Kaposi sarcoma in an patient with atopic dermatitis treated with ciclosporin

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SUMMARY
There are four clinical subtypes of Kaposi sarcoma (KS): classic, endemic, epidemic and iatrogenic. The geographical prevalence of the endemic variant matches areas of human herpes virus type 8 (HHV8) seroprevalence. The iatrogenic variant, seen in immunosuppressed patients, can be associated with significant morbidity and mortality. This is the first report of KS described in the context of atopic dermatitis (AD) treated with ciclosporin (CSA). We report a case of KS in an HHV8 seropositive Congolese patient following immunosuppression with CSA for AD. Treatment has been challenging, protracted and associated with significant morbidity. Immunosuppressive therapies are increasingly used for inflammatory dermatological conditions, including AD. This case highlights the importance of HHV8 screening of patients from endemic regions or those with other risk factors. It also highlights the importance of early recognition of a condition associated with significant morbidity and even mortality to facilitate appropriate treatment.

BACKGROUND
This case highlighted a number of important messages:

- It is important to reconsider a diagnosis, particularly in the context of treatment failure.
- Immunosuppressive therapy is a potent and potentially life-altering treatment; however, its prescription requires vigilant monitoring.
- Even when a side effect is not previously described in a certain context, familiarity with the literature regarding drug use in other circumstances is important to identify rare complications.
- This case has implications for screening in dermatology, where immunosuppression is ever more frequently prescribed.
- This case and discussion have important messages regarding the mechanism and potential complications of immunosuppression in general, and the discussion provides a useful review of immunosuppression and Kaposi sarcoma (KS) in a dermatological setting that has not been documented elsewhere, to our knowledge.

CASE PRESENTATION
A 42-year-old Congolese man, who had emigrated to Ireland 11 years previously, presented with a 7-month history of an itchy rash on the temples and beard area that had subsequently spread to involve the forearms and thighs. His medical history included type 2 diabetes diagnosed 6 months previously. Medication included metformin, Levemir, Novorapid and lansoprazole. Examination revealed papular, lichenified skin in the beard and temple areas and patchy lichenification of the inner thighs and forearms. A diagnosis of follicular eczema was made. The patient was treated with mometasone furoate 0.1% ointment to the limbs and 1% hydrocortisone cream to the face and neck.

Eight weeks later, the trunk had cleared and only a mild papular eruption on the cheeks, chin and chest persisted. One year after the initial presentation, a more pronounced papular and follicular rash, with hyperpigmented papules on the mandible and with hyperpigmentation of the chin and cheeks, was present. Dry patches on the thighs and shins were noted. Biopsy of the facial rash

identified moderate spongiosis and lichenification. The papular rash on the face progressed significantly over the next few months and was clinically consistent with heavy lichenified eczema. This was confirmed on skin biopsy.

A trial of daily clobetasol propionate 0.05% cream application was started but was ineffective over the subsequent 4 weeks, even with occlusive dressings and nurse education. In view of the recalcitrant and distressing lichenified facial eczema, ciclosporin (CSA) 150 mg twice daily (4 mg/kg/day) was started with the intention of completing a 3-month to 6-month course. Within 2 weeks, an improvement was noted; however, this was limited by persistent and frequent rubbing of the beard area. A repeat biopsy at this time remained consistent with lichen simplex chronicus/nodular prurigo with melanin incontinence; no fungal organisms were seen on the Periodic Acid Schiff stain.

Within 8 weeks of CSA treatment, the patient's face had improved considerably with the patient and the physician's global assessments improving by 80%. Treatment duration of 6 months was planned at this stage. After 12 weeks of treatment, the patient presented with a progressively worsening left calf pain following minor trauma. This pain was limiting mobility, despite analgesia with paracetamol and ibuprofen. Examination revealed hyperpigmented papules, nodules and plaques on the legs (figure 1). There was lymphoedema of his left calf. He had inguinal lymphadenopathy. He was admitted for treatment with intravenous tazobactam and gentamicin for a suspected infected flare of eczema and pain control. The indurated area on his left calf was a matter for concern and was biopsied. Histopathology of this area was diagnostic of KS with a proliferation of atypical spindle cells forming slit-like blood vessels with prominent red cell extravasation (figure 2A,B). HHV8 serology was positive and HHV8 immunostain performed on biopsied tissue was also positive (figure 2C). CT of the thorax, abdomen and pelvis revealed only reactive inguinal lymphadenopathy. Of note, HIV serology was negative.

