MINIREVIEWS

Enterolithiasis

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Abstract

Enterolithiasis or formation of gastrointestinal concretions is an uncommon medical condition that develops in the setting of intestinal stasis in the presence of the intestinal diverticula, surgical enteroanastomoses, blind pouches, afferent loops, incarcerated hernias, small intestinal tumors, intestinal kinking from intra-abdominal adhesions, and stenosing or stricturing Crohn's disease and intestinal tuberculosis. Enterolithiasis is classified into primary and secondary types. Its prevalence ranges from 0.3% to 10% in selected populations. Proximal primary enteroliths are composed of choleic acid salts and distal enteroliths are calcified. Clinical presentation includes abdominal pains, distention, nausea, and vomiting of occasionally sudden but often fluctuating subacute nature which occurs as a result of the enterolith tumbling through the bowel lumen. Thorough history and physical exam coupled with radiologic imaging helps establish a diagnosis in a patient at risk. Complications include bowel obstruction, direct pressure injury to the intestinal mucosa, intestinal gangrene, intussusceptions, afferent loop syndrome, diverticulitis, iron deficiency anemia, gastrointestinal hemorrhage, and perforation. Mortality of primary enterolithiasis may reach 3% and secondary enterolithiasis 8%. Risk factors include poorly conditioned patients with significant obstruction and delay in diagnosis. Treatment relies on timely recognition of the disease and endoscopic or surgical intervention. With advents in new technology, improved outcome is expected for patients with enterolithiasis.

Core tip: We review classic descriptors and latest developments in the enterolithiasis. The article focuses on detailed description of medical epidemiology, classification, pathophysiology, etiology, clinical presentation, differential diagnoses, clinical diagnosis, management, complications, and prognosis of the enterolithiasis. We mention latest trends in endoscopic approach to patients with symptomatic disease. Our paper serves a first comprehensive review of the syndrome for a practicing gastroenterologist.

INTRODUCTION

Enterolithiasis, or presence of stone concretions in the gastrointestinal tract, is an important but relatively uncommon clinical condition that has recently gained significant attention with advances in the gastrointestinal field. Primary enteroliths arise in areas of intestinal stasis in the setting of diverticular disease, surgical enteroanastomosis, blind pouches, and intestinal stenosis or strictures seen in the infectious or inflammatory bowel diseases. Secondary enteroliths include gallbladder and renal stones that may

migrate into the gastrointestinal tract as a result of fistula formation. Clinical enterolithiasis is largely affected by its etiology, underlying conditions, age, gender and geographic distribution. Presentation is often nonspecific, but typically includes "tumbling" abdominal pain, nausea, and vomiting related to the bowel obstruction, and may potentially lead to the gastrointestinal bleeding and perforation. To date, enterolithiasis was largely reported in single case observations or case series. In this latest review, we discuss history, epidemiology, classification, pathophysiology, etiology, clinical features, diagnosis, treatment, complications, and prognosis of this gastrointestinal disease.

HISTORY

Enterolithiasis was first described by a French physician Chomelin J in 1710 in the medical series of *Historie de l' Academie Royal*[1] as a case of stone formation in a duodenal diverticulum that was discovered during an autopsy. This entity received more attention in the early twentieth century with additional reports of patients presenting with small bowel obstruction due to a lodged stone in the distal ileum. Described by Williams in 1908 and later consolidated in a literature review of existing 15 cases by Edwards[2] in 1930, this syndrome has gained momentum with the rapid development of gastrointestinal and radiology fields. Sjoqvist initially reported on chemical composition of enterolith in 1908[3]. Pfahler *et al*[4] acknowledged the first radiologic diagnosis of alimentary stone in 1915. By the mid of the century, De Witt *et al*[5] reported his experience with enterolithiasis across a wide age populationand further light was shed by additional individual case reports. It has then become readily recognized that calculus formation in the intestine was a result of an acquired anatomic pathology that predisposes to stasis in the intestinal tract and leads to elemental clumping and aggregation. Diverticular disease of the small bowel was a leading etiology, followed by stricturing of the intestine from infectious (tuberculosis) or inflammatory (Crohn's disease) processes. In 1947, Grettve[3] proposed classification of enteroliths into primary and secondary types, with primary enteroliths being formed inside the gastrointestinal tract and secondary enteroliths introduced from outside the bowel. However, with increased attention to this syndrome, Frink[6] reported on only fewer than 25 cases of enteroliths in the literature up to 1952. In their classic 1960 paper, Atwell and Pollock[7] have managed to further organize primary enteroliths into distinctive true and false subcategories having paid particular attention to the analysis of chemical composition of the stones as related to their location in the gastrointestinal tract. The topic of enterolithiasis has continued to expand and by the second decade of the twenty first century, over a hundred cases have been reported, although not critically reviewed in a dedicated manner.

