rhinitis, asthma, atopic dermatitis and eosinophilic esophagitis. The clinical presentation and the continued demonstration of the allergic disease process are intimately tied to tissue based mast cell activation. In some situations, the over-production of mast cell mediators results in anaphylaxis or a constellation of anaphylaxis-associated symptoms (secondary mast cell activation syndrome) [13].

The literature supports increased mast cells in the allergic diseases, and a published report in adults suggested a cut-off of <20 mast cells/HPF (as measured in GI tissue) as within normal limits; and if examined the specific markers of CD25 and CD2+ are negative [11,14].

**Case Reports**

**Case 1**

The first patient, an 8-month-old Caucasian male presented to our specialty clinic had very early medical concerns. He was put on antibiotics at day 2 through day 4 of life for GI tract symptoms. Subsequently, he was diagnosed as having milk-soy protein enterocolitis and he was switched to EleCare. He was gaining weight. He had mucous based diarrhea with many foods. Review of systems was otherwise negative. He had no respiratory symptoms, no skin symptoms or rash. His first endoscopy and biopsy of upper and lower GI tract at age 1 was histologically normal. With continued symptoms at 4 years his gastrointestinal biopsy showed increased colonic mast cells (only) Cecum: 62 HPF (max), transverse/descending 42 /HPF (max) and sigmoid/rectum 28 HPF (max). Mast cells were identified by CD117. Eosinophils were not elevated. CD25 staining was negative. At 4 years he was on EleCare with very few foods that he only can eat without diarrhea. At 4 years his IgE was 36 and extensive ImmunobocAP RAST IgE allergy testing to foods was negative and serum tryptase was 4.8 micrograms/l. At age 6 he maintained similar GI symptoms with no additional medical issues and repeated allergy tests were negative and serum tryptase was in the same normal range.

**Case 2**

The second case, a 12-year-old Caucasian male presented to our specialty clinic had a periodic fever syndrome as a younger child. He had outgrown that issue but had fever/exercise-associated facial angioedema with red flushed face, and itching. He did not have cutaneous lesions. Serum IgE was 1025. Shortly after that visit, he had an endoscope for abdominal pain. Biopsies of his duodenum, ileum, right colon and left colon, showed up to 53 mast cells/HPF. Eosinophils were not elevated. Diseases in the family included clotting disorders, hemochromatosis, and polycythemia vera. His serum tryptase were normal. His reference laboratory urinary 2,3-dinor 11B-Prostaglandin F2a was elevated. Urinary Leukotriene E4 and N-Methylhistamine were not ordered.

**Case 3**

The third case, a 3-year-old Caucasian male presented with eosinophilic esophagitis (EoE) symptoms, which was proved to have the diagnosis of EoE (on a PPI) and had abnormal mast cell numbers in a GI-tract biopsy at
another specialty center. His mother had EoE. A previous tryptase was >10 micrograms/L; a serum IgE was elevated (220 kU/L). A c-kit analysis was negative for Asp816val mutation. At our specialty clinic at age 5 he was using a food-based avoidance for EoE. No skin lesions were seen. A repeat upper gastrointestinal tract biopsy showed active eosinophilic esophagitis (30 eosinophils/HPF) and elevated mast cells using CD117; esophagus (15 max), stomach (50 max); duodenum (30 max); descending colon (20 max); retosigmoid colon (30 max). A CD25 staining was negative. His repeated tryptase was 11.3 micrograms/L. Allergy tests were positive for several foods (<0.35 KU/L). Reference laboratory levels of Urinary N-Methylhistamine, 2,3-dinor 11B-Prostaglandin F2a, and Leukotriene E4 were not elevated.

**Discussion**

The standard association of increased mast cells in gastrointestinal biopsies has an immediate connection with systematic mastocytosis [8-12], including children [6]. However, there is a limited literature for less ominous explanations. Establishing the normal occurrence of gastrointestinal mast cells in children is therefore important.

