Case Report
Olgu Sunumu
DOI: 10.4274/turkderm.galenos.2020.34356
Turkderm-Turk Arch Dermatol Venereol 2021;55:92-5

Diffuse large B-cell lymphoma that develops after adalimumab using adalimumab in a patient with psoriasis

Psoriazisli hastada adalimumab kullanımı sonrasında gelişen diffüz büyük B hücreli lenfoma

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Abstract

Psoriasis is a polygenic, systemic inflammatory disease seen in 2% to 3% of the population and leads to a serious deterioration in the quality of life. As a result, studies on the pathophysiology of this disease have led to the development of cytokine-targeted therapies, especially the widespread use of treatments targeting tumor necrosis factor-alpha (TNF-α). The role of TNF-α in inflammation and important physiological pathways has increased safety concerns. In the literature, it has been reported that infections, cardiac failure, neurological diseases, and malignancies may develop related to the use of anti-TNF-α agents. In this case report, a 59-year-old male patient was started on adalimumab as a biological agent for erythrodermic psoriasis. Twenty-four months after starting biological agent therapy, hard nodules occurred under his skin in both the inguinal and axillary regions. The patient was diagnosed with diffuse large B-cell lymphoma based on his histopathological and laboratory examinations. This case report aims to discuss the specific malignancies that may develop from anti-TNF-α agents and the potential pathophysiological mechanisms suggested in the current literature.
Keywords: Psoriasis, adalimumab, lymphoma

Öz

Psoriazis toplumun %2 ile %3'ünde görülen, yaşam kalitesinde ciddi bozulmalara yol açan poligenik, sistemik enflamatuvar bir hastalıktır. Hastalığın patofizyolojisinin aydınlatılması ile ilgili çalışmalar sonucunda, sitokin hedefli tedaviler geliştirilmiş, özellikle tümör nekroz faktör-alfayı (TNF-α) hedef alan tedavilerin kullanımı yaygınlaşmıştır. TNF-α'nın sadece enflamasyonda değil, aynı zamanda önemli fizyolojik yolaklarda rol oynaması güvenlik endişelerini artırmıştır. Literatürde anti-TNF-α ajanların kullanımına bağlı enfeksiyonlar, kardiyak yetmezlikte artış, nörolojik hastalıklar ve malignitelerin gelişebileceği bildirilmiştir. Bu olgu sunumunda 59 yaşında erkek hastaya eritrodermik psoriazis nedeniyle biyolojik ajan olarak adalimumab başlanmıştır. Biyolojik ajan tedavisine başlandıktan 24 ay sonra hastanın her iki inguinal ve aksiller bölgesinde deri altında sert nodüller meydana gelmiştir. Yapılan histopatolojik tetkikler ve laboratuvar incelemeleri neticesinde hastaya diffüz büyük B-hücreli lenfoma tanısı konulmuştur. Bu olgu sunumu ile anti-TNF-α ajan kullanımına bağlı gelişebilecek malignitelerin neler olabileceği, olası patofizyolojik mekanizmaları güncel literatür bilgileri eşliğinde tartışılması amaçlanmıştır.
Anahtar Kelimeler: Psoriazis, adalimumab, lenfoma

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Cite this article as: Yıldırım Bay E, Moustafa E, Oğuz Topal İ, Yalçın Ö, Demirel N. Diffuse large B-cell lymphoma that develops after adalimumab using adalimumab in a patient with psoriasis. Turkderm-Turk Arch Dermatol Venereol 2021;55:92-5.

Introduction

Psoriasis is a polygenic, systemic inflammatory disease that leads to serious impairment in the quality of life. It is seen in 2% to 3% of the population. The disease is characterized by sharply demarcated erythematous-scaly plaques[1,2]. After the studies on the disease pathophysiology, cytokine-targeted therapies were developed, especially biological therapy targeting tumor necrosis factor-alpha (TNF-α), which has gradually increased in the last two decades. One of these agents, adalimumab, is a human monoclonal antibody that targets TNF-α[2,3].

