Pulmonary and hematological alterations in idiopathic ulcerative colitis

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Background: Patients with idiopathic ulcerative colitis (IUC) may suffer from one or more extraintestinal manifestations. We decided to prospectively study the prevalence of extraintestinal manifestations among patients with IUC, with special reference to pulmonary and hematological alterations. Methods: Fifty-one consecutive patients with IUC attending the gastroenterology services of our tertiary-care referral center were evaluated prospectively. A detailed clinical evaluation of the musculoskeletal system, eye and skin, X-ray examination of the sacroiliac joints and chest, liver function tests, coagulation profile, hemogram, pulmonary function tests (PFT) and diffusion capacity for carbon monoxide (DLCO) were done in all patients. ERCP, liver biopsy and high-resolution computed tomography (HRCT) of the chest were performed whenever indicated. Results: Nearly half (24/51; 47%) the patients had one or more extraintestinal manifestations; these included pulmonary function abnormalities (14 patients; 27%), sacroiliitis (8; 16%), arthritis (5; 10%), ocular complications (4; 8%), and pyoderma gangrenosum and Budd-Chiari syndrome (one patient each). Of the 14 (27%) patients who had abnormal pulmonary function, isolated PFT abnormalities were seen in 8 (restrictive pattern in 7, obstructive pattern in 1), decreased DLCO in four, and both the above in two. All patients with decreased DLCO (n=6) were asymptomatic and had normal chest X-ray and HRCT chest. Thirteen (25%) patients had thrombocytosis, 19 (37%) increased fibrinogen level, and one patient had decreased antithrombin levels. Disease activity had significant association with decreased DLCO (p=0.008), increased platelet count (p<0.0001), increased fibrinogen level (p=0.016), low antithrombin levels (p=0.046) and arthritis (p=0.002). Conclusion: Extraintestinal manifestations of IUC were seen in 47% of patients. Asymptomatic pulmonary interstitial involvement was seen in 12%, more often among patients with active disease. [Indian J Gastroenterol 2003;22:176-179]

Key words: Coagulation abnormalities, extraintestinal manifestations, pulmonary function test

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Table 2: Disease activity and laboratory parameters

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Normal values</th>
<th>Disease activity</th>
<th>p value*</th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td>Active (n=12)</td>
<td>Remission (n=39)</td>
</tr>
<tr>
<td>ESR (mm in 1st h)</td>
<td>&lt;20</td>
<td>18 (2-80)</td>
<td>18 (2-52)</td>
</tr>
<tr>
<td>Platelet count (x 10^9/µL)</td>
<td>1.5-4.0</td>
<td>4.2 (2.0-5.4)</td>
<td>2.4 (1.2-5.0)</td>
</tr>
<tr>
<td>Fibrinogen (mg/dL)</td>
<td>200-400</td>
<td>480 (200-600)</td>
<td>360 (200-600)</td>
</tr>
<tr>
<td>Antithrombin (% of healthy controls)</td>
<td>70-125</td>
<td>104 (76-188)</td>
<td>85 (60-143)</td>
</tr>
</tbody>
</table>

All values as median (range). *Mann-Whitney U test

Table 1: Prevalence of extraintestinal manifestations in idiopathic ulcerative colitis (n=51)

<table>
<thead>
<tr>
<th>Manifestation</th>
<th>No. (%) of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary function abnormalities</td>
<td>14 (27)</td>
</tr>
<tr>
<td>Thrombocytosis</td>
<td>13 (25)</td>
</tr>
<tr>
<td>Hyperfibrinogenemia</td>
<td>19 (37)</td>
</tr>
<tr>
<td>Antithrombin deficiency</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Bilateral iridocyclitis</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Episcleritis</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Pyoderma gangrenosum</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Bilateral sacrolitis</td>
<td>6 (12)</td>
</tr>
<tr>
<td>Unilateral sacrolitis</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Periarterial arthritis</td>
<td>5 (10)</td>
</tr>
</tbody>
</table>

Obstructive defect, 4 (8%) had decreased DLCO, and 2 (4%) had a combination of restrictive defect and decreased DLCO. All patients with abnormal DLCO (range 65.8% to 78.8%; normal >80%) had normal HRCT chest. Two patients (4%) had history of smoking; both had normal PFT and DLCO. Patients with active disease more often had decreased DLCO (4/12; 33%) than those in remission (2/39; 5%; p=0.008).

Thirteen patients (25%) had thrombocytosis (platelet count >4 x 10^9/µL) and 19 (37%) had increased fibrinogen levels (normal 200-400 mg/dL). One patient had low AT level of 69% (normal 70%-125% of that in healthy individuals). PT, PTT and APTT values were within the normal range in all patients. Patients with active disease had higher platelet counts, higher fibrinogen level and lower AT levels.

Eight (16%) patients had radiological evidence (radiological grade III in 4 patients, grade II in 3, and grade I in one) of sacroiliitis, of whom 6 had low backache. Disease activity was not related to sacroiliitis. Five patients had peripheral arthritis; disease activity was positively related to arthritis (p=0.002). One (2%) patient with active severe pancolitis of 6 years' duration had abnormal liver function with ascites. She had occlusion of the right and the middle hepatic vein and narrowing of the inferior vena cava on magnetic resonance venography, and had low AT level. Liver biopsy was consistent with Budd-Chiari syndrome and ERCP showed no evidence of primary sclerosing cholangitis.

