CASE REPORT

Pulmonary Kaposi sarcoma and disseminated *Mycobacterium genavense* infection in an HIV-infected patient

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SUMMARY

We report a case of Kaposi sarcoma (KS) and disseminated infection by *Mycobacterium genavense* in a 40-year-old HIV-positive man with CD4+ T-cell count 5/μL. He presented with anorexia, diarrhoea, cachexia and multiple firm violaceous nodules distributed over the face, neck and upper and lower extremities. Biopsy of a skin nodule was performed, confirming KS. Immunoperoxidase staining for human herpesvirus 8 was strongly positive. Endoscopic examination revealed erosive duodenopathy. Multiple biopsy samples showed numerous acid-fast bacilli at direct microscopic examination. Real-time PCR (RT-PCR) identified *M. genavense*. A CT scan showed diffuse pulmonary infiltrates with a 'tree-in-bud' appearance, striking splenomegaly and abdominal lymphadenopathy. A bronchoscopy was performed, revealing typical Kaposi's lesions in the upper respiratory tract. RT-PCR of bronchial aspirate identified *M. genavense* and *Pneumocystis jirovecii.* Despite treatment with highly active antiretroviral therapy, antimycobacterial therapy and trimethoprim/sulfamethoxazole, the outcome was fatal.

BACKGROUND

Mycobacterium genavense is a fastidious, non-tuberculous mycobacterium (NTM), responsible for disseminated infection among severely immunocompromised HIV-positive patients.[1] It remains a diagnostic challenge for physicians and microbiologists, due to its remarkable clinical similarities to *Mycobacterium avium* complex (MAC) infection.

Kaposi sarcoma (KS) is the second most frequent cancer in HIV-infected patients worldwide and occurs in more than 50% of cases in late stages of HIV infection.[2] Opportunistic infections have been associated with the induction and/or exacerbation of pre-existing KS, but few cases have been reported.[3]

CASE PRESENTATION

In September 2014, a 40-year-old HIV-positive man was admitted to the hospital, with 3 months of progressive weight loss, diarrhoea and decreased appetite. He denied fever, night sweats, abdominal pain, cough, haemoptysis or dyspnoea.

He was known to be HIV positive for 15 years, and started highly active antiretroviral therapy (HAART) in August 2009, but was non-adherent to treatment. In April 2011, he restarted HAART, and 4 months later his CD4+ T-cell count was 188/μL and HIV viral load was 311 copies/mL. He withdrew from treatment the following months.

Clinical examination revealed a cachectic, afebrile man, with pale and dry mucous membranes. Cardiopulmonary auscultation was normal. Abdominal examination was characterised by moderate ascites and painful splenomegaly. Multiple firm, non-ulcerated, violaceous nodules scattered over the face, neck (figure 1), and upper and lower extremities, were also noted.

Laboratory findings were sodium 127 mEq/L, albumin 1.7 g/dL, serum iron 10 μg/dL, ferritin 1055 ng/mL, transferrin 111 mg/dL, folic acid 1.6 ng/mL, haemoglobin 5.8 g/dL, platelets 53,000/μL, white cell count 1,400/μL, reticulocyte count 0.2% and C reactive protein 120 mg/L. The patient's CD4+ T-cell count was 5/μL and HIV viral load was 19 509 copies/mL. Serological evaluation for hepatitis B and C, cytomegalovirus, parvovirus and Toxoplasmosis was negative. Stool and blood cultures failed to reveal any organism. Chest radiography showed peribronchial thickening and septal lines (figure 2).

Biopsy of a skin nodule over the left hand was performed. Histopathological examination showed proliferation of small vessels around which elongated spindle cells were observed, confirming KS. Immunoperoxidase staining for human herpesvirus 8 (HHV-8) was strongly positive.

