



Natural Killer-Like T-Cell Lymphoma Localized to the Terminal Ileum: Case Report

Ümit BAYOL¹, Süheyla CUMURCU¹, Kerem KARAMAN², Cem TUĞMEN², Çağlar AKDENİZ¹,
Özlem AKMAN¹, Saime ÜNLÜOĞLU¹

Departments of ¹Pathology and ²General Surgery, Tepecik Training and Research Hospital, İZMİR, TURKEY

ABSTRACT

Intestinal intraepithelial lymphocytes are non-organized lymphoid populations that are composed of heterogeneous subsets with diverse ontogeny and phenotypes, and the differential diagnosis is crucial. A 43-year-old male patient underwent an emergency laparotomy due to a perforated mass of the terminal ileum. A right hemicolectomy plus small bowel resection was performed. Histopathological examination showed medium to large cells with vesicular nuclei, including marked nucleoli with large, colorless cytoplasm. No signs of celiac disease were found in the adjacent mucosa. The tumor cells were immunohistochemically CD45+, CD3+, CD4+, CD8+, CD56+, Pan-Cytokeratin-, CD20-, CD79a-, CD5- and CD30-. Endomysial antibody and antigliadin antibody, IgM and IgG tests; and anti-Ebstein Barr virus latent membrane protein all proved negative. Finally, the histopathological diagnosis of tumor mass was natural killer-like T-cell lymphoma. Primary intestinal cytotoxic natural killer-like T-cell lymphoma is a rare entity, which is difficult to distinguish from other T-cell lymphomas. In addition to microscopic evaluation, immunohistochemical analysis and serological tests are essential to reach a definitive diagnosis.

Key Words: Natural killer T-cells, Lymphoma, Celiac disease

INTRODUCTION

Gastrointestinal non-Hodgkin's lymphomas (NHL) are the most common type of primary extranodal lymphomas with the majority being of B-cell lineage (1). In contrast to their B-cell counterparts, primary intestinal natural killer and T-cell lymphomas (PINKTL) are very rare and generally more aggressive with various subtypes, and the 5-year survival is usually less than 10% (1-3). Intestinal intraepithelial lymphocytes make up one of the largest non-organized lymphoid populations (4). They consist of heterogeneous subsets including T-cells or natural killer (NK) cells and neoplastic counterparts of each with diverse ontogeny and phenotype. Additionally, there are systemic T-cell or NK cell lymphomas [such as $\gamma\delta$ T cell lymphoma and extranodal natural killer-like T-cell lymphoma (NK/T-cell lymphoma), nasal type] that may involve the intestine and the differential diagnosis is crucial (5-12). We report a case with a perforated mass of the terminal ileum diagnosed as NK/T-cell lymphoma.

CASE REPORT

A 43-year-old male patient was admitted to the emergency clinic with complaints of abdominal pain, nausea and vomiting. His physical exam revealed generalized peritonitis with rebound tenderness. A giant mass (>20cm) originating

from the small bowel and filling the lower abdominal cavity was detected by abdominal computerized tomography (Figure 1). The patient underwent an emergency laparotomy due to suspicion of perforation. During the operation, a perforated mass of the terminal ileum, which had invaded the cecum and other parts of the small bowel, was found. A right hemicolectomy plus small bowel resection was performed and the restoration of the gastrointestinal tract was provided with an ileo-colonic anastomosis. A second exploration was performed on the fifth postoperative day for anastomotic leakage after detecting intestinal content in drains. An end ileostomy plus Hartman's procedure was performed and the abdominal cavity was irrigated and cleaned with saline before abdominal closure. No complication developed in the postoperative period and the patient was discharged on the 15th postoperative day.

Histopathological examination of the resected ileal mass revealed T-cell lymphoma. Microscopically, medium to large sized cells with vesicular nuclei including marked nucleoli with large, colorless cytoplasm were seen. No signs of celiac disease were found in the adjacent mucosa. The tumor cells were immunohistochemically positive with CD45, CD3, CD4, CD8, CD56 and negative with pan-cytokeratin (panCK), CD20, CD79a, CD5 and CD30 (Figure 2A-D). After a careful anamnesis, no history or

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Correspondence: Kerem KARAMAN

Tepecik Eğitim ve Araştırma Hastanesi, 3. Cerrahi Kliniği,
Yenişehir, 35170, İZMİR, TURKEY