EPIDEMIOLOGY

The reported prevalence of primary and secondary enterolithiasis in selected populations varies widely from 0.3% to 10% and is largely dependent upon clinical presentation, etiology, and underlying risk factors. Intraluminal stone formation of various sizes is more common than anticipated, typically remains underreported in absence of clinical symptoms or due to its diminutive size that permits intermittent passage, and may not be visualized on conventional radiologic imaging in majority of the cases. However, clinically significant enteroliths are more likely to develop in certain medical conditions. Primary enteroliths are classically formed in the areas of stasis within the bowel in the presence of the intestinal diverticula, surgical side-to-side enteroanastomoses, blind pouches (cul-de-sac), afferent loops in the Billroth Ⅱ gastrojejunostomy and Roux-en-Y procedures, incarcerated hernias, small intestinal tumors, intestinal kinking from intra-abdominal adhesions, or proximal to the intestinal strictures encountered in cases of Crohn's disease and intestinal tuberculosis[8-18].

It is difficult to quantify true incidence of the enterolithiasis in the setting of small intestinal diverticular disease. In fact, significant primary enteroliths remain uncommon medical phenomena, with isolated case series or reports in the setting of typical duodenal and jejunal diverticulosis as well as in special cases of Meckel's diverticulum of the ileum. It should be noted that while the described incidence of jejunal diverticulosis varies from 0.06% to 1.3% in older patients[19], diverticulosis-associated enterolithiasis should be even less common. Prevalence of enterolithiasis in patients with Meckel's diverticulum is best studied to date, and is estimated at 3%-10%[20-22]. Fifteen cases have been reported of post-surgical enteroliths forming after hepatojejunostomy, Billroth Ⅱ gastrojejunostomy, Roux-en-Y gastroenterostomy, and Whipple's procedures[10,23]. There are over 80 cases of enterolithiasis reported in association with intestinal tuberculosis, although most were described by Bery in a single study[24,25]. Small early series of Indian tuberculosis patients showed radiopaque enteroliths in 3% of the patients[26]. However, true prevalence of enterolithiasis in intestinal tuberculosis remains unknown, with large cohorts in studies by Prakash and Deka describing only select cases of the enterolithiasis[24,25,27]. By the turn of the 21st century, there have been an estimated 30 cases reported in association with Crohn's disease[28]. Improved surgical techniques, medical management of chronic intestinal conditions, dietary consumption of calcium products, and finally wide spread use of acid suppressive therapy may alter conventional norms of traditional enterolith formation. Therefore, the true incidence and prevalence of primary enterolithiasis remain to be determined. Additional epidemiological and histological studies are necessary to delineate etiological relationships of enterolithiasis in selected patient popula-

tions. Most cases of enterolithiasis are discovered in symptomatic patients, who present with abdominal pain or small bowel obstruction; thus, the prevalence of asymptomatic enteroliths is still largely unknown. A study by Pantongrag-Brown *et al*[29] in 1996 evaluated 84 patients with Meckel's diverticulum and described 8 (10% prevalence) cases of enteroliths at the time of surgery, a much higher rate than what had been previously reported. Alternatively, a review of 1476 adult patients found to have Meckel's diverticulum during surgery in the Mayo clinic found that enteroliths were seen in 6% of symptomatic and 0.7% of asymptomatic patients at the time of surgery[30].

Gallstone ileus remains the most common form of secondary enterolithiasis. This condition arises in estimated 0.3%-0.5% of general cholelithiasis[31,32]. It accounts for approximately 1%-4% of all cases of mechanical bowel obstruction, while significantly increasing to 25% in geriatric population[31,32-39]. Over-diagnosis of intestinal obstruction due to migrated gallstone has been reported in the literature, largely due to under-recognition of primary "pseudogallstone" enterolithiasis. There are two case reports in the literature of secondary enterolithiasis due to renal stones from an underlying fistulizing disease[40,41].

Gender and age remain important epidemiologic factors in enterolithiasis. As a rule, gender predilection seems to be largely dependent upon the etiology of the stone formation and typically parallels gender predisposition of the underlying condition. Enterolithiasis of Meckel's diverticulosis shows a 3:1 male to female ratio, at least partially due to the 2:1 male to female ratio classically seen in this condition[29]. In contrast, enterolithiasis associated with intestinal tuberculosis and gallstone ileus have shown a female preponderance, likely due to the greater incidence of these diseases in females[11,34]. A review of the 34 cases of enterolith ileus in jejunal diverticulosis reported nearly equal gender distribution[42]. Gallstone ileus clearly has female and geriatric predilection[38].