Endoscopic examination revealed diffuse inflammation of the mucosa of the duodenum. Multiple biopsy samples were submitted for histological and molecular biological analysis. Profound macrophage infiltration, without granuloma, and the presence of numerous acid-fast bacilli were found. Molecular biological analysis of samples taken

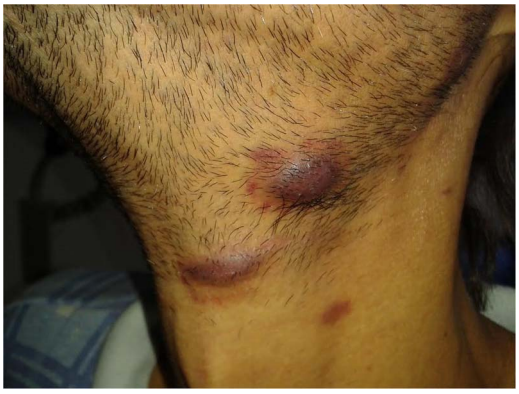

Figure 1 Cutaneous Kaposi lesions.

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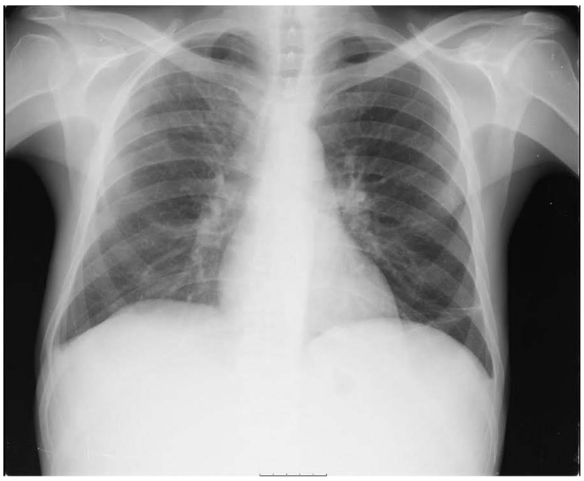

Figure 2 Chest radiography showing peribronchial thickening and septal lines.

directly from the biopsy material, using real-time PCR (RT-PCR), led to the identification of *M. genavense*.

A CT of the chest and abdomen showed diffuse pulmonary infiltrates with a 'tree-in-bud' appearance (figure 3), numerous large lymph nodes in the abdomen, moderate volume ascites, heterogeneous splenic parenchyma with multiple hypodense nodules and striking splenomegaly. A bronchoscopy was performed, revealing cherry-red, slightly raised tracheal lesions (figure 4), typical of KS. Owing to the potential risk of bleeding, biopsy was avoided. Bronchial aspirate direct smear was positive for acid-fast bacilli, and *M. genavense* and *Pneumocystis jirovecii* were identified using RT-PCR. Bronchial aspirate Löwenstein-Jensen and mycobacterial growth indicator tube cultures failed to reveal any organism.

Unlike the diagnosis of KS with pulmonary involvement, which was confirmed by skin biopsy and bronchoscopy, disseminated *M. genavense* infection diagnosis was not so clear. This organism was isolated from non-sterile sites, such as the respiratory and gastrointestinal (GI) tracts, however, a high number of colonies were present. Moreover, the patient was severely immunocompromised and presented disseminated disease (weight loss, pancytopenia, splenomegaly, lymphadenopathy),

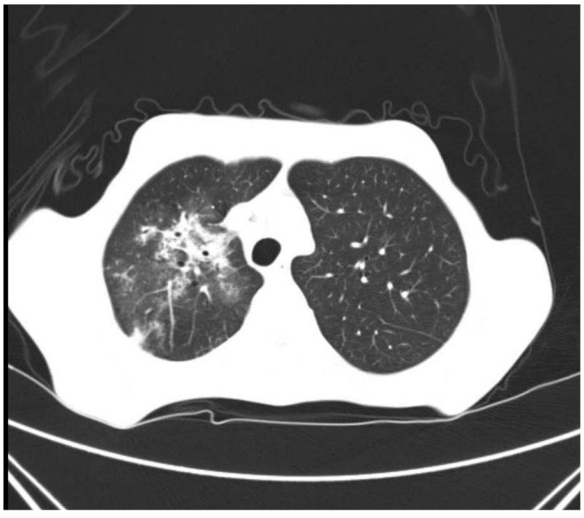

Figure 3 CT of the chest showing diffuse pulmonary infiltrates with a 'tree-in-bud' appearance.

