SHORT REPORT

Dysplasia and colorectal cancer in a patient with ulcerative colitis and primary sclerosing cholangitis: A case report and a short review of the literature

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KEYWORDS
Ulcerative colitis; Primary sclerosing cholangitis; Dysplasia and colorectal cancer

Abstract
Primary sclerosing cholangitis is a chronic progressive disorder which involves the medium size and large ducts in the intrahepatic and extrahepatic biliary tree. The great majority of cases have underlying inflammatory bowel disease, mainly ulcerative colitis. A higher risk of colorectal cancer has been described among ulcerative colitis patients with primary sclerosing cholangitis. Here we report a case of a primary sclerosing cholangitis in a young male with a newly diagnosed ulcerative colitis presenting with colonic dysplasia. Surveillance for colorectal cancer should be strongly recommended in this group of patients.

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1. Introduction
Primary sclerosing cholangitis (PSC) is a chronic progressive disorder of unknown etiology that is characterized by inflammation, fibrosis and structuring of medium size and large ducts in the intrahepatic and extrahepatic biliary tree. The great majority of cases have underlying inflammatory bowel disease, mainly ulcerative colitis (UC); the prevalence may be as high as 90% when rectal and sigmoid biopsy are routinely obtained. Conversely, it has been estimated that PSC occurs in approximately 5% of UC patients and 3% of...
Crohn’s disease (CD) patients. A higher risk of colorectal cancer (CRC) has been described among IBD patients with PSC. Chemoprevention and surveillance for CRC have been strongly recommended in this group of patients.

2. Case report

A 26 year-old male presented to the hepatology outpatient clinic with abdominal pain and bloody diarrhea. The patient had been diagnosed with PSC/autoimmune cholangiopathy 10 years ago. The liver biopsies at diagnosis showed infiltration of the bile ducts by lymphocytes with degeneration of the epithelial cells of the bile ducts. He was on methylprednisolone 8 mg per 24 hours, ursodeoxycholic acid (UDCA) 15–20 mg/kg per 24 hours and azathioprine 50 mg per 24 hours. The laboratory results showed a cholestatic pattern of abnormal biochemical tests with moderate increases in serum aminotransferase levels (aspartate transaminase: 180 U/L, alanine transaminase: 210 U/L), an elevation of alkaline phosphatase (730 U/L), γ-glutamyl transferase (750 U/L) and serum bilirubin (2 mg/dL). The ultrasound showed no data of portal hypertension. An ileocolonoscopy was performed; from the anus to cecum, the colonic mucosa had erythema, edema and superficial ulcers. The patient was diagnosed with UC with moderate to severe activity (Fig. 1a). The patient was then referred to the IBD Unit. The dose of methylprednisolone was increased to 0.8 mg/kg per 24 hours, and the dose of azathioprine to 2.5 mg/kg per 24 hours. Oral and topical 5-aminosalicylates (5-ASA) were added to the treatment. High-grade dysplasia (HGD) with severely active inflammation was observed in two of the biopsies taken during the endoscopy. The biopsies were reviewed by the pathologist; as there was a severely active inflammation, the biopsies were finally classified as indeterminate for dysplasia. We decided to treat the endoscopic and histological inflammation, and to repeat the colonoscopy short later on.

The Mantoux test, and the serology for HCV and HIV were negative in this patient. Anti-HBs were positive (due to previous vaccination). The chest X-ray was normal. In October 2009 the treatment with infliximab 5 mg/kg was started. Co-trimoxazole was added to the treatment for the prevention of Pneumocystis jiroveci infection, due to the immunosuppression. The patient had an excellent response to the therapy and he was in remission after the second induction dose of infliximab. In December 2009, after the three induction doses of infliximab (at 0, 2 and 6 weeks), a colonoscopy was performed. The colonic mucosa was slightly friable, but without ulcers or erosions, with a great improvement compared with the previous endoscopy. No dysplasia was observed in any of the multiple random biopsies that were taken.

The patient remained in remission with azathioprine 2.5 mg/kg, infliximab 5 mg/kg every 8 weeks, 5-ASA 4 g per 24 hours and UDCA for the treatment of the PSC and co-trimoxazole. In October 2010, after a year of combination therapy (azathioprine plus infliximab), a colonoscopy was performed to decide if the patient could be left with azathioprine monotherapy. The colonic mucosa was completely normal (Fig. 1b), although the random biopsies showed multifocal low-grade dysplasia (LGD) (Fig. 2). The diagnosis of LGD was confirmed by a second pathologist; therefore a colectomy was recommended to the patient, and he accepted.