Anti-TNF-α agents often have fewer side effects and are better tolerated than conventional treatments[4]. However, since TNF-α plays a role in inflammation and important physiological pathways, serious safety concerns have been raised[3,4]. Hematological malignancies such as Hodgkin lymphoma, cutaneous T-cell lymphoma, predominant B-cell lymphoma, and diffuse large B-cell lymphoma (DLBCL) may develop using anti-TNF-α agents[4].

This case report aims to discuss the malignancies related to the use of anti-TNF-α agents and review the potential mechanisms accompanied by current literature.

Case Report

A 59-year-old male patient was followed up in our psoriasis outpatient clinic with a diagnosis of psoriasis applied to us with a rash on the right chest area and palpable masses in the axilla.

On physical examination of the patient, purplish, erythematous, irregularly bordered, diffuse plaque lesions with accompanying intact skin islets, and maculopapular areas were observed on his right lateral thoracic region. Also, different-sized plaques with silvery scales on an erythematous background were present on both arms, hands, legs, feet, and trunk (Figure 1).

In addition, pathologically enlarged lymph nodes were detected bilaterally in the axillary and inguinal regions on palpation. The liver was palpable 1 cm below the rib. Systemic examinations of the patient revealed that he had no fever or night sweats, but he had lost 8 kg in the last 1.5 months.

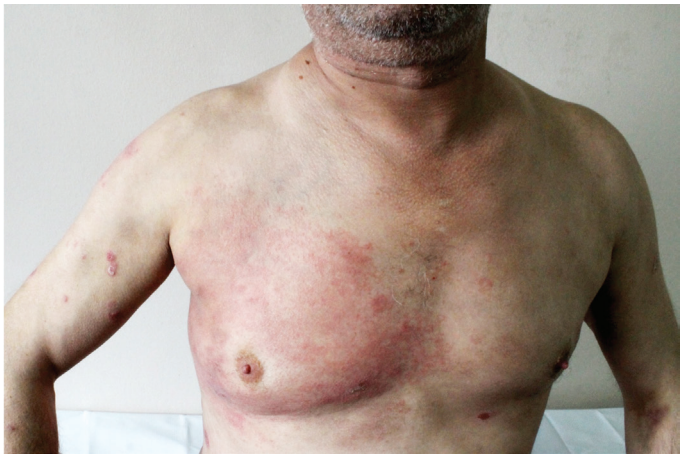

Figure 1. Lipid-colored, erythematous, irregularly demarcated, indurated plaque lesion in the right thoracolateral region

The patient was diagnosed with plaque psoriasis in 2007. BMI of the patient was 27 kg/m^2 and had skin type 3. Previously, after psoralen and ultraviolet A therapy, he had used methotrexate 15-20 mg/week for 18 months.

Afterward, the patient's psoriasis area and severity index was calculated as 17.8. Then, methotrexate and adalimumab (40 mg/week) combination therapy due to erythrodermic psoriasis was started, and therapy continued for 12 months.

Due to methotrexate-related gastrointestinal symptoms, methotrexate was discontinued, and acitretin (35 mg/day) was added to his treatment. This combination therapy (adalimumab and acitretin) was continued for 12 months. After 24 months of initiating biological therapy, subcutaneous nodules appeared in his axillary and inguinal regions.

The patient had hypertension, a 35 pack-year history of smoking. He had not used alcohol. In his family history, his aunt had psoriasis, and his sister had a history of stomach cancer.

