Laryngeal Kaposi’s Sarcoma Complicated by the Immune Reconstitution Inflammatory Syndrome in an HIV-infected Patient

Hirofumi Kato,1,2 Naoki Yanagisawa,1 Hiroshi Morioka,1,3 Shugo Sasaki,1 Noritaka Sekiya,4 Akihiko Suganuma,1 Akifumi Imamura,1 and Atsushi Ajisawa1,5

Abstract

We herein report a case of laryngeal Kaposi’s sarcoma (KS) complicated by immune reconstitution inflammatory syndrome in a human immunodeficiency virus (HIV)-infected patient. The patient initially presented with KS involving the larynx, which was successfully treated with pegylated liposomal doxorubicin (PLD) and antiretroviral therapy (ART). PLD was discontinued after 2 courses because of a marked clinical improvement; however, the patient experienced progressive odynophagia and dyspnea 2 months after the initiation of ART. Laryngoscopy revealed a severely swollen, inflamed epiglottis. The readministration of PLD was successful, and the patient was thereafter discharged without any subsequent complications.

Key words: Kaposi’s sarcoma, immune reconstitution inflammatory syndrome, HIV


Introduction

Kaposi’s sarcoma (KS) is one of the common malignancies among human immunodeficiency virus (HIV)-infected individuals (1). KS is a multifocal tumor that manifests most frequently in the lower extremities, face, trunk and gingiva. KS also commonly involves the lymph nodes and visceral organs, especially the respiratory and gastrointestinal tracts. Laryngeal involvement is a somewhat infrequent manifestation (2) and should be managed cautiously due to the risk of airway obstruction.

A proportion of HIV-infected patients experience a paradoxical clinical worsening of existing opportunistic infections or malignancies in the initial weeks after beginning antiretroviral therapy (ART). This phenomenon is referred to as immune reconstitution inflammatory syndrome (IRIS). IRIS has been reported to be associated with a wide range of infections and malignancies including KS (3). We herein report a case of laryngeal KS that was complicated by IRIS and treated successfully with pegylated liposomal doxorubicin (PLD).

Case Report

A 43-year-old Japanese man was admitted to our hospital with complaints of anal pain persisting for the previous 3 months. His past medical history was unremarkable, and there was no history of smoking, ethanol abuse or illicit drug use. A physical examination revealed an inflamed anal ulcer accompanied with condyloma acuminatum. In addition, numerous purple-red plaques and nodules, ranging in diameter from 0.5-3 cm, were observed on the face, trunk, extremities, and in the oral cavity (Fig. 1). These lesions were clinically diagnosed as KS, according to its typical distribution and characteristics.

1Department of Infectious Diseases, Tokyo Metropolitan Komagome Hospital, Japan, 2Field Epidemiology Training Program, Infectious Disease Surveillance Center, National Institute of Infectious Diseases, Japan, 3Department of Infection Control and Prevention, Nagoya University Hospital, Japan, 4Department of Clinical Laboratory, Tokyo Metropolitan Komagome Hospital, Japan and 5Toshima Hospital, Tokyo Metropolitan Health and Medical Treatment Corporation, Japan

Received for publication May 22, 2015; Accepted for publication July 22, 2015
Correspondence to Dr. Naoki Yanagisawa, naokiy-97@umin.ac.jp
Figure 1. Purplish plaques were observed in the gingiva and the hard palate of the patient, which was clinically diagnosed as Kaposi’s sarcoma.

The admission laboratory data are presented in Table. The results were notable for an elevated C-reactive protein level, but other values, including liver and kidney function tests, were essentially within the normal limits. Antibody for HIV was positive, which was later confirmed by a Western blotting analysis. The CD4 cell count and HIV-RNA viral load were 186/μL and 2.5×10⁵ copies/mL, respectively. The syphilis serology test was positive as well. The plasma KSHV-DNA viral load was 8.3×10⁸ copies/mL.

A further workup revealed pathologically-confirmed KS lesions in the upper gastrointestinal tract (Fig. 2). The patient denied any respiratory symptoms, laryngoscopy demonstrated a swollen epiglottis surrounded by white plaques (Fig. 3a). A laryngeal biopsy was not performed due to the fear of exacerbating the condition, however, laryngeal KS was strongly suspected from the appearance and the clinical situation. A computed tomography scan was prominent for a perianal abscess, but did not reveal any abnormalities in the visceral organs, including the lungs.

Ceftriaxone and metronidazole were initiated for treatment of the perianal abscess. Temporal colostomy was performed as well, resulting in clinical improvement. Subsequently, ART including tenofovir disoproxil fumarate, emtricitabine, and raltegravir was initiated in conjunction with PLD (20 mg/m² every 3 weeks). After 1 course of PLD, the pharyngolaryngeal lesions resolved dramatically, confirming the diagnosis of laryngeal KS (Fig. 3b). The cutaneous KS lesions also began to flatten and fade out. No major side effects of ART or PLD were observed. The patient was discharged after a total of 2 courses of PLD. Only antiretroviral agents were administered thereafter, as a therapeutic response to both HIV and KS were expected.

