Concurrent development of HIV-negative Kaposi's sarcoma and mycosis fungoides in an elderly Inuit from Canada

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SUMMARY

An 88-year-old Inuit man from Northern Canada presented with an extensive skin rash associated with numerous violaceous skin nodules on his palms and lower extremities. Biopsy of a skin nodule revealed Kaposi's sarcoma (KS), a human herpesvirus 8 (HHV8)-associated malignancy, whereas biopsy of the erythematous skin showed an atypical infiltrate of CD4-positive T-cells that, together with TCR gene rearrangement and presence of clonal T-cells in peripheral blood by flow cytometry, was consistent with a T-cell lymphoma, mycosis fungoides (MF) subtype. Serology was negative for HIV and HTLV-I/II and no immunodeficiency syndrome was identified. The patient was successfully treated with an oral retinoid for KS, and with topical hydrocortisone and ultraviolet B (UVB) phototherapy for MF. This case highlights the existence of HHV8-related lesions in native persons of Northern Canada, and also that MF-induced immunosuppression combined with immunosenescence may play a role in the development of non-HIV-related KS.

BACKGROUND

Human herpes virus-8 (HHV8), also known as Kaposi sarcoma-associated herpesvirus, is the causative agent of Kaposi's sarcoma (KS) but also of a spectrum of uncommon lymphoproliferative disorders, most characteristically HHV8-positive multicentric Castleman disease and HHV8-positive diffuse large B-cell lymphoma and primary effusion lymphoma (PEL).[1 2] These conditions occur mainly in immunosuppressed patients, most often related to HIV infection.[1] The most common among them is KS, a malignant proliferation of endothelial cells with an inflammatory component, presenting as cutaneous or mucosal lesions.[3 4]

Primary cutaneous T-cell lymphoma (CTCL) typically presents in the skin with no evidence of extracutaneous involvement at the time of diagnosis. Mycosis fungoides (MF) is the most common CTCL subtype, closely related to the leukemic counterpart Sézary syndrome.[5] Patients with MF appear to be at increased risk of secondary malignancies, including Hodgkin's and non-Hodgkin's lymphoma, acute myeloid leukaemia and lung cancer, among others.[6 7] However, the coexistence of KS and MF in the same patient is a rarely described phenomenon.[8–10]

CASE PRESENTATION

An 88-year-old Inuit man from a village in Northern Quebec, Canada was transferred on 8 November 2019, to the McGill University Health Centre in Montreal, Quebec for violaceous subcutaneous nodules on his palms and lower extremities,

Figure 1 Violaceous subcutaneous nodule of Kaposi's sarcoma on the patient's right lower extremity at the time of diagnosis.

preceded a few months before by a rapid onset of total body erythematous, pruritic and scaly skin lesions. He also had problem of a 6 kg weight loss, night sweats, and fever for the last 4 months. His medical history was limited to cholecystectomy in 2012 and myocardial infarction in 2015, and he was receiving medication for hypertension, gout, dyslipidaemia and chronic obstructive pulmonary

Figure 2 Scaly erythematous lesion of mycosis fungoides covering the left upper extremity of the patient at the time of diagnosis. This figure was taken 2 weeks after diagnosis, and 1 week after starting topical hydrocortisone.

Table 1 Laboratory testing on the patient's peripheral blood at the time of initial presentation and after therapy before being discharged home

