Rare, disseminated Kaposi sarcoma in advanced HIV with high-burden pulmonary and skeletal involvement

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Accepted 17 October 2021

To cite: Connolly SP, McGrath J, Sui J, *et al*. *BMJ Case Rep* 2021;**14**:e245448. doi:10.1136/bcr-2021-245448

SUMMARY

We describe the case of a 30-year-old man who presented to our institution with hypoxia and widespread pulmonary infiltrates managed initially as COVID-19 before receiving a new diagnosis of HIV-associated Kaposi sarcoma (KS) with widespread pulmonary and skeletal involvement. Initial differential diagnoses included *Pneumocystis jirovecii* pneumonia, disseminated mycobacterial infection and bacillary angiomatosis. A bone marrow biopsy showed heavy infiltration by spindle cells, staining strongly positive for human herpes virus-8 (HHV-8) and CD34, suggesting symptomatic, disseminated KS as the unifying diagnosis. The patient commenced cytotoxic therapy with weekly paclitaxel, with a clinical and radiological response. To our knowledge, this case is among the most severe described in the literature, which we discuss, along with how COVID-19 initially hindered developing a therapeutic allegiance with the patient.

BACKGROUND

Although caseloads remained high in the initial waves of COVID-19 and acute medical services overwhelmed, it has been recognised that the diagnosis of other serious infections may be delayed.[1]

We describe a severe and rare manifestation of Kaposi sarcoma (KS), the diagnosis of which was delayed due to the COVID-19 pandemic due to the initial assumption of a diagnosis of severe SARS-CoV-2 infection. KS is a human herpes virus-8 (HHV-8)-associated neoplasm which manifests in immunocompromised individuals and is most commonly confined to skin, but may uncommonly disseminate to involve extracutaneous sites such as the gastrointestinal (GI) tract and lungs.[2] It is classically suggested that a pattern of diffuse skeletal involvement should direct the physician away from KS in favour of bacillary angiomatosis, a multisystem, opportunistic bacterial infection also seen in advanced HIV caused by *Bartonella quintana*.[3] It is for this reason that biopsy of such lesions is highly recommended, which is illustrated by this case.

CASE PRESENTATION

A 30-year-old heterosexual man presented to the emergency department in May 2020, during a period of high COVID-19 incidence and intensive societal restrictions. He described a 4-day history of dry cough and exertional dyspnoea, denying sore throat, anosmia, fever or chest pain. He denied any medical history, and was taking no regular prescribed medication. On presentation, the patient was hypoxic on room air, SpO_2 92%. He was afebrile and normotensive; however, tachycardic at 117 beats/min, with a regular pulse. His examination was strikingly abnormal, with evidence of severe lower limb and scrotal oedema; a disseminated pigmented rash on his torso; extensive, non-tender cervical lymphadenopathy and marked cachexia (45 kg). He disclosed a large degree of unquantified weight loss over the preceding year.

INVESTIGATIONS

Initial radiographic examination yielded a markedly abnormal chest radiograph, with extensive airspace opacification involving the upper-mid and lower zones bilaterally, with more marked involvement of the middle zone and left base.

Initial blood testing was notable for a low albumin level of 29 g/L, a C reactive protein level of 73 mg/L, a slightly raised ferritin of 395 μg/L and a grossly elevated D-dimer of 4.79 mg/L. Transthoracic echocardiography indicated a reduced left ventricular ejection fraction of 20%–25%.

The patient was placed in isolation and underwent two negative nasopharyngeal swabs for SARS-CoV-2 via real-time PCR (RT-PCR) before undergoing CT scanning of his thorax to better delineate his airspace disease. Rather than indicating the peripheral, ground-glass attenuation expected of COVID-19, the patient's imaging demonstrated nodular interlobular and peribronchial interstitial thickening, with diffuse thickening of the major fissures, without cavitation. Additionally, innumerable, multifocal lytic bone lesions were seen on further scanning centred predominantly in the pelvis and cervical, thoracic and lumbar spine (figure 1).

CT-guided biopsy of a bony lesion on his iliac crest was performed, demonstrating bone infiltrated by spindle cell proliferation, strongly positive for CD34 and HHV-8 on immunohistochemistry (figure 2). This confirmed a diagnosis of widely disseminated HIV-associated KS.

HIV serology was positive, and total CD4 +T-helper lymphocyte count was 116 cells/μL (9%). Initial viral load measured 87 272 copies/mL. Through giving a guarded social history, the mode of acquisition of the virus remained unclear, and was presumed to be via heterosexual acquisition, having denied intravenous drug use or sex with other men.

