he patient was admitted to the hospital for further treatment with azathioprine. During a six months period the patient received a total of five doses of 5mg/kg of infliximab intravenously, under concomitant azathioprine therapy. Nevertheless, Crohn’s disease remained as well (2004). From 2005 to May 2008 he was on regular dilatation due to intestinal obstruction (2000) and colectomy, long period of time (from 1998 until 2005) and further required therapy was introduced due to symptoms evolution. However, initially treated with steroids and one year later azathioprine taken at colonoscopy, is reported. At diagnosis, the patient was Crohn’s disease, by radiography and histology of mucosal biopsy inflammation process.

**Abstract**

Crohn’s disease is a type of inflammatory bowel disease implying the immune system. The disease by itself might evolve in deteriorating symptoms that are overwhelming for the patient, such as generalized enteritis, which cannot be easily put into remission. In addition, a correlation between Crohn’s disease and lymphoma presentation, especially Hepatosplenic-T cell lymphoma, has been reported in young males. Symptoms of the disease can be controlled with mild medication such as aminosalicylates or corticosteroids while persisting symptoms or recurrent episodes can be furtherly managed with immune modulators such as azathioprine, methotrexate or anti-TNF monoclonal antibodies like infliximab. A case of a patient with Crohn’s disease, resistant to conventional immunosuppressive therapies, including azathioprine, presenting lymphoma while on anti-TNF therapy is reported.

**Keywords:** Crohn’s disease; Lymphoma; Immunomodulators; Immunosuppression; Hepatosplenic T-lymphoma

**Introduction**

Hepatosplenic T-cell Lymphoma (HSTCL) is an extranodal and systematic neoplasm derived from cytotoxic T-cells usually of γδ T-cell receptor type. HSTCL is a rare lymphoma (<1% of all non Hodgkin’s lymphomas-NHL) which origin has been correlated with chronic immune suppression. Patients with Crohn’s disease, a condition involving autoimmunity, present with an increased risk of lymphoma [1]. Furthermore, rare cases of Hepatosplenic T-cell lymphomas have been reported in adolescent and young adult patients with Crohn’s disease treated with infliximab [2]. Infliximab is a chimeric IgG monoclonal antibody known as a biological response modifier directed against tumor necrosis factor-α (TNF-α), a cytokine which plays an important role in the inflammaton process.

The case of a 33-years old man diagnosed in 1997 with Crohn’s disease, by radiography and histology of mucosal biopsy taken at colonoscopy, is reported. At diagnosis, the patient was initially treated with steroids and one year later azathioprine therapy was introduced due to symptoms evolution. However, the patient had poor compliance to the therapeutic protocol for a long period of time (from 1998 until 2005) and further required dilatation due to intestinal obstruction (2000) and colectomy, as well (2004). From 2005 to May 2008 he was on regular azathioprine therapy. Nevertheless, Crohn’s disease remained active despite therapy, and infliximab was initiated in May 2008. During a six months period the patient received a total of five doses of 5mg/kg of infliximab intravenously, under concomitant treatment with azathioprine.

After the 5th infusion of infliximab (November 2008) he presented with pyrexia, mainly during afternoon, and fatigue. The patient was admitted to the hospital for further investigation. On physical examination, no specific findings other than hepatosplenomegaly were found. Full blood examination did not reveal any abnormal finding. Biochemical analysis revealed abnormal liver functions: aspartate aminotransferase: 522 IU/L (normal values: 5-37IU/L), alanine aminotransferase: 690 IU/L (5-40IU/L), γ-glutamyl transferase: 201 IU/L (7-49IU/L), alkaline phosphatase: 453 IU/L (35-129IU/L), lactate dehydrogenase: 1615 IU/L (<255IU/L). Regarding coagulation parameters, prothrombin time was 14.5 sec (normal range 11-14sec), International Normalizing Ratio: 1.15, activated Partial Thromboplastin Time: 34.4 sec (normal range: 20-40 sec). Inflammatory markers such as C reactive protein levels or erythrocyte sedimentation rate were within the normal range. No pathogens were found in blood cultures and active viral infection was not demonstrated. Abdominal computed tomography confirmed splenomegaly and hepatomegaly (15cm and 19cm, respectively). No pathologic enlargement of lymph nodes was detected.

Microscopic examination of the liver core biopsy revealed T-Hepatosplenic Lymphoma which was further confirmed with bone marrow biopsy. Specifically, bone marrow biopsy showed infiltration of the marrow with lymphocytes having immunohistochemical characteristics: CD3 (+), CD (2) +, CD5 (+), CD4 (-), CD8 (+). The percentage of these pathological lymphocytes was 40%. Nolastic changes were noted. Immunophenotypic analysis of the marrow sample also showed that the amount of CD3 (+), TCR γδ was about 70% of the pathological lymphocytes, a finding consistent with Hepatosplenic T-cell lymphoma (HTCL). Patient’s karyotype analysis was normal (46XY). Due to progressive disease despite initial chemotherapy (cyclophosphamide, Adriamycin, vincristine, prednisolone), a salvage regimen was initiated and the patient underwent an allogenic transplantation from a matched unrelated donor but he finally died because of...
complications related to transplantation.

We describe the case of a patient with Crohn’s disease who had been treated with immunodulatory drug, such as infliximab. Infliximab has shown great efficacy in the treatment of moderate to severe Crohn’s disease by binding and blocking the effects of TNF-alpha, a chemokine messenger involved in the autoimmune process [3]. TNF-alpha enhances inflammatory cytokines, such as interleukins and facilitates leukocyte migration in tissues. Additionally, it is thought to provide protection against cancer and infections, mainly via influencing apoptosis and cell survival [4,5]. Taking the above mechanisms of action of TNF-alpha into consideration, several reports in the literature have correlated the block of TNF-alpha through anti-TNF biological agents, with cancers and lymphomas, especially hepatosplenic lymphoma, in patients with Crohn’s disease. Actually, the risk of cancer development is increased three-fold in patients taking anti-TNF therapy compared to the control group [6-8]. Most of these cases have occurred in patients on concomitant treatment with azathioprine or 6-mercaptopurine [7]. On the other hand HSTCL occurring in Crohn’s disease patients receiving mu tagens such as azathioprine or 6-mercaptopurine without taking infliximab is also reported. This fact indicates that causal association between infliximab and HSTCL has not been clearly established [9-12].

Additionally, the relative risk of lymphomas and other cancers in patients with Crohn’s disease is increased [1]. The patients with Crohn’s disease and other autoimmune diseases have a predisposition of developing lymphomas due to their underlying basic intrinsic disease [13-15]. Lymphoma presentation can occur from weeks to months after infliximab administration, as reported in our patient [16].

Conclusion

All the above indicates that the issue of association of Crohn’s disease, especially in patients taking various immunosuppressive therapies other than biological agents and lymphoma presentation while on infliximab distribution in patients with moderate or severe disease is complicated. Immunity of these patients is altered due to the combination of all the reasons referred. Nevertheless, HSTCL which is a particular type of NHL and the use of infliximab in patients with Crohn’s disease is more closely correlated [15-19]. Anti-TNF therapy is indicated in resistant patients, so as to enhance remission of symptoms and therefore may improve their quality of life. So, more surveillance may be warranted by clinicians in order to reach safe conclusions and keep these innovative drugs, such as biological therapies in the therapeutic armamentarium while avoiding aggressive deteriorations like hepatosplenic lymphoma presentation, mainly occurring in young patients.

References