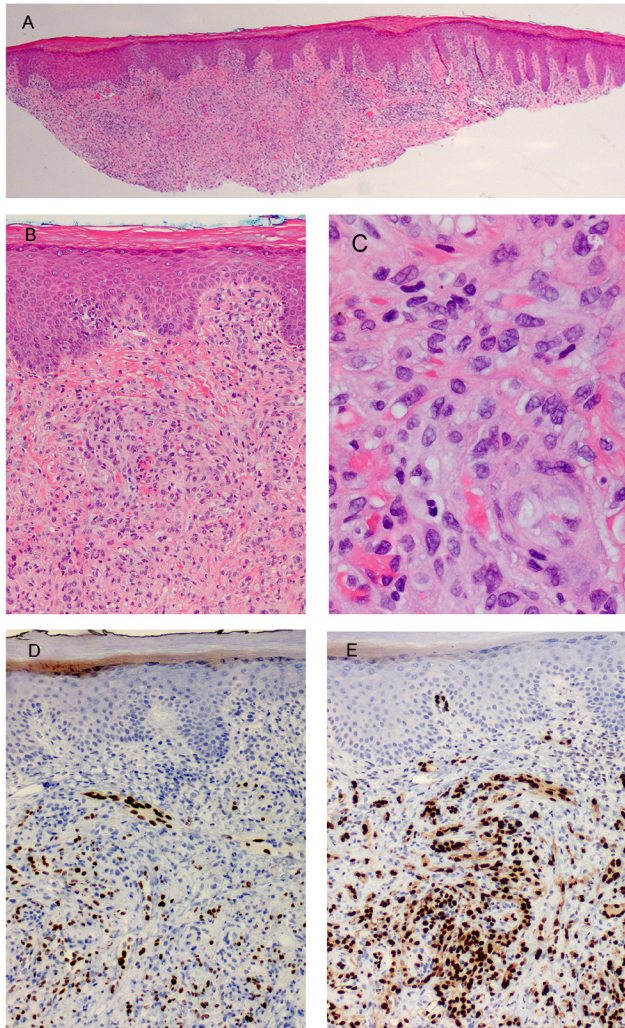|	Hemoglobin (Hb) (g/L) (135–175)	Neutrophils (10^9/L) (1.80–7.70)	Eosinophils (10^9/L) (0.00–0.45)	Lymphocytes (10^9/L) (1.00–4.80)	Lactate dehydrogenase (U/L) (110–210)	IgG G/L (7.00–15.00)	IgA G/L (0.80–4.00)	IgM G/L (0.50–3.00)	Beta2 microglobulin mg/L (0.00–3.50)
8 November	104	4.4	0.98	1.5	321	25.08	6.88	1.61	9.7
17 February	102	3.67	0.30	1.10	132	20.06	5.09	1.28	7.2

Figure 3 Histological examination of a superficial biopsy from a violaceous skin nodule reveals a malignant vascular proliferation in the dermis, with narrow vascular spaces and spindle cells that are positive for human herpesvirus 8 (HHV8), consistent with Kaposi sarcoma (KS). (A–C) H&E stained at 20×, 100× and 400× magnification, respectively; (D) the vascular spaces and spindle cells are positive for HHV8 and (E) the endothelial cell marker ETS-related gene (ERG) by immunohistochemistry, consistent with the diagnosis of KS.

disease. The physical examination revealed generalised scaly erythematous plaques, accompanied with about 60 violaceous nodules affecting the trunk and upper and lower limbs. The patient denied any travel outside his hunting area near his village and had no history of sexually transmitted infections. Physical examination revealed a small left cervical lymph node (LN) (<1 cm) in the absence of hepatosplenomegaly.

INVESTIGATIONS

Laboratory results showed normocytic anaemia with haemoglobin 104 g/L, and platelets 175 10^9/L, neutrophils 4.4 10^9/L, lymphocytes 1.5 10^9/L and with moderate eosinophilia of 0.98 10^9/L with normal creatinine, transaminases and mild elevation of lactate dehydrogenase (LDH) 321 U/L (table 1). Serologies were negative for viral hepatitis, syphilis, HIV, and human T-lymphotropic virus (HTLV)-I/II and were positive for Epstein-Barr virus (EBV). PCR testing on the peripheral blood was positive for HHV8 (non-quantitative) and EBV (4786 copies /mL), while PCR for HIV and cytomegalovirus (CMV) was negative (below the detection level). His CD4 cell count was 665 cells /mm^3 with CD8 at 374 cells /mm^3, with a normal CD4/CD8 ratio of 1.7. Stool analysis and culture were negative for ova and parasites.

Histological examination of a skin biopsy from a violaceous nodule on his left palm revealed a malignant vascular proliferation and spindle cells that were positive for HHV8 by immunohistochemistry, consistent with KS (figure 1). Concurrently, a biopsy of a scaly erythematous skin lesion on his right arm (figure 2) revealed an atypical infiltrate of predominantly CD4-positive T-cells with mild epidermotropism and partial loss of CD7 expression assessed by immunohistochemistry (figure 3). Molecular studies performed on the latter biopsy showed clonal TCR gene rearrangement, indicating the presence of a T-cell clonal population, most consistent with CTCL.

