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Case Report

Kaposi's Sarcoma in an Ankylosing Spondylitis Patient Treated With Anti-Tumor Necrosis Factor-Alpha Therapy

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ABSTRACT

Tumor necrosis factor-alpha (TNF-α) inhibitors are immunosuppressive agents used in a variety of inflammatory diseases, including rheumatoid arthritis (RA), spondyloarthritis, psoriasis, and inflammatory bowel disease (IBD). Kaposi's sarcoma (KS) is an angioproliferative disease associated with the human herpes virus 8 (HHV-8). We present a 46-year-old male patient with ankylosing spondylitis (AS) treated with TNF-α inhibitor and developed KS during follow-up. The coexistence of anti-TNF-α treatment with KS is a rare condition. This case is presented to address this rare association. Therefore, keeping in mind KS, which is a type of skin tumor, in such HIV-negative patients in whom immunosuppressive agents are initiated, is essential in terms of early diagnosis, treatment, and prevention of complications.

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Introduction

Ankylosing spondylitis (AS) is a chronic inflammatory disease that damages the spine by causing structural changes, including bone growth and fusion. Anti-tumor necrosis factor (TNF) agents use has greatly improved the AS treatment, with anti-TNFs are now routinely recommended by clinical practice guidelines for AS patients with persistently high disease activity following first-line therapy with nonsteroidal anti-inflammatory drugs' (NSAIDs) description added to introduction section.[1] Tumor necrosis factor-alpha (TNF-α) is synthesized by activated macrophages and T cells. TNF-α is important for macrophage activation, phagosome activation, differentiation of monocytes to macrophages, recruitment of neutrophils and macrophages, and granuloma formation and function.[2] TNF-α, a pleiotropic inflammatory cytokine, is now

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recognized as a key pathogenic mediator of infectious and inflammatory diseases.[3] TNF-α with monoclonal antibodies or soluble receptors (etanercept, infliximab, adalimumab, golimumab, certolizumab pegol) has been developed novel treatment options for certain rheumatic diseases. During the past decades, biological agents in rheumatic diseases resulted in better control of disease activity and improved quality of life. However, TNF-α inhibitors are potentially associated with severe side effects. Injection site reactions, infusion reactions, neutropenia, infections, demyelinating disease, heart failure, skin reactions, autoimmunity induction, malignancy.[4] Kaposi's sarcoma (KS) is divided into four types according to the clinical conditions in which it develops: classical (the type originally defined by Kaposi that typically occurs in middle age and old age), endemic (various forms identified in sub-Saharan indigenous Africans), epidemic type immunodeficiency syndrome (AIDS), iatrogenic type (the form associated with immunosuppressive drug therapy typically seen in renal allograft recipients).[5] The iatrogenic variant of KS is classically reported in organ transplant patients undergoing immunosuppressive therapy or those receiving long-term steroids. However, over the past few decades, the use of biological agents such as TNF-α inhibitors has led to an increase in KS cases. Herein, we report a case of iatrogenic KS caused by adalimumab in AS patients receiving TNF-α inhibitor therapy.

Case Report

A 46-year-old male patient, who was followed up in our clinic for 4 years with a diagnosis of AS. The patient had grade 3 bilateral sacroiliitis. Spinal involvement and enthesitis were not present. As a result of genetic analysis, HLA-B27 was found to be negative. The patient who was unresponsive to NSAID treatment received etanercept treatment for 1 year, and then adalimumab treatment was started due to secondary unresponsiveness to etanercept. Adalimumab treatment was interrupted due to coronavirus disease 2019 (COVID-19) infection. He had not been using adalimumab for the last year. While using adalimumab one year ago, purple-black patch-like lesions developed in a limited area on his hand *(Figure 1)*. The patient, who did not come for follow-ups, presented to our outpatient clinic when new lesions developed in both hands and feet in the last 2 months, similar to those at the beginning *(Figure 2)*. There was a history of lobectomy due to tuberculosis 20 years ago in his medical history. No signs of disease activation were detected in the patient, who was followed up regularly for pulmonologist. There was no known systemic disease except AS.