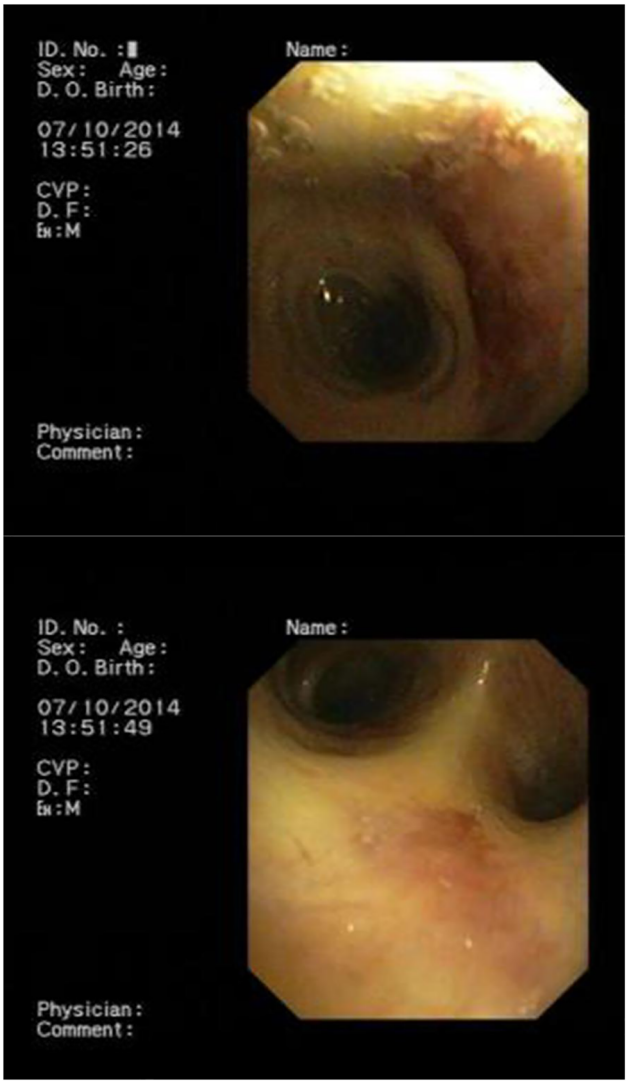

Figure 4 Bronchoscopy showing violaceous patches in the trachea.

supporting the diagnosis of disseminated *M. genavense* infection, rather than colonisation. Also, even though the patient did not present respiratory symptoms, *P. jirovecii* pneumonia was assumed, due to its isolation from bronchial aspirate and the presence of diffuse pulmonary infiltrates.

TREATMENT

The patient was started on antiretroviral treatment with darunavir/ritonavir plus abacavir/lamivudine. The direct molecular diagnosis of *M. genavense* and *P. jirovecii* enabled immediate treatment of the patient with antimycobacterial therapy (rifabutin, ethambutol and clarithromycin) and co-trimoxazole (trimethoprim/sulfamethoxazole).

Four days after beginning treatment, the patient presented a non-pruritic, annular, erythematous skin eruption involving the upper and lower extremities, and trunk (figure 5). Mucous membranes were not involved. We assumed a drug-induced skin eruption due to co-trimoxazole, since it spontaneously resolved and did not recur after desensitising the patient using a regimen of gradual incremental exposure over a 14-day period. Unfortunately, it was not possible to perform a timely skin biopsy to confirm the diagnosis.

