

A Case of Kaposi's Sarcoma Associated with Disseminated AIDS: The Management Challenges

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Background: As a malignant tumor derived from vascular endothelial cells, Kaposi's sarcoma (KS) is quite common in AIDS patients. Nonspecific clinical symptoms often lead to timely diagnosis or wrong treatment, leading to recurrent disease and poor prognosis. Anti-retroviral therapy (ART) could significantly reduce its morbidity and aggressiveness. As one of the ARTs, liposome anthracyclines are the preferred chemotherapy regimen for disseminated KS with multiple organs or tissue invasion. The curative effect is highly related to the degree of immunosuppression. This is the first case of AIDS with Kaposi's sarcoma, who was cured after ART and two consecutive chemotherapy with doxorubicin liposome without recurrence. This case may provide new ideas and methods for the clinical management of AIDS with Kaposi's sarcoma.

Case Description: The patient, a male aged 60 years, was hospitalized on 21/11/2018 following having a cough, expectoration, and difficulty breathing. He was infected with HIV eight years ago and presented symptoms of blood-stained sputum. The patient complained that he had not received ART before. After admission, he was diagnosed as KS with disseminated AIDS after multiple biopsies and histopathological examinations. The patient was treated with ten months of ART (lamivudine+tenofovir+dolutegravir) and 14 times of chemotherapy with doxorubicin liposome (20 mg/m², three times per week, seven times per course of treatment). The patient's disease was finally alleviated, and there was no recurrence during the follow-up.

Conclusion: The reconstitution of immune function and consecutive chemotherapy with doxorubicin liposome play a vital role in treating KS. In addition, for the early general symptoms of AIDS patients, such as thrombocytopenia and hemorrhagic purple papules, it is necessary to increase vigilance and obtain the results of histopathological verification as soon as possible to diagnose KS patients at an earlier stage and realize clinical intervention in time.

Keywords: AIDS, Kaposi's sarcoma, human herpesvirus 8, doxorubicin liposome

Introduction

According to the incidence of cancer patients with AIDS, Kaposi's sarcoma, non-Hodgkin's lymphoma, and invasive cervical cancer were classified as AIDS-related tumors by the CDC in the US in 1993.¹ KS is the most common malignant tumor related to AIDS, which is vascular endothelial cells characterized by red or purple-brown maculopapular lesions. KS can occur alone or involve the oral gastrointestinal tract and respiratory systems. Human herpesvirus 8 (HHV-8) was closely related to the occurrence of KS.²

The standard therapy method for late-stage KS is still anti-retroviral therapy (ART) combined with systemic chemotherapy.³ A case of disseminated AIDS-KS was diagnosed and treated in the Second Department of Infection in Xixi Hospital, Hangzhou. The lesions of this case involve the skin and mucosa, respiratory system, and bone marrow hematopoietic function. The early clinical manifestations include hemorrhagic purpura and thrombocytopenia. Before diagnosis, the patients have been treated with idiopathic thrombocytopenic purpura and pulmonary infection. After hospitalization, the patient was significantly relieved by ART and 14 times of chemotherapy of doxorubicin liposome. This is the first case of AIDS with Kaposi's sarcoma, who was cured after ART and two consecutive chemotherapy with doxorubicin liposome without recurrence. Hence, the reconstitution of immune function and consecutive chemotherapy with doxorubicin liposome play a vital role in treating KS.

Case Presentation

The patient, a male aged 60 years, was hospitalized on 21/11/2018 following having a cough and expectoration for more than one month and having difficulty breathing for more than four days. He was infected with HIV eight years ago and presented symptoms of cough and sputum one month ago and blood-stained sputum two weeks ago. The patient complained that he had not received ART before.

The patient was first hospitalized at a community hospital and Zhejiang Provincial People's Hospital with a cough and expectoration. His pulmonary CT showed interstitial changes in both lungs. The laboratory examination showed a platelet count of $10 \times 10^9/L$, diagnosed as pneumonia and thrombocytopenia. One week after treatment, the platelet count was $174 \times 10^9/L$. Then, the patient presented difficulty breathing four days ago and was admitted to our hospital.

The physical, laboratory, imageological, and histopathological examinations were performed after admission. The physical examination parameters are as follows: temperature of $36.9^\circ C$; pulse of 127 times/min; respiration of 20/min; blood pressure of 118/76 mmHg. The acute sickly look and congestion of the throat were visible. The large purple-red macules could be observed on the oral mucosa (Figure 1A). The dark brown and dark red scattered petechiae can be seen in the neck, chest, abdomen, and lower limbs (Figure 1B). Breath sound was slightly rough, with no lung dry, moist rales. Heart rate was consistent, with no murmur. The abdomen was soft without tenderness, the liver, spleen, and ribs were unaffected, and there was no prominent edema in both lower limbs.

The laboratory examination results were as follows: WBC of $11.11 \times 10^9/L$, RBC of $4.22 \times 10^{12}/L$, Hb of 135 g/L, PLT of $9 \times 10^9/L$, CRP of 25 mg/L, PCT of 0.2 ng/mL. The occult blood test (stool) was positive (+). The antiplatelet antibody was negative (-). Lymphocyte subset test results showed a total lymphocyte count of 550/ μL , CD4+/CD8+ of 0.08, CD4+T of 34/ μL , and HIV-RNA of 1.12×10^5 IU/mL. TB infects T-cells was 2.4 pg/mL. EB-DNA with whole blood was 2.28×10^4 cp/mL.

