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What's New in Diagnosing Diverticular Disease

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ABSTRACT

In this session different issues for the diagnosis of diverticular disease (DD) were considered including "Biomarkers", "Computer tomography", "Ultrasonography in detecting acute diverticulitis", "Endoscopy" and "The DICA classification: a new predictive tool in managing diverticular disease". Most patients affected by DD suffer from recurrent attacks of abdominal pain without evidence of an active inflammatory process, causing a difficult differential diagnosis with other intestinal conditions. Several biomarkers, serological, fecal, urinary and genetic were considered, but recent studies confirmed that only CRP and fecal calprotectin are matching with the criteria for an ideal biomarker for DD. Colonoscopy still remains the gold standard for the diagnosis of DD, playing a key role in many clinical settings, such as colonic diverticular bleeding, or to differentiate inflammatory bowel disease (IBD) and segmental colitis associated with diverticulosis (SCAD); Moreover, in 2015 has been developed the DICA (Diverticular Inflammation and Complication Assessment) endoscopic classification that considers 10 different parameters, each one with a score, and the sum of items scores represents the severity of the disease; in this way the endoscopic exam would be able to predict the outcome of DD for each patient. On the other hand, computer tomography (CT) is the gold standard for acute diverticulitis (AD) with an excellent sensitivity and specificity; recently, metanalysis of prospective studies have shown that intestinal ultrasonography (IUS) and CT have the same sensitivity for the diagnosis of an AD and the advantage is that IUS is less expensive, non-invasive and easily accessible.

Key words: diverticular disease – acute diverticulitis – colonoscopy – DICA classification – computer tomography – ultrasonography – fecal calprotectin.

Abbreviations: AD: acute diverticulitis; CRP: C reactive protein; CT: computer tomography; CTC: computer tomographic colonography; DD: diverticular disease; DICA: Diverticular Inflammation and Complications Assessment; ESR: erythrocyte sedimentation rate; FC: fecal calprotectin; IBD: inflammatory bowel diseases; IUS: intestinal ultrasonography; LGIB: lower gastrointestinal bleeding; SCAD: segmental colitis associated with diverticulosis.

BIOMARKERS IN THE DIAGNOSIS OF COLONIC DIVERTICULAR DISEASE

Clinical evaluation alone of DD results in a wrong diagnosis in 34-68% of the cases and may lead to inadequate treatment, unneeded investigations, unnecessary hospital stay and increased costs. The use of imaging techniques may help clinicians. However, ultrasound is examiner-dependent and (CT) is expensive and potentially harmful. Biomarkers are measurable indicators of some biological conditions and may allow the characterization of disease subtypes. Ideal biomarkers should be, accurate, reproducible, non-invasive and low cost. Nowadays, serum, fecal, urinary and genetic biomarkers have been proposed for DD.

Serum biomarkers

C reactive protein (CRP), eritrocytes sedimentation rate (ESR), white blood cell counts (WBC), fibrinogen, β-2-globulin, α1-acid glycoprotein were increased in patients with AD. However, by a multivariate analysis only CRP >50 mg/dl was an independent predictor of AD [1]. Further, CRP > 150 mg/dl significantly discriminated uncomplicated diverticulitis from complicated diverticulitis [2]. High levels of serum procalcitonin, a marker of bacterial infection, differentiated (sensitivity 80%

specificity 91%) complicated versus uncomplicated diverticulitis when combined with CT scans [3].

Fecal biomarkers

When there is inflammation in the gastrointestinal tract, calprotectin is delivered by neutrophils in the stool. High levels of fecal calprotectin (FC) may differentiate IBS from IBD, thus it is a sensitive marker of activity in IBD. FC correlates with mucosal leucocytes density and may distinguish symptomatic DD from IBS [4]. Further, FC may be useful in assessing response to therapy and in predicting diverticulitis recurrence [5]. Microbiota imbalance is a risk factor for the occurrence of DD. Patients with DD showed higher amount of Enterobacteriaceae [6], a depletion of microbiota members with anti-inflammatory activity and metabolome profiles linked with inflammatory pathways and gut neuromotor dysfunction [7].

Urinary biomarkers

Because of dysbiosis, it is hypothesized that specific urinary metabolic pathways might identify patients with DD. Hippurate and methanol showed significant differences among health controls and patients with AD and symptomatic uncomplicated DD (SUDD) [8].

