Case Description

In July 2013, a 38-year-old white man was referred to the Chronic Viral Illness Service at McGill University Health Centre, Montreal, QC, with a 5-year history of persistent cutaneous nodular KS on the lower limbs, coupled with an 8-year history of HIV infection. The patient had, elsewhere in 2005, been diagnosed with HIV infection; he had continued to receive ART since then. He became aviremic—with a CD4+ T-cell count exceeding 500/μL—shortly after initiation of ART. On presentation, he was on a regimen of tenofovir, emtricitabine, and raltegravir. His viral load was undetectable (<40 copies/mL), and his CD4+ T-cell count was 749/μL.

The patient developed cutaneous nodular KS on his lower limbs in 2008 while his HIV infection continued to be well controlled. Biopsy and pathology examination of the lesion on his right thigh revealed characteristic spindle cells and high vascularity, with positivity for the human herpesvirus type 8, determined to be KS (Figure 1). He
had since been treated over a period of 5 years with multiple cycles of liposomal doxorubicin, paclitaxel, vinorelbine, and bortezomib, and had failed to sustain partial response for more than 6 months after chemotherapy.

When referred to our centre in 2013, the patient had left lower limb KS lesions aggravated by prominent pain and swelling, and he had difficulty in moving. Physical examination revealed dark violet nodular lesions on both thighs, the left being more prominent and the biggest measuring 15×12 cm, with swelling and tenderness. Blood tests for immunoglobulin G antibodies to cytomegalovirus were positive, and tests for cytomegalovirus antigen, hepatitis B or C antigen, and syphilis were negative. Magnetic resonance imaging and ultrasonography of the lower limbs were confirmative of soft-tissue infiltration by KS (Figure 2).

The patient received 8 cycles of paclitaxel with the mTOR (mammalian target of rapamycin) inhibitor sirolimus as an immunomodulator for 1 year, which resulted only in transient and partial tumour control. Because of tumour progression, treatment options were discussed with the patient, including re-initiation of previously used chemotherapy, immunomodulators such as thalidomide, and imatinib. After consideration, the patient decided to receive imatinib. Oral imatinib 400 mg daily was therefore prescribed with liposomal doxorubicin beginning in September 2014.

The patient was closely followed in clinic, and major regression of the lesions started to take place 1 month after imatinib initiation—something not previously observed. At the beginning of imatinib therapy, the patient reported mild swelling of the eyelids and lower limbs and extreme fatigue and malaise, which were treated with furosemide and nonpharmacologic measures. The symptoms gradually improved after the first 2 months. Chemotherapy was stopped after 2 cycles, and the symptoms continued to improve on imatinib monotherapy. At his last visit (after 9 months of treatment), all KS lesions had completely resolved for the first time since the KS diagnosis.

DISCUSSION

HIV-KS in the Context of Virus-Controlled HIV Infection

Patients with KS typically present with a CD4+ T-cell count below 350/μL in absence of ART. However, new-onset or unremitting KS has been reported in HIV-infected patients with an undetectable viral load and restored CD4+ T-cell count. In 1999, the first 2 cases of HIV-KS in the setting of viral suppression were reported by Chan et al.5, followed by several case series of HIV-KS with CD4+ T-cell counts exceeding 300/μL and an undetectable HIV viral load6,7. Still, KS persistence despite effective ART remains rare.

In addition, our patient was unique because of the onset of KS with a CD4+ T-cell count exceeding 600/μL combined with 3 years of HIV viral suppression. However, unlike the indolent course of KS usually reported in controlled HIV infection, the KS lesions in our patient were progressive and refractory to multiple chemotherapies despite a well-restored CD4+ T-cell count. Those observations raise questions about the interplay between human herpesvirus type 8, HIV, and the development of KS, especially in the context of effective ART.

Factors that have been postulated to play a role in the development or persistence of KS in such patients include older patient age, duration of HIV infection, and type of ART used6,8. More recently, Unemori et al. observed that
increased frequencies of immunosenescence phenotypes (CD57+ and CD28−) and lower frequencies of naïve T cells (CD27+, CD28+, CD45RA+) are associated with the presence of KS in ART-treated patients, indicating a role for “immune aging” in relation to an increasing vulnerability to KS. Nevertheless, more investigation in this population is required to elucidate the underlying mechanisms. Furthermore, whether an approach other than chemotherapy in addition to ART will better target such KS lesions remains unknown. In that sense, our case suggests a treatment option for recurrent and refractory KS in patients treated with long-term ART.

Imatinib As a Pathogenesis-Based Therapy
A reduced incidence and remarkable regression of KS have been reported in HIV-infected patients treated with ART or with chemotherapy. However, none of the KS treatments to date are curative. The development of KS is currently well recognized to be an inflammation-driven angiogenic and oncogenic process in which a number of cytokines and growth factors with autocrine and paracrine growth effects create a favourable microenvironment for KS formation. Targeted therapies based on antiangiogenic agents and cytokine signalling pathway inhibitors have therefore been regarded as a priority in treatment development.

Activation of the receptor tyrosine kinases such as PDGFR and c-Kit receptor has been proposed to play a role in mediating the growth of HIV-KS. As a multikinase inhibitor, imatinib has shown activity against PDGFR and c-Kit in treating gastrointestinal stromal tumours with activating mutations in PDGFR and c-Kit. The response of HIV-KS to imatinib has also been investigated (detailed in Table 1). In 2005, a pilot study by Koon et al. evaluated the clinical and histologic effects of imatinib on 10 patients with progressive cutaneous HIV-KS despite chemotherapy or ART, or both. After 4 weeks of oral imatinib (300 mg twice daily), 5 of 10 participants experienced a partial response. In addition, biopsies of lesions in the responders demonstrated histologic regression, correlated with inhibition of PDGFR and its downstream effector, extracellular receptor kinase. However, a phase II study by the same group, in which 30 patients received imatinib 400 mg daily for an intended 52 weeks, failed to identify a link between clinical outcomes and the alteration in PDGFR or c-Kit downstream effectors, despite an observed partial response in one third of participants. Those results raise the question of the operating mechanisms underlying imatinib’s efficacy.

