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Paper Accepted* **ISSN Online 2406-0895**

Case Report / Приказ случаја

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Iatrogenic Kaposi's sarcoma following immunosuppressive treatment of the recurrent longitudinally extensive transverse myelitis

Јатрогени Капошијев сарком као последица имонусупресивне терапије рекурентног лонгитудиналног екстензивног трансверзалног мијелитиса

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Received: December 13, 2016
Accepted: August 8, 2017
Online First: August 11, 2017
DOI: https://doi.org/10.2298/SARH161213162L

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SUMMARY

Introduction Iatrogenic Kaposi's sarcoma (KS) represents a multifocal, angioproliferative tumor that develops in patients undergoing immunosuppressive treatment and is considered to be induced by activation of latent human herpes virus type 8 (HHV8) infection.

The aim of this report was to present patients with iatrogenic KS due to immunosuppressive treatment.

Case outline We present a 69-year-old male non-HIV patient, previously treated of anti-aquaporin-4 antibody negative recurrent longitudinal extensive transverse myelitis with prednisolone and azathioprine for 1 year. The patient developed bluish and violet plaques and nodules on his face, trunk and extremities. Skin biopsy findings (histopathology and immunohistochemical detection of CD31 expression and anti-HHV8 antibodies in the spindle cells) confirmed the diagnosis of KS. The reduction of immunosuppression and a topical treatment with imiquimod resulted in a partial, but significant regression of skin lesions, but the patient had another relapse of myelitis following the cessation of azathioprine and a reduction in the dose of prednisolone.

Conclusion To our best knowledge, this is the first case of an inflammatory and demyelinating central nervous system disease treated with corticosteroids and azathioprine that was associated with iatrogenic KS. The efficient treatment of both conditions is highly challenging and can be troublesome in specific cases.

Keywords Kaposi's sarcoma; longitudinally extensive transverse myelitis, immunosuppression; human herpes virus 8; imiquimod

Сажетак

Увод Јатрогени Капошијев сарком (КС) представља мултифокални, ангипролиферативни тумор који се најчешће јавља код пацијената који примају неки вид имуносупресивне терапије и сматра се да је последица реактивације латентне хумане херпес вирус 8 (ХХВ8) инфекције.

Циљ овог рада је био да прикаже болесника са јатрогеним КС услед имуносупресивног лечења.

Приказ болесника Приказујемо ХИВ негативног мушкарца старог 69 година, који је претходно лечен годину дана преднизолоном и азатиоприном због анти-аквапорин-4 негативног рекурентног лонгитудиналног екстензивног трансверзалног мијелитиса. Код пацијента је дошло до појаве ливидних папула и нодулуса на носу, лицу, трупу и екстремитетима. Хистопатолошки и имунохистохемијски налаз биоптата коже потврдио је дијагнозу КС (позитивност ћелија на *CD31*, а такође и на ХХВ8 антитела). Редукција имуносупресије и локална терапија имиквимодом довела је до парцијалне регресије кожних промена, али се развио релапс мијелитиса због искључивања азатиоприна и смањења дозе преднизолона.

Закључак На основу доступне литературе, ово је први описани случај јатрогеног КС удруженог са инфламаторним и демијелинизационим обољењем централног нервног система. Ефикасно лечење оба стања је изузетно комплексно и тешко у одређеним случајевима, као што је и наш.

Кључне речи: Капошијев сарком; лонгитудинални екстензивни трансверзални мијелитис; имуносупресија; хумани херпес вирус 8; имиквимод

INTRODUCTION

Kaposi's sarcoma (KS) represents a multifocal, angioproliferative tumor that is currently recognized in four different clinical types: classical, endemic in Africa, epidemic associated with Acquired Immune Deficiency Syndrome, and iatrogenic. Iatrogenic KS develops in patients undergoing immunosuppressive treatment and is considered to be induced by an activation of the latent human herpes virus type 8 (HHV8) infection [1, 2].

The aim of this report was to present patients with iatrogenic KS due to immunosuppressive treatment.

CASE REPORT

We describe a 69-year-old man who developed multiple KSs on his face, trunk and extremities following long-term immunosuppressive therapy for recurrent longitudinally extensive transverse myelitis (LETM).