After optimising HAART, our goal was to initiate systemic chemotherapy for pulmonary KS. However, this was

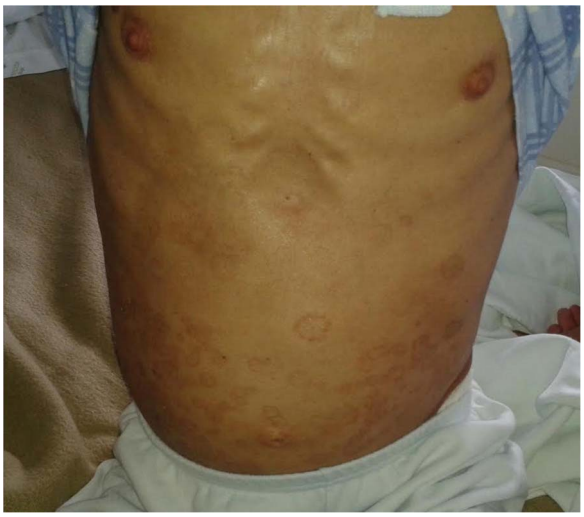

Figure 5 Annular erythematous eruption of the trunk (resolution phase).

unbearable, due to the patient's severe pancytopenia and the concurrent risk of chemotherapy-induced myelosuppression.

OUTCOME AND FOLLOW-UP

The patient experienced a prolonged hospital stay, as he presented severe cachexia and pancytopenia, with regular need of red blood cell transfusion. He completed 21 days of treatment with co-trimoxazole and was continued on HAART and antimycobacterial therapy. Four months later, his CD4+ T-cell count was 6/μL and HIV viral load was 434 184 copies/mL. He was assumed to be non-adherent to treatment and died the following month.

DISCUSSION

M. genavense is a fastidious NTM that is believed to be acquired through ingestion of the organism from an environmental source. It has been isolated from the respiratory and GI tracts of immunocompetent humans.[4] This finding supports the hypothesis that *M. genavense* may colonise the gut and disseminate from it with progressive immunodeficiency. *M. genavense* infection has been reported almost exclusively in patients with AIDS and an absolute CD4+ T-cell count <100/μL.[4 5] It is responsible for 12.8% of all NTM infections in patients with AIDS and has been described as a pathogen-causing disease with significant morbidity and mortality.[6]

M. genavense infection typically presents as a disseminated disease, with massive adenopathy and organomegaly, especially splenomegaly, without respiratory symptoms or pulmonary involvement. Clinical presentation is strikingly similar to that of disseminated MAC infection.[7] Charles *et al*[8] conducted a retrospective multicentre study in France, which illustrated the variety of clinical presentations of *M. genavense*: weight loss (79%), fever (75%), abdominal pain (71%), splenomegaly (71%), lymphadenopathy (62,5%), diarrhoea (62,5%) and hepatomegaly (62,5%).

Owing to the extreme fastidiousness of *M. genavense*, routine cultures fail to isolate this organism. Therefore, in most cases, molecular methods such as RT-PCR and 16S ribosomal RNA gene sequencing are necessary. Human isolates can be recovered from cultures of blood, bone marrow, liver, spleen and other tissue, but require supplemented media for growth.[9] In our case, early diagnosis of *M. genavense* infection was possible due to *Mycobacterium* seen at direct microscopic examination of duodenum samples and bronchial aspirate, and confirmation with RT-PCR. However, blood, stool and bronchial aspirate cultures remained negative, confirming the particular difficulty in growing this organism using standard mycobacterial culture methods.

When *M. genavense* is isolated from a usually sterile site, such as blood, bone marrow, lymph nodes or synovial fluid, the diagnosis of true infection is usually clear. However, when it is isolated from non-sterile sites, such as the respiratory or GI tract, the diagnosis can be less definitive. A case series from Spain, conducted between 1998 and 2005, identified 26 HIV-infected patients with NTM isolates from sputum.[10] As in our patient, they used clinical criteria to establish a diagnosis of colonisation versus infection; some of the factors associated with disease were CD4+ T-cell count <50/μL, weight loss, haemoglobin <11 g/dL and duration of symptoms longer than a month.

