OLGU SUNUMU CASE REPORT

DOI: 10.5336/dermato.2017-57068

Cutaneous T Cell Lymphoma in a Patient with Primary Biliary Cholangitis

Primer Biliyer Kolanjitli Bir Hastada Kutanöz T Hücreli Lenfoma

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Geliş Tarihi/*Received:* 21.06.2017
Kabul Tarihi/*Accepted:* 23.10.2017

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ABSTRACT Primary biliary cholangitis (PBC) is an autoimmune and cholestatic, liver disease characterized by chronic nonsuppurative destructive cholangitis, circulating antimitochondrial antibodies and interlobular bile duct destruction. Autoimmune disorders including PBC seems to have an elevated risk of lymphoma. Mycosis Fungoides, the most common type of Cutaneous T- cell lymphoma (CTCL) is also a neoplasm of the immune system. There is little information about the risk of developing lymphoma including CTCL in PBC patients. Here, we present the second case of CTCL as much as we know, reported in the literature that occurred in an adult patient with PBC.

Keywords: Mycosis fungoides; liver cirrhosis, biliary

ÖZET Primer biliyer kolanjit (PBK), kronik ve supuratif olmayan, destruktif kolanjit, dolaşımda antimitokondrial antikor varlığı ve interlobuler safra yollarının yıkımı ile karakterize otoimmün ve kolestatik bir karaciğer hastalığıdır.. Dolaşımdaki antimitokondrial antikor varlığı ve interlobuler safra yollarının yıkımı tipiktir. PBK de dâhil olmak üzere otoimmün hastalıklarda, lenfoma gelişimi riski yüksektir. Kutanöz T hücreli lenfomanın en sık görülen tipi olan Mikozis Fungoides de bir immün sistem neoplazmıdır. PBK hastalarında KTHL de dahil olmak üzere lenfoma gelişme riski hakkında çok az bilgi vardır. Bu makalede, PBK'li erişkin bir hastada görülen ve bildiğimiz kadarı ile literatürde bildirilen, ikinci kutanöz lenfoma olgusunu sunuyoruz.

Anahtar Kelimeler: Mikozis fungoides; karaciğer sirozu, biliyer

Primary biliary cholangitis (PBC) is an autoimmune and cholestatic, liver disease characterized by chronic nonsuppurative destructive cholangitis, circulating antimitochondrial antibodies and interlobular bile duct destruction by cytotoxic T-cells. The rate of disease progression is quite variable, but typically the disease is slowly progressive. Anti-mitochondrial M2 antibodies (AMA-M2) are present in approximately 95% of the cases.[1]

Autoimmune disorders including PBC seems to have an elevated risk of lymphoma. The increased risk may be related to the disturbance of immune function or immunosuppressive therapies used to treat the disease. To the best of our knowledge, 20 cases of non-Hodgkin Lymphoma (NHL), 4 cases of Hodgkin's disease, 3 cases of primary hepatic lymphoma and only one

case of CTCL have been reported in PBC patients.[2-7] The only case of cutaneous T cell lymphoma (CTCL) was reported in a patient with primary biliary cholangitis and secondary Sjögren syndrome.[7] In this report, we describe a 58 -years-old female patient having the diagnosis of CTCL, mycosis fungoides (MF), eight years following PBC diagnosis.

CASE REPORT

A 58-year-old female patient with a history of PBC for 8 years was admitted to our department because of multiple erythematous and scaly plaques involving the legs, buttocks and abdominal wall. Her symptoms were started almost 5 years ago but she was diagnosed as dermatitis and prescribed emollients, with no improvement. However, given the persistence and progression of the skin lesions, she was referred to our hospital. Upon dermatologic examination, the patient was found to have multiple pink, scaly patches and plaques on the trunk and lower extremities, clinically suggestive of CTCL (Figure 1). A biopsy of the plaque at the right proximal lower extremity, stained with hematoxylin-eosin revealed enlarged lymphocytes with hyperchromatic irregular nuclei with epidermotropism (Figure 2). The papillary dermis was hyalinized. The lymphocytes were highlighted on CD3 staining, and most cells expressed CD4 with little CD8 expression. There was no palpable lymphadenopathy or hepatosplenomegaly. Staging tests revealed localized cutaneous disease and the patient was diagnosed with MF, stage Ia (T1N0 M0B0). She was treated with narrow-band ultraviolet B (nbUVB) phototherapy, 3 times weekly, with good response after 16 weeks.