The patient was admitted to our dermatology department with multiple violaceus plaques and nodules, some of which were ulcerated. The lesions were present on his face, neck, and trunk (Figure 1. A, B). During the previous 1 year-period, the patient was treated by neurologist for a recurrent, anti-aquaporin 4 (AQP4) antibody negative LETM, affecting six vertebral segments on thoracic spinal

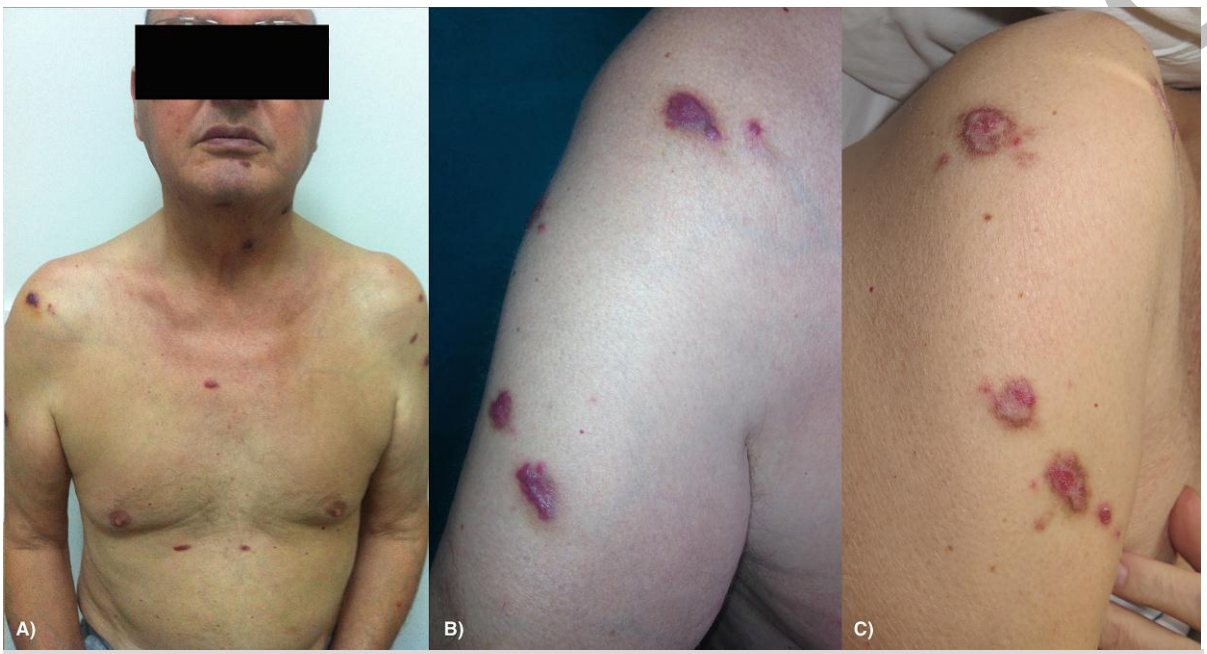

Figure 1. A) Violaceus plaques present on the patient's face, trunk and extremities; B) Close-up of the lesions, infiltrated violaceus plaques with telangiectasia on the periphery of the lesions C) Almost complete resolution of the lesion during the immunosuppression-free period.

cord magnetic resonance imaging with no clinical or subclinical signs of optic nerve or brain involvement. As part of the neurological work-up, neurosarcoidosis, systemic autoimmunity and paraneoplastic conditions were considered, but could not have been confirmed. The patient has been also tested negative for syphilis, Borrelia Burgdorferi, hepatitis B virus, hepatitis C virus and human immunodeficiency virus (HIV). Cerebrospinal fluid tests for herpes simplex virus type I and II, varicella zoster virus and cytomegalovirus were also negative, while tests for human T-lymphotropic virus type I or II could not have been performed due to technical limitations. Prior to the skin lesion eruption, the patient had five attacks of myelitis over the period of 3 years. At his first myelitis attack, the patient was treated with high-dose methylprednisolone (1000mg/day) for five days, intravenously, followed by oral steroid taper. However, a reduction in the maintenance dose of prednisolone below 30mg/day was always associated with a relapse of myelitis and therefore azathioprine was introduced as steroid-sparing agent. Prior to the first skin eruption, the patient was treated with azathioprine in

addition to corticosteroids for one year. At the time of skin lesion eruption, the patient received oral prednisolone (50 mg/day) in addition to azathioprine (2.5mg/kg/day).

