Abnormal mucus in cap polyposis

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Abstract

Background—Cap polyposis is a rare disease characterised by mucoid and bloody diarrhoea, with polyps covered by a cap of mucoid and fibrinopurulent exudate. The pathogenesis is not known.

Aims—To throw some light on cap polyposis pathogenesis, by examining the mucus of patients and analysing the expression of five mucin genes, MUC2, MUC3, MUC4, MUC5AC, and MUC5B.

Patient and methods—The study was performed on biopsy specimens taken from a patient with recurrent cap polyposis. Histological examination, electron microscopy, and mRNA in situ hybridisation were used.

Results—The mucus of cap polyposis differed in three respects from that of normal adult colon: abnormal ultrastructure of the mucus in the goblet cells, predominance of non-sulphated mucins, abnormal expression of the MUC4, MUC3, and MUC5AC genes.

Conclusions—Most of these abnormalities have been reported for other pathological situations, suggesting that the abnormalities observed in the mucus of this patient with cap polyposis are probably secondary phenomena rather than primary. However, the mucin abnormalities detected, which reflect deregulation of the expression of three apomucin genes, abnormal glycosylation, and abnormalities of the secretion process, are also probably involved in the clinical manifestations of cap polyposis.

(Gut 1998;42:135–138)

Keywords: cap polyposis; mucins; histochemistry; ultrastructure; in situ hybridisation

Cap polyposis is a rare disease described by Williams et al. It is characterised by mucoid and bloody diarrhoea, with polyps covered by a cap of mucoid and fibrinopurulent exudate. Very few cases have been reported. It has been postulated that abnormal colonic motility leading to mucosal prolapse may be an important cause. No specific viral or bacterial agent has been identified.

The mucus present in the dilated cystic glands and in the mucopurulent cap has not previously been analysed. We made a systematic study of the mucus of the characteristic polyps by histochemical and electron microscopic examination and looked at the expression of five mucin genes, MUC2, MUC3, MUC4, MUC5AC, and MUC5B for a review, see), using in situ hybridisation, in a patient with recurrence of cap polyposis. The results were compared with those found on samples of normal adult colon.

Patient and methods

PATIENT

A 42 year old woman complained of mucus and bloody diarrhoea with abdominal and rectal pain three days after operation for a uterine myoma in December 1991. A first sigmoidoscopy in January 1992 showed a flushed oedematous mucosa with abraded areas in the sigmoid colon but not in the rectum. Biopsy samples suggested non-specific inflammatory colitis. Small sessile inflammatory polyps were found 15–35 cm from the anal margin in following sigmoidoscopies. The patient’s symptoms worsened despite treatment with 5-aminosalicylate. A sigmoid colectomy was performed in March 1993, and the diagnosis of cap polyposis was established on the basis of the appearance of the polyps, which were formed from hypertrrophic colonic mucosa with dilated glands containing mucus and granulocytes, covered by a cap formed from mucus, fibrin, and leucocytes. The patient remained well for ten months. Recurrence of mucoid diarrhoea began in January 1994 under treatment with 5-aminosalicylate. A colonoscopy performed in March 1994 showed three small polyps located on the colorectal anastomosis (fig 1).

METHODS

The three polyps were resected and immediately cut into two halves. One half was fixed in 4% paraformaldehyde in cacodylate buffer and further processed for paraffin embedding for histological and histochemical examination and in situ hybridisation; the other one was...
Results

The mucus in cap polyposis differed from that of normal colon in its ultrastructural characteristics and in its composition, as ascertained by histochemical examination and in situ hybridisation.

Histochemically, the differences were found in the polyps and about 1 cm of the surrounding mucosa. In these areas, all the mucus-containing epithelial cells, whether in the glands or superficial epithelium or the mucoid superficial cap, stained only for non-sulphated mucins (fig 2A). The same areas were negative for sulphomucins. In normal colonic mucosa,
Both non-sulphated and sulphomucins were expressed in the goblet cells, with a predominance of sulphomucins (fig 2B). Sulphomucins were more abundant in the lower part of the glands and non-sulphated mucins were present in the upper part.

Under the electron microscope, the epithelial cells of the polyp mucosa were covered by a thick layer of mucus on their surface. This mucus layer was in close continuity with the mucus located at the apical pole of the goblet cells. However, this superficial mucus layer showed no sign of adhesion to the cytoplasmic membrane of epithelial cells, but not by adhesion to the cytoplasmic membrane of epithelial cells. The adhesive properties of this mucus might be linked to abnormalities in the packaging of mucin droplets, since, in this case of cap polyposis mucus, droplets coalesced and were extruded in conglomerated masses. This phenomenon may also be related to the abnormal biochemical composition of this mucus and/or altered structure of the mucus. This was not found in biopsy specimens of normal colonic mucosa. However, similar packaging abnormalities have been found in familial polyposis,

Discussion

In the present study of the mucus in a case of cap polyposis, we found differences in the histochemistry, ultrastructure, and mucin gene expression when compared with normal colonic mucosa.

Histochemical analysis of the mucus in cap polyposis showed exclusive expression of non-sulphated mucins in the characteristic polyps and in the adjacent mucosa, while both non-sulphated and sulphated mucins were expressed in normal colonic mucosa. A similar predominance of non-sulphated mucins has been reported as characteristic of “transitional mucosa” associated with colorectal adenocarcinoma by Filipe.9–11 However, further studies also found a predominance of non-sulphated mucins in other types of colorectal carcinomas,12 as well as in familial polypsis,13 colorectal adenomas,11 and ulcerative colitis with dysplastic changes.14 15 It would thus appear that a predominance of non-sulphated mucins is found in areas of colonic mucosa associated with a wide range of pathological situations.