The diagnosis of PBC was based on the following criteria at presentation: elevated cholestatic enzymes namely gamma-glutamyl-transpeptidase (155 U/l; upper normal limit: 40 U/l) and alkaline phosphatase (184 U/l; upper normal limit: 104 U/l), normal ultrasound of the upper abdomen, liver histology with typical PBC lesions (stages I and II according to Ludwig's histological classification) and positivity for AMA. PBC was diagnosed clinically and histologically according to the criteria proposed by the Japanese Joint Research Group for

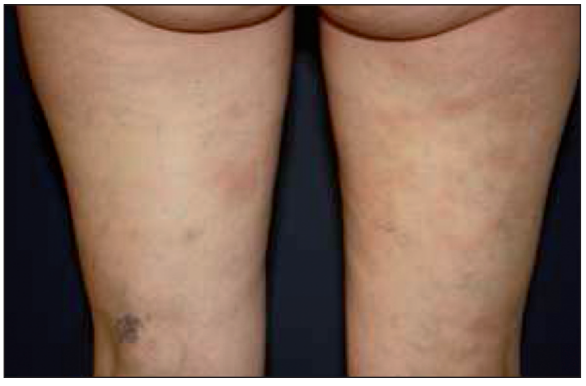

FIGURE 1: Cutaneous T cell lymphoma. Multiple plaques on the extensor aspect of lower extremities 8 years after the initial diagnosis of primary biliary cirrhosis.

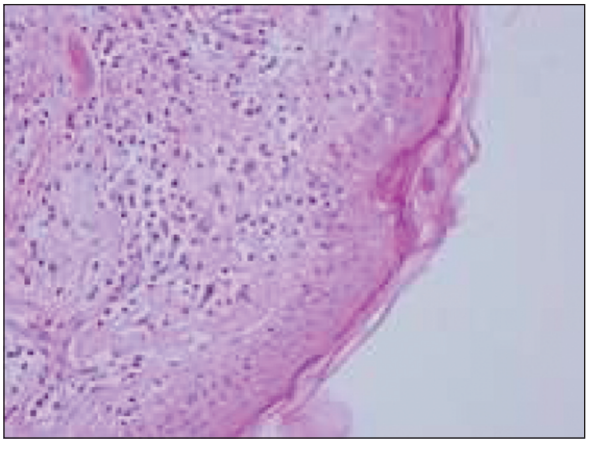

FIGURE 2: Hematoxylin and eosin, ×40. Biopsy revealed an atypical perivascular lymphocytic infiltrate with epidermotropism.

Autoimmune Hepatitis.[8] Hematological data showed normal white and red blood cell counts. Erythrocyte sedimentation rate was 25 mm/h. Blood biochemical data were total bilirubin 1.3 mg/dL (normal range (NR): 0.2-1.2 mg/dL), direct bilirubin 0.3 mg/dL (NR: 0.0-0.2 mg/dL), aspartate aminotransferase 49 IU/L (NR: 8-46 IU/L), alanine aminotransferase 76 IU/L (NR: 0-35 IU/L), alkaline phosphatase 216 IU/L (NR: 35-104 IU/L), gamma glutamyl transferase 55 IU/L (NR:5-36 IU/L), blood urea nitrogen 13 mg/dL (NR:5-24 mg/dL), creatinine 0,6 mg/dlL(NR: 0.40-1,40 mg/dL), Hepatitis B surface antigen and anti-hepatitis C virus antibody were both negative. She was positive for anti-M2 anti-mitochondrial antibodies at 1:144 (NR: 1:7). Thyroid stimulating hormone and free thyroxin were within normal ranges.

