ADVANCES IN IBD

Current Developments in the Treatment of Inflammatory Bowel Disease

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Silent Crohn's Disease

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G&H Can you give some background about what defines "silent disease"?

DB Silent disease is disease that does not have the overt symptoms that make a patient feel poorly. This is a fairly well-established concept in medicine. Perhaps the best example of a correlate to silent Crohn's disease is silent ischemia in the context of heart disease. For example, diabetic patients may show electrocardiographic (ECG) changes but not have the classic anginal chest pain that is associated with cardiac ischemia. Symptomatically, they may feel fine but have objective evidence of pathology based on testing.

Several seminal papers in cardiology, published in the 1980s, found a significantly higher rate of myocardial infarction and death in asymptomatic persons whose ECG findings revealed silent ischemia, compared with persons with normal ECG findings. These study findings alerted physicians to the need to be more aware that some patients are not able to report their symptoms accurately.

In the context of inflammatory bowel disease (IBD), particularly Crohn's disease, there are patients who feel quite well but simultaneously have objective evidence of inflammation. These patients report that things are going fine when they present to the doctor's office, but laboratory work will show evidence of a biochemical inflammatory signal with elevated C-reactive protein (CRP) levels and perhaps a sedimentation rate elevation, or endoscopy performed for surveillance purposes will show evidence of active inflammatory disease.

Endoscopically, the physician can see friability and ulcerations, changes that are very consistent with an active disease process, but the patient is not able to report this due to a lack of symptoms. Therefore, my colleagues and I investigated whether silent disease can occur in patients with Crohn's disease in the context of routine clinical care. The goal of the research was 2-fold: first, to determine what the rate of silent disease was among a group of Crohn's disease patients who were being followed in a tertiary referral setting and, second, to determine whether patients demonstrating a pattern of silent Crohn's disease were at risk for developing an increased rate of complications.

G&H How does a practitioner know to look for Crohn's disease if it is silent?

DB The best way to identify such patients in the routine clinical setting is not known. Historically, a physician will ask the patient how he or she feels, and self-reported symptoms have been the major mainstay of how treatment decisions are guided. The Physician Global Assessment may include information from laboratory findings or recent imaging or endoscopy, which will show evidence of the patient's actual state of health.

At our IBD center at the University of Pittsburgh, we obtain routine laboratory testing at the time of clinic visits. This includes fairly simple tests, such as a blood count and liver function tests, but we also monitor CRP levels and erythrocyte sedimentation rates at the time of clinic encounters. We have been using this strategy since 2009

and have a cohort of patients who have signed registry consent, allowing us to use their routine clinical information for research purposes.

Using the University of Pittsburgh Medical Center IBD Registry database, we are able to identify patients who have objective evidence of inflammation, defined as an elevated CRP measure at the time of a clinic visit. In parallel with this standardized laboratory testing, we routinely ask patients to fill out validated metrics, including a previously published version of the Short IBD Questionnaire (SIBDQ; from Jowett SL, Seal CJ, Barton JR, Welfare MR. *Am J Gastroenterol*. 2001;96(10):2921-2928.). This version of the SIBDQ has a scoring system that ranges from 10 to 70, with 10 being the lowest score and 70 being the perfect score. Based on the literature as well as our experience using this tool, a score above 50 suggests that the patient is doing well.

Approximately half of our patients will come into clinic with SIBDQ scores greater than 50, but these scores are assessed in parallel with a laboratory score that allows us to come up with a 2×2 grid in which patients fall into specific categories. The CRP level is either elevated or normal, and the patient is either feeling well or having more difficulties with disease-related quality of life.

Using this structured approach to clinical management, we have learned that two-thirds of patients are very accurate in reporting symptoms related to inflammation. In contrast, the remaining one-third of Crohn's disease patients will not accurately report the relationship between symptoms and inflammation. Approximately one-sixth of patients are "overreporters," or they will describe abdominal symptoms that are suggestive of active Crohn's disease but fail to demonstrate objective evidence of inflammation. These individuals have historically been described as having irritable bowel syndrome (IBS) or functional symptoms in the setting of IBD ("IBS in IBD"). The remaining one-sixth of patients have objective evidence of inflammation but otherwise do not report it, and these individuals comprise the subgroup we have labeled "silent Crohn's disease."

G&H What markers best identify silent Crohn's disease, and how are they being captured?

DB We do not know which biomarker will be the perfect marker, but we know that there are a number of strategies to identify inflammation in Crohn's disease, and these strategies for monitoring have different levels of sensitivity. The use of biomarkers to gauge inflammation is an active area of investigation in IBD, and we are currently learning the performance characteristics of blood markers such as CRP level as well as fecal markers such as calprotectin. The recent investigation carried out by our research group did not compare various biomarkers but instead focused on 1 parameter, CRP level, which has been used to identify inflammation. We know, however, that endoscopy is very sensitive for identifying active inflammation and is the most sensitive diagnostic resource to assess patients who have colonic disease. We also have growing evidence that some of the fecal biomarkers of inflammation might be quite sensitive.