3. Discussion

The increased risk of CRC in UC has been recognized for decades, although the estimates of the magnitude of that risk vary considerably in the literature. Several studies have recognized PSC as a risk factor for CRC in UC patients; however, this has not been proven in all studies (Table 1). Soetikno et al. performed a meta-analysis and they described an odds ratio of 4.09 (95% confidence interval, 2.89–5.76) when compared patients with UC and PSC to UC patients without PSC. This finding has led to the recommendation of closer surveillance in this unique high risk subset of UC patients.

The mechanism by which PSC induces CRC remains unclear. It has been hypothesized that alterations in the bile salt pool and a high concentration of bile acid in the colon may, at least partially, be responsible for the increased risk. This hypothesis would explain the preponderance of right-sided cancers.

Figure 1 Endoscopic response to the treatment with infliximab: a) at diagnosis, the mucosa had erythema, edema, spontaneous bleeding and superficial ulcers; b) after 1 year of combination therapy (azathioprine plus infliximab), the mucosa was completely normal. However, biopsies showed multifocal low-grade dysplasia.
which are increased in PSC patients, probably due to a high concentration of carcinogenic secondary bile acids delivered to the colon. On the other hand, some groups have questioned whether the risk is increased by PSC itself or whether it is because the associated colitis in these patients is often a pancolitis with a subclinical course. As a result, the colitis tends to be diagnosed late and tends not to need colectomy for medically controlled flare-ups, thereby increasing the risk of colorectal neoplasia, purely for the increased extent and duration of the colitis.

3.1. Endoscopic surveillance

Periodic surveillance colonoscopy is the basis of our current approach to cancer prevention in IBD. As previously mentioned, in PSC patients, UC is often subclinical. For this reason, they should undergo a colonoscopy at the time of diagnosis, even if they are asymptomatic. Some authors recommend repeating the colonoscopy after a few years despite having a normal initial colonoscopy. However, other authors recommend repeating the endoscopic examination only when there are new symptoms suggestive of colitis. As patients with PSC represent a subgroup at higher risk of CRC, surveillance should be performed annually from the time of PSC diagnosis.

Dysplasia is defined as the unequivocal neoplastic alteration of the epithelium without invasion into the lamina propria. Microscopically, according to the IBD Dysplasia Morphology Study Group, dysplasia is divided into three categories: 1) negative for dysplasia, 2) indefinite for dysplasia, and 3) positive for dysplasia, which is further divided into LGD and HGD. It is traditionally recommended that any diagnosis of dysplasia be confirmed by a second pathologist. A finding of indefinite dysplasia should prompt accelerated surveillance with a repeated endoscopic/histological examination in 3 to 6 months. Management of low-grade dysplasia is a subject of debate among experts, with no clear consensus on the optimal management. Data from St. Mark’s Hospital indicate that the 5-year cumulative probability of progressing from LGD to HGD or CRC is as high as 54%. Strikingly similar results were obtained from the Mount Sinai Hospital, within a 5-year progression rate of 53% among patients with initial flat LGD. Likewise, a series of 18 LGD patients followed at the Mayo Clinic demonstrated a 33% 5-year progression rate. Despite these rather similar results from three different patient populations, some authors have reported a substantially lower rate of progression. Different studies have failed to achieve consensus on the proper management of flat LGD. Hence, available options should be discussed with each patient. A patient confirmed to have multifocal flat LGD (two or more biopsies with LGD from a single screening or surveillance examination) – as the patient presented in this report – or the presence of flat LGD in two or more examinations with at least a single focus of LGD, should be strongly encouraged to undergo prophylactic total proctocolectomy. Furthermore, even for patients with confirmed unifocal LGD (only one biopsy positive for LGD in a screening or surveillance examination) the option of undergoing prophylactic proctocolectomy should also be offered, since evidence indicates that a 5-year rate of progression to HGD or CRC in this patient group seems to be similar to that of multifocal LGD. The finding of HGD dysplasia should prompt referral for immediate total proctocolectomy attributable to the high rate of concurrent or subsequent malignancy.