Owing to the difficulties of growing *M. genavense* in culture, in vitro data on drug susceptibility are scarce. Previous studies, reviewed in the American Thoracic Society Statement, suggest that most isolates are susceptible to amikacin, rifamycins, fluoroquinolones, streptomycin and macrolides.[9] Ethambutol and isoniazid have limited activity against *M. genavense*.[7] Optimal treatment has not been established, but therapeutic regimens of at least three antimycobacterial drugs, including clarithromycin, during 12–18 months, appear to be more effective.[9] In our case, despite following these guidelines, the outcome was fatal after 5 months of treatment. However, we believe that the patient's non-adherence to treatment and his severe immunosuppression contributed in a large scale to this result.

Besides the diagnosis of disseminated *M. genavense* infection, our patient also presented a skin biopsy and bronchoscopy confirming the diagnosis of KS with pulmonary involvement. KS is one of the AIDS-defining skin diseases and is the second most common neoplasm seen in HIVinfected patients worldwide. It has reached epidemic proportions in some parts of the world, such as Southern Africa.[2]

KS is an angioproliferative cancer of endothelial origin, and is characterised by its notable clinical heterogeneity, varying from minimal to fulminant disease, as well as by its ability to progress or regress based on host-immune factors.[11] Its development is strongly associated with HIV infection, mainly the CD4+ T-cell count, which seems to be the most important factor, and HHV-8 infection.[12] HIV infection is believed to create a deficient immunological environment within which other oncogenic viruses, such as HHV-8, can escape immune control and induce tumour growth.[13]

Unlike classical forms of KS, which are generally slowly progressive and limited to the skin, AIDS-related KS is frequently more aggressive, involving lymph nodes and visceral organs, which confers significant morbidity and mortality. Cutaneous KS is characterised by a few or widespread multifocal violaceous or dark red colour patches, papules, plaques and/or skin nodules. The range of colours associated with these lesions is owed to their vascularity. Typically, the lesions are bilateral, symmetrically distributed and involve mainly the lower extremities, face (especially the nose) and genitalia.[14] Although these lesions present a characteristic appearance, KS diagnosis should be confirmed by a biopsy whenever possible. Histological examination is usually characterised by neoangiogenesis and proliferating spindle-shaped cells combined with an inflammatory infiltrate of lymphocytes, plasma cells and macrophages.[13] Identification of HHV-8 is possible using immunohistochemical staining.

In HIV-infected patients, it is common for KS to spread to extracutaneous sites, such as the mucosal membranes, lymph nodes and visceral organs, including the GI tract, lungs, liver and spleen. The oral cavity is frequently affected (33% of cases). In 40% of cases, GI involvement is present at initial diagnosis and can occur without cutaneous disease.[3] GI lesions may cause weight loss, abdominal pain, nausea, vomiting and bleeding, or may be asymptomatic. Likewise, pulmonary KS is also common, and in 15% of cases, may occur in the absence of mucocutaneous disease.[15] Patients with pulmonary KS may present with shortness of breath, cough or haemoptysis. In those who are asymptomatic, pulmonary KS may be found on a chest radiograph (nodular, interstitial or alveolar infiltrates, pleural effusion or isolated pulmonary nodule).[16] Biopsy of these lesions should be avoided, due to the potential risk of bleeding. Therefore, as demonstrated in our case and supported by the literature, the finding of cherryred, slightly raised endobronchial lesions at the time of bronchoscopy is generally sufficient for a presumptive diagnosis of pulmonary KS.[17]

AIDS-related KS is usually staged according to the AIDS Clinical Trials Group classification system, which characterises cases as good or poor risk prognosis, considering both the KS and HIV infection.[18] Patients are categorised taking into account tumour burden, immune status (measured by CD4+ T-cell count) and the presence of systemic illness. Those patients, such as ours, who present with extensive oral cavity involvement or visceral disease, CD4+ T-cell count lower than 200/μL, and a history of opportunistic infection, thrush or B symptoms (fever, night sweats, weight loss, diarrhoea), are considered to have a poor prognosis. However, those who do not present any of these factors are considered to have a better prognosis.

