

Kaposi's Sarcoma after Long-Acting Steroids: Time until Remission and Drug Washout

D. Nassar^a N.E.C. Scharztz^a C. Bouché^b A. Lévy^a D. Kerob^a F. Agbalika^d M. Lafaurie^c
C. Lebbé^a

Departments of ^aDermatology, ^bEndocrinology and ^cInfectious Disease, and ^dLaboratory of Virology,
Hôpital Saint-Louis, AP-HP, Paris, France

Key Words

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Abstract

Long-acting steroids (LAS) are widely used to treat various inflammatory diseases and allergies. They have many adverse effects including the inhibition of the hypothalamo-pituitary axis that can last several months. LAS are also strong immunosuppressors and can result in severe opportunistic infections and immunodeficiency-related malignancies. However, the time needed for immune recovery after withdrawal of LAS is unknown. Here we report a case of Kaposi's sarcoma (KS) and severe immunosuppression after a chronic triamcinolone acetonide (TA) treatment. Six months after withdrawal, traces of TA were still detected in the serum by HPLC mass spectrometry. At 8 months, the drug became undetectable, and clinical and biological signs of immune recovery – beginning of KS regression, normalization of IgG levels and CD4 T lymphocyte counts – became noticeable. We then provide a review of the literature on the time until remission of KS after immunosuppression reduction. We also reviewed the cases of KS induced by TA, and the metabolic side effects of TA when compared to standard glucocorticoids.

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Introduction

Long-acting steroids (LAS) are widely used to treat inflammatory and allergic diseases. After a single intramuscular injection in humans, plasma levels of triamcinolone acetonide (TA) are detectable for 14–21 days, and the suppression of pituitary-adrenocortical function lasts for 4 weeks [1]. After long-term administration, intramuscular TA inhibits the hypothalamic-pituitary-adrenal axis for up to 10 months after the last dose [2]. LAS are also strong immunosuppressors and can result in severe opportunistic infections and immunodeficiency-related malignancies [3–6]. The time needed for immune recovery after withdrawal of LAS remains unknown. Here, we report a case of Kaposi's sarcoma (KS) secondary to a long-term administration of intramuscular TA, in which we monitored clinical and biological parameters of drug washout during 12 months.

Case Report

A 62-year-old Ethiopian physician was admitted to the department of dermatology for an HIV-negative steroid-induced KS. He had been using self-administered intramuscular injections of LAS TA (Kenacort retard®) for nearly 2 years to relieve

chronic back pain and arthralgias. The estimated cumulative injected dose of TA was 2.4 g. He presented with severe amyotrophy, Cushing-like facies, abdominal obesity, insulin-requiring diabetes – negative for anti-glutamic-acid-decarboxylase, anti-insulinoma-associated protein-2 and anti-islet-cell-antigen autoantibodies – and adrenal blockade necessitating a steroid substitution. He had invasive ulcerative skin KS nodules on the legs and feet, especially on the plantar surface and on the toes (fig. 1) with a debilitating lymphedema. The human herpesvirus 8 DNA load in peripheral blood was 524 copies/ml. He also had severe immunosuppression, with hypogammaglobulinemia (IgG 4.6 g/l) and low CD4 T lymphocyte count in peripheral blood (116/mm³, 12% of the total lymphocyte count) which led to several infections during 8 months following LAS withdrawal: 2 *Pseudomonas aeruginosa* sepsis, a catheter-related *Staphylococcus aureus* sepsis, cytomegalovirus viremia, leg cellulitis and *Aspergillus fumigatus* spondylodiscitis confirmed by vertebral biopsy. These severe and opportunistic infections contraindicated chemotherapy for KS except for 2 infusions of paclitaxel (100 mg/m² at a 2-week interval) and 2 courses of bleomycin (10 mg at a 2-week interval) with intravenous immunoglobulin in the first 5 months of follow-up. Despite these therapies, the KS dramatically worsened.



Fig. 1. a Severe invasive KS secondary to a chronic TA treatment. Clinical improvement of the cutaneous KS lesions started 8 months after LAS withdrawal (**b**), and remission occurred after 12 months (**c**).

