Expression of cyclooxygenase-2 in gastritis and gastric premalignant lesions

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Cyclooxygenase (COX)-2, the protein that plays a key role in gastric carcinogenesis, is being evaluated as a pharmacological target for both the prevention and treatment of cancer [1,2]. Tumor promotion may be attributed to the stimulation of cell proliferation and migration, the inhibition of apoptosis, the increase in malignant cell invasiveness and the induction of angiogenesis [1-3].

We aimed to immunohistochemically evaluate COX-2 expression in patients with chronic gastritis and premalignant lesions and to assess its possible association with the sequence of normal epithelium, inflamed epithelium, atrophic gastritis, intestinal metaplasia and gastric dysplasia.

A total of 153 patients who underwent upper gastrointestinal tract endoscopy due to dyspeptic symptoms between December 2010 and June 2012 were included in the study. There were 84 males and 69 females, whose mean age was 59 (range: 28-89) years.

Biopsies were obtained from pyloric antrum, incisura angularis, and gastric corpus in order to determine their histological status. The diagnosis of gastritis and premalignant lesions was based on the Houston modification of the Sydney classification. COX-2 expression was detected by a monoclonal antibody from the Santa Cruz Biotechnology Company, California, USA. Immunohistochemical staining was scored by two independent observers with a concordance of 80% on a scale of 0-3, based on the number and intensity of stained cells. It should be taken into account that in each of our specimens, COX-2 immunoreactivity was graded after examination of all available tissue including areas of atrophy, metaplasia and dysplasia, when observed. For each specimen the percentage of stained cells was determined. In cases with different percentages scored by the two observers, the slides were reexamined under simultaneous microscopy and a final percentage was determined.

Of the 153 patients, 106 were diagnosed with mild, 35 with moderate and 12 with severe gastritis (Table 1), while 89 (58%) of them had precancerous lesions.

Based on the τ-Kendall correlation test, there was a statistically significant link between severity of gastritis and COX-2 expression scores, meaning that the COX-2 expression scores increased with the severity of gastritis (from mild to moderate τb= 0.166, P<0.05), but COX-2 expression decreased from moderate to severe gastritis (τb= -0.32, P<0.05), in part agreement with the study of Hokari et al [4]. The results of the latter study suggest that the level of lipocalin-type prostaglandin D synthase mRNA expression (a specific enzyme that synthesizes prostaglandin D₂ from precursor prostaglandin H₂, synthesized by COX-2) decreased as gastritis became more severe.

Moreover, there was a weak correlation between COX-2 expression scores and presence of atrophic gastritis, intestinal metaplasia, or dysplasia in patients with chronic gastritis (χ² = 6.98, P<0.10).

In conclusion, COX-2 expression scores exhibited considerable variation among the three groups for severity of gastritis, tending to increase from mild to moderate gastritis states and to decrease from moderate to severe gastritis states, while there was a weak association between COX-2 expression scores and precancerous lesions in patients with chronic gastritis.

Table 1 Cyclooxygenase (COX)-2 in relation to severity of gastritis

<table>
<thead>
<tr>
<th>Gastritis</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
<th>Total</th>
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<tr>
<td>COX-2 Expression scores</td>
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<td></td>
<td></td>
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<tr>
<td>Negative</td>
<td>30</td>
<td>3</td>
<td>6</td>
<td>39</td>
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<tr>
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<td>0%</td>
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References


Conflict of Interest: None

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Red pepper: an aid for gut functional diseases with pain?

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Functional dyspepsia and irritable bowel syndrome (IBS), as well as other gut functional diseases characterized by visceral hypersensitivity and pain, may render quality of life very poor and account for about 1/3 of visits to gastroenterology departments. They also represent a high cost for society in terms of prescriptions and sick leave. Following an emerging trend some attempts have been made to pharmacologically decrease visceral hypersensitivity with a number of drugs, but with little clinical success. In recent years, however, visceral hypersensitivity and pain have been described in most cases to hyperactivity of transient receptor potential vanilloid 1 (TRPV1) nociceptive fibers, that transfer the pain sensations to central nervous system (CNS), which are activated by noxious thermal, mechanical or chemical stimuli and these may be a new target for treatment of visceral pain [1].