His laboratory examination results were hemoglobin: 14 g/dL [reference range (RA): 11.5-15.5], white blood cell: 8x10^3/μL (RA: 4.5-10.5), C-reactive protein: 52 mg/L (RA: 0-5), sediment: 61 mm/h (RA: 1-15), lactate dehydrogenase: 427 U/L (RA: 125-220), and beta-2 microglobulin, serum: 4.17 mg/L (RA: 1.09-2.53). His positron emission tomography/computed tomography (PET/CT) showed multiple lymph

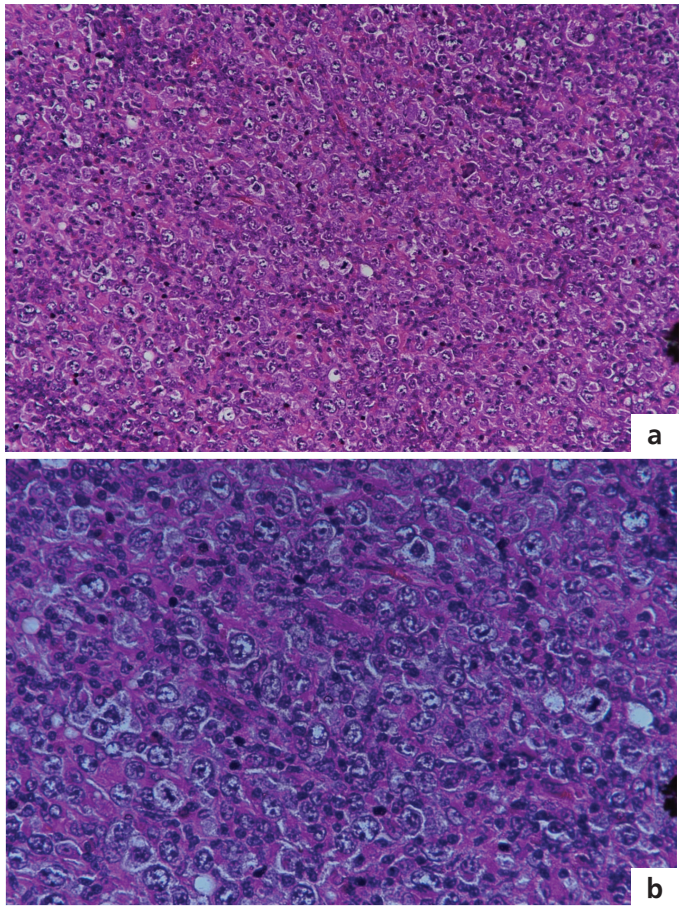

Figure 2a. Diffuse infiltration consisting of pleomorphic, bizaar cells in lymph node excisional biopsy specimen (hematoxylin and eosin, x200) **b.** Diffuse infiltration of pleomorphic, bisaar cells in lymph node excisional biopsy specimen (hematoxylin and eosin, x400)

nodes and involvement of his liver, spleen, and musculoskeletal system. Histopathological examination of a 4 mm punch biopsy obtained from the right lateral thoracic region showed edema in the superficial dermis. It also showed capillary dilatation and perivascular neutrophil and lymphocyte infiltration in the deep dermis. Histopathological examination of the lymph node sample excised from the inguinal region revealed a diffuse infiltration consisting of pleomorphic and bazaar cells (Figure 2a, b).

While these cells showed positive immunoreactivity with CD20 (Figure 3), CD45 (Figure 4), B-cell lymphoma-2 (Bcl-2), and MUM1, they did not stain with CD3, CD5, CD10, CD15, CD30, and Bcl-6. The patient was diagnosed with DLBCL based on these features these features. The patient was referred to the hematology outpatient clinic with his results.

A bone marrow (BM) biopsy was performed by the department of hematology. Involvement of the BM was not detected. A biopsy was performed from the liver mass lesion. The results of his biopsy were reported as DLBCL.