Since little is known about LAS wash-out after long-term administration, we monitored the blood levels of TA by HPLC mass spectrometry. Traces of the drug (1.2 pg/ml) were detected up to 6 months after withdrawal and became undetectable at 8 months. At that time point we started to notice flattening of the KS nodules and a decrease in lymphedema. Interestingly, CD4 T cells and IgG plasma levels also returned to normal values 8 months after withdrawal (table 1). At the same time, blood glucose levels returned to normal values, and insulin administrations were no longer needed. Interferon α (3 million IU, 3 times per week) was added 2 months later in order to accelerate improvement. At 12 months, the patient's KS lesions had improved considerably, and he did not develop any further infections and regained his autonomy. Nevertheless, there was still adrenal blockade upon Synacthen[®] stimulation.

Discussion and Review

This observation provides interesting pharmacological data concerning wash-out of TA after a long-term parenteral

treatment. In our patient, after 2 years of monthly 100 mg i.m. TA, serum levels became undetectable 8 months after withdrawal. Interestingly, this coincided with clinical evidence of drug clearance, as steroid-induced complications started to regress, including diabetes, cushingoid facies and amyotrophy. Clinical evidence of immune recovery could be reflected by the regression of KS lesions and the return of CD4 T cell counts and IgG levels to normal values. And these parameters also occurred 8 months after TA withdrawal. Moreover, new opportunistic infections no longer occurred after that time. Of notice, the traces of TA (1.2 pg/ml) detected in the blood at 6 months are well below the concentrations of glucocorticoids that induce immunosuppression in vitro and in vivo [7–9]. However, all experimental data in the literature on glucocorticoid-induced immunosuppression are done after short-term exposures. In our patient, the very low traces of TA detected at 6 months after a very long exposure were accompanied by low IgG levels and CD4 T cell counts (table 1). Nevertheless, our observation lacks immunological functional tests for a more accurate evaluation of biological immune recovery.

In transplant-related KS, the time to complete or partial clinical remission after the first reduction of immunosuppressive therapy was estimated to be 11.2 months (range 4–20) in a short series [10], but stable disease is generally noted within 3–6 months. Duman et al. [11] have reported that complete remission occurred after 6 months of immunosuppression reduction in 8 of 11 renal-transplant patients who developed KS. Clinical remission is achieved in 3–3.9 months after a switch of immunosuppression to rapamycin [12, 13]. In HIV-related KS patients, time to response to highly active antiretroviral therapy is extremely variable, ranging from 3 to 9 months with the possibility of a paradoxical initial deterioration [14].

KS was reported to develop after standard glucocorticosteroid therapy alone for a wide variety of inflammatory diseases in various doses and treatment periods [5, 15–21]. In most of the reported cases, spontaneous regression occurred after treatment discontinuation. When specified, the time to achieve clinical remission ranged from 4 to 7 months [15, 22, 23].

Moreover, KS has been described to develop secondary to oral, intra-articular, topical and intralesional skin injections of

Table 1. Clinical and biological follow-up from a patient who developed KS secondary to a chronic treatment with intramuscular TA

	At presentation	6 months after TA withdrawal	8 months after TA withdrawal	12 months after TA withdrawal
Clinical evaluation	cushingoid features, severe invasive KS, diabetes	cushingoid features, worsening of KS, opportunistic infections, diabetes	improvement of KS, immune restoration, improvement of cushingoid features and diabetes	no cushingoid features, no diabetes, significant improvement of KS
Lymphocyte count, n/mm ³	2,500	967	1,817	3,800
CD4 T cells, %	13 (325/mm ³)	12 (116/mm ³)	34 (618/mm ³)	ND
IgG (normal 7–15), g/l	6.1	4.6	6.2	8.0
Insulin dose per day, IU	30	30	24, daily dose gradually decreased and insulin stopped after 10 months	no insulin or any other diabetes drug
ACTH levels (normal 20–80), pg/ml	<5	2	ND	ND
Cortisol level, mg/ml				
Baseline (normal 60–245)	12	6	9	52
After Synacthen (normal 195–400)	ND	81	32	104
TA levels, pg/ml	ND	1.2	undetectable	undetectable

The drug washout and the clinical signs of immune recovery occurred around 8 months after withdrawal. ND = Not determined; ACTH = adrenocorticotropin.