Digital dermoscopy revealed a vascular lesion consisted of homogenous whitish and reddish formations and multiple telangiectasia. Histopathological analysis of the skin biopsy showed multiplied and dilated vascular formations comprised of spindle cells with numerous extravagated erythrocytes and siderophages, admixed with lymphocytes and eosinophils. Additional immunohistochemistry analysis revealed high intensity expression of CD31 and HHV8 nuclear antigen in the spindle cells (Figure 2). The tests for HIV infection were repeated (both anti-HIV antibodies and tests for HIV antigens) and were consistently negative.

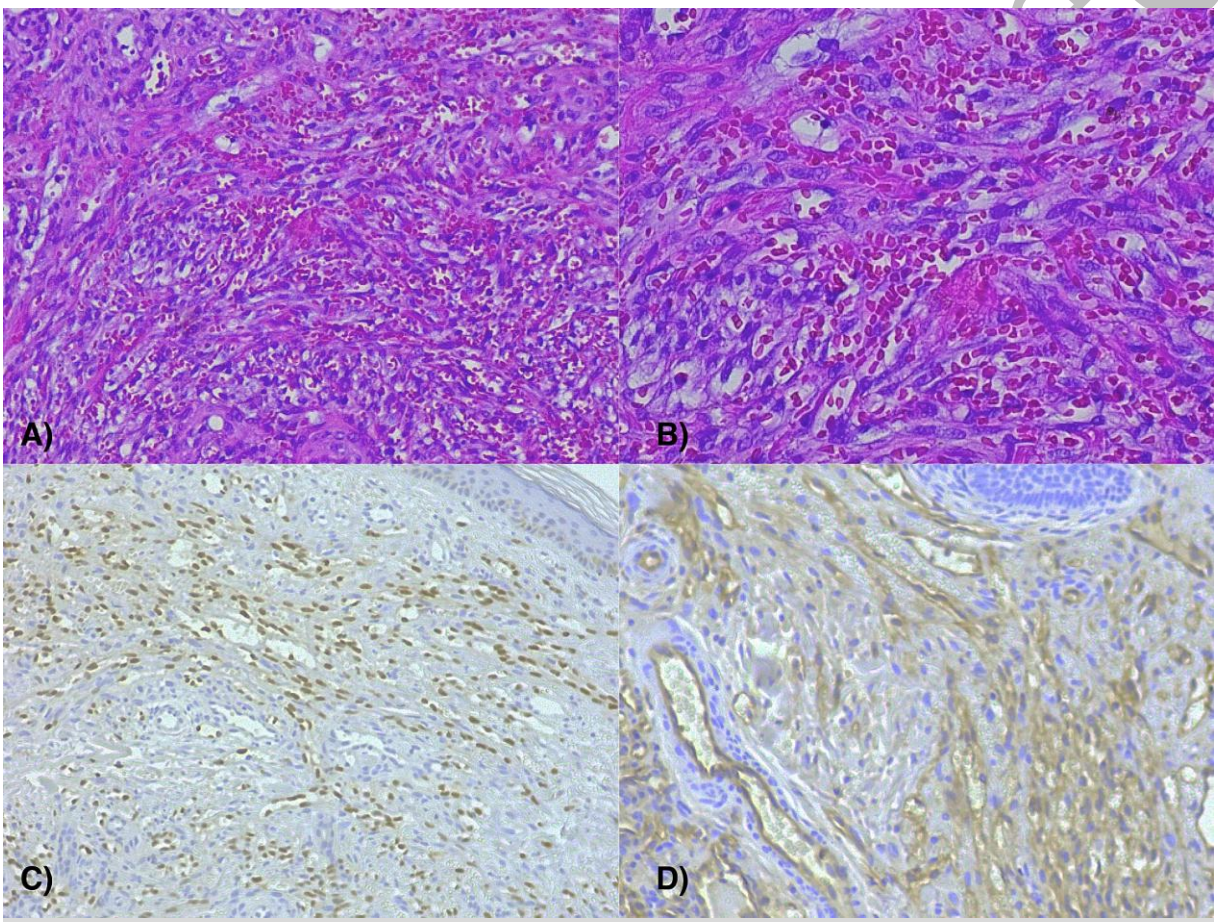

Figure 2. A) and B) Multiplied and dilated vascular formations comprised of spindle cells with numerous extravagated erythrocytes and siderophages, admixed with lymphocytes and eosinophils ((H&E, A) ×100, B) ×200); C) IHH HHV8 positive cells, ×100; D) IHH CD31 positive cells, ×100.