The patient was reviewed by medical oncology and considering his significant symptoms due to KS, liposomal doxorubicin was started. Analgesia in the form of pregabalin and opiates was increased. Within 72 h of cycle 1 doxorubicin, there was an improvement in symptoms and cutaneous appearances. The most significant clinical change was noted with the first two cycles of therapy, followed by a minor improvement noted with subsequent cycles. By the ninth cycle of liposomal doxorubicin (cumulative dose 180 mg/m2), there was a flattening of the plaques on the lower limbs and some improvement in the lymphoedema. Unfortunately, the patient developed congestive cardiac failure (CCF) with echocardiography demonstrating an ejection fraction (EF) of 35–40% and anteroseptal hypokinesia. All investigations supported a possible diagnosis of doxorubicin-induced cardiomyopathy, perhaps compounded by small vessel disease due to poorly controlled diabetes. Multiple admissions were required to stabilise the patient's profoundly symptomatic CCF. Doxorubicin was discontinued 26 months after diagnosis and 8 months after cessation of a 6 month course of daunorubicin, the cutaneous disease remains stable (figure 3) and there has been no evidence of extracutaneous KS on further imaging. His CCF remains well controlled symptomatically and objectively (EF 25% and moderate pulmonary hypertension; pulmonary artery pressure, systolic, 45 mm of mercury above right atrial pressure).

INVESTIGATIONS

Contained within the main body + figures for histology.

DISCUSSION

In 1872, Moritz Kaposi described multiple purplish tumours affecting the lower extremities of elderly men from the Mediterranean. Four clinical subtypes of KS have since been identified: epidemic, classic, iatrogenic and endemic variants. The epidemic or AIDS-associated variant is the most common presentation of the condition and was first noted by Friedman-Kien et al[1] in 1981 in a group of homosexual men. The classic variant primarily affects elderly men of Eastern European and Mediterranean origin, and has a male: female ratio between 10:1 and 15:1.[2–4] The endemic type affects those in area high HHV8 seroprevalence such as East and Central Africa; this can be associated with a more aggressive course with patients presenting at a younger age and with more extensive involvement.[5] Iatrogenic KS is typically described in solid organ transplant recipients where its

incidence is estimated to be between 84 and 500 times the rate in the general population, with studies demonstrating that the ability of cytotoxic T cells to respond to Kaposi's sarcoma-associated herpesvirus (KSHV) proteins is lost as immunodeficiency becomes more profound.[2 6–9] KS has also been reported in a range of conditions where the patient has been immunocompromised, such as Wegener's granulomatosis, polymyositis/dermatomyositis, rheumatoid arthritis, vasculitis, systemic lupus erythematosus, polymyalgia rheumatica, Behcet's syndrome, ulcerative colitis, Crohn's disease, aplastic anaemia, myasthenia gravis, chronic membranous glomerulonephritis, giant cell arteritis, systemic sarcoidosis and bullous pemphigoid.[4 10–18]

In 1994, Chang et al identified herpesvirus-like DNA sequences in patients with AIDS-associated KS, confirming it as the causative agent for all forms of KS.[19] Further studies identified a strong correlation between the geographical prevalence of KS and the seroprevalence of KSHV/HHV8.[20] Further evidence has shown that while not all patients who are HHV8+ will develop KS (1 in 17 000 in the general US population in 1998), other cofactors significantly increase that risk, such as HIV, where the risk increases by a factor of 20 000–50 000.[21] There is no known curative therapy; however, it is possible to render patients free of detectable disease. Both local and systemic therapeutic modalities exist. Treatment choices are dependent on patient-related and disease-related factors. Prognosis can be strongly linked to the clinical subtype, ranging from a smouldering course over many years in classic KS to being a more progressive life-threatening in African or AIDS-associated KS.

To our knowledge, KS has only been documented in atopic dermatitis (AD) on two previous occasions, and never in the context of treatment with ciclosporin (CSA). In the first case, a 7-year-old girl with a history of AD since late infancy developed KS on the extremities that progressed rapidly.[22] The immunosuppression identified was short courses of topical and oral corticosteroids, in which the latter were stopped 1 month prior to presentation. In this respect, the authors felt that their patient could not be categorised under the existing four clinical subtypes of KS, and instead suggested a new category: 'atopic dermatitis-associated KS'. Alternatively, noting the altered immune response present in those with AD and subsequent increased propensity to viral skin infections, they felt that it may be that HHV8 may have 'increased aggressiveness in atopic dermatitis'. The other case of KS in a patient with AD was a man who was HIV-negative who had sex with men, but who had been treated with azathioprine for AD.[23]