In the physical examination of the patient, vital signs were stable. Head and neck examinations were normal. Respiratory system examination did not reveal respiratory sounds in the upper lobe of the right lung. Cardiovascular system, abdominal and rheumatological examination

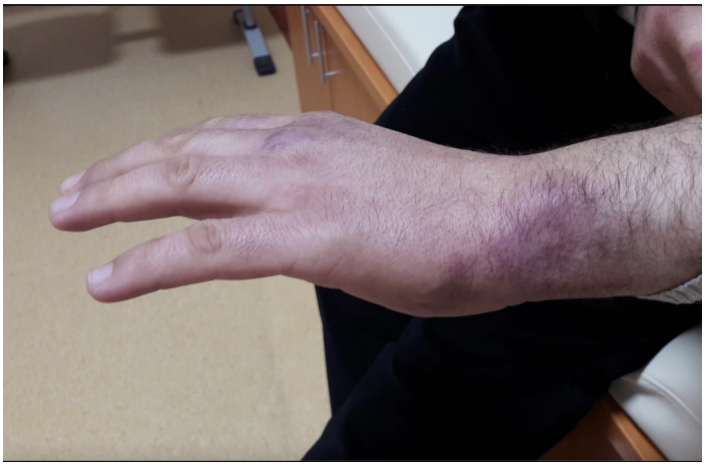

Figure 1. Purple-black patch-like on the patient's hand.

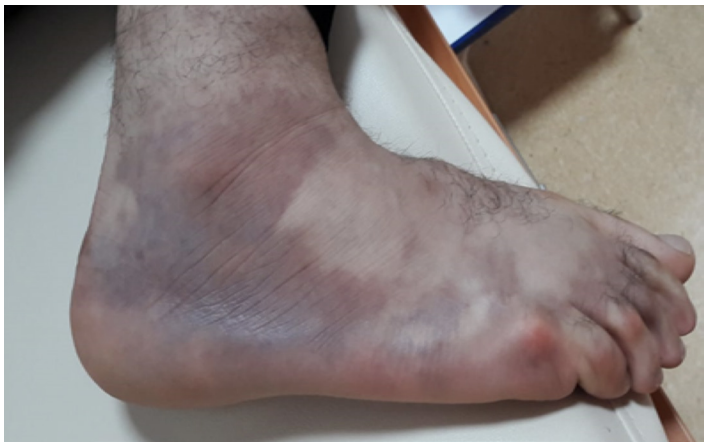

Figure 2. Purple-black patch-like on the patient's foot.

were normal. In the dermatological examination, there were bilateral livingoid patches on the hands and feet; no lesions were found elsewhere on the body. Laboratory parameters; leukocyte 4.0 K/uL, neutrophil 2.6 K/uL hemoglobin 14.2 g/dL, platelet 185 K/uL, blood urea nitrogen 41 mg/dL, creatinine 1.2 mg/dL, alanine aminotransferase 28 U/L, aspartate aminotransferase 29 U/L, lactate dehydrogenase 164 U/L, vitamin B12 642 pg/mL, folic acid 6.03 ng/mL, TSH 1.93 µIU/mL and ferritin 23.6 ng/mL, C-reactive protein (CRP) 8 mg/L, erythrocyte sedimentation rate 11 mm/hour. ANA, RF, anti-CCP, F-ANCA, anti-dsDNA, cold agglutinins, HBsAg, anti-HCV, anti-HIV ELISA tests were found to be negative. The patient was diagnosed with iatrogenic KS as a result of the skin biopsy performed from the foot lesion. Histopathological examination showed expansion of spindle cell vascular processes, and the tissue was stained positive for human herpes virus 8 (HHV8) *(Figure 3)*. The patient did not report any family history of endemic KS. No involvement was observed in the endoscopy and tomography of the neck, thorax, and abdomen in terms of possible involvement. Chemotherapy was initiated for the patient, and he was followed up in the outpatient clinic.