Red pepper has been used for many years, transdermally to alleviate osteoarticular and neuropathic pain and its analgesic property is connected to its content in capsaicin, a transient stimulator of TRPV1 fibers (sensitization), which locks their neuronal membrane in a depolarized state that prevents subsequent depolarization, with consequent decrease of pain sensation (desensitization). Until about ten years ago the analgesic effect of capsaicin was exploited only through cutaneous application to reach the TRPV1 of the somatic nociceptive nerves.

The novel idea was to reach the TRPV1 of the gastrointestinal nociceptive fibers by ingesting red pepper and was described for the first time in a study of the effect of red pepper on painful symptoms of functional dyspepsia in 2002 [2]. In fact the epigastric pain of patients who ingested a daily amount of 2.5 g of red pepper containing 0.7 mg/g of capsaicin for five weeks, started to significantly decrease after three weeks with respect both to basal period and to patients who received placebo randomly and in a double blind manner. This paper represented the first clinical application of TRPV1 channel desensitization to treat visceral pain. Subsequently, because an increase in TRPV1 nerve fibers was found in colonic mucosa of IBS patients that was correlated with pain [3], a double blind controlled study on the effect of red pepper in these patients was carried out by administering red pepper enteric-coated pills, which demonstrated a significant improvement in abdominal pain after five weeks [4]. Although these results suggest a novel way of dealing with these frequent and distressing functional diseases, this approach was not clinically put into practice. One reason may be that the analgesic effect of red pepper is obtained at the expense of an initial, although transitory, exacerbation of pain in the first weeks of treatment in some patients [2,4].

Perhaps gastroenterologists are waiting for TRPV1 antagonists that, instead of desensitizing TRPV1, directly block its activation [5]. This way, however, is more risky, because TRPV1, is expressed not only in visceral neurons, but also in the CNS and in non-neuronal cells, where it is involved in many other important physiological functions of the body [6]. The appearance of serious side effects with these TRPV1 antagonists, such as hyperthermia and insensitivity to noxious heat, has prevented their experimentation in man. Desensitization of TRPV1 receptors through capsaicin administration is surely less dangerous than TRPV1 blockers; because red pepper is recognized as safe by the FDA for oral use, and millions of persons in the world, especially in south-east Asia, consume large quantities of capsaicin with red pepper (2.5-8 g/person) every day for life without evident adverse consequences. On the contrary, a beneficial effect on functional gut diseases may be inferred considering that these functional diseases, and in particular IBS, have a markedly lower prevalence in these countries than in western countries [7]. For these reasons the use of capsaicin should be promoted in the clinical management of this kind of visceral pain, including pain due to esophageal and rectal hypersensitivity, at least until TRPV1 antagonists have reached a level of safety.

References

Probiotics, prebiotics, synbiotics and naturally fermented foods: why more may be more

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We read with interest the review article of Gionchetti et al [1], which elegantly summarizes the data surrounding probiotics in pouchitis. Probiotics are live microorganisms that, when ingested, confer health benefits. In recent years, others have expanded on this concept, and introduced the words ‘prebiotics’ and ‘synbiotics’ to the lexicon. Respectively, they are “a non-digestible food ingredient that beneficially affects the host by selectively stimulating the growth and/or activity of one or a limited number of bacteria in the colon [2]” and a product that combines pre and probiotics synergistically. A final and relatively underexplored hypothesis is the role naturally fermented foods may play in health.

While the popularity of probiotics has surged in recent years, the idea that living organisms in food can be salutary is not a new concept. As early as Genesis, it was noted that “Abraham owed his longevity to the consumption of sour milk,” and Plinius, a Roman, advocated fermented milk products for the treatment of gastroenteritis [3].

Prebiotics and synbiotics are logical next steps. Indigestible foodstuff, prebiotics, such as fructooligosaccharides, inulin, and transgalactosylated oligosaccharides, selectively promote bifidobacteria growth, and may enhance its efficacy. Synbiotics, combinations of bacteria such as Bifidobacterium longum and proprietary prebiotics (Synergy 1, an inulin-oligofructose growth substrate), have been tested in small trials for the treatment of gastrointestinal illness [4].

Many of these studies however have yielded conflicting results. While there is significant evidence for the benefit of probiotics concerning antibiotic-associated diarrhea, rotavirus-associated diarrhea and pouchitis, results are merely suggestive for irritable bowel syndrome and ulcerative colitis, and the evidence is altogether equivocal for Crohn’s disease and constipation [5]. Synbiotics have also yielded mixed conclusions. One double blind, randomized controlled trial of 18 patients evaluated the efficacy of a synbiotic for the treatment of active ulcerative colitis. The study found an improvement in mucosal inflammatory markers, and improved clinical appearance of inflamed areas; however, no significant difference was found in the clinical activity index between the treatment group, and placebo [6].