CSA has been shown to promote cutaneous carcinogenesis in a dose-dependent manner[24–26] by inhibiting Langerhans cells,[27 28] dermal dendritic cells (DCs),[29 30] T-cell signalling and proliferation, and ciclosporin directly promotes tumour development.[26 31 32] In a number of the autoimmune conditions noted above, in addition to solid organ transplantation, CSA has been specifically associated with the subsequent development of KS. The transplant literature describes an association between KS and most immunosuppressant medications, including mycophenolate mofetil, azathioprine and the calcineurin inhibitors tacrolimus and CSA, though CSA by far carries the greatest risk.[33] Sirolimus (SRL) is a mammalian target of rapamycin (mTOR) inhibitor that has a known antineoplastic effect which may share a common mechanism of action with its immunosuppressant action.[34] KS resolution in patients with a transplant switched from CSA to SRL has been described, with conflicting reports as to whether resolution is more likely due to SRL introduction than CSA withdrawal, but clinical trials of mTOR inhibitors and other tyrosine kinase inhibitors in KS are underway.[35 36] Of note, there have, however, also been reports of recurrence of KS on dose elevation of SRL.[37]

There is evidence to suggest that methotrexate (MTX) may prevent viral transforming gene transcription with respect to KS.[38] Though methotrexate has not been specifically associated with KS development, it has formed part of treatment regimens where KS occurrence has been attributed to other medication. Of note, KS development and progression have been documented in association with oral steroid use in AD and other conditions such as giant cell arteritis.[17 22]

Tumour necrosis factor (TNF) is known to have a paradoxical role in carcinogenesis and can act both as a tumour necrosis factor and as a tumour promoting factor.[39] It has been shown to induce KS cell proliferation, with neutralising monoclonal antibodies directed against TNF receptor blocker 1 (TNFR-1) completely inhibiting its development, though neutralising anti-TNFR II had little or no effect on growth.[40] Thalidomide, in addition to known significant antiangiogenic activity, is a selective inhibitor

of TNF-α that has shown some efficacy in treatment of KS.[41] The monoclonal antibodies infliximab and adalimumab have been temporally related to the development of KS on three and two occasions, respectively; however, risk factors for the development of KS such as HIV, endemic risk profile and other immunosuppression, including MTX in two cases, were noted in all cases.[18 42–44] Interestingly, to our knowledge, etanercept, a fusion protein that fuses the TNFR-2 to the constant end of the immunoglobulin IgG1 antibody, has never been reported in association with KS.

In summary, we describe the case of a 42-year-old patient from an HHV8 endemic area with severe follicular eczema. When treated with ciclosporin, he developed KS. We feel that our patient represents an overlap case, spanning the clinical subtypes of endemic and iatrogenic KS. Unfortunately this case also highlights the morbidity that may arise from KS. Immunosuppression can be considered as **'**a complex function whose major determinants are the immunosuppressive programme and the presence or absence of infection with a group of immunomodulating viruses**'**.[45] We feel that our case is an example of this and provides an argument for the consideration of pretreatment screening for HHV8 in patients with AD who are being considered for treatment with CSA, especially in those from endemic areas. Given the varied case reports noted above, it may also be of benefit to screen at-risk patients to be treated with CSA or profound immunosuppression for other dermatological conditions, to enable early recognition and treatment of a disease that can be associated with significant morbidity and mortality.

Learning points

- Treatment failure should prompt reconsideration of a diagnosis.
- Ciclosporin is particularly associated with development of Kaposi sarcoma in at-risk patients and this should be considered prior to initiation of treatment.
- Treatment of Kaposi sarcoma can be difficult and is associated with significant morbidity and even mortality.
- It is important to consider the lessons learnt within other specialties with respect to drug complications, even when side effects have been undocumented in the setting within which the medication is being prescribed.

Figures

Figure 1 The patient's left leg showing Kaposi sarcoma manifesting as hyperpigmented macules, papules, nodules and plaques.

