

Childhood non-Hodgkin's lymphoma arising as a complication early in the course of Crohn's disease

Ayşen Aydoğan¹, Funda Çorapçioğlu¹, E. Levent Elemen², Selim Öncel¹, Yeşim Gürbüz³, Melih Tugay²

Departments of ¹Pediatrics, ²Pediatric Surgery and ³Pathology, Kocaeli University Faculty of Medicine, Kocaeli, Turkey

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The neoplastic change in patients with Crohn's disease is usually seen in the form of adenocarcinoma. Primary gastrointestinal lymphoma complicating chronic inflammatory bowel diseases is thought to be uncommon. This report describes a case of gastrointestinal lymphoma in a 12-year-old boy with Crohn's disease of one-year duration that initially manifested as an abdominal mass. Although Crohn's disease may present as a palpable abdominal mass, changing symptomatology should always warrant consideration of developing lymphoma complicating inflammatory bowel diseases. It is our hope that this case report gives the clinician an insight into the possibility of lymphoma development, even in the early course of the disease, and stresses the importance of obtaining a reliable histological diagnosis whenever possible.

Key words: Crohn's disease, gastrointestinal lymphoma, childhood.

The risk of neoplastic change in patients with Crohn's disease (CD) is well described and is usually seen in the form of adenocarcinoma¹. Primary gastrointestinal lymphoma complicating chronic inflammatory bowel diseases (IBDs) is thought to be uncommon². Most lymphomas described are of non-Hodgkin's type (NHL)³. The mechanism underlying lymphoma complicating CD is not described clearly. Alterations in immune surveillance, chronic inflammatory condition, immunosuppressive therapy, exposure to radiation, and Epstein-Barr virus (EBV) infection have all been suggested^{3,4}.

This report describes a case of gastrointestinal lymphoma in a 12-year-old boy with CD of one-year duration that initially manifested as an abdominal mass.

Case Report

A 12-year-old boy with a five-year history of abdominal pain was first admitted to our hospital for recently developing paleness, fatigue and headache. The patient had been evaluated for chronic periumbilical and

lower abdominal quadrant pain at a pediatric gastroenterology unit one year previously. He had been found to have a palpable 5×5 cm firm mass on the right abdominal quadrant and had undergone upper gastrointestinal endoscopy and colonoscopy, which revealed aphthous lesions on the terminal ileum and multiple hyperemic areas on the colonic mucosa. Tissue examination had revealed germinal center hyperplasia in the terminal ileum, minimal glandular distortion in the colon and normal findings at the duodenum. Terminal ileum wall thickness and several lymph nodes, the largest of which was 2 cm in diameter, were determined on abdominal computed tomography (CT). The patient was thought to have CD, and laparoscopic surgery and biopsy for certain differential diagnosis were advised before initiation of immunosuppressive therapy. The family had refused surgery and took their child to another center, where mesalamine was started. Within the previous year, abdominal pain had significantly improved and the patient had been able to attend school until the last two months when the drug therapy was discontinued by the family. Thereafter, the pain

increased progressively and the patient began to complain about headaches. He had never experienced fever, diarrhea, arthralgia, or ocular or dermatological problems except for recurrent oral aphthous lesions for the last five years. The family history was unremarkable.

On admission, his weight and stature were 43 kg (25th-50th percentile) and 155 cm (50th-75th percentile), respectively. The patient was afebrile, pale and tachycardic. There was a palpable firm and tender mass (8×8 cm) on the right lower quadrant. No respiratory or cardiac problems were encountered. The complete blood count revealed: hemoglobin 4.6 g/dl, mean corpuscular volume 59 fl, white blood cell count 2,800/μl and platelet count 754,000/μl. Albumin, C-reactive protein (CRP) concentration and erythrocyte sedimentation rate (ESR) were 2.8 mg/dl, 3.98 mg/dl and 18 mm/hour, respectively.

Abdominal CT revealed a grossly thickened intestinal wall resembling a mass at the distal ileum (Fig. 1). We agreed with the former diagnosis of CD, based on the combination of the chronicity of the clinical history and the past radiologic, endoscopic and histologic features. The patient was started on treatment with steroid and azathioprine. At the beginning of the therapy, ESR, CRP and albumin concentrations were 44 mm/hour, 13.6 mg/dl, and 2.7 mg/dl, respectively. Immunoglobulin levels and lymphocyte counts were in normal ranges for his age during the follow-up period.

