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CASE REPORT

Mast cell deposition and activation may be a new explanation for epiploic appendagitis

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SUMMARY

Epiploic appendagitis is as an acute painful condition of the fat on the outside of the intestine. Thus far, there have been no publications to our knowledge that appendagitis can be caused by mast cells or can be associated with chronic pain. A patient with multisystemic disorders suffered with both chronic and acute attacks of abdominal pain for a year. The worst attack led to surgical resection of an enlarged sigmoid colon epiploic appendage. Careful review of her complex medical history and mast cell stains of gastrointestinal biopsies led to the diagnosis of mast cell activation syndrome. Re-examination of the resected appendage using an immunohistochemical stain demonstrated a high mast cell density which is a new histopathological finding. Treatment of mast cell activation syndrome and other related syndromes led to marked improvement in her health, including all types of chronic abdominal pain.

BACKGROUND

Epiploic appendages are rows of adipose structures found on the surfaces of the small and large intestine and are composed of fat and have a central vein and artery and a peritoneal covering.[1] Epiploic appendagitis (EA) can be caused by an idiopathic inflammatory disease and/or disease caused by torsion of the appendage.[1] The classic presentation is sudden onset of dull or sharp abdominal pain which is referred directly from the inflamed peritoneal surface of the appendage which usually is located in the right or left lower quadrant.[2] Attacks of EA occurs in both genders between ages 20 and 50 and generally resolves with conservative therapy; however, it can require hospitalisation and, rarely, surgery.[3] Originally thought to be rare, EA is actually relatively common and furthermore it is often misdiagnosed and can be mistaken for both common acute and recurrent diseases.[4–7] In a large study, the CT was reviewed retrospectively in 660 patients with lower abdominal pain (348 suspected diverticulitis and 312 suspected appendicitis) and 11 (2%) met CT criteria for EA.[4] In a study of 45 patients with EA, a presumptive clinical diagnosis was acute appendicitis (n=13), acute cholecystitis (n=2), acute diverticulitis (n=19), renal colic (n=7) and ovarian pathology (n=4).[7] Obesity is the only identifiable risk factor associated with EA.[1 2 8] A retrospective CT study of 100 patients with EA versus 100 patients with acute abdomen demonstrated significantly greater abdominal adipose volume, visceral adipose area and subcutaneous adipose area in the EA group.[8]

A patient with numerous syndromes and obesity led us to consider that a mast cell (MC) disease was responsible for EA and acute and chronic abdominal pain. MC deposition or activation has not hitherto been reported in EA. MCs are also thought to play an inflammatory role in the development of obesity which ties into EA.[9] Under normal circumstances, MCs are produced from haematopoietic precursors in the marrow, circulate briefly in the blood and soon site themselves in peripheral tissues to guide normal growth and development of tissues.[10] The function of normal MCs are to sense insults such as trauma and infection and then quickly respond by degranulation of premanufactured stores of mediators.[11] Through interactions with specific receptors on other cells locally and distantly, mediators effect adjustments in function to assist the body with resistance to, and recovery from, the insult. Pathological behaviour from MCs occurs when there are genetic mutations in the regulatory KIT protein and subsequently disease states develop according to the location of MC deposition.[12] Gastrointestinal (GI) tract MCs have been associated with burning mouth syndrome, heartburn, chest pain, nausea, abdominal pain, diarrhoea, constipation and a form of irritable bowel syndrome (IBS).[13–16] Proximity of MCs to GI sensory nerves and local release of inflammatory mediators from MCs have been proposed to explain chronic pain which has been demonstrated in man and in animal models.[14 15]

Mast cell activation syndrome (MCAS) is a prevalent, recently recognised, highly heterogeneous syndrome of chronic multisystem polymorbidity.[17 18] This syndrome produces general themes of inflammation±allergic type phenomena±abnormalities in growth and development.[19] The same spectrum of effects from chronic inappropriate activation of MCs is seen in the rare disease of mastocytosis which is distinguished from MCAS by neoplastic MC proliferation in the bone marrow and a high tryptase level.[20] Although autoimmune mechanisms of primary MCAS likely exist (eg, via anti-IgE or anti-IgE-receptor autoantibodies), preliminary genetic investigations have demonstrated a large menagerie of mutations to be present in the MCs of patients with MCAS in KIT, a transmembrane tyrosine kinase receptor and the dominant MC regulatory element.[12] Biopsy recognition of MCs is generally not seen by via routine H&E staining. It requires special histochemical stains (eg, tryptase, giemsa, toluidine blue, alcian blue)