A study by Ertmer et al. showed that treatment with imatinib could lead to a dose-dependent activation of cellular autophagy, which was likely induced by inhibition of c-Abl rather than by inhibition of PDGFR or c-Kit receptor. Autophagy is a cellular catabolic mechanism involved mainly in the recycling and turnover of cytoplasmic constituents. Regarded as a double-edged sword in tumour progression, autophagy can promote cell adaption and survival in some circumstances and induce autophagic cell death and growth arrest in tumours in others. Imatinib is known for its effect of inducing tumour cell apoptosis by inhibition of oncogenic tyrosine kinase signalling and subsequent enhanced CD8 cytotoxic function and decreased regulatory T-cell inhibition, as demonstrated in the case of gastrointestinal stromal tumours. However, imatinib might also have the capacity to shift the balance between apoptosis and autophagy in KS tumour cells. Basciani et al. provided evidence that imatinib results in increased autophagy in multidrug-resistant KS cells, indicating that autophagy might represent an additional mechanism of tumour regression in KS.

Given that resistance or unresponsiveness to chemotherapeutic agents results predominantly from defects in the apoptotic signalling pathway, agents such as imatinib that can induce autophagy could be important in managing recurrent KS such as that experienced by our patient. In addition, previous studies have indicated that autophagic activity is inversely correlated with virus production in HIV infection, and pharmacologically induced autophagy...
TABLE I  Summary of clinical studies of imatinib mesylate in Kaposi sarcoma (KS)

<table>
<thead>
<tr>
<th>Reference</th>
<th>Pts (n)</th>
<th>Study details</th>
<th>Drug regimen</th>
<th>Clinical outcome</th>
<th>Safety</th>
</tr>
</thead>
<tbody>
<tr>
<td>Koon et al., 2005</td>
<td>10</td>
<td>Patients with progressive cutaneous HIV-KS were eligible. All received ART for a mean duration of 37.5 weeks; 7 had received prior single-agent chemotherapy for KS.</td>
<td>Oral imatinib 300 mg twice daily for 4 weeks</td>
<td>Partial clinical response (by tumour measurements) was observed in 5 of the 10 patients. Histologic regression was demonstrated in 4 of 6 patients, and inhibition of PDGFR was observed in 4 of 4 patients.</td>
<td>Gastrointestinal (drug withdrawn in 5 patients; dose reduction applied in the rest)</td>
</tr>
<tr>
<td>Koon et al., 2014</td>
<td>30</td>
<td>Patients with HIV-KS were eligible. ART had been received by 77% (23 of 30), and prior therapy for KS, by 60%.</td>
<td>Oral imatinib 400 mg for daily up to 52 weeks, with dose escalation up to 600 mg daily at the 3rd month, if stable</td>
<td>Partial response was observed in 10 of 30 patients, and stable disease in 6 (20%). No significant decrease in ERK phosphorylation was observed in post-treatment biopsies. No mutation in PDGFR or c-Kit receptors was identified.</td>
<td>Grade 3 or 4 imatinib-related adverse events were reported in 8 patients; 5 of those patients terminated the therapy.</td>
</tr>
</tbody>
</table>

Pts = patients; ART = antiretroviral therapy; PDGFR = platelet-derived growth factor receptor; ERK = extracellular receptor kinase.

in infected CD4+ T cells could lead to a significant decline in viral replication\(^{17,18}\). In that sense, whether imatinib might generate a synergistic effect in terms of viral control and reservoir eradication in HIV-ks patients would be of special interest.

SUMMARY

We report a rare case of highly chemoresistant KS in well-controlled HIV infection, which was successfully treated using imatinib. Imatinib can be a treatment option for multiresistant HIV-ks, and its operating mechanism needs more investigation.

ACKNOWLEDGMENTS

We thank the patient for his consent to publish this case report. We acknowledge Jacque Sas and Jim Pankovich for coordinating the research with the support of Canadian Institutes of Health Research (CIHR), CIHR Canadian HIV Trials Network (CTN). We thank Angie Massicotte for coordination and assistance during the writing of this case report.

WC is supported by the 2014 CIHR CTN International Post-doctoral Fellowship. BR is supported by Fondation Philanthropia and the Catherine and Stuart Townsend Hematology Fellowship Award. JPR is holder of the Louis Lowenstein Chair in Hematology and Oncology, McGill University.

CONFLICT OF INTEREST DISCLOSURES

We have read and understood Current Oncology’s policy on disclosing conflicts of interest, and we declare that we have none.

AUTHOR AFFILIATIONS

*Chronic Viral Illnesses Service, McGill University Health Centre, Montreal, QC; †Research Institute, McGill University Health Centre, Montreal, QC; ‡Department of Infectious Diseases, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences, Beijing, PRC; §Institut de Cancérologie Gustave Roussy, Villejuif, France; †Institut national de la santé et de la recherche médicale (INSERM), Villejuif, France; ‡Department of Pathology, Centre hospitalier universitaire de Sherbrooke, Sherbrooke, QC.

REFERENCES


