Sarcoma di Kaposi indotto da terapia steroidea in paziente con infezione da HIV affetto da glomerulopatia a lesioni minime, durante terapia antiretrovirale con alti linfociti T CD4+ e viremia non rilevabile.

Steroid induced Kaposi Sarcoma in an HIV living person affected by minimal change disease nephropathy, undergoing antiretroviral treatment with undetectable viral load and high CD4+ cell count.

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Riassunto

Mentre la prevalenza del Sarcoma di Kaposi (SK) tra le persone che vivono con l'HIV sta significativamente diminuendo grazie all'introduzione della terapia antiretrovirale, forme di SK iatrogeno sono in aumento a causa dell'ampio uso di terapie immunosoppressive per malattie autoimmuni, neoplasie e trapianti.

Gli steroidi sono la forma più utilizzata di terapia immunosoppressiva e casi di SK indotti da terapia steroidea sono stati riportati anche in pazienti senza infezione da HIV. Il contesto, la patogenesi, la gestione e la prognosi di questi casi rimangono, ad oggi, poco conosciuti. Solitamente, il trattamento del SK iatrogeno richiede la sospensione o la riduzione della dose di immunomodulatori, ma questo spesso si associa al rischio di riacutizzazione della patologia sottostante.

Riportiamo il caso di un uomo con infezione da HIV in terapia antiretrovirale, con carica virale per HIV non rilevabile e elevata conta di cellule CD4+, che ha sviluppato SK cutaneo, dopo l'avvio del trattamento con corticosteroidi per glomerulopatia a lesioni minime.

La gestione di questo caso è stata piuttosto impegnativa per il delicato equilibrio tra terapia immunosoppressiva e rischio di progressione della patologia opportunistica.

Abstract

While the prevalence of Kaposi Sarcoma (KS) among people living with HIV has significantly decreased since the introduction of Antiretroviral Therapy, iatrogenic KS is increasing due to the wide use of immunosuppressive therapies for autoimmune diseases, cancers and transplants. Steroids represent the most widely used form of immunosuppressive therapy, and steroid-induced KS cases have also been reported in patients without HIV infection, but the typical background, management, and prognosis remain unknown. Usually, treatment of iatrogenic KS requires withdrawal or a dose reduction of immunomodulators, but this is frequently associated with the risk of underlying condition relapse.

We present the case of a man living with HIV infection on antiretroviral therapy with undetectable HIV viral load and high CD4+ cell count, who developed cutaneous KS, after corticosteroid treatment for minimal change disease (MCD) nephropathy. The management of this case was quite challenging to achieve a fine balance between immunosuppressive therapy and the progression of KS.

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Introduction

Kaposi sarcoma (KS) is a rare angioproliferative tumor caused by human herpesvirus 8 (HHV8) and Kaposi sarcoma–associated herpesvirus (KSHV) in the context of immunodeficiency, such as that induced by HIV infection or immunosuppressive therapy.

While the prevalence of KS among people living with HIV (PLHIV) has significantly decreased since the introduction of Antiretroviral Therapy (ART), iatrogenic KS is increasing due to the wide use of immunosuppressive therapies for autoimmune diseases, cancers and transplants.

Steroids are the most widely used form of immunosuppressive therapy, and steroid-induced KS cases have also been reported in patients without HIV infection, but the typical background, management, and prognosis remain unknown.

We herein report a case of steroid-induced cutaneous KS in a man living with HIV in stable antiretroviral therapy and high CD4+ cell counts.

Case Report

A 50-year-old male was diagnosed with HIV in 2003 and started ART in 2011 with TDF/FTC/EFV with a nadir CD4+ cell count of 469cells/mmc. No resistance-associated mutations were present at baseline genotyping. Over the following years, ART was changed for toxicity and simplification purposes, but he never experienced virological failure nor AIDS-defining events. HIV-RNA remained undetectable since the beginning of the treatment, with CD4+ cell count increasing to 900cells/mmc, therefore in September 2011 he started lamivudine/dolutegravir as a simplification strategy. The patient reported a history of acute hepatitis A, he was treated for late latent syphilis with Benzathine Penicillin G and was negative for HCV and vaccinated for HBV. He also was overweight, with a BMI of 28, he was being treated with ACE-inhibitors for hypertension and with alpha-blockers for benign prostatic hyperplasia.