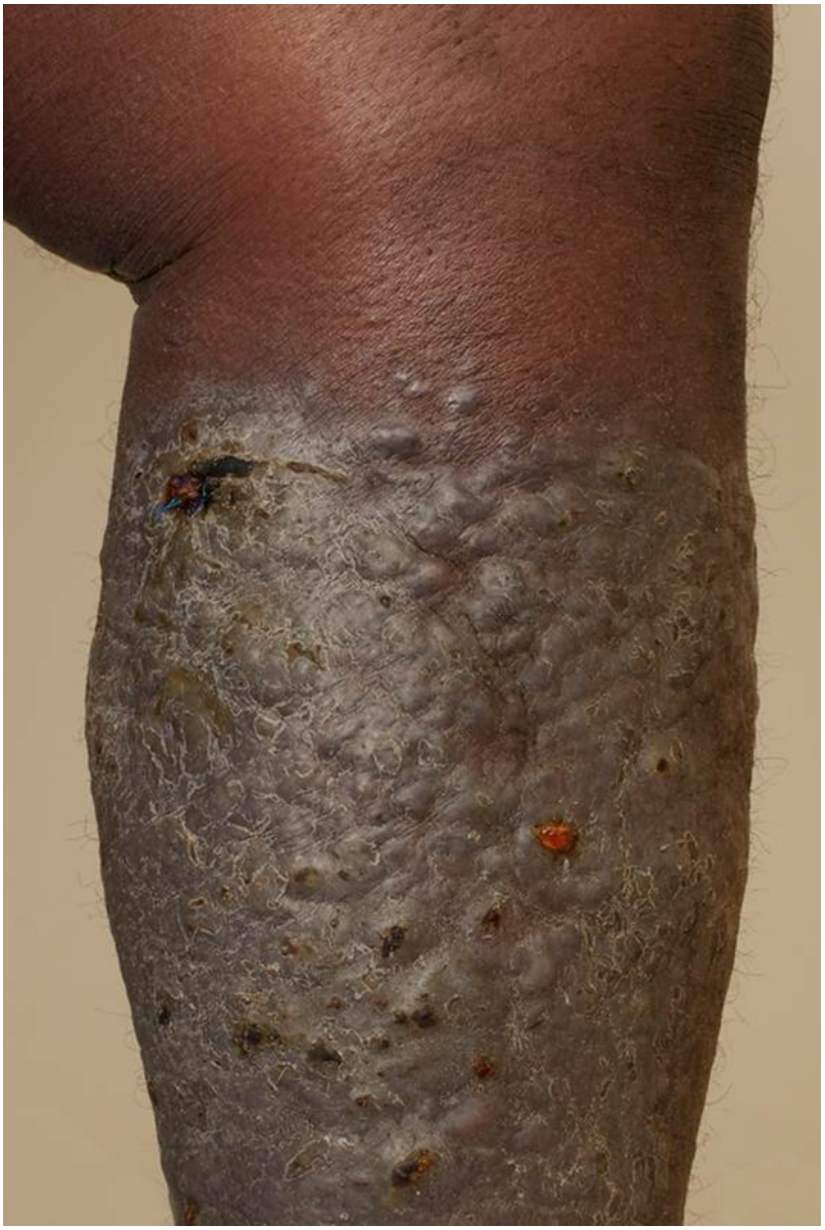


Figure 2 (A) Dermal infiltrate of Kaposi sarcoma with a dermal proliferation of atypical spindle cells (H&E x 40). (B) The spindle cells form slit-like vascular channels. Red cell extravasation is a prominent features (H&E x 200). (C) Immunostaining shows nuclear positivity for HHV8 latent nuclear antigen (Novacastra).

