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Do mast cells play a pathogenetic role in neurofibromatosis type 1 and ulcerative colitis?

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ABSTRACT

Concurrent association of neurofibromatosis type I and ulcerative colitis has been reported in one clinical case (Tavakkoli et al., 2009). Although this association may represent a casual finding, a common pathophysiology is postulated. Mast cells have been implicated in the pathogenesis of both neurofibromatosis type 1 and ulcerative colitis (He, 2004; Yoshida et al., 2010). Mast cells are typically present in neurofibromas microenvironment where they appear to contribute to tumor initiation, progression and angiogenesis (Staser et al., 2010, 2013). Moreover, interaction of mast cells with nerves throughout the gastrointestinal tract has been correlated with progression and maintenance of ulcerative colitis (Stoyanova and Gulubova, 2002). We describe a 14 year-old male with history of neurofibromatosis type 1 and new onset of ulcerative colitis diagnosed on clinical and histological findings. On gross examination the entire colonic mucosa appeared edematous showing a peculiar granular pattern, with focal erythema, shallow ulcers and multiple sessile polyps. Hematoxylin and eosin stained tissue biopsies from the colonic mucosa showed chronic inflammatory bowel disease, severe activity, consistent with chronic ulcerative colitis. Immunohistochemistry stain of the intestinal lesions revealed high expression of Neuron Specific Enolase (NSE) and S100 highlighting the presence of a Schwann cell component. In addition, c-kit/CD117 positive stain indicated a marked increase of mast cells in the lamina propria. This pattern of cellularity in the lamina propria showing increased mast cells and augmented Schwann cell component was absent in the colonic mucosa of a normal control or a patient with ulcerative colitis alone. Our observation supports the evidence of a pathogenetic role of the mast cell in ulcerative colitis associated with neurofibromatosis type 1. Further investigations are warranted to confirm the significance of this correlation as it may impact therapeutic approaches of these pathologies.

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Introduction

Concomitant association of histologically proven ulcerative colitis (UC) and neurofibromatosis (NF) type 1 is a rare finding documented in one adult clinical case by Tavakkoli et al. (1) Previous literature identified mast cells as important elements involved in both pathogenesis of inflammatory bowel disease and development of neurofibromas (2, 3). Here we report a pediatric case of newly diagnosed UC in NF type 1. We evaluated the presence of mast cells and Schwann cells in the colon tissue biopsy diagnosed with UC by immunohistochemistry (IHC). Mast cells were identified by expression of CD117/c-kit, and Schwann cells by expression of Neuron Specific Enolase (NSE) and S100. As control tissue, we utilized a colon biopsy from a pediatric patient with UC alone and a colon biopsy from a pediatric patient without evidence of the disease.

Case report

A 14 year-old male presented to the emergency department of our hospital with one-day history of sudden onset of explosive loose stool associated with tenesmus and spotting of fresh red blood and one month history of increasing fatigue. Past medical history was significant for NF type 1 diagnosed in the first year of life based on clinical manifestations and positive family history in maternal grandmother and aunt. The patient also had history of Attention Deficit Hperactivity Disorder (ADHD) pharmacologically treated and resolved three years prior. The patient appeared pale and showed multiple “café au lait” spots on the trunk and extremities. Rectal exam showed erythema without evidence of anal fissures or rectal masses. The initial vital signs were within normal limit (temperature 98.8 °F, blood pressure 124/79, respiratory rate 23, pulse oximetry 99%), except for mild tachycardia (pulse 99). The base line laboratory data confirmed a significant microcytic anemia with hemoglobin 5.1 g/dl, Mean Corpuscolar Volume (MCV) 48 fL, reticulocyte count 2.3%, iron 11 mcg/dl, Total Iron Binding Capacity (TIBC) 399 mcg/dl, and ferritin 1.7 ng/ml. The patient received 1 L normal saline

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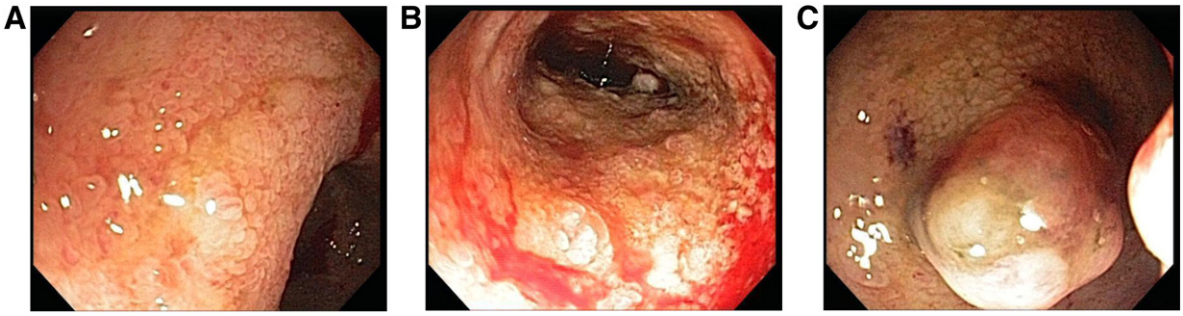

Fig. 1. Sigmoid mucosa, ileocolonoscopy.

and 2 units of packed red blood cells. Following blood transfusion the hemoglobin increased to 7.6 g/dl and the MCV increased to 56.6 fL. Peripheral blood anti-neutrophil cytoplasmic antibodies (ANCA) screen was positive. The atypical perinuclear (P)-ANCA titer was 1:640 units (reference range: <1:20 units). The inflammatory bowel disease panel showed normal levels of myeloperoxidase antibody (<1.0 unit, (normal range <1.0 unit)), Proteinase-3 antibody (<1.0 unit (normal range <1.0 unit)), anti-Cerevisiae IgG and anti-Cerevisiae IgA (4.5 units and 5.8 units, respectively, (normal range <20 units)).