Flow cytometry was performed on his peripheral blood using the EuroFlow panels. Gating on the lymphoid region (7.1% nucleated cells), no clonal B-cell population was detected but T-cells comprised 94% of lymphocytes with a CD4/CD8 ratio of 2.7. Gating on the CD4+CD8 T-cell population demonstrated that CD4+CD26 cells were increased up to 72% (normal <30%) with an immunophenotype consistent with the presence of circulating Sézary/MF cells (table 2).[11]

MRI showed normal-sized liver and spleen, however, also revealed symmetrical and mildly enlarged (1.0–1.5 cm) axillary, mediastinal and hilarLNs. The positron emission tomography (PET) scan demonstrated mildly hypermetabolic LN in the right submandibular area with standardised uptake values (SUVs) up to 4.5, and right and left axillary and inguinal LN with SUVs up to 3. Due to his skin condition, focal PET imaging was also performed on his upper or lower limbs and no hypermetabolic activity was noted. Such symmetrical and mildly enlarged LN with low metabolic activity was considered reactive.

DIFFERENTIAL DIAGNOSIS

In sum, the patient presented with two biopsy-proven rare skin conditions occurring synchronously; an HIV-negative KS and a primary CTCL consistent with the MF subtype. Distinguishing these two entities from other diseases with similar cutaneous presentations, such as psoriasis and severe eczema, was challenging. It required a thorough review of clinical findings and extensive laboratory testing including flow cytometry on peripheral blood and histopathological assessment of separate skin

Flow cytometry	CD3 (%)	CD4 (%)	CD8 (%)	CD5 (%)	CD20 (%)	CD19 (%)	CD56 (%)	CD38 (%)	Kappa CD19 POS	Lambda CD19 POS	CD45 (%)
Table 2 Flow cytometry performed on the patient's peripheral blood at the time of the initial presentation											
November 19	91	60	26	88	1	1	8	33	0	0	97
February 20	84	45	30	81	5	5	10	40	3	2	97

Gated on the lymphoid region (14.3% of nucleated cells).

biopsies in combination with immunohistochemistry and molecular studies. As only few circulating Sezary cells were present, the diagnostic of MF was established.

According to the American Joint Committee on Cancer,[6] the patient's MF was classified as T4, N0, M0 and B1. Skin lesions involved at least 80% of his total skin surface area (T4). The patient did not have cancer spread to nearby LNs (N0), no metastasis was detected (M0), and had circulating Sezary cell count below 1000 cells/m^3 (B1). Thus, the prognosis classification in this patient was IIIB.

TREATMENT
The patient was prescribed oral acitretin (a second-generation retinoid) 10 mg daily for 4 weeks and then increased to 30 mg daily for 8 weeks for KS lesions. The extensive MF skin lesions were treated with 1% hydrocortisone topical (cream) applied two times per day on total body surface followed by UVB phototherapy. Due to penicillin allergy, oral clindamycin 300 mg two times per day was also prescribed to treat infected excoriated skin lesions.

OUTCOME AND FOLLOW-UP
After treatment, blood tests showed a decrease in LDH, beta2 micro globulin, and IgG levels, partial improvement of anaemia, with normalisation of eosinophil count (table 1). A post-treatment assessment of circulating lymphocytes by flow-cytometry showed a decrease in CD4 cells with a slight increase in CD8 cells. The B cell (CD19+, CD20+) population increased with a higher expression of kappa and lambda light chains. Globally, these findings indicated a reduction in Sézary cell count and partial improvement in B cell count and function. The patient's skin lesions also resolved on treatment for both KS and MF and he was discharged home after a follow-up with a nurse.

DISCUSSION
KS is caused by HHV8 and has distinctive clinical and epidemiological forms: (1) the classic form of KS, first described in 1872 in Vienna by Moritz Kaposi, is a relatively indolent disease that affects predominantly elderly men of East European and Mediterranean descent; (2) the endemic form of KS affects HIV-negative individuals of Eastern and Central Africa and may present with visceral involvement; (3) the epidemic or AIDS-associated KS is the most aggressive form and affects HIV-infected patients, particularly men having sex with men (MSM) in Western countries, or irrespective of sexual orientation in sub-Saharan Africa; (4) the iatrogenic form of KS occurs in transplant recipients, and persons receiving immunosuppressive therapy for a variety of diseases; and (5) the non-epidemic form of KS affecting HIV-negative middle-aged MSM with no identifiable immunodeficiency which has been recently recognised, presenting with cutaneous lesions and an indolent course.[12 13]