In May 2022, a nephrology consultation was asked for severe proteinuria of 600 mg/dl (8.1 g per day). Urine analysis also showed: albuminuria >400 mg/dl (5.47 g daily), UACR (Urine albumin-to-creatinine ratio) 603 mg/mmol. Serum creatinine and creatinine clearance were normal, 1.04 mg/dl and 138.4 ml/min, respectively.

A kidney biopsy was performed, which was consistent with minimal change disease (MCD). As a first line treatment he started prednisone 75 mg (0.8 mg/kg) and acetylsalicylic acid as antiplatelet and endothelial cell protection for severe proteinuria.

After 14 weeks of steroid treatment, proteinuria significantly reduced (24-h proteinuria 1.65 g, 189 mg/dl) but the patient presented right lower limb edema and a bluish nodular lesion at his right ankle. A skin biopsy confirmed KS suspicion, then prednisone was rapidly tapered.

Further analysis showed HHV8: 4162 copies/ml, reduced CD4 cell count to 281cells/mmc (CD4/CD8: 0.8) with undetectable HIV-RNA.

Total body FDG PET evidenced bilateral inguinal adenopathy of 15 mm of maximum diameter with increased radiotracer uptake.

No gastrointestinal KS lesions were found at the gastroscopy and colonoscopy examination.

A lymph node biopsy revealed KS localization and very few findings related to multicentric Castleman disease.

After prednisone reduction at 7.5 mg/day, we observed a flattening of the skin nodules and no appearance of new lesions, HHV8 viremia resulted negative, HIV-RNA undetectable and CD4+ count raised up to 537 cells/mmc, but proteinuria increased again at nephrotic range level of 3850 mg daily (154 mg/dL). After two months there was a further increase of proteinuria at 8284 mg daily (414 mg/dL), so it became necessary to increase immunosuppression.

Considering the undergoing KS and the risk of HHV8 reactivation, cyclophosphamide 150 mg was started instead of cyclosporine and prednisone was reduced to 5 mg daily.

During the following months, daily proteinuria improved to 1.7 g (84 mg/dL), but in the fourth month of cyclophosphamide treatment we also saw a CD4+ cell count decline to 297 cells/mmc, HIV-RNA became slightly detectable with 29 copies/mL, HHV8 viremia increased up to 115 cp/mL. The dose of cyclophosphamide was reduced to 100 mg and then stopped after having completed 6 months of treatment. A low prednisone dose of 5 mg/2.5 mg was continued every other day.

During the following months, proteinuria remained almost stable with a prednisone dose of 5 mg/2.5 mg every other day, HHV8-DNA and HIV-RNA remained undetectable with CD4+ cell counts at 450 cells/mmc.

Table 1. Nephrological and immunovirological parameters during immunosuppressive therapy. **TND:** target not detected.

	Baseline	1 month	3 months	4 months	6 months	8 months	9 months	12 months	13 months	14 months	15 months	20 months	25 months
albuminuria mg/dl	327	113	57	41	89	231	182	71	55	44	29	44	31
24h albuminuria g	6,22	2,5	1,26	0,83	2,2	4,62	3,19	1,46	1,42	1,32	0,92	1,3	0,94
proteinuria mg/dl	427	163	75	59	154	414	299	84	75	59	40	65	49
24h proteinuria g	8,12	3,6	1,65	1,1	3,8	8,2	5,2	1,73	1,92	1,77	1,3	2,01	1,47
HIV RNA copies/ml	<20	TND	<20		<20	TND		29	<20	<20	<20	TND	TND
HHV8 DNA copies/ml				4162	<250	<250	<98	115	215	<98	TND	946	<350
LTCD4 n /mmc (%)	940 (32%)	281 (33%)	454 (30%)		537 (33%)	442 (34%)		163 (26%)	295 (30%)	317 (29%)	272 (33%)	411 (34%)	453 (33%)
CD4/CD8	0,8	0,8	0,7		0,8	0,96		0,47	0,66	0,61	0,76	0,88	0,82
Prednisone dose mg/day	75	75	62,5	37,5	7,5 / 5	5	5	5	5	5	5	5 / 2,5	5 / 2,5
Cyclophosphamide dose mg/day						150	150	150	100	100			

The patient continued ART with lamivudine/dolutegravir with no specific adverse events nor virological failure, with the exception of the above-mentioned detection of 29 cp/ml.