In 2010 a brief report of the number and distribution of mast cells in the pediatric gastrointestinal tract of healthy children was published [15]. Thirty-two children without histological abnormalities were studied were reported using tryptase or CD117 staining, and the mean and maximum results were reported. The maximum numbers were: Esophagus 3 mast cells (MC)/HPF, gastric mucosa 2 MC/HPF, and gastric lamina propria (LP) 29, duodenal villous LP maximum 29, intercryptal LP the maximum was 36. In the terminal ileum villous LP was 19 and 42 for intercryptal, the highest colonic MC were in the cecum/ascending colon with 19 MC/HPF, with decreasing numbers to the rectum. In a separate report, colonic mast cells in 41 non-atopic children with endoscopic and histological studies were reported [16]. The highest colonic lamina propria mast cell number in children was in the descending colon at 15.5 ± 7.3 /HPF. A third study of healthy Canadian children using a Geimsa stain revealed low numbers of mast cells in the gastrointestinal tract, in fact the highest level in any one child was 11 /HPF in the ileum lamina propria [17]. These three pediatric based studies would strongly suggest, in children, mast cells should not be clustered, or in surface epithelium, and likely never exceed 30/HPF in the lamina propria.

Exaggerated, non-systematic mastocytosis associated gastrointestinal mast cells have been described to be increased in a limited number of adult disease circumstances [18]. These include mastocytic enterocolitis, gastrointestinal food allergy, and diarrhea-predominant irritable bowel syndrome [18-21].

A report by Jakate termed their adult patients with elevated gastrointestinal mast cells and chronic intractable diarrhea as having mastocytic enterocolitis [19]. Their subjects had significantly more mast cells in the gastrointestinal tissue as compared to controls and subjects with inflammatory gastrointestinal disease.

A single older report demonstrated increased mast cells in adults with gastrointestinal food allergy [20].

A number of reports have documented increased gastrointestinal mast cells in adult subjects with diarrhea-predominate irritable bowel syndrome [18,21,22]. Likely these reports and the group reported by Jakate et al. have over-lap.

Therefore, there is good support for mast cells involvement in functional bowel disease in adults [19,21,22]. The frequency and maximal levels of CD117+ mast cells, with concomitant CD25 negativity, needs additional study, and a 2013 case report emphasizes the importance of specific mast cell staining in the diagnosing gastrointestinal associated systemic mastocytosis conditions [23].

There are also limited studies of increased mast cells in pediatric gastrointestinal tissue in association with a non-systemic mastocytosis conditions. A report from Iran in 2009 terms a group of children (abdominal pain/vomiting) and increased gastric mast cells expressed as mast cell gastritis, and only reported children above a
The mast cell number was determined after geimsa stain, and at 1000X magnification in 10 fields with a Zeiss standard light microscope and the number of mast cells (density) was calculated (a measurement of 0.25 mm²). Gastritis cases were not clinically variable between subjects with increasing mast cell numbers (max 93/0.25 mm²) [24].

A second Iranian study in 2012 proposed an explanation for recurrent abdominal pain and gastritis was associated with increased mast cells in the gastric biopsy specimen [25]. Their summary and the actual data was conflicting, as mast cells were lower in gastritis patients as compared to controls, and the maximum number of mast cells seen was <15 (counting methodology not specified) in either population.

An American study of mast cells in children with chronic, non-inflammatory abdominal pain and children with inflammatory gastrointestinal disease, revealed higher colonic mast cells in the non-inflammatory subjects, but mean mast cells were 3.54/ HPF (± 2.92), and 2.63 HPF (± 1.83); and in neither group were mast cells counts >15 HPF [26]. Therefore, this study did not support high mast cells in pediatric abdominal functional pain syndrome [26].

The three pediatric children reported here had markedly increased mast cells in different areas of their gastrointestinal tract. Case 3 had known eosinophilic esophagitis, and a modestly elevated tryptase. Case 1 and 2 had no other diagnosed allergic disease, and had more GI based issues. The author has followed case 1 for 6 years, case 2 for 2 years, and case 3 for 2 years. Because of mast cell activation episode(s) in case 2 and 3, a broad-based approach to mast cell mediator activity suppression had been instituted (antihistamine and anti-leukotriene prophylaxis). Retrospective CD25 staining in case 3 was negative. Case 1 retrospective CD25 staining was negative. Case 2 changed specialty providers.

With only a limited literature for explaining gastrointestinal pediatric mast cell exaggeration as reference, the discovery of elevated gastrointestinal mast cells raises concerns. Adding CD25 staining at the time of elevated mast cell discovery would reveal a less worrisome mast cell accumulation and was done in 2 of the 3 cases. I present these three cases, uncovered in an academic Allergy-Immunology specialty clinic with extensive exposure to gastrointestinal endoscopy and histological reports, to expand the repertoire of mast cell processes in the pediatric population, and bring explanation in situations where an exclusive pediatric gastrointestinal mast cell accumulation is discovered.

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References