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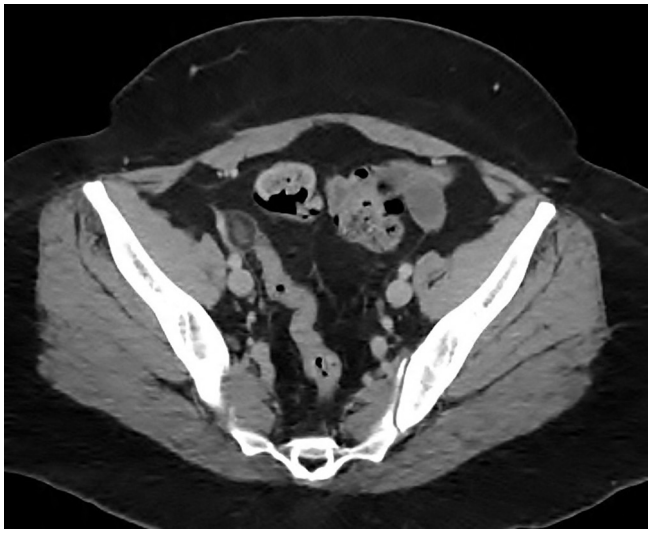

Figure 1 Classic CT scan finding of epiploic appendagitis with a rim-enhancing, oval structure on the exterior of the sigmoid colon located in the right lower abdomen.

or, immunohistochemical staining for CD117, the extracellular domain of KIT. One theoretical question raised in this report is whether or not appendages can cause chronic abdominal pain owing to activation of MCs on the peritoneal surface of the intestinal appendage. Our theory is that the MCs cause chronic pain in appendages due to local MC secretion of mediators of nociception such as histamine, tryptase, cytokines and/or other chemicals.

CASE PRESENTATION

A 40-year-old Caucasian woman with a history of migraines, gastro-oesophageal reflux, nausea, IBS–diarrhoea and many other idiopathic syndromes suffered with constant abdominal pain with episodic attacks of severe abdominal pain over the past year. The pain had peaks of labour-like contractions lasting 5 min. This pain was sharp and migratory but most often was located in the right lower quadrant. It was worse with pressure, palpation and movement. Over the same time period, she had worsening headaches, fatigue and cognitive dysfunction. This pain was clearly differentiated by the patient from her 8-year history of IBS which was characterised by postprandial crampy pain, bloating, foul gas and diarrhoea which responded to periodic 2-week courses of the antibiotic rifaximin. Over the course of the year, rifaximin was prescribed but did not help this pain.

The patient presented for evaluation in the GI clinic after 4 days of extremely severe, sharp right lower abdominal pain that awoke her from sleep and was associated with a 100°F temperature. The right lower quadrant was markedly tender with guarding. The white blood count was normal. The CT was abnormal (figure 1). Despite administration of acetaminophen and ibuprofen, the pain worsened and after 7 days of unremitting pain, laparoscopic surgery was performed. Gross findings included an enlarged area of fat near the normal appendix that had a small amount of superficial focal fat necrosis. After surgical resection of the appendage, the right lower pain immediately abated and she was discharged. Standard H&E stain showed adipose tissue with patchy areas of fat necrosis with repair. The appendectomy specimen was normal.

Colonoscopy was performed 2 weeks after surgery owing to haematochezia. On review of systems obtained immediately prior to this procedure, she endorsed 44 of the 48 symptoms reported most commonly seen in MCAS.[19] The colon and ileum were grossly normal. Internal haemorrhoids were present. The CD117 stain was used to determine MC density (as described in the Investigation section). The ileum had 40–50 diffuse and