Table 1 summarizes nephrological and immunovirological parameters during immunosuppressive therapy.

Discussion

Here we present the case of a man living with HIV infection on antiretroviral therapy with undetectable HIV viral load and high CD4+ cell count, who developed cutaneous KS, after corticosteroid treatment for MCD nephropathy.

MCD is a major cause of idiopathic nephrotic syndrome (NS), is characterized by intense proteinuria leading to edema and intravascular volume depletion. In adults, it accounts for approximately 15% of patients with idiopathic NS. First line treatment requires steroids, but about 10%–20% of cases of adult MCD are steroid-resistant. Treatment of steroid-resistant diseases includes calcineurin inhibitors and cyclophosphamide. In adults, relapses are frequent, occurring in about 56%–76% of patients requiring further immunosuppressive treatment courses (1).

KS is an opportunistic, angioproliferative tumor, closely related to HHV-8 and KSHV replication with cutaneous, mucosal and visceral involvement. HHV-8 and KSHV replication is also associated with the pathophysiology of primary effusion lymphoma, HIV-associated multicentric Castleman disease, and Kaposi sarcoma inflammatory cytokine syndrome.

Its incidence has dramatically fallen in PLHIV since the introduction of antiretroviral combination therapy 30 years ago due to the restoration of immunity and better control of HIV replication. However, KS is still one of the most frequently occurring cancers in PLHIV, in particular in men who have sex with men and in sub-Saharan Africa, where it is still endemic.

Even in the context of restored immunity, the risk of KS is still more than 30 times higher in PLHIV than in the general population (2).

Immune restoration after antiretrovirals start leads to KS lesions regression in several months in localized non-aggressive forms, while in more aggressive form systemic treatments are needed, which may rely on chemotherapeutic agents such as liposomal doxorubicin, taxanes, or immune-modulating therapy (interferon alpha or PEG-interferon), or antiangiogenic agents.

Iatrogenic KS is a variant that is associated with immunosuppression or transplant, developing after immunosuppressive therapy.

KS generally develops 2–3 years after transplantation and is largely due to HHV8 reactivation in transplant recipients, although HHV8 can also be transmitted by donor organs (3).

Post-transplantation KS is generally managed by reducing immunosuppressive treatment to the lowest levels compatible with allograft function or by changing the immunosuppressive agent, such as switching from calcineurin inhibitors to mTOR inhibitors (2).

In a recent review, Endo and colleagues reported 33 cases of iatrogenic KS excluding HIV and transplant patients (4).

The underlying diseases included autoimmune disorders such as pemphigus vulgaris, bullous pemphigoid, rheumatoid arthritis, Behçet's disease, ulcerative colitis, and Crohn's disease. KS most frequently developed on the skin in 26 cases, followed by the gastrointestinal tract in 11 cases, half of them had ulcerative colitis or Crohn's disease. The most commonly used steroid was prednisolone, and the amount of steroid used ranged from 2.5 to 80 mg/day.

In 20 of 33 cases, discontinuation or tapering of steroid dose was selected for treatment. Of these 20 cases, 14 (70%) showed improvement, while 6 (30%) did not.

Treatment of iatrogenic KS requires withdrawal or a dose reduction of immunomodulators, but this is frequently associated with the risk of relapses of the underlying condition.

Indeed, in the case we are describing, reduction of prednisone after the first cutaneous KS appearance, led to a proteinuria increase, on the other hand, high doses of prednisone or cyclophosphamide were followed by reactivation of HHV8 increasing the risk of the opportunistic disease evolution.

PLHIV, even if on stable ART treatment and high CD4+ cell counts, present an immunological impairment due to the lack of a complete restoration overlaying chronic immune activation. These conditions made the case quite challenging for the achievement of the fine balance between immunosuppressive therapy, required by the kidney disease, and the progression of KS. Closed monitoring and a longer follow up is necessary to define the outcome of both the glomerulopathy and the opportunistic disease. ■

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