HHV8 is chiefly horizontally transmitted and repeated contact is needed to establish transmission, through sexual intercourse or mother-to-child interaction.[14–16] Whereas sexual transmission between MSM remains the main transmission route and HHV-8

seroconversion correlates with the number of sexual contacts,[14] other routes of transmission are exceptional and include blood transfusions.[17] Immunosuppression or immunosenescence is required for the development of KS, along with HHV8.[18] Immune factors associated with KS development include low CD4 T-cell counts and the elevation of dysfunctional T-cells expressing the senescence marker CD57.[18 19] 'Inflammaging', which encompasses ageing and chronic conditions associated with inflammation, and the accumulation of senescent cells in tissues contribute to a senescent associated secretory phenotype. This proinflammatory environment is associated with elevated cytokines and angiogenic factors which are associated with cancer development including KS.[9 12]

The association between KS and MF has been rarely reported.[1] Bariani et al in 2016 reported a 53-year-old Caucasian man from Brazil who developed non-HIV KS after 2 years of UVB phototherapy to treat his MF. Interestingly, negative immunohistochemistry for HHV8 in the initial MF lesions of the patient strengthened the hypothesis that the virus has no relation with the development of this lymphoma, whereas MF-induced immunosuppression and phototherapy were considered as contributing factors for the onset of KS.[10] Similarly, Samuelov et al in 2016 reported a case of a 55-year-old Caucasian man born in Ukraine and survivor of the Chernobyl disaster that developed a T-cell rich B-cell lymphoma, before developing KS and MF.[3] The development of KS in this patient was thought to be caused by previous exposure to radiation from the Chernobyl accident as well as the systemic chemotherapy received for the treatment of his lymphoma.[3 20]

Although Bigi et al showed that EBV coinfection with HHV8 played an essential role in the pathogenesis of PEL in a cell culture model, EBV coinfection with HHV8 has not been established as a contributing factor for the development of KS.[13 21] Therefore, although the increased EBV levels in the blood of our patient raise the possibility that EBV played a role in the development of KS, it could alternatively suggest an underlying immunodeficiency allowing replication of both EBV and HHV8.

As the classic form of KS often affects patients over 75 years of age where the course is generally indolent, the use of treatments with limited side effects is appropriate and may include radiotherapy, immunotherapy or chemotherapy. Among chemotherapeutic agents, the use of pegylated liposomal doxorubicin is well tolerated with low cardiac toxicity and is generally the first-line treatment.[22] Retinoids are derivatives of vitamin A and mediate their biological effect through interactions with cellular nuclear receptors, modulating cell growth, differentiation, and apoptosis. Retinoids are used in the treatment of tumours including cancers of the head and neck, bladder, and also in CTCL and KS, where inhibition of vascular smooth muscle cell proliferation by these compounds has been reported in the latter.[23] Furthermore, acitretin, among a panel of other retinoid compounds, had the highest ability to inhibit the growth of KS cells in cell culture.[24 25] Corbeil et al demonstrated that acitretin at low concentrations was sufficient to inhibit the growth of rapidly dividing early passage KS cells. Higher concentrations induced KS cells

Table 3 Mycosis fungoides (MF) as a dermatological masquerader: different dermatological, clinical and haematological MF presentations.

Dermatologic presentation	Clinical sign	Differential diagnosis
Classical MF	Eczematous	Seborrheic, dyshidrotic, atopic eczema
	Scaling	Psoriasis
		Parapsoriasis
		Tinea corporis and pedis
	Erythematous	Erythema multiforme or annular
	Alopecia	Alopecia areata
Erythrodermic MF	Erythrodermic	Adult T-cell leukaemia
		Atopic dermatites
		Drug reaction
		Psoriasis
Tumorous MF	Tumorous	Lupus erythematosus
		B-cell lymphoma
		Lymphomatoid papulosis
Adnexotropic MF	Adnexotropic	Rosacea
		Eczema
		Seborrheic dermatitis
		Comedones,
		Epidermal cysts
		Follicular hyperkeratosis
		lupus erythematosus
Granulomatous MF	Granulomatous	Granuloma annulare
		Rosacea
		Sarcoidosis
Other	Skin atrophy	Pityriasis versicolor or alba
	Hypopigmented	Vitiligo
	Hyperpigmented	Acanthosis nigricans
	Hyperkeratotic	Palmoplantar pustulosis
	Pustular	
Constitutional or systemic presentation	Pruritus	
	Fever	
	Weight loss	
	Enlarged liver and or spleen	
Haematological presentation	Anaemia	
	Lymphocytosis	
	Presence circulating Sezary cells	