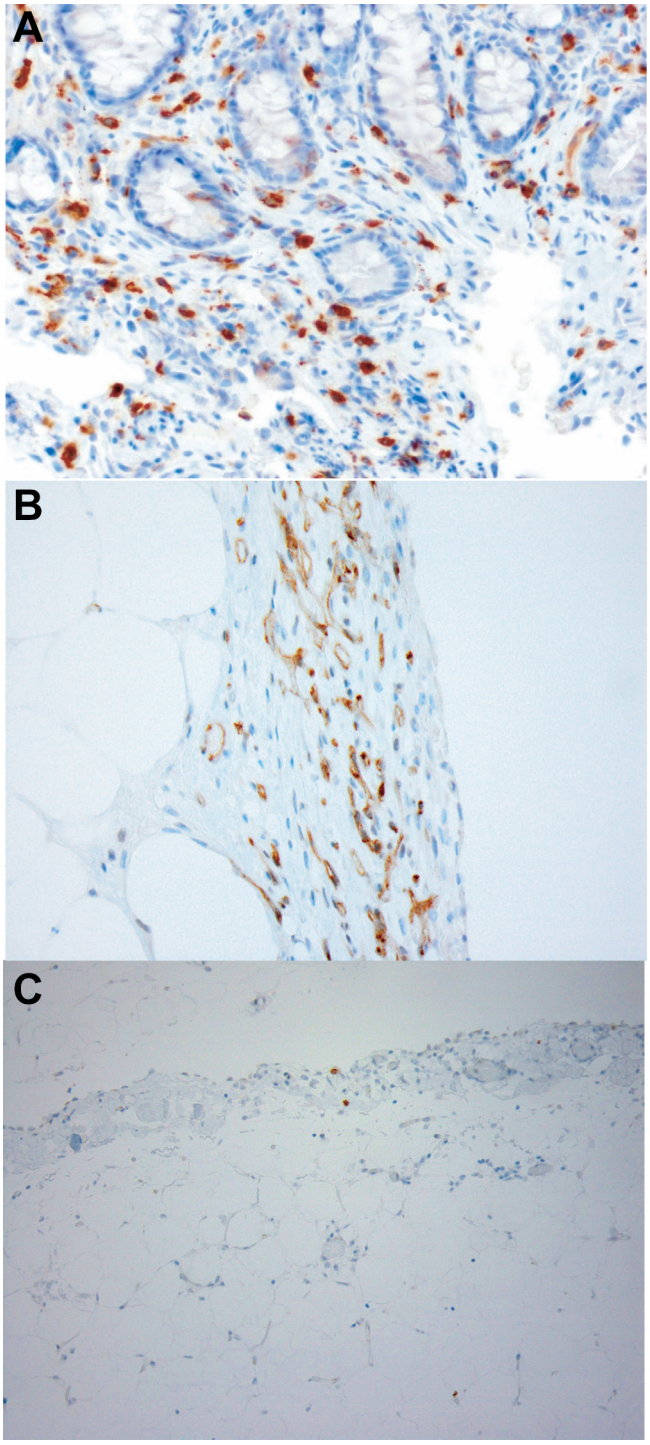

Figure 2 Immunohistochemical stain showing increased CD117 positive mast cells (MCs) in: (A) terminal ileum with >80 MCs/high-power field (×40/0.65 objective magnification; part of field shown); (B) epiploic appendage peritoneal surface with 60 MCs/high-power field (×40/0.65 objective magnification); and (C) control case epiploic appendage peritoneal surface with 2 MCs/high-power field (×20/0.65 objective magnification).

70–80 focal MC/high-power fields (HPF) (figure 2A). The colon had <20 diffuse and 30–40 focal MC/HPF. Reaccession of the cell blocks of the EA surgical specimen led to discovery of an average of 60 diffuse MC/HPF in the peritoneal surface of the epiploic appendage (figure 2B).

Five days after colonoscopy, the patient underwent more thorough evaluation, including a complete, life-long medical and travel history, detailed review of medical records of all 18 hospitalisations since age 20, physical examination and laboratory studies. As a child, she had subluxation of her hips. At age 18, she worked at a camp insect stings and tick bites caused skin rashes. At age 28, she found a deer tick 2 weeks after returning from a camping trip. The tick caused a Red Bull's eye rash, fever, chills, fatigue and was treated with three courses of antibiotics. Other cocampers had antibody-confirmed Lyme disease.

MEDICAL HISTORY

Complex migraine with recurrent patterns of dysarthria and/or hemiplegia (five admissions starting at age 31), near syncope (three admissions starting at age 34), nausea (two admissions), dyspnoea (two admissions), atypical/frequent infections (adult onset cystic acne, tonsillitis, sinusitis, cellulitis after insect bite and three episodes of herpes zoster), fibromyalgia syndrome, chronic fatigue syndrome, IBS, pelvic floor dysfunction, restless legs syndrome, Bechet's syndrome, Raynaud's phenomenon and morbid obesity (increase of body mass index (BMI) 34.7–38.3 kg/m^2 over 5 years which failed to respond to a 1200 calorie diet for the last year). Three pregnancies required admissions for nausea. Urinary retention occurred after each C-section requiring catheterisation for ≥5 weeks and intermittently over the last 10 years. She had three miscarriages, cholecystectomy for abdominal pain and gallstones, and hysterectomy for severe pain and bleeding. She was allergic to six medications.

Family history

Son, Ehlers-Danlos syndrome (EDS). Father, life-time syncope/near syncope. Mother, adrenal insufficiency and myasthenia gravis.