E-mail: karaman_kerem@yahoo.com.tr Phone: +90 264 444 54 00

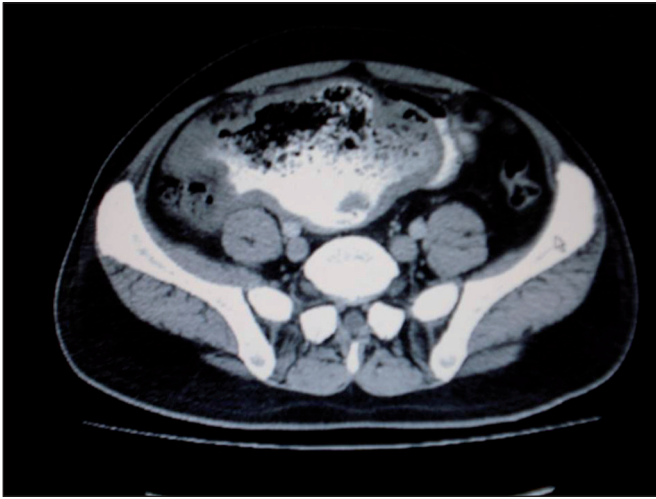


Figure 1: Abdominal computerized tomography demonstrates the giant mass, which filled the lower abdominal cavity.

association with celiac disease was determined and the endomysial antibody and antigliadin antibody IgM and IgG tests were negative. Epstein-Barr virus (EBV) antibodies IgM and IgG were positive for EBV viral capsid antigen (VCA) and EBV virus nuclear antigen (EBNA). However, no additional tumor was detected by screening in the nasopharynx, skin and soft tissues or other parts of the gastrointestinal tract. Further, immunohistochemically, anti-EBV latent membrane protein (anti EBV-LMP; Daco, Denmark) was also negative. Hence, the histopathological diagnosis of the tumoral mass was NK/T-cell lymphoma, and the patient was referred to medical oncology where he was placed on a Hyper-CVAD (cyclophosphamide, vincristine, doxorubicin, dexamethasone) chemotherapy regimen. At the end of the six-month follow-up, the patient is now symptomless and is coming for routine check-ups.