We do not yet have as clear of a signal, however, that fecal biomarkers will be as robust in patients who have small bowel disease as in those with colonic disease. The literature suggests that some patients will have endoscopic evidence of inflammation and that CRP levels will not elevate until a more extensive degree of mucosal injury is encountered. Therefore, CRP elevation represents a more significant threshold of mucosal damage compared with endoscopic assessment. Confounding issues also exist in regard to the interpretation of CRP elevation in Crohn's disease management. If a person has an infection, such as a vital illness or upper respiratory infection, his or her CRP level will rise very rapidly.

G&H What imaging tools are the most efficient for detecting silent Crohn's disease?

DB Imaging is a very effective strategy for identifying activity in IBD, and we have a number of modalities. Historically, radiology with computed tomography (CT) scans have been used to assess inflammation. Some of the newer CT radiology protocols, such as CT enterography, may provide some of the best images, and we can get a wealth of data from that type of study. The downside is that radiation exposure during abdominal pelvic CT scanning is substantial. Extreme care is needed in young patients because radiation exposure will potentially contribute to complications, specifically the development of cancers in later adult life.

A newer modality that is gaining popularity is magnetic resonance enterography (MRE). MRE is extremely effective in detecting inflammation in the bowel, particularly in patients who have small bowel disease that is not easily amenable to a colonoscopy or that is located in the regions that are in between the reach of upper endoscopes and colonoscopes. There are some drawbacks to MRE, though. Expertise is limited; not all centers have radiology staff members who are experienced with this protocol. MRE is more expensive than CT radiology, the testing takes longer, and patients have to be in the scanner for a longer period of time than with a CT scan, which may discourage use among some patients who are claustrophobic. The assessment of luminal bowel in the abdomen and pelvis can be achieved with the same CT study but will require 2 separate, dedicated MR studies due to technical

issues regarding image acquisition. However, despite these limitations, MRE provides very clear and objective data of inflammatory activity in the bowel.

G&H In clinical practice, how can a person with silent Crohn's disease be identified outside of a university research setting?

DB If the patient has a history of Crohn's disease, he or she is typically followed for a long time by gastroenterologists in the community. It is not uncommon for patients who are quite stable to be seen once or twice a year, and most patients are reliable about keeping appointments and reporting their symptoms. The key to identifying silent Crohn's disease is to obtain a routine, objective biomarker assessing inflammation when the patient is being seen in these follow-up visits. Relying entirely on the patient's symptoms will fail to identify inflammation if the patient is stoic and/or simply cannot sense that bowel inflammation is active. Physicians need to be aware that approximately one-quarter of patients with active disease are asymptomatic. Physicians may consider adopting a system similar to the one used by the University of Pittsburgh, in which quality of life is assessed using numeric scores that can easily be filled out by patients in 2 minutes, and routinely checking CRP levels.

It is important to keep in mind that underreporting of symptoms has important ramifications in that the asymptomatic patient who nevertheless has an objective marker of inflammation is at substantial risk for a complication that will require hospitalization within 2 years. An underreporter will likely persist in underreporting; therefore, once we identify such a patient, we have to be more vigilant about using objective markers in him or her. We have yet to show, however, whether acting on the detection of CRP level elevation will have an impact on preventing complications or whether the inflammatory process needs to be caught at an earlier stage. We need to see whether increased vigilance, in the form of more diagnostic testing, will help asymptomatic patients avoid complications.

G&H How does a physician convince a patient who is feeling well but shows signs of disease that he or she should take medication?

DB Studies similar to ours will help to inform both the treating gastroenterologist as well as patients. If we can describe the natural history of disease to patients with undertreated inflammation and let them know that there is a substantial chance of complications that will require hospitalization, this can motivate both the patient and physician to act in a preemptive fashion. In our study, 37% of the silent Crohn's disease cohort at our center required hospitalization within 2 years compared with 7% of patients who felt well and had no elevation in CRP level. The use of objective markers to guide diagnostic testing and treatment is the emerging strategy for IBD management, and these data on silent Crohn's disease represent an additional facet of that evolution to optimize management.

G&H How does increased vigilance, in the form of increased testing, impact cost concerns or insurance issues?

DB Physicians are very conscious of cost issues in medicine nowadays. The best strategy both to be cost-effective and to improve outcomes in patients is to prevent complications that would lead to hospitalization. As discussed above, half of patients with Crohn's disease feel well in a random clinic encounter, but if we track those patients over the next 2 years, we will find that 14% will be hospitalized. In order to avoid these high-cost interventions, it would be very desirable to identify which patients will fall into that 14%. Our study on silent Crohn's disease found just that—we can identify which patients are at risk of hospitalization (37% vs 7%) based on an elevated biomarker of inflammation, CRP level.

In our study, we found that we could identify a subgroup of patients who had a much higher rate of hospitalization than other patients through use of fairly inexpensive blood tests. Now, we hope that we can use that lead time to perhaps do some investigation that would help those patients get on a better course of medical therapy that might prevent the natural history of their disease from progressing to a complication that requires hospital-based care.

Dr Binion has no relevant conflicts of interest to disclose.

Suggested Reading

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