Extraintestinal Manifestations of Inflammatory Bowel Disease. Hematological, Vascular and Coagulation, Renal, Pulmonary

A. Ilias, Th. Maris

SUMMARY

Extraintestinal manifestations of inflammatory bowel disease (IBD) have been joined with almost every system. Over 100 extraintestinal manifestations have been described. Many of these problems are common in Crohn’s disease and ulcerative colitis but they are more prevalent in Crohn’s disease than in ulcerative colitis.

The incidence of extraintestinal manifestations has been estimated from 20% to 40%. It has been shown that if a patient presents with one manifestation, the possibility to develop one more is greater than that expected by chance. This phenomenon suggests a common pathophysiological mechanism of all these conditions. The exact pathophysiological mechanism of extraintestinal manifestations is not known, but generally they could be chronic immune reactions to circulating autoantibodies.

For educational reasons, extraintestinal manifestations may be divided into two groups, manifestations associated with active bowel disease (either small or large) and problems that occur independently of the presence of inflammation.

Hematological complications

Anaemia, is generally defined as a hemoglobin value <10 g/Dl and severe anaemia as Hg<10 g/dL. The prevalence of anemia in patients with inflammatory bowel disease ranges from 10% to 70%. The anaemia results in many chronic symptoms, especially fatigue. Even mild to moderate anaemia has significant symptomatology and significant impact on quality of life.

The main causes of anaemia are iron deficiency and anaemia of chronic disease. Others reasons include B12 deficiency, haemolytic anaemia and allergic drug reaction.1

In normal subjects, daily iron loss amounts reach 1–2 mg. This loss requires a similar total amount to be taken from diet. Anaemia of iron deficiency is mostly due to excessive loss of iron through intestinal bleeding without balancing with an adequate intake with food. It has been shown that even in non active disease the loss of iron is important.2

Assessment of the iron status is made by combination of serum iron concentrations and serum transferrin and ferritin concentrations.

The anaemia of iron deficiency is generally treated with oral iron supplements. Iron supplementation may probably lead to a worsening of inflammatory activity and deterioration of the disease through the production of reactive oxygen species.3,4

Many patients are intolerant of oral iron therapy and others do not respond to this way of administration. Correction of anaemia through the administration of intravenous iron saccharate and supplemental erythropoietin has been shown to improve the hematologic profile as well the quality of life of these patients. Future studies are needed to find out which exact treatment has the most beneficial effect.5,6

Anaemia of chronic disease results from decreased erythropoiesis, secondary to increased levels of proinflammatory cytokines (IL-1, IL-6, TNF), reactive oxygen metabolites and nitric oxide. The best treatment for anaemia of chronic disease is the treatment of the underlying disease and the reverse of inflammation. The adminis-
tration of erythropoietin has been shown to improve the hematologic picture in many studies.7

Coagulation and Vascular Complications

A prothrombotic status has been shown in both ulcerative colitis and Crohn’s disease. The hypercoagulable state may result from many possible reasons. Etiological factors include dehydration, immobility, thrombocytosis, increased levels of fibrinogen, factor V mutation, factor VIII, antithrombin III deficiency and free protein S deficiency. The prothrombotic tendency is generally associated to active bowel inflammation but a prothrombotic status also remains in non active disease.

The V Leiden mutation was found in patients with ulcerative colitis and thromboembolic episodes. No increase of this mutation was found in patients with ulcerative colitis without thrombotic complications.

Methylenetetrahydrofolate reductase deficiency is more prevalent in patients with IBD than the general population. This finding in combination with folate and vitamin B12 deficiency, may result to hyperhomocysteinemia, which is a well known prothrombotic state.8,9,10

Patients may present with venous deep vein thromboses thromboembolism or, less commonly, arterial thrombosis. Pulmonary emboli are a rare, dangerous and probably fatal complication of IBD and especially of ulcerative colitis.

The cause of the thromboembolism is multifactorial. Etiological factors include the above stated prothrombotic status plus immobility, and malnutrition. Systemic vasculitis may contribute to thrombosis. In more than 50% of patients who present with a thrombotic episode however, no predisposing factor can be detected.

Patients with these complications should be treated with anticoagulants, initially heparin or low molecular weight heparin, followed by warfarin. Anticoagulation treatment is generally effective with no complication by intestinal bleeding.11,12,13 In more severe cases colectomy may be considered.

Renal Manifestations

Some of the renal manifestations are only the side effects of 5 ASA therapy. Among real complications nephrolithiasis tops the list.

In patients with perforating Crohn’s disease, fissures have been described stretching on the bladder and other anatomic structures.

Uric acid and oxalate stones are common in patients with Crohn’s disease. The pathophysiology of uric acid stone formation is volume depletion and a hypermetabolic state of these patients.

The aetiology of oxalate stone is more complex. Malabsorption of fat from intestinal resection or extensive small bowel disease results in luminal calcium binding of free fatty acids, thereby decreasing calcium available to bind and clear oxalate. Increased oxalate is absorbed, resulting in hyperoxaluria and calcium oxalate stone formation. Moreover the production of stones is also induced by the intestinal loss of crystallisation inhibitors (citrate, magnesium).

More rare renal complications of IBD include membranous glomerulonephritis, nephritic syndrome and renal amyloidosis.14,15

Pulmonary Manifestations of Inflammatory Bowel Disease

Pulmonary Manifestations of IBD are rare compared to manifestations of other systems. Although some authors suggest that these cases are only coincidental findings, it seems that some of them are really extraintestinal complications of IBD. However in any case the possibility of drug-induced pulmonary disease must be ruled out e.g a side effect of such a drug (mesalamine, methotrexate).

Pulmonary disease in IBD ranges from life threatening interstitial fibrosis presenting with severe symptoms to subclinical or asymptomatic pulmonary function abnormalities, only detected by specific pulmonary function tests. The most common pulmonary manifestations are pneumonitis, pleuritis and chronic bronchitis. Chest X-ray, spirometry and blood gas analysis belong to the basic examinations of IBD patients. More sophistic pulmonary investigations are reserved for patients with abnormal spirometry, and persistent symptomatology from the respiratory system.

Bronchodilators, antibiotics and in severe cases corticoids are the treatment of choice.16,17,18

REFERENCES

3. Oldenburg B, Koningsberger JC, Berge Henegouwen GP,