The abdominal pain initially decreased in the first two weeks and laboratory parameters improved by one month (hemoglobin 11.8 g/dl, CRP 0.67 mg/dl, ESR 26 mm/hour, and albumin 3.5 g/dl); however, the pain increased with time and laboratory parameters deteriorated again during the following two weeks. Pleural fluid and ascites, detected only by imaging techniques, arose by the sixth week. There were no additional findings on the repeated abdominal CTs. The patient underwent double balloon ileocolonoscopy, but it was not possible to reach the involved part of the ileum because of the altered anatomical configuration of the intestines due to the mass. No suspicious macroscopic or histopathologic findings were detected within the visible small intestines. We concluded that the patient was

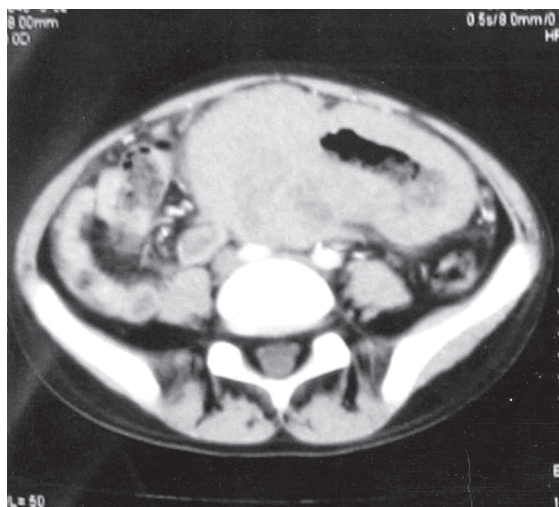


Figure 1. Thickened intestinal wall.

unresponsive to medical therapy and suggested surgery. Although an abdominal mass can be a presenting feature of CD, considering the radiologic findings and accompanying pleural fluid and ascites, malignant lymphoma should be excluded before surgery. However, cytological examination of ascites could not be done because ascitic fluid was detectable only by imaging techniques. We suggest that abdominal exploration in such cases gives much greater diagnostic knowledge and when necessary, gives the surgeon the opportunity for surgical treatment of CD.

The abdominal exploration revealed degenerated and edematous intestines and omentum with multiple adhesions in between. Abscess formation and a closed perforation of the ileum were encountered. Small bowel with concomitant ileocecal valve and ascending colon resection were performed, leaving a segment, 140 cm in length, of healthy small intestine, and an ileostomy was constructed.

Macroscopically, there was a tumoral mass measuring 10×5×2 cm in the terminal ileum. In the microscopic examination, the ileal wall and characteristics of CD could not be differentiated because of the excessive tumoral infiltration. The tumor was composed of diffuse infiltrating small cells with narrow cytoplasm, nucleus with multiple small basophilic nucleoli and clumped chromatin (Fig. 2). The diagnosis was mature B-cell lymphoma expressing CD10, CD20, CD19 and sIgM.

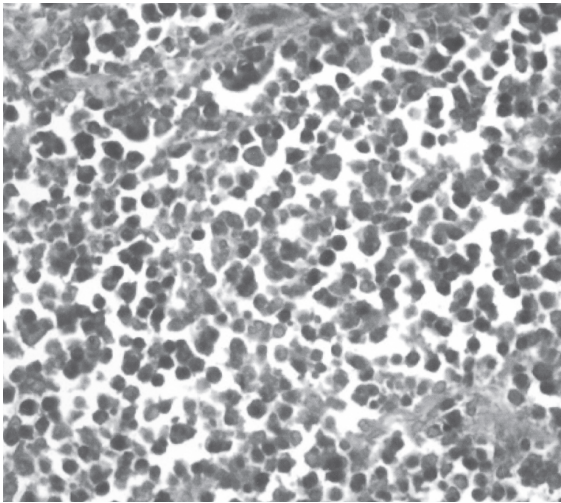


Figure 2. Diffuse infiltrating tumor cells (hematoxylin & eosin, X400).

The patient, with a lactate dehydrogenase concentration of 793 IU/L, was accepted to be at stage III and risk group 3, and the courses of prephase+AA+BB+CC+AA+BB were planned according to the BFM-95 protocol, which consists of high-dose methotrexate and cytosine arabinoside⁵. However, because of serious cicatrization problems encountered around the ileostomy orifice and at the incision site, all chemotherapeutics were given with 50% dose reduction for the following two courses. The patient received the calculated total dose in the last three courses and has been in complete remission for four months since the cessation of chemotherapy.

Discussion

Because of the similarity of symptoms of malignancies and active IBD, the diagnosis of abdominal malignancies is difficult in patients with CD, and abdominal malignancies may be erroneously diagnosed as CD⁶. Although the patient responded to mesalamine therapy clinically, the initial mass did not disappear. The presence of the mass in the previous year without clinical deterioration excluded malignancy or tuberculosis to a large extent. He seemed to have a CD attack based on the clinical signs and the laboratory tests at presentation. In the sixth week of the immunosuppressive therapy, the patient was diagnosed as mature B-cell lymphoma. We do not think that lymphoma had accompanied CD from the beginning of

the presentation of the mass, because B-cell NHL has a high proliferative index and grows rapidly. Rather, a diagnosis of an IBD attack for reasons related to the emerging lymphoma complicating IBD would be appropriate, and the immunosuppression might have had an accelerating role in this setting.