Ultrastructurally, the characteristic cap found on the polyps in cap polyposis was composed of a thick layer of mucus. The adhesion of this mucus layer to the underlying epithelium was mediated by a close continuity with the mucus of goblet cells, but not by adhesion to the cytoplasmic membrane of epithelial cells. The adhesive properties of this mucous might be linked to abnormalities in the packaging of mucin droplets, since, in this case of cap polyposis mucus, droplets coalesced and were extruded in conglomerated masses. This phenomenon may also be related to the abnormal biochemical composition of this mucous and/or altered structure of the mucus. This was not found in biopsy specimens of normal colonic mucosa.

Table 1  Expression of the mucin genes in cap polyposis and normal colon

<table>
<thead>
<tr>
<th>Probes</th>
<th>Tissues</th>
<th>MUC2</th>
<th>MUC3</th>
<th>MUC4</th>
<th>MUC5AC</th>
<th>MUC5B</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cap polyposis</td>
<td>S:+++*</td>
<td>S:+</td>
<td>S:++</td>
<td>S:+ †</td>
<td>S:−</td>
</tr>
<tr>
<td></td>
<td>C:+++</td>
<td>C:−</td>
<td>C:++</td>
<td>C:+/++</td>
<td>C:−</td>
<td>C:−</td>
</tr>
<tr>
<td>Normal colon (n = 8)</td>
<td>S:+++</td>
<td>S:++/+++</td>
<td>S:+/++</td>
<td>S:−</td>
<td>S:−</td>
<td></td>
</tr>
<tr>
<td></td>
<td>C:+++</td>
<td>C:−</td>
<td>C:++</td>
<td>C:+/++</td>
<td>C:−</td>
<td>C:−</td>
</tr>
</tbody>
</table>

S, surface epithelium; C, crypt epithelium.

*Labelling intensity: −, absent; +, weak; ++, moderate; ++++, strong.

†Focal labelling.
been reported in the ultrastructural study of six cases of "transitional mucosa" adjacent to colonic carcinomas. The expression of the five mucin genes studied by in situ hybridisation also differed in this case of cap polyposis from normal colonic mucosa. MUC4 was expressed at a high level in the polyps in cap polyposis, whereas it is expressed only at a moderate level in normal mucosa. So far, the only known pathological condition to show such an overexpression of MUC4 is ductal pancreatic adenocarcinoma. After MUC2, MUC3 is the predominant mucin gene expressed in normal colon as well as in normal small intestine. In this case of cap polyposis, MUC3 was clearly poorly expressed compared with the situation in normal colon. The MUC3 gene has been observed to be deregulated in other pathological situations. In colon cancers, a discrepancy is observed, since MUC2 and MUC3 are expressed at a high level in colloid cancers and at a low level in other types of colon cancer. MUC3 has been reported to be expressed at a very low level in ulcerative colitis, as in this case of cap polyposis. Interestingly, a case has been recently reported of a patient with cap polyposis who had been treated for ulcerative colitis for seven years. The data, taken together, suggest that a common mechanism might occur in the pathogenesis of cap polyposis and ulcerative colitis.

MUC5AC is abnormally expressed in a few cells in this case of cap polyposis. It is normally expressed in both bronchial and gastric superficial epithelium, but not in normal intestinal mucosa. We recently reported aberrant expression of MUC5AC in rectosigmoid villous adenomas. Moreover, we showed that MUC5AC mRNA expression decreased as the grade of dysplasia advanced, suggesting that MUC5AC gene expression is an early event in the multistep process of colonic tumorigenesis. The finding of MUC5AC in fetal intestine at an early stage of development (unpublished observation) reinforced our suggestion that the expression of MUC5AC is linked to the degree of intestinal epithelial cell differentiation. The expression of MUC5AC in a few cells in this case of cap polyposis might reflect an abnormal differentiation process.

Thus cap polyposis secretes mucus in abundance, but this mucus is qualitatively abnormal. The ultrastructural features of the mucus in the goblet cells is also altered. Mucus in cap polyps differs from that of normal colon by quantitative disequilibrium between the expressed apomucins, by a large predominance of non-sulphated mucins and a large decrease in sulphated mucins. Unfortunately, so far nothing is known about the relationship between glycosylation, as studied by histochemistry, and the different apomucins. The most likely explanation for the lack of sulphomucins in cap polyps is a reduction in sulphotransferase activity, leading to dramatic changes in the carbohydrate chains and charge of mucin gene products. The abundant secreted mucus may be a direct consequence of the overexpression of MUC4 and MUC5AC.

In conclusion, we have shown that the mucus in this case of cap polyposis differs from that of normal colon. Our data failed to show whether there is direct involvement of mucins in the initiation steps of the pathogenesis of cap polyposis. Non-typical and specific changes in mucins, as observed by histochemical and electron microscopic examination and in situ hybridisation, were detected. Thus we suggest that these alterations are probably a secondary rather than a primary phenomenon. Nevertheless, it is noteworthy that most of these changes have been described in preneoplastic colonic mucosa—for example, transitional mucosa, adenomas. Whatever the mechanism involved, abnormalities detected in the mucus composition and ultrastructure in cap polyposis are likely to have important consequences for mucosal protection and to be involved in the clinical manifestations of cap polyposis.

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