Discussion

In our study, 24 (47%) patients had one or more extraintestinal manifestations. These included sacroiliitis, peripheral arthritis, ocular compli- cations, pyoderma gangrenosum, hepatic venous obstruction, and pulmonary function abnormalities; of these, pulmonary function abnormality was the commonest manifestation.

It was previously believed that extraintestinal manifestations were less common (4%-15%) in Indian patients. However, Kedhkar et al reported extraintestinal manifestations in 35% of their 150 patients. In comparison, reports from Western countries have found a frequency of 25% to 36%. Our results suggest that extraintestinal manifestations are as frequent in Indian patients as in their Western counterparts.
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Six (12%) of our patients had abnormal DLCO; all of them were asymptomatic and had normal chest X-ray and HRCT chest. This suggests a latent interstitial pulmonary involvement, which has been reported by Marvisi et al.12 Eade et al.13 reported asymptomatic decrease in DLCO in patients with IUC. Sharma et al.14 from India reported a reduction in forced expiratory volume (FEV,) and maximum expiratory volume (MEFR) and maximum ventilatory volume (MVV), suggesting sub-clinical restrictive-obstructive ventilatory involvement; however, these reductions were not statistically significant. Higenbottom et al.15 reported 10 patients with IUC and unexplained cough, including four with restrictive pattern and three with minor obstruction on pulmonary function testing.

In our study, there was significant association between decreased DLCO and disease activity, suggesting that pulmonary inflammation commonly accompanies inflammation of the bowel. Tzanakis et al.16 also found significantly lower DLCO in the absence of pulmonary symptoms during exacerbations of bowel disease. The pathogenesis of inflammatory bowel disease (IBD)-related airway disease is unknown. Since both the gastrointestinal tract and bronchial tree originate from the primitive gut, this association may represent inflammation at two sites with common embryological origins.4,17 This hypothesis is supported by the fact that patients with IUC develop sclerosing cholangitis; the biliary tract is also derived from the primitive gut. Furthermore, the pathologic pattern of disease in IBD-associated airway disease has been reported to be similar to that in sclerosing cholangitis.18 Another hypothesis suggests that many of the extraintestinal manifestations of IBD, including lung disease, are secondary to circulating inflammatory mediators and reactive oxygen species released by inflamed bowel mucosa.19

Patients with active IUC had higher fibrinogen levels than those in remission. In one study, coagulation parameters, such as fibrinogen, fibrinogen-degradation products and antithrombin level were changed in patients during active disease.20 The results were comparable to studies demonstrating activation of blood coagulation and activated fibrinolysis in patients with IUC.21 Fibrinogen is an acute-phase protein, levels of which increase with inflammation. Also a significant relationship between disease activity and increased platelet count was observed; a similar observation was made in a study by Linskens et al.22

Several authors have demonstrated low plasma levels of antithrombin.23,24 In our study, AT levels were significantly lower in patients with active disease than in those in remission. However, AT levels of both these groups were within normal limit. In a previous study, no coagulation abnormalities were found in patients with chronic stable disease.25 Other investigators, however, have found low plasma levels of AT in patients with active IBD.26 Previously, decreased AT levels have been interpreted as sustained consumption secondary to thrombin generation, with reduction in AT levels being the greatest in patients with active disease, thus indicating more intensive activation of coagulation pathway.24 It is known that reduced AT plasma levels increase the risk of thromboembolic complications.26

Radiological evidence of sacroiliitis was found in 16% of our patients, which compares well with a reported incidence of 12%-15%.27 Peripheral arthritis was seen in 10% of our patients, which has been reported in 10%-15% of patients.28 Exacerbation of bowel disease and flares of peripheral arthritis tend to coincide in IUC, as in our study.27 We encountered ocular complications in 4 (8%) patients, comparable with the 4%-7.5% reported from the West.23 and 8% reported by Kochhar et al.2 One (2%) patient had pyoderma gangrenosum in our study, which is rare and reported in 1%-2% of patients.28

One patient in our study had abnormal liver function tests and was diagnosed as having Budd-Chiari syndrome after investigation. Budd-Chiari syndrome has been reported previously in association with IUC.29 We did not encounter any patient with primary sclerosing cholangitis, which is reported in 2%-8% of cases from Western countries.30 This complication has only rarely been reported from India and its exact incidence is unknown.31 Kochhar et al.27 noted two cases of primary sclerosing cholangitis in their 150 cases.

In conclusion, extraintestinal manifestations of ulcerative colitis are frequent in Indian patients. Flares of peripheral arthritis, unlike sacroiliitis, tend to coincide with exacerbation of bowel disease. Latent interstitial pulmonary involvement was seen during the course of IUC (especially active disease), despite absence of symptoms or radiological alterations. There appears to be a mild hypercoagulable state in those with active disease compared to those in remission.

References
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Received May 12, 2003. Received in final revised form August 11, 2003. Accepted August 14, 2003