AIDS-related KS treatment decisions depend on the disease stage, symptoms and concurrent complications of HIV infection. HAART, either alone or in combination with systemic chemotherapy, is recommended for all patients with AIDS-related KS, as it plays a crucial role in preventing disease progression and reducing tumour burden. It has multiple effects on KS, which include the inhibition of HIV replication, the improvement of the immunoresponse against HHV-8 and possibly some direct antiangiogenic activity of protease inhibitors.[19] Systemic chemotherapy is generally indicated for patients not responding to HAART and/or with widespread, symptomatic, rapidly progressive or life-threatening disease.[20] The recommended first-line chemotherapy for KS treatment is pegylated liposomal doxorubicin or liposomal daunorubicin.[21] Other agents that have been used include paclitaxel, bleomycin, vinblastine, vincristine and etoposide.[22]

In our patient, the concurrent presence of extensive cutaneous KS lesions with pulmonary involvement, severe immunosuppression, disseminated *M. genavense* infection and *P. jirovecii* pneumonia, contributed to a poor prognosis. The patient was immediately started on HAART, but systemic chemotherapy was never initiated, due to the patient's severe pancytopenia and the concomitant risk of chemotherapy-induced myelosuppression. Similar to that described with corticosteroid therapy, opportunistic infections have been associated with the induction and/or exacerbation of pre-existing KS, but few cases have been reported.[23 24] In our case, we believe that the patient's disseminated *M. genavense* infection and *P. jirovecii* pneumonia probably contributed to these effects on KS, since a high level of proinflammatory cytokines was observed in this setting.

Learning points

- *Mycobacterium genavense* infection must be considered as a differential diagnosis of any HIV patient with an absolute CD4+ T-cell count <100/μL presenting with fever, diarrhoea, abdominal pain, weight loss and lymphadenopathy.
- Since of its culture growth limitations, early diagnosis relies mostly on molecular methods, such as real-time PCR and 16S ribosomal RNA gene sequencing, which allow rapid identification of the *Mycobacterium*.
- Therapeutic regimens should consist of at least three antimycobacterial drugs, including clarithromycin.
- AIDS-related Kaposi sarcoma (KS) is frequently aggressive and presents with disseminated disease, more often affecting the oral cavity, the gastrointestinal and respiratory tracts, which confer significant morbidity and mortality.
- Highly active antiretroviral therapy is recommended for virtually all patients with AIDS-related KS, since it is essential for prevention of disease progression and tumour burden reduction.

Competing interests None declared.

Patient consent Obtained.