### Table 1

<table>
<thead>
<tr>
<th>Authors</th>
<th>Overall risk of dysplasia and CRC in UC patients</th>
<th>CRC risk in PSC patientsa [odds ratio (95% CI)]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bergeron et al.</td>
<td>5% at 10 years 19% at 25 years</td>
<td>2.54 (1.4–4.7)</td>
</tr>
<tr>
<td>Gupta et al.</td>
<td>15.6% at 16 years 1.9% at 5 years 5.1% at 15 years 9.2% at 25 years</td>
<td>1.1 (0.2–8) 5 (1.1–23)</td>
</tr>
<tr>
<td>Jess et al.</td>
<td>5.5% at 10 years 0.6% at 10 years 5.4% at 20 years 7.5% at 30 years</td>
<td>No increased risk 9.5 (2.2–40.5)</td>
</tr>
<tr>
<td>Kekilli et al.</td>
<td>5%</td>
<td>No increased risk</td>
</tr>
<tr>
<td>Lakatos et al.</td>
<td>5.5%</td>
<td>9.5 (2.2–40.5)</td>
</tr>
<tr>
<td>Rutter et al.</td>
<td>NR</td>
<td>4 (0.7–21.8)</td>
</tr>
<tr>
<td>Shetty et al.</td>
<td>NR</td>
<td>3.15 (1.4–7.3)</td>
</tr>
<tr>
<td>Soetikno et al.</td>
<td>NR</td>
<td>4.79 (3.5–6.4)</td>
</tr>
<tr>
<td>Velayos et al.</td>
<td>NR</td>
<td>1.1 (0.5–2.3)</td>
</tr>
</tbody>
</table>

CI, confidence interval; NR, not reported.

a Comparing patients with UC and PSC vs. patients with UC without PSC.

Figure 2  Histological view of the colon wall showing signs of low-grade dysplasia: nuclear enlargement with hyperchromasia, increased mitotic figures and decreased intracellular mucin without surface maturation.

Table 1  Risk of dysplasia and colorectal cancer (CRC) among patients with ulcerative colitis (UC) and primary sclerosing cholangitis (PSC).
Although it is recommended, the adherence to endoscopic surveillance remains low, even among high-risk patients. The prevalence of surveillance among UC patients in population studies is approximately 25%, and only 40% among PSC patients.

The use of random biopsies during endoscopic surveillance is being increasingly criticized, as despite improvements in optical resolution of modern endoscopes, surveillance colonoscopy has suboptimal sensitivity for detecting flat dysplasia. Itzkowitz and Harpaz report that a typical random biopsy strategy samples less than 0.05% of the colon, highlighting the potential for sampling error associated with this procedure. Currently, methylene blue or indigo carmine chromoendoscopy has been recommended as an alternative to random biopsies in surveillance guidelines, as it is superior to random biopsies for the detection of neoplastic lesions.

3.2. Chemoprevention

The idea that CRC risk among patients with UC can be reduced by therapy with 5-ASA was first suggested by Pinczowski et al. in 1994. Since then, a large number of observational studies have been published on the topic showing conflicting results. Unfortunately, none of the observational studies published on this topic is sufficiently robust to definitively answer the question of whether 5-ASA therapy can reduce the risk of CRC in UC patients. At present, the protective effect of 5-ASA therapy on the risk of UC related CRC remains plausible, though unproved.

As with studies evaluating the question of chemoprevention of 5-ASA, there is inconsistency in the data set evaluating thiopurines. However, unlike 5-ASA, thiopurines carry significant risks that need to be weighed against their efficacy. To date, there are insufficient data to recommend azathioprine or mercaptopurine for chemoprevention of CRC in UC patients.

Several years ago, Pardi et al. published a prospective randomized placebo controlled trial evaluating the effect of UDCA in the high-risk subset of UC patients with coexisting PSC. Compared to the placebo group, patients who received UDCA (13–15 mg/kg) had a relative risk of 0.26 for developing CRC or dysplasia. In contrast with these results, a recent randomized placebo controlled trial by Eaton et al. showed that a high dose of UDCA (28–30 mg/kg) increases the risk of CRC in patients with UC and PSC. Other medications, such as corticosteroids, non steroidal anti-inflammatory drugs or folates have been explored as potential chemo preventive agents, but none of them have yielded satisfactory results.

4. Conclusions

In conclusion, we would like to emphasize that: 1) the higher risk of CRC in IBD patients with colonic involvement makes necessary the adoption of surveillance strategies with the goals of reducing morbidity and mortality associated with IBD-related CRC; 2) the presence of dysplasia should be actively investigated, mainly in patients with simultaneous UC an PSC; 3) all patients with PSC should undergo colonoscopy at the time of the diagnosis of the disease and, in those who have UC concomitantly, a colonoscopy should be annually repeated; and 4) lastly, the management of dysplasia depends on the degree and location of dysplasia.

Conflict of interest statement

Authors have nothing to declare.

References


