Hodgkin’s Disease with Nephrotic Syndrome as a Complication of Ulcerative Colitis: Case Report

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We describe a case of a 32-year-old patient with ulcerative colitis complicated by Hodgkin’s disease who presented with nephrotic syndrome. The patient had suffered from relapsing ulcerative colitis for 6 years before he developed Hodgkin’s lymphoma. He was treated for Hodgkin’s disease with 9 cycles of combined chemotherapy (COPP/ABV) and achieved the stable remission of lymphoma, nephrotic syndrome, and ulcerative colitis. To the best of our knowledge, this is the first report on ulcerative colitis associated with Hodgkin’s disease and nephrotic syndrome.

Key words: colitis, ulcerative; Hodgkin’s disease; lymphoma; nephrotic syndrome

In contrast to the carcinoma of the colon, lymphomas rarely complicate inflammatory bowel disease (1). Type of lymphoma found in such cases is usually non-Hodgkin lymphoma developing at extraintestinal sites (1-5). Hodgkin’s disease, if found, accompanies Crohn’s disease (6-9). Gastrointestinal lymphomas developing in Crohn’s disease comprise a heterogeneous group of tumors of both B and T cell lineages. On the other hand, gastrointestinal lymphomas complicating ulcerative colitis have all been polymorphic B-cell lymphomas (9).

Primary Hodgkin’s disease of the gastrointestinal tract is rare and constitutes less than 0.5% of all cases of Hodgkin’s disease (10). These patients usually present with one or more of the following symptoms: lymphadenopathy, fever, weight loss, splenomegaly, or hepatomegaly. Some patients present with more unusual symptoms, such as pruritus in 10-15% of the cases, hemolytic anemia in 2-3%, alcohol-related pain in 1-2%, cutaneous manifestations in 1-2%, nephrotic syndrome in 0.4%, and finally, idiopathic thrombocytopenia purpura, osteolytic changes, and central nervous system involvement in less than 1% of patients (11).

We report a case of Hodgkin’s disease that developed as a complication of ulcerative colitis in a patient presenting with a nephrotic syndrome.

Case Report

A 32-year-old man was referred to our Department of Medicine in January 1998 due to lymphadenopathy and heavy proteinuria. He had been diagnosed to suffer from ulcerative colitis in February 1991 and treated with sulphasalazine. He had had three relapses of the disease, with more than six bloody stools per day. In September 1997, he developed febrile catarrh with enlarged cervical lymph nodes. Lymphadenopathy persisted despite antibiotic treatment. In December 1997, he was found to have proteinuria of 16.5 g/24 h (Table 1).

Table 1. Laboratory data of the patient with ulcerative colitis complicated by Hodgkin’s disease on admission to Zagreb University Hospital Center and follow-up examinations

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<tbody>
<tr>
<td></td>
<td>Erythrocyte sedimentation rate (0-12 mm/h)</td>
<td>90</td>
<td>12</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>Copper (12.0-24.6 mmol/L)</td>
<td>32</td>
<td>22</td>
<td>18</td>
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<tr>
<td></td>
<td>Haptoglobin (0.6-1.6 g/L)</td>
<td>3.21</td>
<td>1.65</td>
<td>1.12</td>
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<tr>
<td></td>
<td>Lactate dehydrogenase (150-240 U/L)</td>
<td>288</td>
<td>381</td>
<td>254</td>
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<tr>
<td></td>
<td>Alkaline phosphatase (30-50 U/L)</td>
<td>165</td>
<td>59</td>
<td>82</td>
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<tr>
<td></td>
<td>Albumins (39-48 g/L)</td>
<td>15.3</td>
<td>30.6</td>
<td>36.2</td>
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<tr>
<td></td>
<td>C-reactive protein (0-5 mg/L)</td>
<td>100</td>
<td>8</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Proteinuria (0-0.15 g/24 h)</td>
<td>16.5</td>
<td>1</td>
<td>0</td>
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</table>

On admission to the Division of Nephrology, physical examination revealed cervical and axillary lymphadenopathy. Lymph nodes were up to 2x2 cm in size. Liver and spleen were not enlarged. The erythrocyte sedimentation rate was 90 mm/h. Concentration of lactate dehydrogenase was normal (288 U/L), whereas the concentrations of alkaline phosphatase (165 U/L) and C-reactive protein (100 mg/L) were increased (Table 1). Kidney biopsy revealed focal segmental glomerulosclerosis, with thickened capillary basement membranes and dilated glomerular capillaries in affected glomeruli (Fig. 1).