Enterolithiasis remains a disease of the adulthood, but differs in time of presentation in various congenital and acquired conditions. Thus, Pantongrag-Brown *et al*[29] and Steenvoorde *et al*[42] reported mean age of 45 and 70 years in Meckel's diverticulum and jejunal diverticular disease related enterolithiasis, respectively. In earlier reports, proximal small bowel enterolithiasis was seen in older adults with average age of 65 years and distal small bowel stone formation was seen in a younger group of patients with average age of 50 years[7]. A series of Crohn's patients showed a mean duration of symptoms 15.7 years before presenting with enterolith, likely reflecting the increasing incidence of stenosis and adenocarcinoma with time[28,43]. In Nakao's analysis of 176 cases of gallstone ileus, the affected patients ranged from 24 to 91 years of age[33] while Ayantunde *et al*[34] reported a mean age of 77 years in patients with this condition.

CLASSIFICATION

Categorization of enteroliths into primary and second-

ary types helped organize classification system that we use today. Primary enteroliths are formed within the gastrointestinal tract and can be further subdivided into the "true" and "false" subtypes. True primary enteroliths are made of substances found in chyme under normal alimentary conditions, may occasionally have a central "fruit pit", and are subdivided into the choleic acid and calcium (calcium phosphate, calcium oxalate, and calcium carbonate) stones. False primary enteroliths are formed from insoluble foreign substances in the bowel and are divided into three types: agglutination of a large amount of indigestible materials (bezoars), precipitation of substances in the intestinal tract that become insoluble because of resorption of their solvents (varnish stones in varnish drinkers), and concentration of water suspended insoluble salts (chalk, lime, barium sulfate). Mixed concretions may be seen in cases of eventual external calcification of false enteroliths in the distal small bowel[7]. Secondary type enteroliths are stones that are formed in the organs outside of the proper gastrointestinal tract and then migrate into the bowel causing obstruction, with the most common type being gallstones[14,28].

ANATOMY AND PATHOPHYSIOLOGY

Anatomy of the intestinal tract plays an integral role in enterolith formation. Luminal pH and microenvironment specific to each segment of the gut, coupled with development of diverticular disease, altered endoluminal propagation and peristaltic functionality are important factors in developing conditions necessary for stone formation. The small intestine is 3 to 7 meters long and is divided into three regions: duodenum, jejunum, and ileum. Physiologic enteral motor and sensory functions play an important role in the proper aboral movement of chyme and indigestible residues along the small intestine. Integrity of the intestinal tract allows for unobstructed and proper peristalsis and is essential in maintaining continuous migration of the chyme and the endogenous secretions. Importantly, endoluminal microenvironment plays a crucial role in its digestive properties. Under physiologic conditions, established small intestinal pH variation is region specific, starting at about pH of 6 in the duodenum and progressively increasing to about pH 7.4 in the terminal ileum[44].

True primary enteroliths are formed from chemical elements already present in the bowel in the anatomically compromised areas of stasis and their composition may indeed vary by location. Choleic acid enteroliths that require lower pH are typically found in the proximal small intestine, largely affected by significant diverticular disease, strictures or stenosis. On the other hand, calcium phosphate, calcium oxalate, and calcium carbonate primary enteroliths are found in the distal small bowel. These salts are soluble in water and acidic environments, requiring an alkaline pH to precipitate and thus are most often formed in the terminal ileum[15,43,45]. Of interest, while distally recovered enteroliths may typically contain a small percentage of choleic acid, proximal stones are entirely

calcium free[7]. Under normal physiologic conditions, microlithiasis that may be formed in various gastrointestinal disorders is ultimately cleared by effective propagation of the endoluminal contents without significant delay in segments of the small bowel. On the other hand, prolonged and significant intestinal stasis creates favorable endoluminal conditions for particulate aggregation leading to enterolith formation. Similar to the proximal enteric region, stasis in the distal small bowel may occur in a variety of clinical conditions, including stricturing or stenotic Crohn's disease, post-surgical anatomical alterations, post-radiation enteritis, gastrointestinal tuberculosis, and congenital or acquired ileo-jejunal diverticular disease.

While also at risk of presenting at the site of underlying enteropathy, false enteroliths have different chemical composition. Some enteroliths are made up of large amounts of indigestible ingested material, such as hair, occurring in trichotillomania or trichophagia. Others may be composed of varnish in cases of varnish drinkers, or barium sulfate, chalk, lime, milk, magnesium, and aluminum antacids. Stones can also be formed of fecal matter[14,46].

The chemical composition of secondary enteroliths depends on the etiology of the stone. Gallstones are primarily made of bile acids, lecithin and other phospholipids, and cholesterol[47]. Anatomic proximity of the gallbladder to the alimentary tract increases the risk of fistula formation and gallstone extravasation into the gut in various entero-vesicular disease states. In gallstone ileus, gallstones migrate through fistulas and become lodged in the gastrointestinal tract with the most common site of obstruction in the ileum (60%), followed by the jejunum (15%), stomach (15%), and colon (5%)[48]. Similarly, but less commonly observed, close proximity of the renal pelvis to the second part of the duodenum may predispose patients to renal stone erosion into the small intestinal tract[40,41].