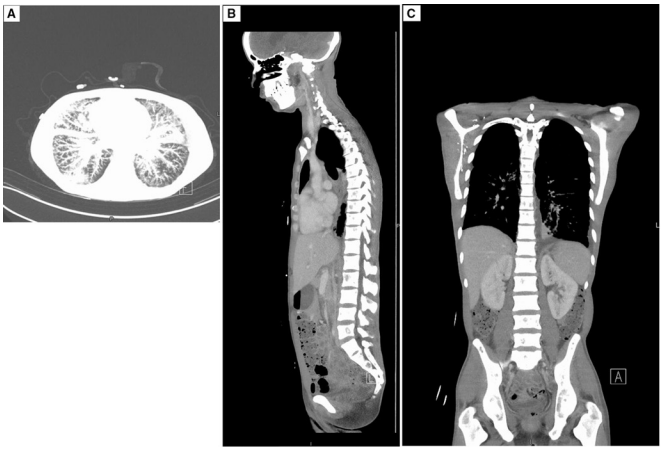

Figure 1 Images obtained from initial CT of patient's thorax, abdomen and pelvis on admission, indicating pulmonary parenchymal disease in (A) transverse section, and disseminated osseous disease involving the axial skeleton in sagittal section. Subsequently staining strongly positive for (B) HHV-8 and (C) CD34.

DIFFERENTIAL DIAGNOSIS

The initial suspicion was that this represented COVID-19 given the high contemporaneous caseloads and abnormal chest radiograph. Following serial negative PCR tests, HIV antibody testing and CT imaging, a wide alternative differential diagnosis existed at this point.

Given the patient's significant immunocompromise, opportunistic infections such *Pneumocystis jirovecii*, cytomegalovirus and tuberculous or non-tuberculosis mycobacteria were all considered. Investigations in effort to help exclude co-existent opportunistic infections and mitigate risk of subsequent immune reconstitution inflammatory syndrome on initiation of combination antiretroviral therapy (cART) were then performed, including serum β-D-glucan and serum cryptococcal antigen, which were negative. The osseous lesions also raised concern for bacillary angiomatosis. In light of the pattern of parenchymal involvement, a malignant process with dissemination to lung and bone was also thought possible, such as lymphoma, bronchogenic neoplasm or KS. Langerhans's cell histiocytosis and disseminated tuberculosis also potentially explained the bone and lung findings.

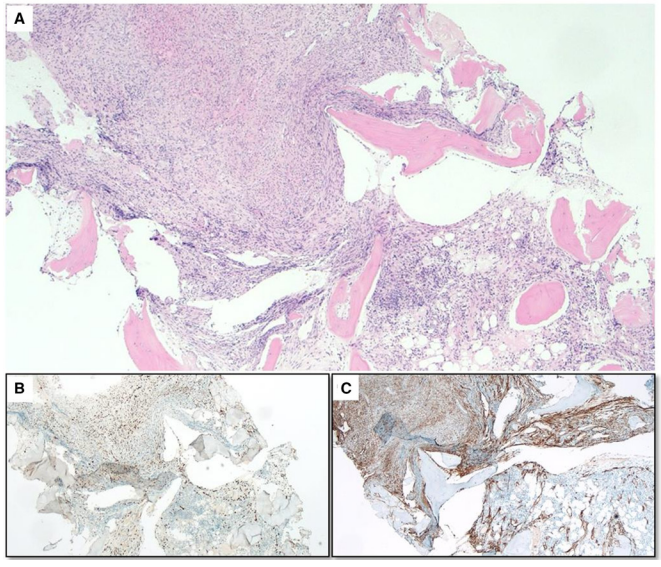

Figure 2 Images obtained from the stained histology slides of bone biopsy taken from the patient, indicating spindle cell proliferation and lymphoid aggregates infiltrating the bone on hematoxylin and eosin (H&E) staining (A), subsequently staining strongly positive for (B) HHV-8 and (C) CD34.

TREATMENT

At this point, the patient was understandably distressed and anxious as the details of his diagnoses were being gradually related to himself and his partner. His severe orthopnoea limited him from lying flat, and he was at that point undergoing an intensive regimen of sequentially added broad-spectrum anti-infective agents, including intravenous trimethoprim-sulfamethoxazole, meropenem, ganciclovir and a cART regimen of bictegravir, tenofovir alafenamide and emtricitabine to accommodate a wide array of differential diagnoses, including opportunistic infections such as *P. jirovecii* and cytomegalovirus.