Genetic markers

Genome wide studies found associations between specific loci and DD (ARHGAP15 and COLQ) and AD (FAM155A and rs9960286 located near CTAGE1) [9,10].

ENDOSCOPY

Colonoscopy plays a key role in different clinical settings of DD: 1) diverticular bleeding; 2) differential diagnosis of colon diseases (SCAD vs IBD); 3) follow-up AD; 4) prognostic tool in patients with DD.

Colonoscopy in Colonic Diverticular Bleeding

Colonic Diverticular Bleeding is the most common cause of lower gastrointestinal bleeding (LGIB) affecting from 3 to 15% of patients with colonic diverticulosis, with mortality rate from 2 to 3 %. In patients with suspected colonic diverticular bleeding colonoscopy is generally indicated: a) electively when bleeding has stopped spontaneously (70-80% of cases): in order to exclude other causes of LGIB. b) as primary intervention in managing colonic diverticular bleeding: urgent colonoscopy, within 24 hours, in order to find signs of diverticular bleeding (active bleeding, visible vessel or adherent clot). c) as primary imaging in patients with recurrent episodes of LGIB in which CT angiography was non-diagnostic [11,12,13]. Unprepared colonoscopy is not recommended because is associated with a low cecal intubation rate (55-70%) and a high risk of bowel perforation. Urgent colonoscopy for acute LGIB is associated with a shorter length of hospital stay and lower hospitalization costs [14,15,16].

Colonoscopy in differential diagnosis of colon diseases (SCAD vs IBD)

Segmental colitis associated with diverticulosis (SCAD) is a chronic inflammatory process localized in the interdiverticular mucosa and therefore mainly in the sigmoid colon. By definition, the diverticular ostia are spared from any inflammation [17]. There are histological similarities between SCAD and IBD, but by endoscopic examination we can easily differentiate SCAD from IBD or other type of colitis: in SCAD the inflammatory process involves the interdiverticular mucosa in the colonic area presenting diverticulosis and therefore mainly in the sigmoid colon, and the rectum and proximal colon are endoscopically and histologically normal; in ulcerative colitis the rectum is always affected; Crohn's disease may affect colon and other gastrointestinal areas [18].

Colonoscopy following Acute Diverticulitis

Regarding the role of endoscopy in AD or following an attack of acute diverticulitis, Galetin and colleagues [19], in a recent systematic review and comparison of guidelines, confirm that there is discordance in performing colonoscopy in acute diverticulitis. Colonoscopy is usually avoided in patients with suspicion of AD because of the high risk of bowel perforation. Expert opinion is in favour of performing these tests when the acute process has resolved, usually after approximately 6 weeks, to rule out the presence of other diseases, such as cancer and IBD. Colonoscopy following AD is useful in the following conditions: a) In persistent symptomatic patients in order to exclude other diseases b) After resolution of an AD if a high-quality examination of the colon has not been recently performed [20].

Colonoscopy as a predictive tool for diverticular disease outcomes

Diverticular Inflammation and Complication Assessment (DICA) is an endoscopic classification that considers four items of DD in a scoring system and is a promising tool for DD outcomes.

THE DICA CLASSIFICATION: A NEW PREDICTIVE TOOL IN MANAGING DIVERTICULAR DISEASE

Diverticulosis of the colon is the most frequent anatomic alteration detected during screening colonoscopy [21]. It can be detected in 32.6% of routine colonoscopies and up to 71.4% of people ≥ 80 years. [21]. Moreover, the SUDD patients having extensive diverticulosis are at higher risk of AD occurrence [22], and the persistence of endoscopic inflammation may be a risk factor for AD recurrence [23]. Despite these data, an endoscopic classification of diverticulosis and DD was absent till 2015. Recently the first endoscopic classification of diverticulosis and DD, called DICA has been developed and validated. This classification takes into account four main items and several subitems: the extension of diverticulosis (left or right), the number of diverticula per each colonic region (≤ 15 or ≥15 diverticula), the presence of inflammation (oedema, hyperaemia, erosions, SCAD), the presence of complications (rigidity, stenosis, pus and bleeding). Each of these items and subitems has a numerical score, and the sum of the scores lead to three different DICA scores: DICA 1 (up to 3 points), DICA 2 (from 4 to 7 points), and DICA 3 (over 7 points) [24]. This classification seems to have a predictive value on the