Table 2. TA-induced KS: clinical features of cases reported in the literature

	TA dosage and duration	Disease	Other immuno-suppressors	KS severity	Opportunistic infections	Evolution
Trattner et al. [5]	TA p.o. 8 mg/day	chronic asthma	none	skin nodules	not reported	spontaneous regression after withdrawal, time not specified
Avalos-Peralta et al. [24]	TA intralesional, 40 mg, 2 injections	pemphigus vulgaris	prednisone, mycophenolate mofetil	skin nodules at the injection site	not reported	lesions completely excised for diagnosis
Selvi et al. [6]	TA intra-articular	psoriatic arthritis	none	skin nodules	not reported	spontaneous regression after withdrawal, time not specified
Pérez et al. [25]	TA topical	erythroblastopenia, thymoma	none	nodule on the tongue	not reported	spontaneous regression after withdrawal, time not specified
Our patient	TA intramuscular, 40 mg every 10 days, 2 years	back pain and arthralgia	none	invasive cutaneous	<i>Aspergillus fumigatus</i> spondylodiscitis	spontaneous regression: began at 8 months, interferon α added at 10 months, remission at 12 months

TA [5, 6, 24, 25]. In 3 of the 4 cases, KS regressed spontaneously after treatment discontinuation; the time until remission was not specified. Available characteristics of these patients as well as of our patient are summarized in table 2.

Our observation is, to our knowledge, the first well-documented KS secondary to long-term intramuscular TA injections.

And that, besides the rare opportunistic *A. fumigatus* spondylodiscitis, reflects the deep immunosuppression that could occur after such a treatment regimen.

Whether long-term parenteral TA induces more side effects than conventional steroids remains unclear. Kurosawa et al. [26] compared the efficacy and safety of 3 corticosteroids in the treatment of alope-

cia areata: (1) oral dexamethasone 0.5 mg/day for 6 months, (2) intramuscular TA 40 mg once a month for 6 months followed by 40 mg once every 1.5 months for 1 year, and (3) pulse therapy using oral prednisone 80 mg for 3 consecutive days once every 3 months. Side effects were reported in 41% of the intramuscular TA group, 30% of the dexamethasone group and 10% of

the pulse oral prednisone group, but these side effects did not include hypertension, peptic ulcer, elevated fasting blood sugar, abnormal serum chemical profiles or lenticular opacities. Impairment in the adrenopituitary axis was noted in 23% of the patients given intramuscular TA and they recovered only 2 months after withdrawal. McLeod et al. [27] compared TA 80 mg i.m. every 4 weeks to daily oral prednisone 10 mg in the treatment of asthma. After 24 weeks, patients treated with intramuscular TA had lower plasma cortisol levels, more bruising, hirsutism and cushingoid facies. Willey et al. [28] compared TA 80 mg i.m. every 4 weeks to daily oral prednisolone 5 mg, during 24 weeks in chronic asthma. They observed less adrenal suppression in the intramuscular TA group, but more menstrual irregularities, muscle pain and hirsutism. Origala et al. [29] compared high doses of TA (360 mg i.m.)

for 3 consecutive days to daily oral prednisone (median dose 12.5 mg) for 30 days. Steroid-induced side effects were more frequent in the intramuscular TA group.

In pediatric patients, monthly TA (1 mg/kg i.m. initial dose, with 10–20% tapering every month) during a mean period of 14 months induced decreased growth velocity compared to oral prednisone 1 mg/kg [30]. Metabolic adverse effects were also observed after repeated local injections of TA especially in children. Adrenal blockade could last up to 7 months after repeated intra-articular injections [31]. Kumar et al. [32] demonstrated the persistence of TA in the plasma and urine up to 4–5 months after intra-articular or intradermal administration, and that it was associated with Cushing's syndrome and adrenal blockade that lasted 4–5 months.