Following an evaluation by a medical oncologist and a series of careful discussions about the likely outcomes and risks of treatment, our patient consented to undergo a treatment course of cytotoxic chemotherapy for his symptomatic visceral KS. Cardiac MRI performed 4 weeks into the admission following initiation of cART showed normalisation of left ventricular

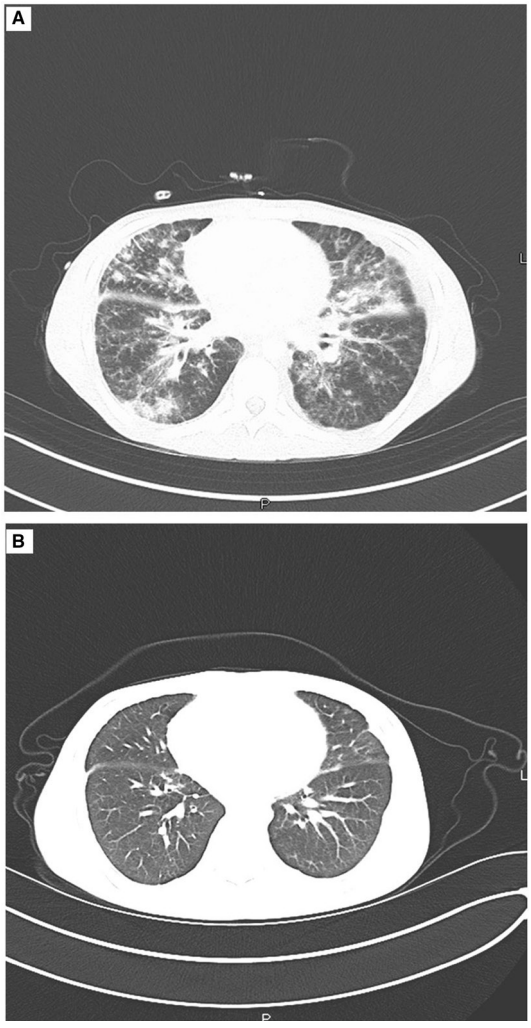

Figure 3 Comparative CT scans of our patient's lung fields at (A) point of diagnosis and (B) 11 months later following chemotherapy and immune reconstitution.

function, indicating either interobserver variability in the initial study or a reversible cardiomyopathy induced by either direct myocardial viral invasion or malnutrition. Nonetheless, in light of a perceived risk of future myocardial dysfunction given the initial echocardiography, single-agent, weekly paclitaxel was selected for his chemotherapeutic regimen, rather than conventional (or indeed liposomal) doxorubicin. The patient underwent the first several weeks of his chemotherapy as an inpatient, awaiting a clinical response, with close involvement of the dietetic and physiotherapy services.

Through a combination of his COVID-19 isolation and subsequent de-isolation, necessitating transfer of wards and intensive rotation of staff members on the infectious diseases team through isolation and on-call commitments, we had yet to establish an effective therapeutic alliance with the patient and he was particularly distrustful of the medical staff. This was gradually achieved through input of our medical social worker and counselling services.

OUTCOME AND FOLLOW-UP

The patient underwent a clinical response to cART and cytotoxic chemotherapy over the course of his 3-month admission, with an improvement in his peripheral oedema, weight and oxygenation. He was discharged home on room air with close follow-up in the infectious diseases clinic. At the patient's most recent review, his viral load had been consistently suppressed since June 2021, his CD4 +count had improved to 221 cells/µL (15%) and he had returned to a healthy weight. Having expressed a wish to discontinue chemotherapy and following a joint discussion with patient and medical oncology, the patient is now under active surveillance by the medical oncology team. His most recent scan at the time of writing indicated a substantial radiological response to his treatment, with a vast reduction in the extent of the nodular interlobular septal thickening throughout both lungs (figure 3). The skeletal lesions remained stable in number and had indicated increased sclerosis implying therapeutic response. The therapeutic relationship with the patient had improved, with the consistency and regularity of care that falling numbers of COVID-19 cases afforded.