outcome of DD in terms of AD occurrence/recurrence and risk of surgery, founding that DICA 3 patients were at higher risk of AD occurrence/recurrence compared with DICA 2 or DICA 1 patients. The same risk was recognized in assessing the surgical risk: DICA 3 patiens were at higher risk of surgery linked to the disease than DICA 2 or DICA 1 patients [25]. A recent study in real life confirms the significant agreement for this classification in clinical settings, even for endoscopists not expert with this disease [26]. DICA classification has become the standard reference for the studies assessing DD by an endoscopic point of view [27-29]. A prospective, international study is currently ongoing. This study will take three years, and the results at one year of follow-up have recently become available: the preliminary analysis seems to confirm the results of the retrospective study, namely DICA 3 patients are at higher risk of AD and surgical procedures disease-related than DCA 2 and DICA 1 patients [30].

COMPUTER TOMOGRAPHY

Computer tomography (CT) is the gold standard in diagnosing and staging patients with AD. CT with i.v. contrast performed within 48 hours after onset of symptoms has excellent sensitivity and specifity (98% and 99%). It is useful for diagnosis, treatment and follow up of patients. There are several CT findings: maximal thickness of the bowel, inflammation of pericolic fat, presence of abscesses, stenosis, fistula, free air and fluid in the peritoneal cavity. It's also able to identify the length of colonic inflammation. CT scan grades the severity of diverticulitis; several CT classifications have been proposed: Ambrosetti, Hynchey, WSES. Currently the modified Hynchey's classification remains the most widely used, but it is insufficient to cover all clinical presentations [31-33]. CT scan should be descriptive taking into consideration the details of all the signs that might play a role in the evaluation of AD. CT is a significant predictor of surgery during the first attack, the presence of extraintestinal gas ≥5 mm being correlated with unfavourable outcome of nonsurgical treatment [34]. Length of involved colon >5 cm and retroperitoneal abscess were associated with diverticulitis recurrence: distant intraperitoneal air is the most important factor predicting surgical treatment [35, 36]. CT colonography (CTC) recently has been proposed as a diagnostic test in patients recovering from an episode of AD; CTC should be performed at least 2 or 3 months after the acute episode of diverticulitis. A DD severity score based on CTC findings has been proposed. The central place of CT in the evaluation of AD severity is proven. A classification system based on CT scan results may drive decisions making [37].

ULTRASONOGRAPHY

Several international guidelines considered intestinal ultrasoography (IUS) the first imaging technique for detecting AD [38]. Meta-analysis of prospective studies have shown that IUS and CT scan have the same sensitivity in diagnosing AD, and both techniques can be used as initial diagnostic tool. However, CT has the advantage of a more panoramic view and it is likely more useful to identify alternative diseases [39]. On the other hand, US is widely available and easily accessible within the emergency department, it has a low cost, it's noninvasive and it can be therefore performed as first exam in patients with abdominal pain, followed by CT scan in inconclusive cases. Another main advantage of IUS is its ability to assess in real-time the site of abdomen with the greatest tenderness, in cases with localized and well-defined abdominal pain. In patients with uncomplicated AD, at the level of areas with maximum tenderness, IUS can detect short-segmental bowel wall thickening (>5 mm), an inflamed diverticulum, and localized hypertrophy of mesenteric fat. The presence of at least 2 of these signs allows the diagnosis of AD with a sensitivity and specificity greater that 90%. In patients with AD complicated by fistulas or abscesses, pericolic hypoechoic or anechoic structures may be observed within the mesenteric fat hypertrophy. Differentiation between phlegmonous and septic fluid collections may be obtained by using color Doppler or contrast-enhanced US, which are able to detect the hypervascularization of the inflammatory areas [40]. A potential limitation of IUS might be the need of an expert sonographer. This issue, namely level of experience of an operator in detecting AD has been assessed in a Dutch study, showing that sensitivity of a radiologists with experience of <500 intestinal exams is only 58% compared with 82% of an expert one. However, the positive predictive values were similar 90% for expert vs. 85% for non-expert radiologists [41]. Anyway, it should be recognized that every diagnostic technique requires experience, and hopefully in future the learning of intestinal US in medical schools will overcome this limitation.

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