CHEMICAL COMPOSITION AND STRUCTURE

Chemical composition of the primary enteroliths varies by the site of the stone formation, length of its migration in the intestine and finally, the location of the site of its impaction. Concentration of choleic acid in the enterolith is inversely related to the distance from the proximal small bowel to the ileocecal valve, with highest saturations (52%-84%) found in the duodenum and jejunum, while effectively decreasing to single digits distally[7]. Free fatty acids and neutral fats effectively follow the pattern and their composition ranges from 9.6% proximally to 0.6% distally. On the other hand, calcium salt composition of the enteroliths increases proportionally with its location in the distal small bowel. Whereas calcium containing enteroliths are not seen in the proximal intestine, its concentration nears 85% in the distal part of the organ. Various calcium salts are present, including calcium oxalate, calcium phosphate, calcium carbonate, and calcium sul-

fate in order of decreasing incidence[7]. Calcium dihydrate and uric acid stones were also reported[49]. However, it should be noted that chemical composition of an enterolith may not follow general rule of site-related chemical composition: in cases of acute migration of proximal stone with resultant bowel obstruction or in special case of Meckel's diverticulum with ectopic gastric mucosa that may predispose to the in-situ choleic stone formation.

Enteroliths may vary in size and number, ranging from few millimeters to 10 cm in greatest dimension. They may appear in a single stone, in a cluster of concretions, or in a disseminated pan-intestinal pattern. Enteroliths may range in number from several stones to nearly a hundred[11], largely depending on underlying pathology. While classically round, oval, discoid, or faceted, they may appear as triangular or rectangular, and a small number of stones may be needle-shaped or a phenomena likely related to the original "nucleus" of the stone, its anatomical origin, and route of migration[11,25]. Size and chemical composition of an enterolith may affect is weight, with larger egg-shaped concretions potentially reaching under 100 g[50].

ETIOLOGY

Primary enterolithiasis is typically multifactorial with numerous anatomical and microenvironmental factors predisposing to development of clinically significant concretions. Variations in structural integrity of the intestine may be seen in the diverticular disease (congenital and acquired)[8,9]; surgical entero-anastomoses[14], afferent or Roux loops[10], blind pouches[13]; stricturing or stenosing disease of the bowel seen in infectious and inflammatory conditions (tuberculosis, Crohn's disease)[11,12]; radiation or eosinophillic enteritis[15,51]; mucosal diaphragmatic disease[52]; intestinal duplication[53,15]; fistula[54]; malignancy[55]; and finally in apparent kinking of the gut that is found in patients with intra-abdominal adhesions, external compressions, or incarcerated hernias[15-18]. Other conditions associated with increased risk of enterolith production include intestinal aganglionosis, intestinal amoebiasis, and ischemic enteritis[15]. Resultant stasis and impedance of the normal intestinal flow may promote microbiome-accelerated precipitation of insoluble chemical salts and effectively lead to the stone formation. Prolonged dietary consumption of a large calcium load has been proposed as a possible contributing factor in the distal ileal stone formation, but still remains a hypothesis[56]. Exogenous particle ingestion is a risk factor for development of false primary enteroliths. Finally, enterobiliary and enterourinary pathology may place a patient at a higher risk of developing secondary enteroliths that may result in gallstone (common) or renal stone (rare) ileus[40,57].

Diverticular disease of the intestine clearly predisposes to enteric stone formation. While duodenal diverticulosis occurs in up to 22% of the adult population[58], ileo-jejunal diverticular disease is quite rare with an estimated incidence of less than 5%[59]. Jejunal diverticulosis

accounts for over 80% of the non-duodenal disease[19]. Non-synchronous alimentary peristalsis, mucosal valve flap at the diverticular margin, pre-existing intestinal motility disorders, lack of muscular wall component, and an apparent area of "ready to catch" reservoir predispose to effective chyme stasis, bacterial deconjugation of soluble bile acids, and finally de-novo enterolithiasis[29,42,60-63]. True and false enteroliths may form, the latter potentially from a significant stagnation of food particles and debris accumulation within a diverticulum. Meckel's diverticulum is the most common congenital abnormality of the gut occurring in 2% of the patients. Wide-neck Meckel's diverticula represent a special subtype of the small intestinal diverticular disease with preservation of all bowel wall layers, maintenance of inherent peristalsis, and frequent presence of an ectopic tissue all of which make enterolith formation more difficult. Decreased pH in gastric mucosa lined diverticulum may prohibit otherwise potential calcium salt precipitation in the ileum. Delayed diagnosis of Meckel's diverticulum, small intestinal tissue lining of the pouch, alkaline environment, neck edema or inflammation, and focal nidus formation are potential risk factors for development of the stones[22,29,64]. Typical calcification of the stones seen in the Meckel's diverticulum follows a periphery-to-center progression[29].