The patient was diagnosed with stage 4B DLBCL by the department of hematology. RCHOP (rituximab: 375 mg/m^2/day, cyclophosphamide: 750 mg/m^2/day, doxorubicin: 50 mg/m^2/day, vincristine: 2 g/day, and methylprednisolone: 80 mg/day) chemotherapy was planned once every three weeks. According to the PET/CT results, the patient was diagnosed as having a complete response to the treatment after four cycles of chemotherapy and eight cycles of chemotherapy were completed. The patient has been in remission for three years. His treatment and controls were performed by the hematology clinic and us.

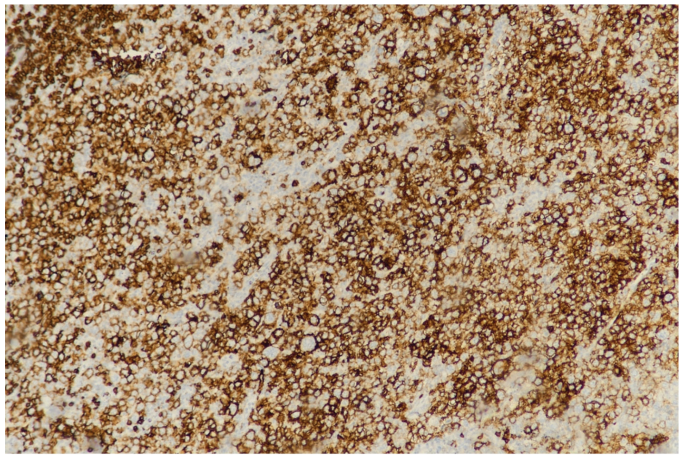

Figure 3. Immunoreactivity of pleomorphic, bizaar, atypical cells with CD20 (CD20, x100)

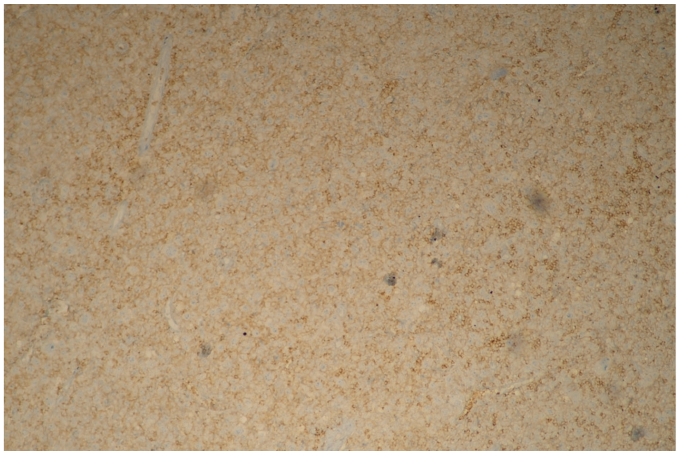

Figure 4. Immunoreactivity of pleomorphic, bizaar, atypical cells with CD45 (CD45, x40)

Discussion

TNF-α is a basic cytokine that plays a role in inflammation and immune response[5]. Since high levels of TNF-α are in psoriatic lesions, other inflammatory diseases, and systemic circulation, TNF-α has been a target cytokine to treat these diseases[6]. Anti-TNF-α agents modulate inflammatory and immune responses by regulating the response of interleukin-23 (IL-23) and T helper-17 in psoriatic skin[7].

TNF-α induces apoptosis by caspases and the Fas-associated death pathway. TNF-α potentializes antineoplastic activity by affecting cell lines directly[5,6,8]. Anti-TNF-α treatment negatively affects cancer immune surveillance mechanisms by decreasing NK cell function, B-cell line lysis, IL-1 beta production, and interferon-gamma secretion. Also, these treatments induce macrophage and T-cell apoptosis[9].

It has been reported that after the use of anti-TNF-α agents, hematological malignancies, such as Hodgkin lymphoma, cutaneous T-cell lymphoma, B-cell predominant lymphoma, DLBCL, and other malignancies such as colorectal cancer, melanoma, and non-melanoma skin cancer may develop[4-6].