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REFERENCES

1 Böttger EC, Teske A, Kirschner P, *et al*. Disseminated "Mycobacterium genavense" infection in patients with AIDS. *Lancet* 1992;340:76–80.
2 Ferla LL, Pinzone MR, Nunnari G, *et al*. Kaposi's sarcoma in HIV-positive patients: the state of art in the HAART-era. *Eur Rev Med Pharmacol Sci* 2013;17:2354–65.
3 Dezube BJ, Pantanowitz L, Aboulafia DM. Management of AIDS-related Kaposi sarcoma: advances in target discovery and treatment. *AIDS Read* 2004;14:236–8, 243–4, 251–3.
4 Doggett JS, Strasfeld L. Disseminated Mycobacterium genavense with pulmonary nodules in a kidney transplant recipient: case report and review of the literature. *Transp Infect Dis* 2011;13:38–43.
5 Böttger EC. Mycobacterium genavense: an emerging pathogen. *Eur J Clin Microbiol Infect Dis* 1904;13:932–6.
6 Pechère M, Opravil M, Wald A, *et al*. Clinical and epidemiologic features of infection with Mycobacterium genavense. *Arch Intern Med* 1995;155:400–4.
7 Thomsen VO, Dragsted UB, Bauer J, *et al*. Disseminated infection with Mycobacterium genavense: a challenge to physicians and mycobacteriologists. *J Clin Microbiol* 1999;37:3901–5.
8 Charles P, Lortholary O, Dechartres A, *et al*., French Mycobacterium genavense Study Group. Mycobacterium genavense infections: a retrospective multicenter study in France, 1996–2007. *Medicine (Baltimore)* 2011;90:223–30.
9 Griffith DE, Aksamit T, Brown-Elliott BA, *et al*. An official ATS/IDSA statement: diagnosis, treatment, and prevention of nontuberculous mycobacterial diseases. *Am J Respir Crit Care Med* 2007;175:367–416.
10 Alvarez-Uria G, Falcó V, Martín-Casabona N, *et al*. Non-tuberculous mycobacteria in the sputum of HIV infected patients: infection or colonization? *Int J STD AIDS* 2009;20:193–5.
11 Uldrick TS, Whitby D. Update on KSHV-epidemiology, Kaposi Sarcoma pathogenesis, and treatment of Kaposi sarcoma. *Cancer Lett* 2011;305:150–62.
12 Rezza G, Andreoni M, Dorrucci M, *et al*. Human herpesvirus 8 seropositivity and risk of Kaposis sarcoma and other acquired immunodeficiency syndrome-related diseases. *J Natl Cancer Inst* 1999;91:1468.
13 Pantanowitz L, Dezube BJ. AIDS-Related Cancer: New Entities, Emerging Targets, and Novel Tactics. *Abstr Hematol Oncol* 2005;8:20–30.
14 Dezube BJ. Acquired immunodeficiency syndrome-related Kaposi's sarcoma: clinical features, staging, and treatment. *Semin Oncol* 2000;27:424–30.
15 Huang L, Schnapp LM, Gruden JF, *et al*. Presentations of AIDS-related pulmonary Kaposi's sarcoma diagnosed by bronchoscopy. *Am J Respir Crit Care Med* 1996;153:1385–90.
16 Aboulafia DM. The epidemiologic, pathologic, and clinical features of AIDS-associated pulmonary Kaposi's sarcoma. *Chest* 2000;117:1128–45.
17 Judson MA, Sahn SA. Endobronchial lesions in HIV-infected individuals. *Chest* 1994;105:1314–23.

18 Krown SE, Metroka C, Wernz JC. Kaposi's sarcoma in the acquired immune deficiency syndrome: a proposal for uniform evaluation, response, and staging criteria. AIDS Clinical Trials Group Oncology Committee. *J Clin Oncol* 1989;7:1201–7.
19 Sullivan RJ, Pantanowitz L. New drug targets in Kaposi sarcoma. *Expert Opin Ther Targets* 2010;14:1355–66.
20 Gbabe OF, Okwundu CI, Dedicoat M, *et al*. Treatment of severe or progressive Kaposis sarcoma in HIV-infected adults. *Cochrane Database Syst Rev* 2014;8: CD003256.
21 Bower M, Collins S, Cottrill C, *et al*. British HIV Association guidelines for HIV-associated malignancies 2008. *HIV Med* 2008;9:336.
22 Lee FC, Mitsuyasu RT. Chemotherapy of AIDS-related Kaposi's sarcoma. *Hematol Oncol Clin North Am* 1996;10:1051.
23 Trattner A, Hodak E, David M, *et al*. The appearance of Kaposi sarcoma during corticosteroid therapy. *Cancer* 1993;72:1779.
24 Gill PS, Loureiro C, Bernstein-Singer M, *et al*. Clinical effect of glucocorticoids on Kaposi sarcoma related to the acquired immunodeficiency syndrome (AIDS). *Ann Intern Med* 1989;110:937.