The patient visited our outpatient clinic for odynophagia 2 months after initiating ART. Laryngoscopy revealed a severely swollen, inflamed epiglottis. The otolaryngologist initially suspected acute viral epiglottitis, and oral prednisolone (20 mg/day) was administered. However, odynophagia was accompanied by progressive dyspnea and the patient was readmitted to our hospital 10 days later. On admission, the vital signs were stable with a respiratory rate of 14 times per minute and oxygen saturation of 97% on ambient air, despite dyspnea. A physical examination revealed an edematous face and neck and reappearance of the purplish lesions on the skin. Laryngoscopy revealed a far-advanced, swollen epiglottis (Fig. 3c). The laboratory data, including the kidney and liver function tests and inflammatory markers, were unremarkable. The CD4 cell count was 196/μL with an undetectable HIV-RNA viral load, demonstrating a good clinical response to ART. The plasma KSHV-DNA viral load had decreased to 20 copies/mL. The clinical diagnosis of KS-IRIS was made, and PLD was readministered immediately. ART was interrupted temporarily for fear of exacerbating the symptoms. PLD resulted in a rapid clinical response, averting tracheotomy, which was considered upon admission. After an additional 2 courses of PLD, the patient was asymptomatic and laryngoscopy demonstrated resolution of the KS lesion. ART was restarted at this time, but IRIS did not occur. Adverse effects of PLD included grade 2 neutropenia, but this recovered without the use of any medication. The clinical course was not complicated for any abdominal symptoms, thus suggesting the occurrence of KS-IRIS of the gastrointestinal tract. Follow-up upper gastrointestinal endoscopy performed after 6 courses of PLD demonstrated complete resolution of the KS lesions. PLD was continued for a total of 10 courses, and the clinical course was stable thereafter.

Discussion

We experienced a case of laryngeal KS complicated by IRIS in an HIV-infected patient. Rapid administration of PLD and interruption of ART resulted in clinical improvement.

The diagnosis of laryngeal KS may be difficult at times, since it is an unusual location for KS to develop. However, clinicians should be well aware of laryngeal KS and its associated symptoms, for a delay in the diagnosis may result in substantial complications. In a case series reported by Mochloulis et al., most patients presented with symptoms associated with upper airway obstruction. Among the 17 patients described, the most frequent symptom was dyspnea (82%), including 1 patient who required tracheostomy for acute airway obstruction. Other symptoms included a nonproductive cough (76%), fever (29%), dysphagia (11%), hoarseness of voice (11%), and hemoptysis (6%). The ma-
majority of the patients (88%) had cutaneous KS as well. Although that report was published in the pre-ART era, it is notable that the survival of the patients was extremely poor (6). In our case, the patient initially lacked any respiratory symptoms, which was not consistent with the previously published findings. However, due to the widespread KS cutaneous lesions throughout the body, endoscopy and imaging studies were undertaken. Previous case reports revealed that the majority of laryngeal KS patients also have cutaneous and visceral KS lesions, which was true for our patient. Clinicians may consider lowering their threshold for performing an extensive workup in such cases.

In this case, we suspected KS-IRIS rather than progressive KS of the larynx. Researchers have proposed criteria for KS-IRIS, which include the following: abrupt KS worsening after ART, compatible time from the start of ART, viral suppression, CD4 cell count increase, agreement between 2 primary investigators, and the exclusion of other causes of worsening signs and symptoms (7). Previous reports have revealed that KS-IRIS frequently occurs within 3 to 6 weeks after initiating ART (8). Because our case met the above criteria and the timing of occurrence, it was reasonable to sus-

**Table. Laboratory Data on Initial Admission.**

<table>
<thead>
<tr>
<th>Hematology</th>
<th>Biochemistry</th>
<th>Infection/Immunology</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC 7,200 /μL</td>
<td>BUN 10 mg/dL</td>
<td>HBs-Ag (-)</td>
</tr>
<tr>
<td>Neu 60.0 %</td>
<td>Cr 0.8 mg/dL</td>
<td>HBs-Ab (+)</td>
</tr>
<tr>
<td>Lym 27.5 %</td>
<td>T.bil 0.3 mg/dL</td>
<td>HCV-Ab (-)</td>
</tr>
<tr>
<td>Hb 11.2 g/dL</td>
<td>AST 161 IU/L</td>
<td>RPR 907 R.U.</td>
</tr>
<tr>
<td>Ht 27.8 %</td>
<td>ALT 12 IU/L</td>
<td>TPLA 8,482 T.U.</td>
</tr>
<tr>
<td>Plt 12.7×10^4 /μL</td>
<td>LDH 203 IU/L</td>
<td>CMV pp65(HRP-C7) (-)</td>
</tr>
<tr>
<td></td>
<td>Na 140 mEq/L</td>
<td>E. histolytica Ab ×100</td>
</tr>
<tr>
<td></td>
<td>K 4.1 mEq/L</td>
<td>HIV-Ab (+)</td>
</tr>
<tr>
<td></td>
<td>Cl 104 mEq/L</td>
<td>CD4 cell count 186 /μL</td>
</tr>
<tr>
<td></td>
<td>Occult blood (-)</td>
<td>Glu 119 mg/dL</td>
</tr>
<tr>
<td></td>
<td>CRP 5.9 mg/dL</td>
<td>HIV-RNA 2.5×10^5 cp/mL</td>
</tr>
<tr>
<td></td>
<td>K 300 cp/mL</td>
<td>KSHV-DNA 8.3</td>
</tr>
</tbody>
</table>