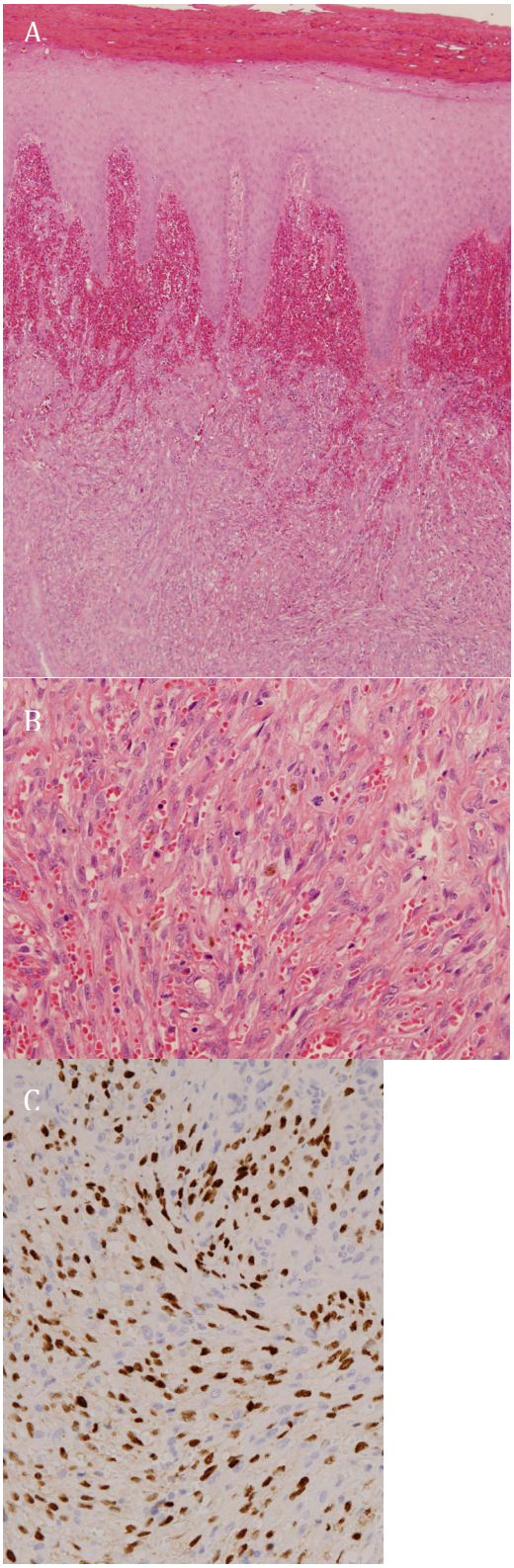
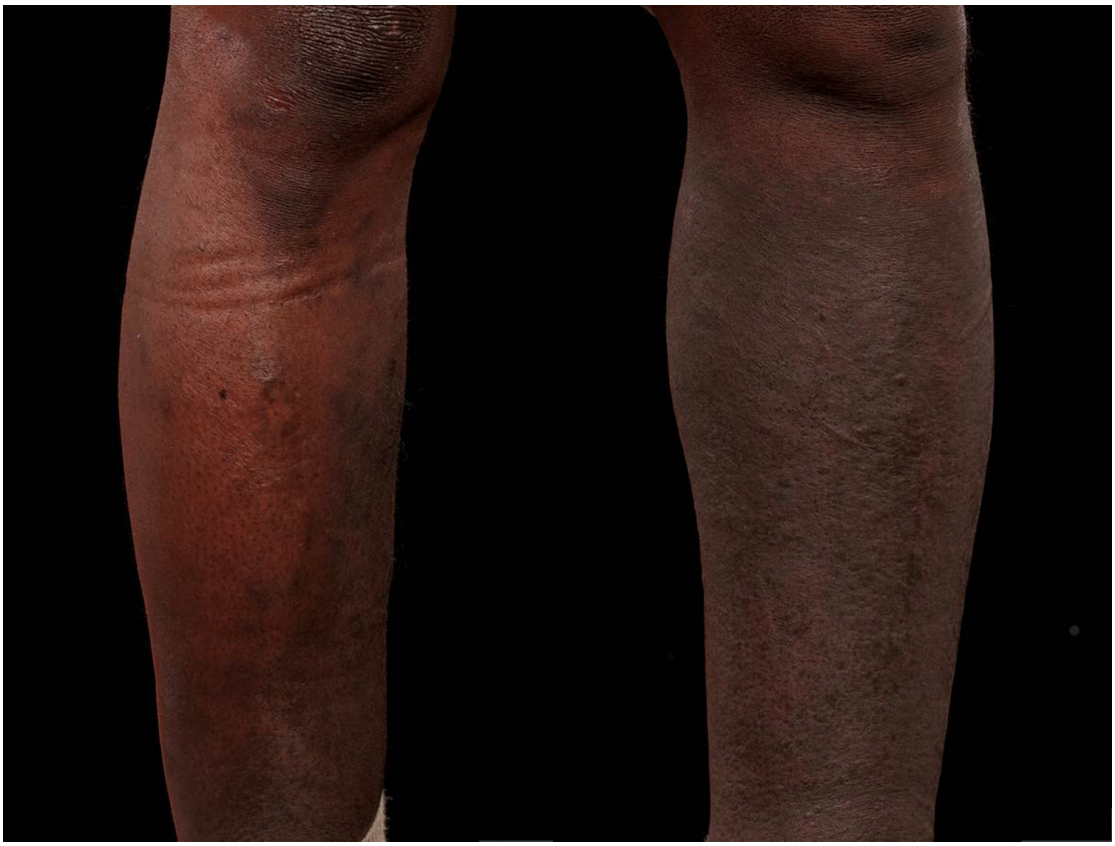


Figure 3 Anterior view of the patient's legs, 26 months after diagnosis and 8 months after cessation of a 6-month course of daunorubicin.



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Competing interests None.

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