The patient underwent esophagogastroduodenoscopy and ileocolonoscopy. The mucosa of the stomach and terminal ileum appeared grossly normal. The entire colonic mucosa however showed diffuse edema with a peculiar granular pattern accompanied by focal erythema, shallow ulcers and multiple sessile polyps (Figs. 1A–C). Multiple biopsies were obtained from the gastric mucosa to the rectum. Microscopic examination of tissues from the colonic mucosa revealed a prominent lymphoplasmacytic infiltrate in the lamina propria, associated with goblet cell depletion, cryptitis, crypt abscesses and pseudopolyp formation (Fig. 2A–B). The degree of chronic inflammation ranged from mild (transverse colon and rectum) to moderate (cecum and descending colon), to severe (ascending and sigmoid colon). Pseudovilli formation was also noted in the sigmoid colonic mucosa (Fig. 2B). The microscopic findings along with the clinical manifestations were consistent with the diagnosis of UC. No significant pathologic changes were observed in the gastric and terminal ileal mucosa. Immunohistochemistry stain of the intestinal lesions with c-kit/CD117 revealed a marked increase in mast cells in the lamina propria (Fig. 3B). In addition, Neuron Specific Enolase (NSE) (Fig. 3C) and S100 positive cells (Fig. 3D) highlighted the presence of a Schwann cell component. This pattern of cellularity showing increased number of mast cells and augmented Schwann cell component in the lamina propria was absent in the colonic mucosa of a normal control (Fig. 4A–D) or a patient with UC alone (Fig. 5A–D). In the latter, however, the level of NSE expression by Schwann cells appeared similar to the one observed in our patient (Figs. 3C and 4C).

Following diagnosis, the patient was discharged home in stable condition, on iron fortified diet, oral 5-aminosalicylic acid (5-ASA), Asacol 800 mg (q 8 h), and daily intake of folic acid 1 mg, and ferrous sulfate 325 mg.

Materials and methods

IHC staining was performed utilizing antibodies purchased from Cellmark AB, Gothenburg, Sweden. The Ventana Benchmark XT and Ventana Benchmark Ultra, Tucson, Arizona, were utilized as automated slide staining system, following the manufacturer's protocol.

Discussion

NF type 1 is a common autosomal dominant disease caused by mutation of the tumor suppressor gene NF-1 leading to multiple neuronal, hematopoietic and skeletal pathologies (Jett and Friedman, 2009). Clinical manifestations include "café au lait" spots, neurofibromas, frecklings, Lisch nodules, optic gliomas, and bone deformities. Hallmark of the disease is the development of neurofibromas, composed of Schwann cells, fibroblasts, extracellular matrix and degranulating mast cells (Jett and Friedman, 2009).

Mast cells are resident leukocytes known to play a key role in type I hypersensitivity (Walls et al., 2001). Characteristic feature is the presence of cytoplasmic metachromatic granules that occupies approximately 40% of the cell volume. These membrane-enclosed secretory granules originate from the Golgi apparatus. Here, preformed mediators including histamine, proteoglicans, neutral proteinases, cytokines, and newly generated mediators such as eicosanoids and platelet activating factor (PAF) (He, 2004). Mast cell activation is fundamental in mast cell function because only activated mast cells can cause pathophysiologic changes. (He, 2004) Anti-Immunoglobulin (Ig)E, ionophores, stem cell factor (SCF), eosinophil cationic protein and tryptase can activate mast cells (He, 2004; Walls et al., 2001).

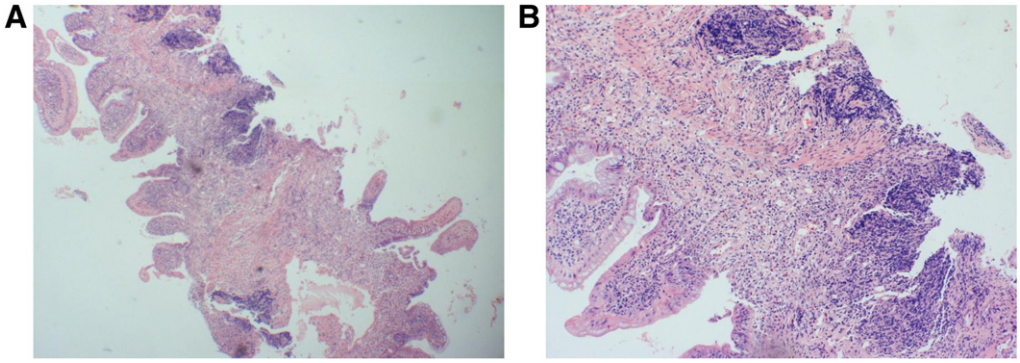

Fig. 2. Ulcerative colitis in neurofibromatosis type 1. Figs. 2A–B: Hematoxylin and Eosin stain of sigmoid colon mucosa, 4× (A) and 10× (B).

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