Although treatment periods with TA in the majority of these studies were short-

er than in our observation, none have reported opportunistic infections or severe immunodeficiency. Trattner et al. [5] noticed that 6 of their 10 patients with steroid-induced KS belonged to an ethnic group known to have a susceptibility to classic KS. Of notice, our patient comes from a region with a high prevalence of KS.

Our observation provides original data on the time until complete drug washout and clinical signs of immune recovery – as shown by KS regression and return to normal CD4 and IgG levels – after long-term intramuscular TA. Such a regimen should be avoided in the treatment of chronic dermatological inflammatory or allergic diseases, especially in patients with a predisposing geographical background for KS.

References

- Kusama M, Sakauchi N, Kumaoka S: Studies of plasma levels and urinary excretion after intramuscular injection of triamcinolone acetate. *Metabolism* 1971;20:590–596.
- Carson T, Daane TA, Weinstein RL: Long-term intramuscular administration of triamcinolone acetate: effect on the hypothalamic-pituitary-adrenal axis. *Arch Dermatol* 1975;111:1585–1587.
- Hafner C, Linde HJ, Vogt T, Breindl G, Tintelen K, Koellner K, Landthaler M, Szeimies RM: Primary cutaneous cryptococcosis and secondary antigenemia in a patient with long-term corticosteroid therapy. *Infection* 2005;33:86–89.
- Sohail MR, Smilack JD: *Aspergillus fumigatus* septic arthritis complicating intra-articular corticosteroid injection. *Mayo Clin Proc* 2004;79:578–579.
- Trattner A, Hodak E, David M, Sandbank M: The appearance of Kaposi sarcoma during corticosteroid therapy. *Cancer* 1993;72:1779–1783.
- Selvi E, De Stefano R, Manganelli S, Marcolongo R: Kaposi's sarcoma in psoriatic arthritis. *Rheumatology (Oxford)* 2003;42:389.
- Mager DE, Moledina N, Jusko WJ: Relative immunosuppressive potency of therapeutic corticosteroids measured by whole blood lymphocyte proliferation. *J Pharm Sci* 2003;92:1521–1525.
- Scheinman RI, Cogswell PC, Lofquist AK, Baldwin AS Jr: Role of transcriptional activation of I kappa B alpha in mediation of immunosuppression by glucocorticoids. *Science* 1995;270:283–286.
- Uhl A, Czock D, Boehm BO, Zellner D, Mertz A, Keller F: Pharmacokinetics and pharmacodynamics of methylprednisolone after one bolus dose compared with two dose fractions. *J Clin Pharm Ther* 2002;27:281–287.
- Barete S, Calvez V, Mouquet C, Barrou B, Kreis H, Dantal J, Dorent R, Durand F, Dimitrov Y, Dupin N, Marcelin AG, Piette JC, Bitker MO, Francès C: Clinical features and contribution of virological findings to the management of Kaposi sarcoma in organ-allograft recipients. *Arch Dermatol* 2000;136:1452–1458.
- Duman S, Toz H, Asci G, Alper S, Ozkahya M, Unal I, Celik A, Ok E, Başçi A: Successful treatment of post-transplant Kaposi's sarcoma by reduction of immunosuppression. *Nephrol Dial Transplant* 2002;17:892–896.
- Stallone G, Schena A, Infante B, Di Paolo S, Loverre A, Maggio G, Ranieri E, Gesualdo L, Schena FP, Grandaliano G: Sirolimus for Kaposi's sarcoma in renal-transplant recipients. *N Engl J Med* 2005;352:1317–1323.
- Lebbé C, Euvrard S, Barrou B, Pouteil-Noble C, Garnier JL, Glotz D, Legendre C, Francès C: Sirolimus conversion for patients with posttransplant Kaposi's sarcoma. *Am J Transplant* 2006;6:2164–2168.
- Krown SE: Highly active antiretroviral therapy in AIDS-associated Kaposi's sarcoma: implications for the design of therapeutic trials in patients with advanced, symptomatic Kaposi's sarcoma. *J Clin Oncol* 2004;22:399–402.
- Trattner A, Hodak E, David M, Neeman A, Sandbank M: Kaposi's sarcoma with visceral involvement after intraarticular and epidural injections of corticosteroids. *J Am Acad Dermatol* 1993;29:890–894.
- Antón E: Kaposi's sarcoma in an immunocompetent patient following corticosteroid therapy. *Eur J Intern Med* 2008;19:226.
- Girelli CM, Serio G, Rocca E, Rocca F: Refractory ulcerative colitis and iatrogenic colorectal Kaposi's sarcoma. *Dig Liver Dis* 2009;41:170–174.
- Celik Y, Turgut N, Turgut B, Pamuk GE, Demir M: Chronic idiopathic demyelinating polyneuropathy (CIDP) associated with Kaposi's sarcoma. *J Neurooncol* 2006;79:323–324.
- Joo M, Soon Lee S, Jin Park H, Shin HS: Iatrogenic Kaposi's sarcoma following steroid therapy for nonspecific interstitial pneumonia with HHV-8 genotyping. *Pathol Res Pract* 2006;202:113–117.
- Burnet SP, McNeil JD: Kaposi's sarcoma in an elderly patient with rheumatoid arthritis after intra-articular corticosteroids. *Rheumatology (Oxford)* 2002;41:107–108.
- Casoli P, Tumati B: Rheumatoid arthritis, corticosteroid therapy and Kaposi's sarcoma: a coincidence? A case and review of literature. *Clin Rheumatol* 1992;11:432–435.
- Monti M, Mancini LL, Ceriani R, Hendrickx I, Guizzardi M: Iatrogenic Kaposi's sarcoma and HCV infection. *J Eur Acad Dermatol Venereol* 2004;18:191–193.
- Kuttikat A, Joshi A, Saeed I, Chakravarty K: Kaposi sarcoma in a patient with giant cell arteritis. *Dermatol Online J* 2006;12:16.