DISCUSSION

KS is a multifocal, angioproliferative neoplastic disease of likely lymphatic origin, associated with HHV-8 and characterised on histology by neoangiogenesis, spindle-shaped cells and a chronic inflammatory infiltrate.[2 4]

Although KS had been described extensively in the literature in the context of the incidence of variants in older men of central European or Mediterranean ancestry (classic KS), in neoplastic disease in sub-Saharan Africa (endemic KS) and in the context of solid-organ transplantation (post-transplant KS), the disease has gained more recognition for—and appears destined to be associated with— advanced HIV infection (epidemic KS).[4] Where HIV infection is readily diagnosed and cART widely available, incidence of KS has become relatively rare. The disease presents most typically as multifocal, pigmented skin lesions; variably affecting lymphatic tissue, the oral cavity and viscera—most commonly the GI tract (manifest as malabsorption of occult blood loss) and lung parenchyma (resulting chiefly in dyspnoea, cough, haemoptysis and chest pain). Presentations with ascites and pleural effusion are also seen.[2] As ever, accounts of KS lesions in visceral sites as obscure as the eye and thyroid gland exist.[5] It is contested that much 'disseminated' disease is in fact explainable by distinct clones emerging in parallel through common risk factors of immunosuppression and active HHV-8 replication rather than distal metastases.[6] Prognosis depends heavily on the extent of the disease. Three-year survival has been reported as ranging from 88% in localised disease, to 53% in the case of symptomatic visceral disease, where cytotoxic chemotherapy is traditionally indicated.[7] Asymptomatic and cosmetically acceptable disease may be treated with immune reconstitution through initiating cART alone. The exact benefit conferred by cytotoxic chemotherapy (adjunctively with cART) is unclear, with response rates of 46% (95% CI 37% to 54%) in one randomised phase III clinical trial.[8] In those such as our patient (for whom the comparatively cardiotoxic anthracyclines were relatively contraindicated), taxanes such as paclitaxel are preferred,although this risk is partly mitigated by use of pegylated liposomal doxorubicin.[9 10] No clear positive impact of adjunctive cytotoxic chemotherapy on survival rates has been demonstrated.[11] Localised osseous pain sometimes necessitates use of external-beam radiotherapy, to which KS lesions are exquisitely sensitive.[12]

Skeletal involvement is relatively rare in KS, constitutes a worse prognosis, and is more typically seen in the setting of locally aggressive head-and-neck lesions that erode through tissue planes into underlying bony structures, as initially described by Kaposi[13] himself. Lesions are characteristically osteolytic, with destruction of the cortex and less commonly, destruction of the entire bone being seen. HIV-associated cases show a greater predilection for the axial skeleton than classic or endemic variants.[14] As stated before, skeletal lytic lesions are thought to favour a diagnosis of bacillary angiomatosis over KS.[3]

KS skeletal lesions are poorly appreciable on plain film imaging, with CT and MRI showing superior sensitivity.[15] An in-depth 2006 review of the published KS cases involving the musculoskeletal system by Caponetti et al[14] yielded 66 case reports, with 28 attributable to HIV-associated KS. Of these, only 12 appear to affect more than one site, and 5 have concomitant lung involvement. Median CD4 +count in those with reported counts was 66 cells/µL (range 0–138 cells/µL). Subsequent to this publication date, a further three cases of widespread multifocal skeletal HIV-associated KS were found,[16–18] only one of which displaying lung parenchymal involvement.[16]

Learning points

- Kaposi sarcoma is an increasingly uncommon manifestation of advanced HIV in developed countries, and uncommonly presents with diffuse skeletal involvement.
- Bone biopsy is warranted in these cases to confirm diagnosis.
- Early multidisciplinary involvement with experienced medical oncologists is integral to achieving favourable outcomes in visceral, symptomatic Kaposi sarcoma.
- Many measures necessitated by the COVID-19 pandemic have adversely affected therapeutic relationships with our more vulnerable patients, with detrimental outcome. As caseloads reduce once more, care should be taken to re-establish and facilitate these relationships with patients.

Acknowledgements We thank the members of our multidisciplinary team who assisted us in managing a complex and instructive case.

Contributors Each of the contributing authors were involved in the clinical care of the above patient and authorship of the manuscript. SPC and JMcG were clinical registrars involved in the diagnosis, work-up and treatment of the patient. SPC drafted the manuscript and obtained the images and informed written consent. JMcG contributed to the writing of the manuscript, including the discussion section. JS is the principal medical oncologist in charge of the patient's care and assisted with the case write up and discussion. EGM is the infectious diseases consultant in

charge of the patient's care and reviewed the manuscript, making suggestions. Each had an opportunity to review the completed manuscript prior to submission.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Consent obtained directly from patient(s)

Provenance and peer review Not commissioned; externally peer reviewed.

Case reports provide a valuable learning resource for the scientific community and can indicate areas of interest for future research. They should not be used in isolation to guide treatment choices or public health policy.

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