Naturally fermented foods (NFF), in contrast to pre, pro or synbiotics, do not consist of isolated species of bacteria or homogenous non-digestible food scaffolds. NFF refer to traditionally prepared items, which may contain multitudes of microorganisms -even some unidentifiable strains- as well as both digestible and non-digestible food. One study of naturally fermented dry Greek salami found no fewer than 348 lactic acid bacteria alone, including Lactobacillus curvatus, L. sake, L. plantarum, Weissella viridescens, W. hellenica, and countless other unidentifiable isolates [7]. Another study of artisanal daily products found 4379 isolates in 35 products [8]. Thus, the sum total of items in NFF may be orders of magnitude greater than pro, pre or synbiotics. Likely NFF represents a novel therapeutic avenue that has been thus far under-investigated.

Some evidence suggests more may be more. A randomized trial by Ishikawa among ulcerative colitis patients showed that the addition of bifido-bacteria-fermented milk (BFM) to standard treatment improved relapse rates from 90% to 27% versus standard treatment alone [9]. In this study, a probiotic and fermented food showed additive benefit when combined with standard treatment. In contrast, a study by Zocco demonstrated that lactobacillus when administered in conjunction with mesalamine showed no benefit over mesalamine alone among ulcerative colitis patients [10]. The latter study used a probiotic in isolation, without a fermented food product.

Another provocative study of HIV patients showed that yogurt supplemented with Lactobacillus rhamnosus Fiti, and produced by local women in a low-income community in Tanzania, resulted in an average increase of CD4 cell counts by 0.13 cells/µL/ day among consumers [11]. Although this was an observational study, it would be interesting to compare, locally produced yogurt, industrially produced yogurt, isolated L. rhamnosus Fiti and placebo capsule in a prospective trial. If NFF offer unique benefits, the former would yield the best results.

NFF, which are inherently a collection of many distinct bacterial species and food substances, may be superior to isolated pro and synbiotics and, if so, would represent a new direction for gastrointestinal research. NFF may also yield other avenues of therapeutic strategy, which may otherwise go ignored in the current ‘one bacteria, one foodstuff’ paradigm. Studies that support NFF would be a vindication of traditionally prepared foods and food rules, a subject that has garnered a large following, and much publicity in the lay press [12]. NFF may offer health benefits that surpass both pro and synbiotics.

References

Vitiligo aggravated after major surgery for Crohn’s disease: a consequence of severe surgical stress?

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Vitiligo is an autoimmune skin disorder characterized by acquired white patches of skin and overlying hair as a consequence of loss of melanocytes and cutaneous pigment from the involved areas [1]. It appears mainly in patients with autoimmune disorders, although it has also been rarely described in patients with inflammatory bowel disease either before or after the establishment of diagnosis of bowel disease [2,3]. Some recent reports claim that vitiligo can also occur during treatment with anti-tumor necrosis factor (TNF)-α factors (infliximab or adalimumab) in patients with either Crohn’s disease (CD) [4] or ulcerative colitis [5].

We describe hereinafter the case of a patient with severe CD who developed extensive vitiligo, following a major surgical procedure performed for complicated CD. A woman, aged 44, developed CD of the small and large bowel at the age of 17. During the subsequent years, the disease was running with exacerbations of mild-to-moderate severity. The main clinical symptom was abdominal pain largely due to incomplete bowel obstruction and signs of impaired nutritional status. She also described vitiligo, covering a very small area of her hands. There was no family history of vitiligo and no known history of an autoimmune disorder. Maintenance treatment included only mesalamine (2.4 g/d) as azathioprine was not tolerated. In April 2010, she underwent right hemicolectomy with resection of 25 cm of the terminal ileum plus end-to-end anastomosis, because of the development of clinical signs of obstructive ileus. On May 25, 2010, she suddenly developed clinical and laboratory signs of acute peritonitis. The WBC was 14,490, the CRP 38 (nv: <3 mg/L) and the Hct 32%. Abdominal CT confirmed the clinical diagnosis of generalized peritonitis due to perforation and leakage at the site of the previous anastomosis. Careful lysis of the abundance of adhesions was performed along with resection of a small part of the large intestine (5 cm) and ileum (10 cm). A lateral anastomosis plus loop ileostomy proximally to anastomosis was performed. Subsequently, she developed septic shock and was transferred to the emergency unit. Total parenteral nutrition plus antibiotics were applied. She gradually improved and finally, she was discharged from the emergency unit after 20 days. Soon after, she noticed large areas of different sized achromic patches occupying most of her body’s skin, localized mainly in her face, upper and lower extremities and trunk (Fig. 1). Cutaneous biopsy showed a typical picture of vitiligo (i.e., absence of melanocytes, increased number of Langerhans’ cells, epidermal vacuolization, T cell inflammatory infiltrate, and neural alterations).