Alterations in normal anatomy seen in post-surgical patients play an important role in enterolith formation. Side-to-side anastomosis and end-to-side anastomoses with circular muscular fiber division and alteration in peristalsis place patients at a higher risk of developing enteral luminal stasis and stone aggregation[14]. Blind pouch of various lengths may lead to changes in intestinal microenvironment, create a segment of reversed peristalsis, and predispose to eventual bacterial overgrowth that results in accelerated enterolith formation described above[65]. Similar hypomotility is seen in the Roux-en-Y anastomosis or Billroth Ⅱ gastrectomy with disconnection from the main pacemaker function of the duodenum or associated vagal denervation. Post-surgical strictures may lead to stasis as well. Chemical composition of post-surgical enteroliths reflects their position in the gut, with preponderance of choleic acid stones in the proximal relatively acidic afferent limbs and calcium stones in the distal relatively alkaline efferent limbs. In all mechanisms, bowel stasis promotes bacterial overgrowth, which can result in deconjugation of bile salts, causing soluble choleic acid to become insoluble deoxycholic acid and precipitate enteroliths[66]. Afferent limbs are more likely to be acidic, given their connection with the stomach, thus enteroliths formed in this area are most often choleic acid stones[23,66,67].

Intestinal tuberculosis is a rare complication seen in 2% of the patients with pulmonary tuberculosis. While consistently decreasing in the developed countries, its incidence remains high in many parts of the world, keeping it as an important etiology in enterolith formation that was recognized back in the early 20th century. Chronic or subacute intentional obstruction in absence of effec-tive medical or surgical therapy may be present. In fact, up to 60% of the patients with tuberculous enteritis may develop a significant obstruction[68], which may eventually lead to a stone formation or be a direct result of a concretion that was already formed. Low dietary intake of calcium and high phytate containing foods in poor socio-economic populations may offset the overall incidence of distal small bowel enterolithiasis in patients with intestinal tuberculosis[25].

Stricturing or stenosing Crohn's disease is more common in the developed countries. The etiology of alimentary track stone formation in chronic active Crohn's disease of the small intestine is in fact similar to multiple stricture forming tuberculous enteritis. Mean duration of the disease symptoms to the enterolith formation is estimated at 15 years[28], largely a result of progressive luminal narrowing. Such enteroliths are most often found within the areas of aneurismal, saccular, or dilated parts of the intestine[43,45]. They may be single or multiple, a concept largely related to the number of stenotic or structuring areas of the intestine, each predisposing to stone formation[12]. Common affinity of the Crohn's disease to the neo-terminal ileum makes calcified enterolith formation there most common[43,52]. Areas of entero-enteric or entero-colic anastomosis in Crohn's disease, with or without disease activity, are risk factors for developing alimentary concretions. Incidentally, enterolith formation may lead to early diagnosis of a location of significant stricture or neoplasm in patients with small intestinal Crohn's disease.

False primary enteroliths are formed from indigestible materials, including trichobezoars that may grow by accumulation of indigestible materials and food rich in cellulose. Intestinal migration of these concretions is rare. Excessive varnish consumption may lead to reabsorption of premixed solvents and significant chemical precipitation in water and digestive juices resulting in varnish stone formation. Effective water resorption from oral solutions of barium sulfate, chalk, lime, milk, magnesium, and aluminum containing antacids may trigger apparent insoluble salt precipitate in the gut. Finally, fecaliths may form in the elderly, psychiatric, bedridden, or narcotic dependent patients with history of chronic constipation[14,46]. Gallstone ileus represents classic type of secondary enterolithiasis. A rare cause of estimated 1%-3% of mechanical small bowel obstructions, its significance raises tremendously in the elderly population where it accounts of up to a quarter of all small bowel obstructions[32]. First described by Bartholin in 1654[34,37], this syndrome gained attention with Dr. Rigler's classic paper in JAMA in 1941[69]. Typical pathogenesis of gallstone ileus begins with acute or chronic cholecystitis, often in the setting of cholelithiasis, which spreads inflammation and adhesion to the alimentary tract, leading to development of a biliary-enteric fistula. Given the anatomic proximity of the duodenal wall, cholecystoduodenal fistula accounts for overwhelming majority (86%-96%) of the tracts, followed by cholecysto-colonic, cholecysto-gastric,

and choledocho-duodenal fistulas[33,34,57,69-74]. Gallstones eventually enter the intestinal tract and may result in clinical obstruction with classic predilection to known areas of stasis in the physiologically narrower distal ileum and ileocecal valve (in 60% to 85% of the cases), proximal small intestine, stomach, and finally colon[34,37,38]. Chemical analysis of the composition of enterolith reveals it gallstone origin; however, secondary depositions may occur in the long standing occult disease and vary by location. Size of the gallstones typically varies between 2.5 to 4.5 cm, but may achieve significantly large dimensions of 10 cm in some patients[34,69]. Reactive substances in the bile juice found in the gallstones may react with intestinal epithelial cells, potentially leading to significant mucosal injuries.