DISCUSSION

Primary cutaneous T-cell lymphomas are a heterogeneous group of skin-homing T lymphocytes malignancies. Mycosis fungoides (MF), the most frequent subtype of CTCL, is classified as an indolent lymphoma, according to the WHO-EORTC classification of PCL.[9] The diagnosis of classic MF is based on typical clinical presentation, histopathology, immunohistochemistry, and T-cell monoclonality. Typical histopathologic picture in MF is the dense infiltrate of atypical lymphocytes in the dermis with epidermotropism (presence of atypical lymphocytes in epidermis). Immunophenotyping shows expression of CD4+ antigen, though CD8+ and double negative CD4–/CD8– variants have been described. Cutaneous lymphomas mimic other skin conditions both clinically and histologically. It is often difficult to diagnose MF in its early phase. Various erythematous patches develop. These lesions are chronic, existing for several years until they become plaques, nodules, erythroderma, or tumors. Classic MF typically exhibits slow progression in the first years after diagnosis and rarely progresses to extracutaneous involvement or disease-related death. Patients with early-stage disease have similar life expectancies to controls matched by age, sex and race.[10]

PBC is commonly associated with changes in the skin. The typical patient is a middle-aged woman with jaundice and pruritus, showing features of cholestasis on liver function tests and the presence of anti-mitochondrial antibodies. The clinical course of PBC is variable, ranging from a few years in rapidly progressive cases to a normal life-expectancy in a proportion of asymptomatic cases. Various case reports exist in the literature describing a frequent association of PBC with autoimmune skin disorders including lichen planus, Raynaud syndrome, scleroderma, and CREST syndrome. Our patient had no other autoimmune disease like Sjögren syndrome other than PBC. In 2006 Koulentaki et al. evaluated dermatologic manifestations of PBC patients and reported multiple coinciding skin lesions. Fungal skin infections (31.5%) were the most common skin disorders observed in PBC patients, followed by neoplastic lesions (e.g. cherry angioma, nevi, basal cell carcinoma 18.4%), dermatitis/-urticaria (15.7%), and disturbances of pigmentation (12.4%). However, review of published studies revealed that CTCL (or MF), in association with PBC, has been reported only once.[11]

PBC appears to be a classic autoimmune disease and all autoimmune disorders are increasingly recognized as risk factor for NHL.[2] Autoantibodies, periductal inflammation, and overexpression of autoreactive CD4+ lymphocytes are characteristic histological features of PBC.[12] It has been suggested that the chronic inflammation caused by infections and persisting immune reactions appears to play an important role in the lymphoma pathogenesis in patients with PBC as in other autoimmune disorders.[13] CTCL is the most common type of cutaneous lymphoma and accounts for approximately 50% of all lymphomas arising primarily in the skin. The clinical course can be protracted and take years or decades. To the best of our knowledge, this is the second report of a case of CTCL associated with PBC. In the dermatology literature a few cases were reported describing the association of MF and lupus erythematosus (LE). Although Nakamura et al. thought that this was a coincidence Veysey and Wilkinson recognized that their case contributed to the growing number of reports describing immune disorders in patients with CTCL. In their report similar features with our patient were observed.[14,15] The patient was diagnosed and treated as LE for many years before the diagnosis of MF was made. Although the diagnosis of PBC and cutaneous lymphoma is generally challenging, the uncommon occurrence of overlapping features of both disorders may lead to a diagnostic and treatment dilemma. In conclusion, this case study suggests that CTCL (MF) may be rarely found in the extensive list of diseases associated with PBC and other autoimmune disorders.

Conflict of Interest

Authors declared no conflict of interest or financial support.

Authorship Contributions

Idea/Concept: *Müge Güler Özden;* ***Design:*** *Müge Güler Özden;* ***Control/Supervision:*** *Müge Güler Özden, Talat Ayyıldız;* ***Data Collection and/or Processing:*** *Müge Güler Özden, Talat Ayyıldız;* ***Analysis and/or Interpretation:*** *Müge Güler Özden, Talat Ayyıldız;* ***Literature Review:*** *Müge Güler Özden, Talat Ayyıldız;* ***Writing the Article:*** *Müge Güler Özden, Talat Ayyıldız;* ***Critical Review:*** *Müge Güler Özden, Nilgün Şentürk;* ***References and Fundings:*** *Müge Güler Özden, Nilgün Şentürk, Tayyar Cantürk;* ***Materials:*** *Müge Güler Özden, Tayyar Cantürk.*

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