It is well known that in some immunodeficiency states, colitis resembling CD can be seen, and there is increased tendency to malignancy in immunodeficient patients⁷. However, we did not diagnose such an immunodeficiency disorder in our patient.

Malignant lymphoma is a well-known complication of chronic inflammatory conditions in the salivary glands, thyroid and stomach, as well as rheumatoid arthritis. In CD, non-pathogenic, commensal intestinal bacteria are thought to trigger a chronic dysregulated immune response against the mucosal barrier function⁸. It has been speculated that altered lymphoid populations, exposure to carcinogens secondary to the disturbed mucosal barrier, accelerated cell turnover with the increased genetic mutations, and reduced immune surveillance secondary to immunosuppression predispose these patients to the development of lymphoma⁹.

Recently, there have been some reports about reactive oxygen species (ROS) and mitogen activated protein kinase (MAPK) activation in the development of Burkitt's lymphoma in CD¹⁰. ROS are conventionally known as cytotoxic and mutagenic in high levels, but lower levels can act as an intracellular mediator of growth and apoptosis¹¹. NADPH oxidase subunits, NOX1, are ROS-producing and have been found to be highly expressed in the colon. NOX1 is suggested to play a potential role in host defense. Lymphocytes in lesions of CD and ulcerative colitis are also strongly positive for NOX1 and have been proposed to be potentially involved in the pathogenesis of IBD¹². NOX1 activates several pathways implicated in growth and angiogenesis, including nuclear factor kappa-B (NFκ-B)-dependent transcription and the extracellular signal-regulated kinases (e.g., MAPK) in part through hydrogen peroxide^{11,13}. It was hypothesized that these pathways could have resulted in tumor proliferation in CD¹⁰.

Controversy exists as to whether the underlying risk of lymphoma is increased and, if so,

whether it is related to IBD or its treatment^{14,15}. Recently, the description of a series of an aggressive and commonly fatal form of lymphoma, a hepatosplenic T cell lymphoma in pediatric and young adult patients under immunomodulator and biological combination therapy, raised the question of the risks of treatment¹⁶. Several studies have examined the risk of lymphoma in IBD patients treated with immunomodulators, particularly azathioprine and 6-mercaptopurine^{9,15}. According to the study design (case reports, population-based or hospital-based studies), sample size, and duration of follow-up, the causal association between lymphoma and immunosuppressive therapy in IBD varies. The current data support that IBD alone is not a risk factor for the development of lymphoma and IBD patients treated with thiopurines are at only slightly increased risk of developing lymphoma than the general population¹⁵. However, this small risk has not been clearly quantified in relation to the extent, duration and severity of disease and the type (monotherapy/combined therapy), dosage or duration of immunosuppressive therapy^{16,17}.

In our patient, the duration of disease was at least one year and the duration of immunosuppressive therapy was six weeks. The association of azathioprine therapy with subsequent NHL diagnosis seems extremely unlikely. Generally, the immunosuppressive effect of azathioprine is not expected to start in the first months of therapy, and although most complications of thiopurines used in the treatment of IBD occur early, neoplasms occur late in the course¹⁸. One of the reports of NHL developing relatively early in the course of azathioprine treatment was of a small cohort of 238 patients with IBD, in which two of four cases of NHL were diagnosed 9 and 14 months after beginning azathioprine¹⁹.

In a case report of Burkitt's lymphoma complicating CD, the literature on lymphoproliferative disorders of the bowel in patients with CD was reviewed, and lymphoma was reported to occur in patients with long-standing CD (mean 9.1 years) and in sites of previous disease involvement in most cases³. This supports the view that chronic inflammation may contribute to the development of lymphoma. Although lymphoma arose much

earlier in our patient than in those reported in the medical literature, chronic inflammation may still have contributed to the lymphoma development.

There is a growing concern regarding the risk of EBV-positive lymphoma in IBD patients treated with immunomodulators²⁰. Making a comment on the relationship between the lymphoma and EBV in our patient is not possible, because we were not able to study the EBV genome in lymphoma tissue.

In conclusion, it is our hope that this case report gives the clinician an insight into the possibility of lymphoma development, even in the early course of the disease, and stresses the importance of obtaining a reliable histological diagnosis whenever possible. Although CD may present as a palpable abdominal mass, changing symptomatology in patients on immunomodulatory treatment should always warrant consideration of developing lymphoma complicating IBD. Larger scale, prospective, population-based studies are necessary to define the actual risk of lymphoma and the influence of immunomodulators on that risk in the pediatric IBD patients who are prone to either complications of the disease or adverse effects of the medical therapy throughout a long life span.

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