Finally, bowel obstruction secondary to migrated renal stone is extremely rare, but has been previously described in patients with significant reno-enteral adhesions and fistulization[40,41].

CLINICAL PRESENTATION

Clinical presentation of enterolithiasis varies according to the etiology, age, location, chemical composition, finally, dimensions of the stone. Primary enterolithiasis should be suspected in a younger patient with underlying inflammatory bowel disease (industrialized countries) or tuberculosis (third world countries) or an older patient with intestinal surgery or small bowel diverticular disease who presents with abdominal pains, distention, nausea, and vomiting of occasionally sudden but often fluctuating subacute nature which occurs as a result of the enterolith tumbling through the bowel lumen[11,28,43]. Fevers or chills may be present and physical examination may be remarkable for attenuated bowel sounds, tympany, and abdominal tenderness. Laboratory analysis may reveal leukocytosis and anemia, both from the underlying disease and enterolith related pressure on the intestinal mucosa. Elevated C-reactive protein and erythrocyte sedimentation rate may be present. Rarely a patient may present with a bowel perforation.

Patients with gallstone ileus behave similarly. Abdominal pain is seen in over 90% of the patients with gallstone ileus, followed by vomiting in 60%-95%, abdominal distention in 54%-84%, and constipation in 54.5%, fever in 41%, jaundice in 7% of the cases[33,34]. Female and geriatric patient predilection may be an early clue and history of gallbladder disease may be present in 27%-50% of the patients. Pre-existing comorbidities including cardiovascular, respiratory, and renal diseases are common, and concomitant malignancy may be present[34,39].

MIMICKERS OF ENTEROLITHIASIS

Non-specificity of the symptoms of enterolithiasis and its rarity may lead to delay in effective diagnosis and management. In absence of clinical suspicion, the differential diagnosis is typically wide and may include common causes of bowel obstruction (hernia, adhesions, inflammatory/infectious conditions, tumors, and intussusception), diverticulitis, appendicitis, duodenitis, peritonitis, pancreatitis, and peptic ulcer disease. Intra-luminal swallowed foreign bodies and extra-luminal calcified pathology including phleboliths, ureteral stones, and lymphadenopathy may erroneously lead to misdiagnosis of enterolithiasis. Biliary and renal calculi, mesenteric teratoma, fat necrosis, calcified fibroids, fecaliths, calcified epiploic appendages, and omental calcifications may confound the clinical diagnosis[4,15,20,43]. Finally, clinically insignificant incidentally noted enteroliths may shift attention from primary non-enterolith related pathology of the patient that may be responsible for a current clinical presentation.

CLINICAL DIAGNOSIS

Detailed history and physical examination are necessary in evaluation of a patient with suspected enterolithiasis. Correct diagnosis is established in appropriate clinical setting after excluding other common pathologic processes. A history of sudden or recurrent abdominal pain, associated with vomiting in a patient who is in a population at risk for enterolithiasis should raise suspicion of a possibility of enteral concretions. Symptom review may help identify patients with acute or indolent disease. Historically, diagnosis of enterolithiasis was made at the time of laparotomy or autopsy. Development of radiological field has tremendously improved early diagnosis and treatment of this disorder. Presence of single or multiple enteroliths on imaging is helpful in establishing correct diagnosis. Mobile nature of the stones and their anatomic location may lead to differentiating between various underlying pathologies, including intestinal strictures/stenosis in infectious or inflammatory bowel disease, post-surgical complications, or Meckel's diverticular disease. Traditionally, plain abdominal roentgenograms are the first step in identifying enteroliths and can detect stones in up to a third of the cases[8]. The visibility of the stone depends on the calcium content, with enteroliths containing a higher proportion calcium salts being more radiopaque and forming in the relatively more alkaline environment of the distal ileum. Choleic acid enteroliths are more radiolucent and form in the more acidic environment of the proximal small bowel[15,43,45]. Clinician's awareness of anticipated chemical composition of the enterolith in a particular bowel segment, will increase the yield of radiologic detection and potentiate proper diagnosis. Important radiographic features of enteroliths include dense rim with pale core in oval, round, or rectangular shadows, "coin-end-on" appearance, and apparent mobility on serial examinations in relation to each other and to a fixed anatomical pathology[75]. Computed tomography (CT) scan with oral contrast may provide two or three dimensional orientation and increase the yield of detection of radiolucent stones. CT scan may also help in identifying the number of enteroliths, their exact location, and narrow the focus on the culprit

stone. Dedicated radiologic imaging may assist in establishing underlying pathology of the intestinal tract that leads to a stone formation or is responsible for stone trapping and clinical obstruction. Diagnosis of small intestinal Crohn's disease, diverticulosis, tumor, anastomotic stricture, fistulizing disease, regional enteritis, altered anatomy and blind loops may provide additional clues in patient care. Finally, particular attention should be directed to the gallbladder and biliary system to rule out gallstone ileus.