Considering the diagnosis of widespread KS, the neurologist ceased azathioprine and tapered the dose of prednisolone to a daily dose of 30 mg. The patient was additionally treated with topical 5% imiquimod cream for 5-months and partial regression of skin lesions occurred.

However, the reduction in immunosupression resulted in another severe relapse of myelitis and high-dose methylprednisolone treatment (1000mg/day over 5 days) was again introduced, followed by oral prednisolone in a daily dose of 1mg/kg . Unfortunately, this treatment was complicated by salmonella enteritidis sepsis and disseminated intravascular coagulation (DIC) syndrome. During the

treatment of sepsis and DIC as life-threatening conditions, steroid treatment has been temporarily stopped for 1 month and after the resolution of both sepsis and DIC, it was again introduced in the dose of 20mg/alternate days of prednisolone. During the immunosuppression-free period, KS lesions resolved almost completely (Figure 1. C), but his neurological condition further worsened to the level of spastic paraplegia.

DISCUSSION

To our best knowledge, this is the first case of an inflammatory and demyelinating disease of the central nervous system (CNS) treated with corticosteroids and azathioprine that was associated with iatrogenic KS.

Until now, majority of the cases of iatrogenic KS were described to develop after 1 year of immunosuppressive therapy with steroids, cyclosporine or azathioprine [3]. There are only a few cases of iatrogenic KS induced by immunosuppression in a neurological disease [4, 5]. In both of these cases the immunosuppressant agent was suspended, with a partial regression of the KS lesions in one case [5], and a total regression after an additional local radiotherapy in the other [4]. The main therapy protocol in iatrogenic KS is the discontinuation of the culprit immunosuppressive agent since it has been demonstrated that a re-activation of the latent HHV8 infection, which can be induced by immunosuppression, is essential for the onset of all KS forms [6]. In our patient, KS lesions partially resolved following the reduction in immunosuppressive therapy and almost completely resolved following a temporary discontinuation of steroids during the severe life-threatening infection.

Kotter et al reported a promising result of treatment KS with interferon (IFN) alpha in a patient with Bechet's disease who developed this malignancy (skin, mucosa, and pulmonary lesions) after a long-term triple immunosuppressive therapy with prednisolone, cyclosporine A, and azathioprine [7]. Although we also considered treatment with IFN alpha in our patient, we have not introduced such a therapy since off-label treatment with IFN alpha was not available in our country. Additionally, type-I IFNs might potentially induce worsening of neuromyelitis optica (NMO) patients [8]. Although our patient was anti-AQP4 antibody negative, and since we have not identified any other neurological condition that might be associated with recurrent LETM, we initially considered this patient to have NMO spectrum disease (NMOSD) according to the definition of Wingerchuk et al. [9]. However, the clinical presentation of the recurrent LETM would not meet the latest NMOSD diagnostic criteria [10]. Another treatment option in our patient was local radiotherapy, which had to be yield considering the large number and dissemination of KS lesions.

To the best of our knowledge, we here present the first case of an inflammatory and demyelinating disease of the CNS associated with iatrogenic KS presenting with typical course followed by the resolution after the complete withdrawal of immunosuppressive drugs. The efficient treatment of both conditions is highly challenging and can be troublesome in specific cases. Since there are no unequivocal treatment guidelines for the cases of an association of the disease needed to

be treated with immunosuppressants, with the disorder caused by immunosuppressants, there is always a necessity to balance the seesaw in order to offer the best possible treatment in such circumstances.

ACKNOWLEDGEMENT

This study was partially supported by a grant from the Republic of Serbia Ministry of Education, Science and Technological Development project number: 175031 (dr. Dujmović and dr. Drulović), 175065 (dr. Škiljević) and 175038 (dr. Medenica)

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