Nosotti et al.[4] reported a 59-year-old patient with moderate plaque psoriasis. The patient started anti-TNF-α agents after conventional treatment. Symptoms, such as fatigue and icterus, appeared in the patient after seven months. On further examination, the patient was diagnosed as T-cell/histiocyte-rich large B-cell lymphoma, a variant of DLBCL. In another case report, after using adalimumab for four months due to psoriasis, the patient experienced dysarthria and tonic-clonic seizures. On further examinations, the patient was diagnosed as primary DLBCL of central nervous system lymphoma[10].

DLBCL developed in our patient 24 months after initiating adalimumab, an anti-TNF-α agent. After using adalimumab in patients with psoriasis, the cases of lymphoma are limited and usually develop between two weeks and six months[4,10,11]. According to a systematic review about the incidence of long-term cancer in patients with psoriasis using biological agents, the median follow-up time for adalimumab is six months[11].

The most important difference of our case from the other cases is the duration of follow-up with adalimumab. The treatment duration of our case with adalimumab was 24 months. A 3-year follow-up without remission after developing lymphoma is very rare in the literature[11]. After the long-time follow-up, the development of lymphoma is important regarding compatibility with the latency of cancer-lymphoma. Similar to the duration of developing lymphoma in our patient, the duration from the initiation of anti-TNF-α treatment to the appearance of lymphoma symptoms was 23.6 months in a prospective case-controlled study[12].

Since anti-TNF treatment duration is very heterogeneous in the literature, it prevents the relationship between anti-TNF-α therapy and cancer-lymphoma from being identified[13]. A prospective case-controlled study found that patients who received adalimumab and infliximab have more risk than those who received etanercept [standard incidence ratio (SIR): 4.1, 3.6 and 0.9, respectively][12].

The development of lymphoma has been reported in 5.7% of the patients in a study dealing with side effects of using biological agents between 2000 and 2012 in Turkey[14].

According to a research study conducted by Wolfe and Michaud[15] in 18,572 patients with rheumatoid arthritis (RA), the SIR of developing lymphoma was 1.9. In contrast, it was 2.9 after the use of anti-TNF-α agents. Although some studies suggest that the risk of malignancy in patients with RA using anti-TNF-α agents is higher than that of bio-naive patients, these studies included small sample sizes and heterogeneous study populations. Most studies suggested that the general cancer incidence did not increase during or after the anti-TNF-α treatment[16]. No significant difference was found in another large-scale Korean study found no significant difference between anti-TNF-α agents and disease-modifying anti-rheumatic drugs[17].

Studies in the literature include patients with inflammatory bowel disease and RA. Some of these patients used immunosuppressive agents, such as cyclosporine, previously. It is found that the activated immunogenic nature of the disease and previous immunosuppressive treatments were related to oncogenic risk in patients with psoriasis. This condition causes a challenge in evaluating the role of anti-TNF-α agents in the development of lymphoma[4,5].

The increased use of anti-TNF-α agents in patients with psoriasis reveals the importance of treatment duration, follow-up of clinical condition, and physical examination in patients who were initiated on biological agents. It is recommended to make routine skin and lymph node examinations. These examinations should be continued and be made at six months intervals in the first year and then once a year[18].

Long-term pharmacovigilance studies are needed to determine whether cancer risk is directly attributable to biological agents. Infrequently the possibility that hematological malignancies may develop related to using anti-TNF-α agents should be kept in mind. Therefore, regular physical examinations of patients using these agents should be made, and follow-up of patients accompanied by laboratory parameters must be provided.

Ethics

Informed Consent: Informed consent form was obtained from the patient.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: E.Y.B., Ö.Y., N.D., Concept: İ.O.T., E.Y.B., Design: İ.O.T., Data Collection or Processing: E.Y.B., İ.O.T., Analysis or Interpretation: E.Y.B., İ.O.T., Literature Search: E.Y.B., E.M., Writing: E.Y.B., E.M., İ.O.T.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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