Imaging of patients with Meckel's enterolithiasis may suggest dilated small bowel with air fluid levels in setting of an obstruction in 40% of the cases on plain abdominal radiographs, single or multiple opaque stones in 88% of the patients. Location of the stones may vary, with nearly 60% present in the right lower quadrant. Majority of the stones have peripheral calcifications with radiolucent centers (89%) and range from 1 to 5 cm in diameter[29]. Yield of enterolith and Meckel's diverticulum detection increases with contrast studies, with both CT enterography and small bowel series/enteroclysis complementing plain film radiography and providing additional advantage in identifying underlying pathology. Nuclear studies aimed at detecting ectopic gastric tissue in the Meckel's diverticulum may be helpful but given the high incidence of symptomatic presentation of such diverticula in childhood that is followed by surgical resection, may not always be diagnostic in older patients who have intestinal tissue lining of the diverticulum. It may, however, provide additional information in select rare cases of radiolucent stones that may be formed within acidic environment of gastric mucosal Meckel's and are not visible on plain roentgen films or a CT scan. Extrusion of the enterolith into the small bowel from the diverticulum may lead to the enteric occlusion and alternatively, distention of the Meckel's diverticulum from the large enterolith may cause Mirizzi-type impression on the adjacent gut, both resulting in signs of small bowel obstruction on CT scan[76].

Gallstone ileus represents a better known category of enterolithiasis. Clinical diagnosis should be suspected in a patient who presents with vague complains of intermittent abdominal distention, pains, nausea and vomiting due to "tumbling phenomena" of the stone passage though the intestinal tract[38]. Additional findings may include weight loss, dehydration, and loss of appetite[77]. Duration of symptoms may vary from days to weeks and the diagnosis is typically delayed for several days. Correct preoperative diagnosis is achieved in only half of the cases[78]. A quarter of cases will have an antecedent gallstone disease[34]. Classic description by Leo Rigler in 1941 of pneumobilia or contrast medium in the biliary tract, partial or complete small bowel obstruction, and a visualized ectopic gallstone that may change position within the bowel (Rigler's triad)[69] is seen in less than 50% of patients with gallstone ileus[31,34,36,38,57,69,73,79,80]. Combined radiologic imaging (X-rays, ultrasound, CT scan) result in increased yield of diagnosis, with positive findings in

nearly 80% of the patients[34].

Importantly, colloquial information obtained from radiologic diagnosis of enterolithiasis may provide an important information on the location of the underlying intestinal pathology, including stenotic segments of Crohn's disease, areas of enteric tumors, significant adhesions, incidental Meckel's diverticulum, and hernias.

Notably, with the advent of radiologic procedures and rapid growth of the medical field, there exists a wider gap in the studies addressing potential increase in prevalence of enteroliths today compared to the mid-late 20th century. Certainly, higher detection rate may aid in differential diagnosis of a number of intra-abdominal pathologies, including establishing early clue of enterolithiasis. However, the definitive diagnosis of an intestinal stone is made through removal of the endolith and its subsequent pathology.

COMPLICATIONS AND PROGNOSIS

Complications related to enterolithiasis should be sought for and recognized early. *De novo* formation and subsequent transit of an enterolith through the gastrointestinal tract may result in acute, subacute, or chronic, intermittent, partial or complete intestinal obstruction[76]. Important risk factors include intraluminal stricturing or stenosis seen in inflammatory bowel disease, tuberculous and radiation enteritis; surgical anastomoses; intestinal malignancy; extraluminal kinking or angulation found in the setting of intra-abdominal adhesions, external compressions, or incarcerated hernias; and finally abnormally narrowed intraluminal diameter in otherwise unremarkable terminal ileum and highly patent ileocecal valve. It is generally accepted that, in the absence of mechanical or structural luminal compromise, stones larger than 2.5 cm in diameter may cause an intestinal obstruction[33]. Single enteroliths smaller than 2 cm in size would typically pass unnoticed through normal small intestine and into the colon; but if retained, may become a nidus for additional calcification and growth and may result in pathogenic obstruction in the future. Impacted enterolith may incite direct pressure injury to the intestinal mucosa, potentially worsened by chemical damage from the reactive substances found on its shell[33]. Intestinal gangrene in association with enterolith has been previously reported[7]. Additional rare complications of enterolithiasis include intussusception of small bowel[81], acute obstructive ascending cholangitis due to periampullary duodenal stone[82], afferent loop syndrome[23,83], diverticulitis[63,84], iron deficiency anemia[85], gastrointestinal hemorrhage[45], and perforation[7,16,19,86,87]. Mortality of uncomplicated primary enterolithiasis is very low, but may rise to 3% in the poorly conditioned patients with significant obstruction and delay in diagnosis[42]. Morbidity from the gallstone ileus in the second half of the twentieth century was reported by Reisner and Cohen[38] to include wound infection in 32% of cases, biliary symptoms in 15%, and recurrence in 5% - all

likely to continue to improve with advances in today's medical care, whereas mortality remained high at 18%. Review of the more recent Japanese literature projects a decrease in mortality to 8%[33]. Continued improvement in medical diagnosis and treatment of enterolithiasis will effectively allow for a steady decrease in its associated complications and overall mortality.