The most frequent presentations and differential diagnoses are shown, where applicable.[27]

while several therapeutic guidelines have been published for the management of KS or CTCL, new treatment options including retinoids have been explored in case reports.[29 30]

The 88-year-old patient described in this case report posed a diagnostic challenge while presenting with both classical KS and MF synchronously, two infrequent skin conditions rarely described in association in the same patient. Lesions of KS and MF were successfully treated using an oral retinoid and a topical steroid combined with UVB phototherapy, respectively. We hypothesise that the development of MF induced an immuno-suppressive and/or inflammatory state, and in combination with a senescent associated secretory phenotype, contributed to the development of KS in this elderly person. In addition, although HHV8 is not known to be endemic in Northern Canada, a handful of cases of HIV seronegative KS in Inuit persons living in the Nunavik region in Canada have been reported and justifies research on HHV8 seroprevalence in this population.[31–34]

apoptosis but are not achievable in vivo with oral therapy. Retinoic acid analogues also inhibit HHV8 replication.[24] Interestingly, a case report by Daadaa *et al*, revealed the efficacy of acitretin as a treatment for KS.[26] However, to our knowledge there is currently no literature available discussing the efficacy of retinoic acid in treating KS with concurrent CTCL.

Moreover, the diagnosis of MF remains challenging as many of its clinical and pathological features are not entirely specific and overlap with several reactive dermatologic processes. The most common MF presentations are listed in table 3.[27] Treatment options include a 'watch and wait' approach or skin-directed therapies with steroids and UVB phototherapy for patients with an indolent presentation, or systemic chemotherapy and radiotherapy for patients with advanced disease.[28] Moreover,

REFERENCES

1 Cesarman E, Damania B, Krown SE, *et al*. Kaposi sarcoma. *Nat Rev Dis Primers* 2019;5:9.
2 Swerdlow SH, Campo E, Pileri SA, *et al*. The 2016 revision of the world Health organization classification of lymphoid neoplasms. *Blood* 2016;127:2375–90.
3 Samuelov L, Gat A, Bergman R, *et al*. Mycosis fungoides associated with Kaposi's sarcoma, T-cell rich B-cell lymphoma, and T-cell lymphoma with angioimmunoblastic features. *Acta Dermatovenerol Croat* 2016;24:218–20.
4 Tajarernmuang P, Fiset P-O, Routy J-P, *et al*. Intractable pleural effusion in Kaposi sarcoma following antiretroviral therapy in a Caucasian female infected with HIV. *BMJ Case Rep* 2020;13. doi:10.1136/bcr-2019-233335. [Epub ahead of print: 28 Feb 2020].
5 Willemze R, Cerroni L, Kempf W, *et al*. The 2018 update of the WHO-EORTC classification for primary cutaneous lymphomas. *Blood* 2019;133:1703–14.
6 American Joint Committee on Cancer. Primary Cutaneous Lymphomas. In: *AJCC cancer staging manual*. 8th ed. New York, NY: Springer, 2017: 967–72.

7   Brownell I, Etzel CJ, Yang DJ, *et al*. Increased malignancy risk in the cutaneous T-cell lymphoma patient population. *Clin Lymphoma Myeloma* 2008;8:100–5.

8   Bariani MCPF, Fleury LFF, Ribeiro AMQ, *et al*. Mycosis fungoides and Kaposi's sarcoma association in an HIV-negative patient. *An Bras Dermatol* 2016;91:108–10.

9   Kreuter A, Bischoff S, Skrygan M, *et al*. High association of human herpesvirus 8 in large-plaque Parapsoriasis and mycosis fungoides. *Arch Dermatol* 2008;144:1011–6.

10   Vangipuram R, Tyring SK. Epidemiology of Kaposi sarcoma: review and description of the nonepidemic variant. *Int J Dermatol* 2019;58:538–42.

11   Horna P, Wang SA, Wolniak KL, *et al*. Flow cytometric evaluation of peripheral blood for suspected Sézary syndrome or mycosis fungoides: international guidelines for assay characteristics. *Cytometry B Clin Cytom* 2020:cyto.b.21878.

12   Schulz TF, Cesarman E. Kaposi sarcoma-associated herpesvirus: mechanisms of oncogenesis. *Curr Opin Virol* 2015;14:116–28.

13   Bestawros A, Boulassel M-R, Michel RP, *et al*. Hhv-8 linked to Kaposi's sarcoma, Castleman's disease and primary effusion lymphoma in a HIV-1-infected man. *J Clin Virol* 2008;42:179–81.