- 24 Avalos-Peralta P, Herrera A, Ríos-Martín JJ, Pérez-Bernal AM, Moreno-Ramírez D, Camacho F: Localized Kaposi's sarcoma in a patient with pemphigus vulgaris. *J Eur Acad Dermatol Venereol* 2006;20:79–83.
- 25 Pérez E, Barnadas MA, García-Patos V, Pedro C, Curell R, Sander CA, Kind P, de Moragas JM, Alomar A: Kaposi's sarcoma in a patient with erythroblastopenia and thymoma: reactivation after topical corticosteroids. *Dermatology* 1998;197:264–267.
- 26 Kurosawa M, Nakagawa S, Mizuashi M, Sasaki Y, Kawamura M, Saito M, Aiba S: A comparison of the efficacy, relapse rate and side effects among three modalities of systemic corticosteroid therapy for alopecia areata. *Dermatology* 2006;212:361–365.
- 27 McLeod DT, Capewell SJ, Law J, MacLaren W, Seaton A: Intramuscular triamcinolone acetonide in chronic severe asthma. *Thorax* 1985;40:840–845.
- 28 Willey RF, Fergusson RJ, Godden DJ, Crompton GK, Grant IW: Comparison of oral prednisolone and intramuscular depot triamcinolone in patients with severe chronic asthma. *Thorax* 1984;39:340–344.
- 29 Ogirala RG, Aldrich TK, Prezant DJ, Sinnett MJ, Enden JB, Williams MH Jr: High-dose intramuscular triamcinolone in severe, chronic, life-threatening asthma. *N Engl J Med* 1991;324:585–589.
- 30 Ulinski T, Carlier-Legris A, Schlecht D, Ranchin B, Cochat P: Triamcinolone acetonide: a new management of noncompliance in nephritic children. *Pediatr Nephrol* 2005;20:759–762.
- 31 Hameed R, Zacharin MR: Cushing syndrome, adrenal suppression and local corticosteroid use. *J Paediatr Child Health* 2006;42:392–394.
- 32 Kumar S, Singh RJ, Reed AM, Lteif AN: Cushing's syndrome after intra-articular and intradermal administration of triamcinolone acetonide in three pediatric patients. *Pediatrics* 2004;113:1820–1824.