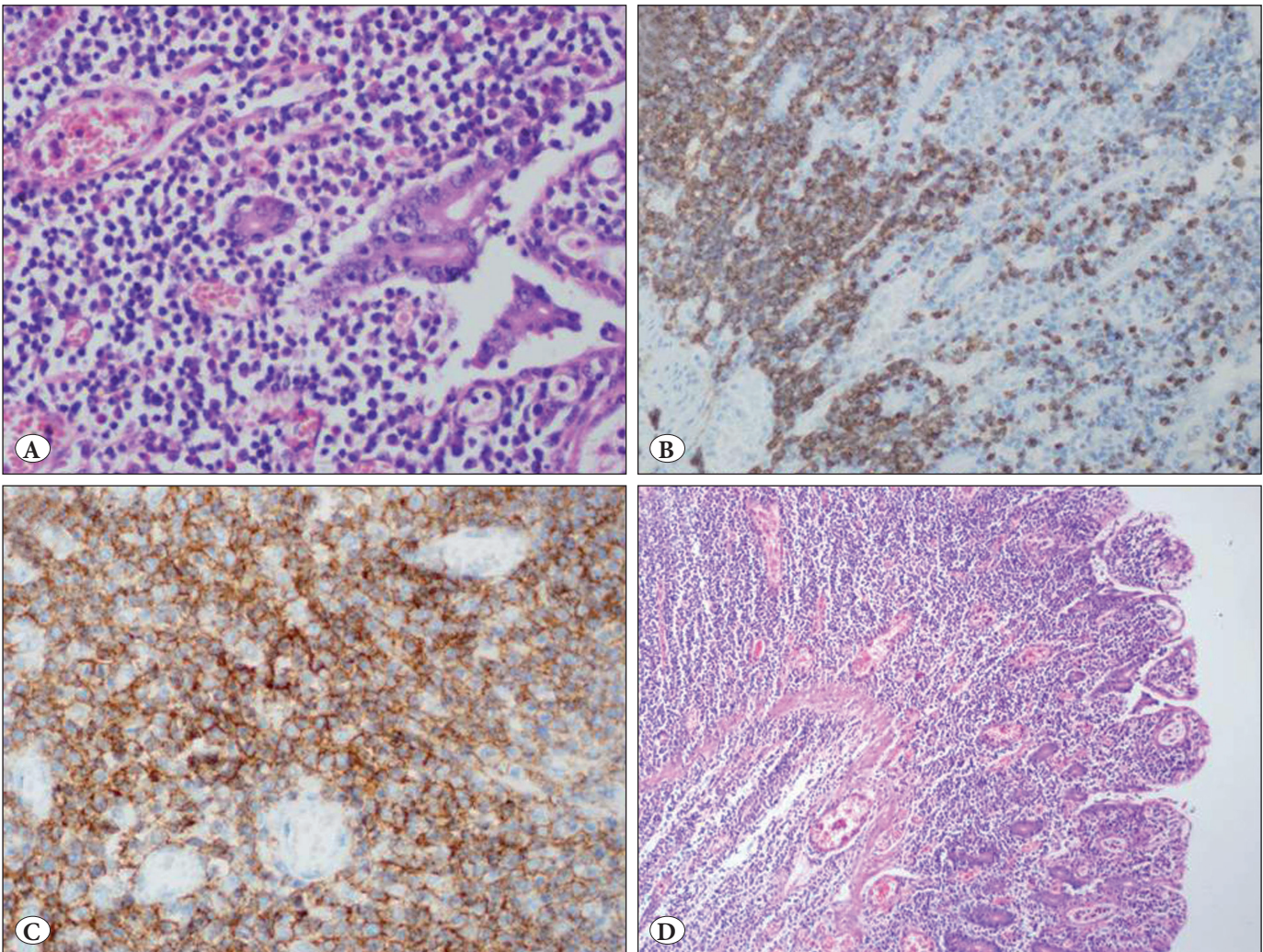


Figure 2: A) Infiltration of the mucosa by tumor cells (H&E; x200). B) CD3+ tumor cells infiltrating the mucosa (CD3; x100). C) CD56+ tumor cells (CD56; x200). D) Transmural infiltration of the bowel wall by neoplastic cells (H&E; x40).

DISCUSSION

Primary intestinal natural killer and T-cell lymphomas (PINKTL) comprise three different entities: enteropathy-associated T-cell lymphoma (EATL), peripheral T-cell lymphoma (PTCL) and NK cell lymphoma. According to the World Health Organization classification (WHO, 2008), EATL is defined as an intestinal tumor derived from intraepithelial lymphocytes. Adjacent to these lesions, villous atrophy and crypt hyperplasia exists in the non-neoplastic small intestinal mucosa (13,14). EATL is frequently localized in the proximal small intestine. In contrast to celiac disease (male/female ratio: 1/2), men are more affected (64%) in EATL. The mean age at diagnosis is approximately 64 years (15). Outcome is very poor with a 2-year survival rate of 15-20% (16-18). Based on morphology, genetic profile and immunohistochemistry, EATL can be divided into two groups. EATL type I has strong association with celiac disease and presents often with malabsorption, weight loss and celiac disease related symptoms. However, EATL type II is not associated with celiac disease, and is presented usually with small bowel obstruction or perforation (19). EATL type II comprises 10-20% of all EATL in Western countries. Although EATL is very rare in the Far East, EATL type II has been reported from Asian countries including Taiwan and Japan (19,20). EATL type I cells are CD3+, CD5-, CD7+, CD8+/-, CD4-, CD56-, CD103+, TCR-beta +/- . The majority of the tumor cells are CD30+. On the other hand, EATL type II cells are CD3+, CD4-, CD8+, CD56+, TCR-β+. Interestingly, CD30 is often negative. Since CD8 and CD56 are critically important in diagnosing EATL type II, these markers should be included in the standard immunological work-up when lymphoma has been diagnosed (14). The NK cells are CD3-, CD7+, CD56+/- and CD57- (21). Primary intestinal cytotoxic NK/T-cell lymphoma should be considered as a distinct entity. These tumors consist of monomorphic small or medium tumor cells that express CD3, CD8 and CD56 without in association with celiac disease (1,9,22). The Revised European American Lymphoma Classification (REAL) system has not accurately defined the phenotype of the tumor cells. It is also difficult to classify NK/T-cell lymphoma. Further, CD56 is not described in intestinal T cell lymphoma by the REAL classification system (23-25). NK/T-cell lymphoma is differentiated from EATL type II by lacking enteropathy and occurring in colon [1]. Our patient displayed CD3+, CD4+, CD5-, CD8+, CD56+, CD30-. Histopathologically, we found no signs of enteropathy in the adjacent tissue during microscopic evaluation and anamnesis revealed any history of celiac

disease. Furthermore, antigliadin antibody IgM and IgG serology and endomysial antibody tests were also negative. The nasal type of the extranodal NK/T-cell lymphoma occurs usually in the nasopharyngeal region; it is CD56 positive CD8 negative, lacks usually T cell receptor (TCR) gene rearrangement, and is strongly associated with EBV (1, 25-27). It is described as "NK/T" rather than "NK" because of some reported cases in which cytotoxic T-cell phenotype was observed (1,14). Although, the present case had positive IgM and IgG antibodies for EBV VCA and EBNA, a diagnosis of a nasal type NK cell lymphoma is eliminated due to absence of nasopharyngeal involvement by the tumor. Additionally, the anti EBV-LMP in the tumor cells was negative. Thus, our case was diagnosed as NK/T-cell lymphoma.

NK/T-cell lymphoma of the terminal ileum is a rare entity that has similar endoscopic features of inflammatory bowel disease, and often invades serosa. Patients usually present at an advanced stage with peritonitis as a result of tumor perforation (24). NK/T-cell lymphomas are reported in a few studies as case series and the true incidence is probably more frequent than expected (26,27). Furthermore, NK/T-cell lymphoma of the terminal ileum can mimic Behçet's enteritis or intestinal tuberculosis and should be considered in the differential diagnosis of these diseases. The true diagnosis can only be established by histopathological evaluation (28,29).

In conclusion, primary intestinal cytotoxic natural killer-like T-cell lymphoma is a rare entity, which is difficult to distinguish from other T-cell lymphomas. In addition to microscopic evaluation immunohistochemical analysis and serological tests are needed to reach a definitive diagnosis.

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