14   Casper C, Krantz E, Selke S, *et al*. Frequent and asymptomatic oropharyngeal shedding of human herpesvirus 8 among immunocompetent men. *J Infect Dis* 2007;195:30–6.

15   Kedes DH, Operskalski E, Busch M, *et al*. The seroepidemiology of human herpesvirus 8 (Kaposi's sarcoma-associated herpesvirus): distribution of infection in Ks risk groups and evidence for sexual transmission. *Nat Med* 1996;2:918–24.

16   Martin JN, Ganem DE, Osmond DH, *et al*. Sexual transmission and the natural history of human herpesvirus 8 infection. *N Engl J Med* 1998;338:948–54.

17   Barozzi P, Luppi M, Facchetti F, *et al*. Post-Transplant Kaposi sarcoma originates from the seeding of donor-derived progenitors. *Nat Med* 2003;9:554–61.

18   Boivin G, Gaudreau A, Routy JP. Evaluation of the human herpesvirus 8 DNA load in blood and Kaposi's sarcoma skin lesions from AIDS patients on highly active antiretroviral therapy. *AIDS* 2000;14:1907–10.

19   Unemori P, Leslie KS, Hunt PW, *et al*. Immunosenescence is associated with presence of Kaposi's sarcoma in antiretroviral treated HIV infection. *AIDS* 2013;27:1735–42.

20   Fahad AS. Prevalence of human herpesvirus-8 (HHV-8) in untreated patients with early stage mycosis fungoides (a retrospective study). *Int J Health Sci* 2010;4:128–38.

21   Bigi R, Landis JT, An H, *et al*. Epstein-Barr virus enhances genome maintenance of Kaposi sarcoma-associated herpesvirus. *Proc Natl Acad Sci U S A* 2018;115:E11379–87.

22   Di Lorenzo G. Update on classic Kaposi sarcoma therapy: new look at an old disease. *Crit Rev Oncol Hematol* 2008;68:242–9.

23   Guruvayoorappan C, Berlin Grace VM. All trans retinoic acid and cancer. *Immunopharmacol Immunotoxicol* 2011;33:241–9.

24   Corbeil J, Rapaport E, Richman DD, *et al*. Antiproliferative effect of retinoid compounds on Kaposi's sarcoma cells. *J Clin Invest* 1994;93:1981–6.

25   Balachandra B, Tunitsky E, Dawood S, *et al*. Classic Kaposi's sarcoma presenting first with gastrointestinal tract involvement in a HIV-negative Inuit male--a case report and review of the literature. *Pathol Res Pract* 2006;202:623–6.

26   Daadaa N, Souissi A, Chaabani M, *et al*. Involution of classic Kaposi sarcoma lesions under acitretin treatment Kaposi sarcoma treated with acitretin. *Clin Case Rep* 2020;8:3340–3.

27   Nashan D, Faulhaber D, Ständer S, *et al*. Mycosis fungoides: a dermatological masquerader. *Br J Dermatol* 2007;156:1–10.

28   Hristov AC, Tejasvi T, Wilcox RA. Mycosis fungoides and Sézary syndrome: 2019 update on diagnosis, risk-stratification, and management. *Am J Hematol* 2019;94:1027–41.

29   Ormerod AD, Campalani E, Goodfield MJD, *et al*. British association of dermatologists guidelines on the efficacy and use of acitretin in dermatology. *Br J Dermatol* 2010;162:952–63.

30   Gilson D, Whittaker SJ, Child FJ, *et al*. British association of dermatologists and U.K. cutaneous lymphoma group guidelines for the management of primary cutaneous lymphomas 2018. *Br J Dermatol* 2019;180:496–526.

31   Krell J, Stebbing J. Broader implications of a stage-guided stratified therapeutic approach for AIDS-related Kaposi's sarcoma. *J Clin Oncol* 2014;32:373–5.

32   Chen J, Mehraj V, Szabo J, *et al*. Multiple remissions of extracavitary primary effusion lymphoma treated with a single cycle of liposomal doxorubicin in a patient infected with HIV. *Curr Oncol* 2018;25:e592–6.

33   Letang E, Lewis JJ, Bower M, *et al*. Immune reconstitution inflammatory syndrome associated with Kaposi sarcoma: higher incidence and mortality in Africa than in the UK. *AIDS* 2013;27:1603–13.

34   Young BM. Cancer patterns in Inuit populations. *Lancet Oncol* 2008;9:1124.