Figure 1 Achromic patches of different sizes and well-defined limits localized on the trunk and upper extremities are visible. The scar on her abdomen from the previous operation can also be seen.
The course of CD following operation was satisfactory with the patient’s main problem being her poor nutritional status. Up to September 2012, the course of vitiligo also remained unaffected. She is on immunomodulating diet (MODULEN IBD) with satisfactory results. So far, no treatment for vitiligo has been applied.

This patient presents some interesting peculiarities which include the sudden aggravation of the pre-existing skin disorder after the stressful major surgical event, and the extremely large area of her body involved by vitiligo in the absence of both family history of vitiligo and underlying autoimmune disorders. We have no obvious explanation for the appearance of this extensive skin lesion. In spite of recent findings implicating oxidative stress and genetic and immune factors in the pathogenesis of vitiligo, it remains largely obscure. It is possible however, that both oxidative stress and psychological stressful events (in our case the stressful event of the major surgical operation) equally contributed to the appearance of this skin lesion. In conclusion, we suggest a possible association between severe surgical stress and the aggravation of pre-existing vitiligo in a patient with CD.

References


Tuberculous abdominal cocoon

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Abdominal cocoon or sclerosing encapsulating peritonitis (SEP) is a rare cause of intestinal obstruction described mostly in young adolescent girls. Thick fibrotic peritoneum encasing the small bowel is a pathognomonic feature. Preoperative diagnosis is rare.

A 37-year-old man with hypertension and chronic renal failure presented with complaints of vomiting and abdominal pain lasting a few days. He had several similar episodes in the past with spontaneous symptomatic relief. He had a history of anorexia, weight loss, low-grade fever and gradual abdominal distension for a few months. Clinical examination revealed distended abdomen with ascites with tenderness and hyperperistaltic sounds. Laboratory studies revealed anemia, hypoalbuminemia, exudate type ascites (SAAG<1.1), significantly raised adenosine deaminase of ascitic fluid and positive PCR for tubercle bacilli. Plain radiograph of the abdomen in supine posture revealed dilated small bowel loops in the mid-abdominal region.
Abdominal ultrasonography revealed clustering of the small bowel loops in the mid-abdominal region with ascites. Contrast-enhanced computed tomography (CT) of the abdomen was performed. It revealed clustered small bowel loops encapsulated within a thick membrane-like sac in the mid-abdomen with dilated stomach and duodenum with moderate ascites (Fig. 1 A, B). Patient was treated conservatively and started on antitubercular medications and is doing well so far on follow up with few episodes of subacute intestinal obstruction settling spontaneously.

Intestinal obstruction secondary to abdominal cooon or SEP is an infrequent clinical entity [1]. The term “abdominal cooon” was first applied by Foo et al in 1978 [2]. The primary or idiopathic abdominal cooon is rare but abdominal cooon secondary to tuberculosis is not uncommon; especially in the tropical and subtropical third world countries like India where tuberculosis tends to be endemic. Prior to the era of CT imaging definitive diagnosis was usually made during surgery. In this case we were able to suspect the diagnosis preoperatively based on CT abdomen findings. Classic CT finding include small-bowel loops congregated in a single area or the concentration of small bowel loops in the mid-abdomen encased by a soft-tissue-density envelope [3]. Other CT findings include the presence of ascites or loculated fluid collections (less common), peritoneal thickening and enhancement, peritoneal calcifications (patients with end-stage kidney disease), thickening of bowel wall and tethering or fixation of bowel loops [4]. Surgery (membrane dissection and extensive adhesiolysis) is the treatment of choice. Once the diagnosis of tuberculosis is established these patients need to be put on standard anti-tubercular treatment.

References


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