Since cytology examination of cervical lymph nodes was positive for Hodgkin disease, the patient was transferred to the Division of Hematology for further diagnosis and treatment. Computed tomography...
(CT) of the chest revealed pleural effusion but no signs of mediastinal lymphadenopathy. Histological analysis of the biopsy sample taken during rectoscopy showed the signs of ulcerative colitis, with infiltration of the mucosa with plasma cells, lymphocytes, and eosinophils, and low-grade dysplasia of cryptal epithelium (Fig. 2).

The histological analysis of extirpated cervical lymph node proved the diagnosis of Hodgkin’s disease of the mixed cellularity type (Fig. 3).

The patient was treated with 9 cycles of hybrid chemotherapy COPP/ABV (cyclophosphamide, vincristine, procarbazine, prednisone/doxorubicine, bleomycine, vinblastine). After the therapy, he achieved complete and stable remission of Hodgkin’s disease, ulcerative colitis, and nephrotic syndrome. In July 2002, he was still in the complete remission.

Discussion

Malignant lymphomas rarely complicate inflammatory bowel diseases. However, there is an increased concern among physicians that frequent use of immunomodulators (infliximab, azathioprine or mercaptopurine) for the treatment of inflammatory bowel diseases may result in increased incidence of lymphomas in such patients. Thus far, there are no data available regarding the possible role of sulphasalazine in the development of lymphomas in patients with ulcerative colitis. Several cases of pseudolymphomatous skin syndrome and angioimmunoblastic lymphadenopathy have been reported in patients treated with sulphasalazine (12,13). However, the possible role of sulphasalazine in the induction of lymphoma has to be clarified, because it might suppress growth of DoHH2 non-Hodgkin’s lymphoma cell line by inhibiting the x(c)-cystine transporter (14).

Studies on incidence of lymphomas in patients with inflammatory bowel disease report conflicting results. A population-based cohort study showed that the absolute risk of malignant lymphomas in such patients was low (0.01% person/year) and similar to the risk in general population (15). Another study revealed that an overall cancer incidence in patients with inflammatory bowel disease was not increased, except for the incidence of Hodgkin’s disease, which was significantly increased in patients with ulcerative colitis (16). Several cases of lymphoma were reported in patients with Crohn’s disease during treatment.
with anti-TNF-alpha antibodies (17,18). Others found an increased risk of non-Hodgkin’s lymphoma and leukemias in patients with inflammatory bowel diseases (19). Recent study demonstrated that patients treated with azathioprine or 6-mercaptopurine had slightly increased risk for the development of Epstein-Barr-positive vs Epstein-Barr negative lymphomas (20). However, there has been no major conclusion since studies are performed on a small number of patients, with short follow-up periods.

Nephrotic changes as part of the paraneoplastic syndrome are rare in lymphoid malignancies. They are mostly observed in Hodgkin’s disease, where they complicate the course of disease in 1 out of 400 patients. The most frequent lesion is lipoid nephrosis (minimal change glomerulonephritis) (21). The membranous nephropathy has been recorded in 10% of patients with Hodgkin’s disease and nephrotic syndrome (21). Some speculate that an abnormality in T cell function leads to minimal change nephropathy in Hodgkin’s disease (21), whereas others suggest involvement of autologous non-tumor antigens, fetal antigen expression, immune complex deposition, viral antigens, or tumor antigens (22). Immunodeficiency-associated lymphoproliferative disorders tend to occur in extranodal sites, particularly in the central nervous system and gastrointestinal tract. They behave as aggressive diseases and progress rapidly. Association with the Epstein-Barr virus has been established, and it seems that in the presence of disturbed T cell function Epstein-Barr virus may induce prolonged proliferation and transformation of B-cells (23).

In case of nephrotic syndrome which does not react to steroid therapy physicians should suspect accompanying Hodgkin’s disease. Finally, any dense lymphocytic infiltrate observed in biopsy specimens from a patient with inflammatory bowel diseases should be thoroughly analyzed to exclude malignant lymphoma.

References