Abnormal physical examination findings

Five days after colonoscopy, the examination was remarkable for: supine pulse 68 beats/min with standing pulses of 96 beats/min after 5 min and 104 beats/min after 10 min (blood pressure unchanged: 129/84 mm Hg); BMI 38.3 kg/m^2; mild epigastric and right lower and left lower quadrant tenderness without rebound or guarding; high oral palate; Beighton joint hypermobility score 5/9 points; velvety skin, mild skin hyperextensibility, bilateral piezogenic papules of the heels and dermatographism.

INVESTIGATIONS

Five days after the colonoscopy, the complete blood count (CBC), comprehensive metabolic profile (CMP), lipid profile, celiac antibody panel, anti-nuclear antibody (ANA), complete anticardiolipin profile, phospholipid level, lupus anticoagulant and activated partial thromboplastin time were normal. The ferritin was normal (50 ng/mL) but unsatisfactory for patients who have restless legs syndrome.[21] Abnormal labs included the cortisol 4.7 μg/dl (4.8–19.5) and ACTH <2.0 pg/mL (7.0–63.0). The following conditions were diagnosed: hypermobile Ehlers-Danlos syndrome (hEDS) by physical examination, MCAS, a clinical diagnosis of postural orthostatic tachycardia syndrome (POTS) and adrenal insufficiency. The diagnosis of MCAS was established by: (1) presence of two of the two major criteria: (a) presence of a constellation of complaints attributable to pathologically increased MC activity in ≥2 organ systems and (b) increased number of MCs in extracutaneous organs (figures 1 and 2); and (2) presence of one of the five minor criteria (response to MCAS therapy).[19] Urinary measurements of N-methylhistamine and prostaglandin G2 were obtained after 6 weeks of MCAS therapy and were normal.

Mast cell density (MCD) was assessed by a standardised systematic approach where MCs were counted in multiple HPF using Nikon BX41 Plan N 40x/0.65 objective magnification. MCD was expressed as a range including <20, 20–30, 31–40, 41–50, 51–60, 61–70, 71–80, 81–90 and 91–100 MCs/HPF. The MCD was categorised as follows: (1) diffuse—MCD reported as least common denominator in any of several microscopic fields, (2) multifocal—highest MCD reported in three or more but not all microscopic fields, and (3) focal—highest MCD reported in <3 mutually exclusive microscopic fields. In the clinic's next two patients who underwent colonic surgery for cancer, an epiploic appendage furthest away from the cancer was stained for MCs. In one patient, two MCs/HPF were seen on the surface and none within the appendage (figure 2C). In the other patient, 0–1 MCs/HPF were seen on the surface and none within the appendage

DIFFERENTIAL DIAGNOSIS

EA can be confused with appendicitis, diverticulitis, cholecystitis, ovarian pathology and renal colic. Differential diagnosis of MCAS includes chronic fatigue syndrome, fibromyalgia, POTS, adrenal insufficiency, allergic disorders (including hives, rash, flushing, asthma, sinusitis and rhinitis), IBS, carcinoid syndrome and pheochromocytoma.

TREATMENT

The patient was given therapy for three disorders: (1) MCAS was treated with histamine H1/H2 receptor blockers (cetirizine and ranitidine) and MC stabilisers (quercetin and vitamins C, D, B_6 and B_{12}); (2) POTS was treated with pyridostigmine, fludrocortisone, propranolol, oral electrolyte solution, periodic intravenous fluids and compressive wear; and (3) adrenal insufficiency was treated with prednisone. Low-dose naltrexone was used as innovative therapy for MCAS, POTS and restless legs syndrome.[22 23]

OUTCOME AND FOLLOW-UP

Treatment for MCAS, POTS and adrenal insufficiency let to rapid clinical improvement in chronic abdominal pain, headaches, nausea, fatigue, light-headedness, restless legs, cognitive dysfunction, muscle pain and dyspnoea. She was able to stop six medications: topiramate, sumatriptan, desvenlafaxine, methylphenidate, gabapentin and hydroxychloroquine. The patient has been followed by bimonthly office visits and numerous emails and telephone calls which have documented excellent clinical improvement.

DISCUSSION

A woman suffered half of her life with numerous disorders owing to unrecognised MCAS. One year of unrelenting abdominal pain came to a crescendo and led to a diagnosis of acute EA. Owing to recent understanding of MCAS, the physicians were able to make the diagnosis and offer a new histological explanation for acute EA and theoretically for chronic abdominal pain.