Abbreviations: RPR: rapid plasma reagin test, TPLA: *Treponema pallidum* latex agglutination, CMV: cytomegalovirus, KSHV-DNA: Kaposi’s sarcoma-associated herpesvirus-DNA

---

**Figure 2.** Biopsy samples of the gastric mucosa. (a) Hematoxylin and Eosin staining showing slit-shaped spindle cells. Immunostaining was positive for (b) D2-40 (c) CD31 and (d) HHV-8 LANA-1. LANA: latency-associated nuclear antigen-1
pect KS-IRIS. Furthermore, Connick et al. suggested that a decrease in the plasma KSHV-DNA level may be correlated with the occurrence of KS-IRIS. A decrease in the KSHV-DNA level suggests that KSHV-infected cells were rapidly cleared by the reconstituted host antiviral response during the early period of ART (9). Our case followed the same clinical course regarding the plasma KSHV-DNA level, supporting the diagnosis of KS-IRIS.

After commencing ART, clinical exacerbation was noted in the larynx but not in the gastrointestinal tract where KS was diagnosed pathologically. The reason for this discrepancy is unclear. A previous report by Bower et al. has demonstrated that the site of KS is not a significant factor for the development of KS-IRIS (4). Variables associated with KS-IRIS include the presence of tumor-associated edema reflective of the inflammatory component of KS (4), as well as T1 KS stage, high HIV viral load, and a detectable KSHV DNA level (10). It is speculated that in patients with high KSHV DNA and HIV viral load, the restored KSHV-specific immune responses may be insufficient in controlling KSHV replication, resulting in cytokine-induced reactive angioproliferation and tumorogenesis (10). In addition, Takeda et al. reported that programmed cell death 1 (PD-1)-positive cells, which are speculated to be associated with IRIS, were less frequent in the tumor after ART on histopathological evaluation, which may suggest the difference between KS-IRIS and other forms of KS (11). Because the pathogenesis of IRIS is not fully understood, further observation is warranted.

The use of corticosteroids might have exacerbated the clinical course in our patient. The primary diagnosis was viral epiglottis, a disease for which corticosteroids are frequently used, however, swelling of the epiglottis worsened subsequently. Corticosteroid use has been reported to be associated with an exacerbation of preexisting KS in HIV-infected patients (12). Achenbach et al. also suggested that the traditional approach toward severe IRIS may not be recommended due to tumor progression (13). In patients with IRIS in the setting of other HIV-related opportunistic infections, such as Mycobacterium tuberculosis or Mycobacterium avium complex, corticosteroids may play an essential role in disease control. However, clinicians should be cautious when using corticosteroids when IRIS is suspected, especially when KS is present.

Treatment with systemic chemotherapy for laryngeal KS-IRIS involving impending airway obstruction should be considered immediately (10). The ART-induced KSHV-specific inflammatory response might result in an increase in an-

Figure 3. Laryngoscopy results. (a) Laryngeal Kaposi’s sarcoma was suspected on initial admission. (b) The appearance after 2 cycles of pegylated liposomal doxorubicin. (c) The appearance 2 months after initiating antiretroviral therapy.
gioproliferative and tumorigenic factors (14), which may contribute to further exacerbation of KSHV (15). Systemic chemotherapy is likely to have a positive impact on KS itself, as well as attenuating reconstituted immune responses by preventing these reactions. On the other hand, previous reports have shown that radiation therapy or intralesional chemotherapy were effective for laryngeal KS and KS-IRIS (16-18). However, these therapies were reported before the introduction of effective systemic chemotherapies, such as PLD or paclitaxel, making it difficult to evaluate which treatment is superior. Moreover, both radiation therapy and intralesional chemotherapy are non-effective for disseminated KS lesions. Accordingly, systemic chemotherapy should be the first-line therapy for KS-IRIS patients, especially when the KS lesions are disseminated or located in the airway.

In summary, we herein described a case of laryngeal KS complicated by IRIS in an HIV-infected patient. Physicians should be aware of this relatively rare, yet significant clinical condition that requires immediate intervention.

The authors state that they have no Conflict of Interest (COI).

References


© 2016 The Japanese Society of Internal Medicine
http://www.naika.or.jp/imonline/index.html