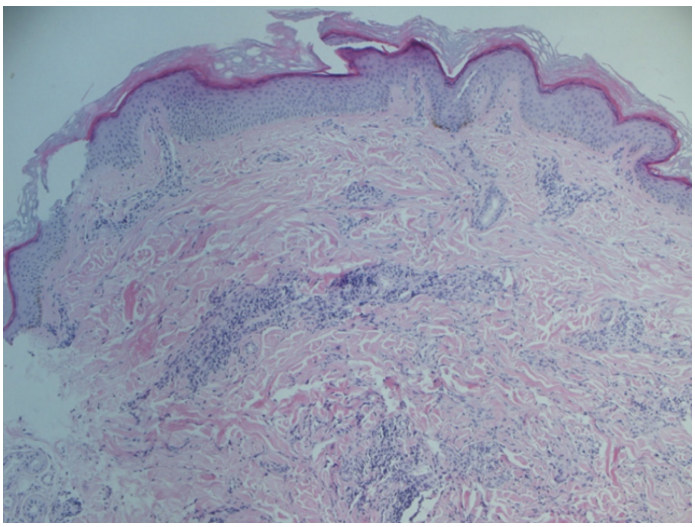

Figure 3. Images of pathology preparations showing Kaposi's sarcoma and images of human herpesvirus 8 stainings.

Discussion

KS is an angioproliferative disease associated with HHV-8.[6] Immunosuppression is a well-defined risk factor for KS. This indicates the presence of cofactors that affect the risk of KS after infection with HHV-8. The iatrogenic variant of KS has traditionally been reported in organ transplant patients receiving immunosuppressive therapy or taking steroids for a long time.[7,8] Iatrogenic CS due to TNF-α inhibitor therapy is rare.[9] Although some meta-analyses of clinical trial data found an increased risk of cancer using TNF-α inhibitor, observational data, especially from registries, generally did not confirm these findings.[10] Overall, there is evidence that TNF-α inhibitors do not increase the risk of most solid tumors, except for some skin cancers. However, uncertainty persists, and study design may affect findings. There is evidence of an increased risk of non-melanoma skin cancer among patients treated with TNF-α inhibitors compared with those who do not receive these agents, including meta-analyses of data from registries, prospective observational studies randomized data.[11-14] In the study, there was no difference in the incidence of malignancy between the three TNF-α inhibitors (infliximab, adalimumab, etanercept) or between different forms of AS, but a significant increase in overall cancer risk was seen. The age at the beginning of treatment with TNF-α inhibitors and the presence and number of comorbidities are also associated with the risk of malignancy, demonstrating that previous malignancy is a significant predictor for a new malignancy. The type of drug was not associated with the risk of malignancy. The data provided by this study are insufficient to determine whether this effect is due to TNF-α inhibitor therapy or other factors.[15] Cancer risk in patients with spondyloarthritis treated with TNF-α inhibitors: a joint study from ARTIS and DANBIO registries In patients with AS, treatment with TNF-α inhibitors was not associated with an increased risk of cancer.[16]

To our knowledge, five KS cases were identified with the use of infliximab, three cases with adalimumab, one with golimumab, and one with certolizumab pegol.[9,17-26] Despite this and the previous report, a casual connection between TNF-α blockade and KS development is still

unclear and should be addressed by appropriate studies. In most of the cases, KS was notably localized to the skin. Except for an ulcerative colitis patient with gastrointestinal involvement of KS.[24] All patients tested negative for HIV. Similar to our patient, in all of the reported cases, KS developed during the use of the biologic agent. Cohen *et al.*[20] described the case of a rheumatoid arthritis patient who developed a typical KS lesion a few weeks after starting infliximab therapy. Kuttikat *et al.*[21] described a case of an older woman with giant cell arteritis (GCA) who developed KS while on a double-blind trial for GCA with an anti-TNF medication. As in the early stages of treatment, cases emerging months and years later, as in our case, have been reported. A close relationship between adalimumab and KS has been emphasized in previous studies.[9,22,23] These patients consisted of rheumatoid arthritis patients. No patients with AS were reported. This AS case is presented to share the association with anti-TNF therapy and KS.

Conclusions

As far as we know, in coincidence with the initiation of TNF-α inhibitory therapy in AS patients, KS has not been reported previously. Due to the rarity of the disease in this patient population, the diagnosis can often be missed or delayed. Therefore, it is significant for patients receiving biologic agents, including anti-TNF-α therapy, to have a close follow-up and receive routine skin evaluation for malignancy. Clinicians should have a high suspicion for KS in such HIV-negative patients starting immunosuppressive agents.

Conflict of Interests

Authors declare that there is no conflict of interest with regard to this manuscript.

Authors' Contribution

Study Conception: SH, DT, SY; Study Design: BS; Supervision: SH, DT, SY; Analysis and Data Interpretation: SH, DT, SY; Literature Review: SH, DT, SY; Manuscript Preparation: SH, DT, SY; Critical Review: SH, DT, SY.

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