MCAS is a heterogenous syndrome often associated with POTS and hEDS which were also retrospectively diagnosed in

this patient.[24 25] Other syndromes and conditions experienced including fibromyalgia, chronic fatigue syndrome, migraines, IBS, cognitive dysfunction, frequent spontaneous abortions, menorrhagia, obesity, numerous allergic disorders and atypical infections could now be explained.[19] Restless legs syndrome was present which is found in approximately 50% of patients with MCAS (G Molderings, personal communication, 2017). This vexing syndrome is associated with many inflammatory and immune disorders, small intestinal bacterial overgrowth and iron deficiency.[26] Postural tachycardia with syncope, pelvic floor dysfunction, small intestinal bacterial overgrowth and urine retention were well explained by POTS which itself could have been mediated by MCAS.[22] A number of the patient's medical problems were preceded and/or exacerbated by a tickborne disease. Lyme disease has been reported as a trigger for both MC activation in rats and POTS in man.[27–29] Lyme disease could not be established by serology in our patient but the workup can have false negative testing.

Chronic abdominal pain without associated abnormal bowel habits is often relegated into a category called functional bowel syndrome which most commonly presents with right lower quadrant pain.[30] This case presents an alternative consideration for such patients. Isolated abdominal pain can be explained by MCs which release mediators locally and thus may be undetectable in the blood and urine. This study suggests that a high MC density in the peritoneal covering of the intestinal appendage is associated with chronic abdominal pain and acute EA. The MCs may cause chronic pain in or near the appendages due to local secretion of mediators of nociception such as histamine and tryptase. The use of non-steroidal therapy for acute EA is often effective which is interesting in that these drugs also stabilise MCs.[17] Via elaboration of a variety of fibrogenic mediators (eg, transforming growth factor-beta), MCAS can affect the development of sclerosis/adhesions as sometimes found already present in patients with MCAS undergoing their initial abdominal surgeries (personal observations, LBA)), furthering the likelihood that MC activation in the epiploic appendage could play a pathological role in the inflammatory process in the peritoneal lining (eg, peritonitis) and in the appendagitis per se.[31]

Patient's perspective

Since the birth of my son in 2008, my health has been in decline. I have had migraines, abdominal pain, joint pain, swelling, depression, traumatic brain injury and debilitating fatigue. Despite the illnesses, I began a Master of Divinity programme to pursue ordination. I began an exercise regimen of swimming, strength training and cardio 5 days a week. I followed this regimen for 2 years with little weight loss. However, the illnesses increased in severity and frequency. Respiratory illness and all-over body pain halted the exercise. I diligently followed treatment plans from the rheumatologist, neurologist, psychiatrist and primary care doctor. The treatments gave intermittent relief but not enough to participate fully in life. At some point, concentrating became a roadblock to reading and writing papers. I flunked out of the programme. Determined to continue my education, I enrolled at a different school that has supported me and given me accommodations.

My primary doctor insisted on a colonoscopy for the abdominal pain and bleeding. From that colonoscopy, many mysteries began to unravel. Thankfully, Dr. Weinstock suspected MCAS and performed the necessary tests. With the identification of MCAS came the treatment of Zantac and Zyrtec. I could not believe the difference these two medicines made. I had energy! I could think clearly! This is the first semester in years I completed my work without needing extensions. The diagnosis of MCAS led to the POTS and EDS diagnoses. I now had explanations for pre-syncopal and syncopal episodes as an adult and the hip pain from my childhood. Treatment for the POTS and EDS has included Low Dose Naltrexone and Florinef. My pain no longer inhibits me from walking through a store or doing errands. I changed my diet to Low FODMAP and SIBO. This change has greatly helped with my abdominal pain and has stopped the daily (sometimes uncontrollable) diarrhoea. I am able to recognise when I am low on fluids and electrolytes. Adding Normalyte to my water and having access to lactated ringers at the infusion centre have helped me address the hydration issues. Until I began treatment, I was recording daily migraines that lasted 6 to 8 hours a day and were incredibly painful. I have yet to have a migraine since treatment began. I am so excited to be back on track to living life and achieving my goals.

Learning points

- Patients with mast cell activation syndrome (MCAS) have a wide array of symptoms, and clinicians need an open mind to entertain the diagnosis.
- Epiploic appendagitis (EA) has always been perceived as an idiopathic acute abdominal pain disorder.
- A patient diagnosed with EA was found to have chronic abdominal pain and mast cell (MC) deposition in the peritoneal covering of a sigmoid appendage.
- Histological examination for MCs in a surgically excised EA may lead to a new, treatable diagnosis of MCAS.
- Chronic abdominal pain could theoretically be due to low-grade peritoneal irritation from localised MC mediator release.

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