TREATMENT

Optimal treatment of enterolithiasis should focus on enterolith removal and correction of underlying pathology to prevent future formation of additional enteroliths. In cases of acute intestinal obstruction, expectant management with serial abdominal examinations, electrolyte correction, appropriate hydration, and nasogastric tube suctioning may be selectively considered for stones less than 2 cm in size in absence of underlying luminal compromise[88]. Spontaneous passage of a larger stone is unlikely and a thorough search for an underlying pathology should be performed. In cases of intestinal stricturing, stenosis, or an anastomotic defect, an attempt at endoscopic segment dilatation and stone retrieval may be considered first[12,89]. Endoscopic electrohydraulic lithotripsy and mechanical lithotripsy have been previously described[84,90]. Surgical management remains the mainstay of therapy in the majority of the cases, with an attempt at digital fragmentation of the stone followed by manual "milking" of the smaller parts into the large intestine being successful in nearly 50% of the cases[9,42]. Alternatively, proximal enterotomy of the non-edematous segment with manual enterolith removal may be performed. Preoperative percutaneous decompression of the afferent limb using ultrasound guidance may be indicated in Billroth II patients[23]. Segmental small bowel resection with intended primary anastomosis should be attempted in the setting Meckel's diverticulum, long complicated strictures, diverticulitis, significant inflammation, intestinal necrosis, perforation, and enteral duplication[20,75]. Most cases described in the literature have been open procedures, although Jones *et al*[76] and Shah *et al*[91] report two cases in which resection was successfully performed laparascopically. This approach decreases the detection rate of additional enteroliths that may need to be sought for and eliminated by milking of the proximal bowel to decrease recurrence of obstruction. Three cases have been reported where surgical removal of Crohn's disease associated enteroliths revealed adenocarcinoma of the bowel[43,45,55], therefore raising awareness for intraoperative evaluation for small bowel tumors.

The procedure of choice in gallstone ileus is still a matter of controversy with possible approached including enterolithotomy alone, in conjunction with simultaneous cholecystectomy and fistula closure, or a two-stage procedure. Higher morbidity and mortality seen in the longer one-stage procedure compared to enterolithotomy alone has led to the latter being the preferred approach in the emergency setting in many centers[34]. However, persistence of biliary-enteric fistula may lead to recurrent gallstone ileus (5%) or cholangitis (11%)[34,57]. Therefore, surgical options should be individualized and if general medical condition of a patient permits, one-step enterolithotomy with cholecystectomy and fistula closure may be considered.

Importantly, enterolith formation may be the first clue to the existence of a compromised intestinal anatomy and every effort should be made to decrease future stone formation by recognizing and treating underlying medical conditions. Medical, endoscopic, or surgical correction of inflammatory, infectious, or structural pathology may provide chronic symptom relief and benefit the long term outcome in many of the cases.

With rapid advances in medical and surgical technology and procedural skills, additional studies are needed to assess the success rate of new approaches to the removal of enteroliths in the twenty first century. Single- and double-balloon enteroscopy with carbon dioxide insufflation may provide additional benefit to the selected patients that were previously managed surgically. This tactic may potentially result in the future shift from surgical into the endoscopically feasible realm, thus decreasing morbidity and mortality associated with surgical intervention and improving patient's outcome.

Finally, "silent" enterolithiasis may occur at increasing rates in the era of radiologic advances. A single or clustered stones may be incidentally visualized in the areas of known diverticulosis including Meckel's diverticulum or strictures/stenosis. Alternatively, finding of an enterolith may an early clue to underlying pathology and further clinical evaluation may be warranted. Incidental enteroliths may potentially lead to complications and will therefore require periodic re-assessment. Endoscopic or surgical retrieval may be considered in select cases.

CONCLUSION

Enterolithiasis remains an important clinical condition with raising incidence and prevalence. Alterations in bowel anatomy and microenvironment play a significant role in pathogenesis of this disease and provide an important clue in its etiologic recognition, chemical classification, and clinical presentation. Distinction between primary and secondary enterolithiasis and identification of underlying enteropathy is crucial in establishing disease process. Clinical diagnosis relies on detailed history and physical examination complemented by radiologic imaging modalities. Mimickers of enterolithiasis should be diligently excluded. Treatment should be aimed at endoscopic or surgical enterolith removal and correction of the underlying intra- and extra-intestinal pathology to prevent additional stone formation. Rapid advances in medical field will continue to lead to improved diagnosis and help expand therapeutic options for the affected patients.

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