The histopathological examination (4/12/2018) was as follows: (skin biopsy) Ill-defined nodular areas were found in the dermis. Novel and immature vessels can be seen in the nodes; hyperplasia for the mesenchymal spindle cells; Angiomatous changes can be observed in the focal area, which follows the character of KS; Immunohistochemical indices: D34(+); Fli-1(+); HHV8(-); Ki-67(30%+); D2-40(+) (Figure 2). Histopathology examination percutaneous pulmonary biopsy (18/12/2018) showed that neovascularization with varying-sized red blood cells could be seen in the alveolar stroma, spindle cell hyperplasia with mild stroma atypia. Immunohistochemical examination/specific stain of pathology of CD34(+), D2-40(+), Fli-1(+) HHV8(+), Ki-67(20%+), PAS(-), acid-fast staining (-), and Silver hexamine staining (-) (Figure 3).

During this period, the patient was treated as follows: moxifloxacin injection was given for 0.4 g qd intravenous drip for anti-bacterial treatment for seven days. SMZ-TMP was given orally for anti-PCP and anti-fungal at a dose of 1.44 g tid and then changed to 0.96 g qd after 21 days of treatment until CD4+T lymphocytes increased to 200/ μL and continued for six months. Fosinate sodium injection was given for 3.0 g intravenous qd for antiviral therapy. Voriconazole tablet was given for 0.2 g oral bid treatment for 15 days. Immunoglobulin 20 g intravenous drip qd treatment for five days. Methylprednisolone treatment was given for anti-inflammatory for 40 mg iv qd, tapering after

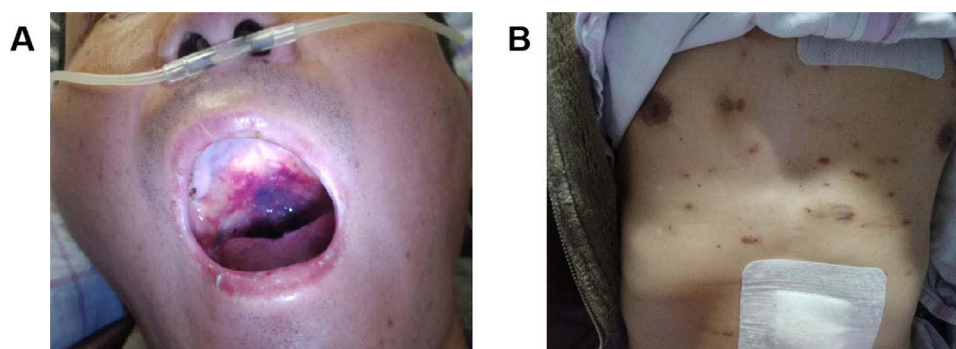


Figure 1 The observation and physical examination of disseminated AIDS-KS. (A) Purple-red macula on the oral mucosa. (B) Dark red maculopapular on chest and abdomen skin.

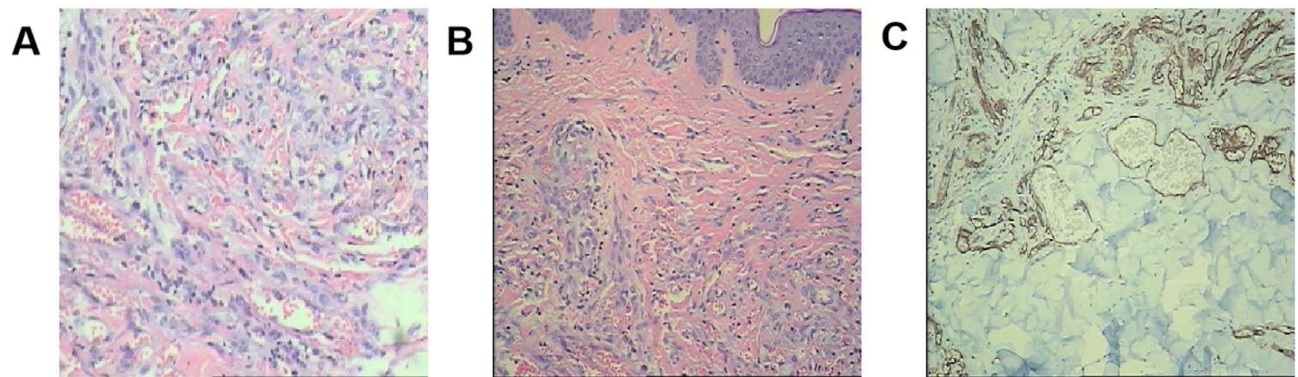


Figure 2 The laboratory examination. (A and B) Ill-defined nodular areas were found in the dermis; novel and immature vessels can be seen in the nodes; hyperplasia for the mesenchymal spindle cells; angiomatous changes can be observed in the focal area, which follows the character of KS; (C) Immunohistochemical examination: CD34(+); Fli-1(+); HHV8(-); Ki-67(30%+); D2-40(+).

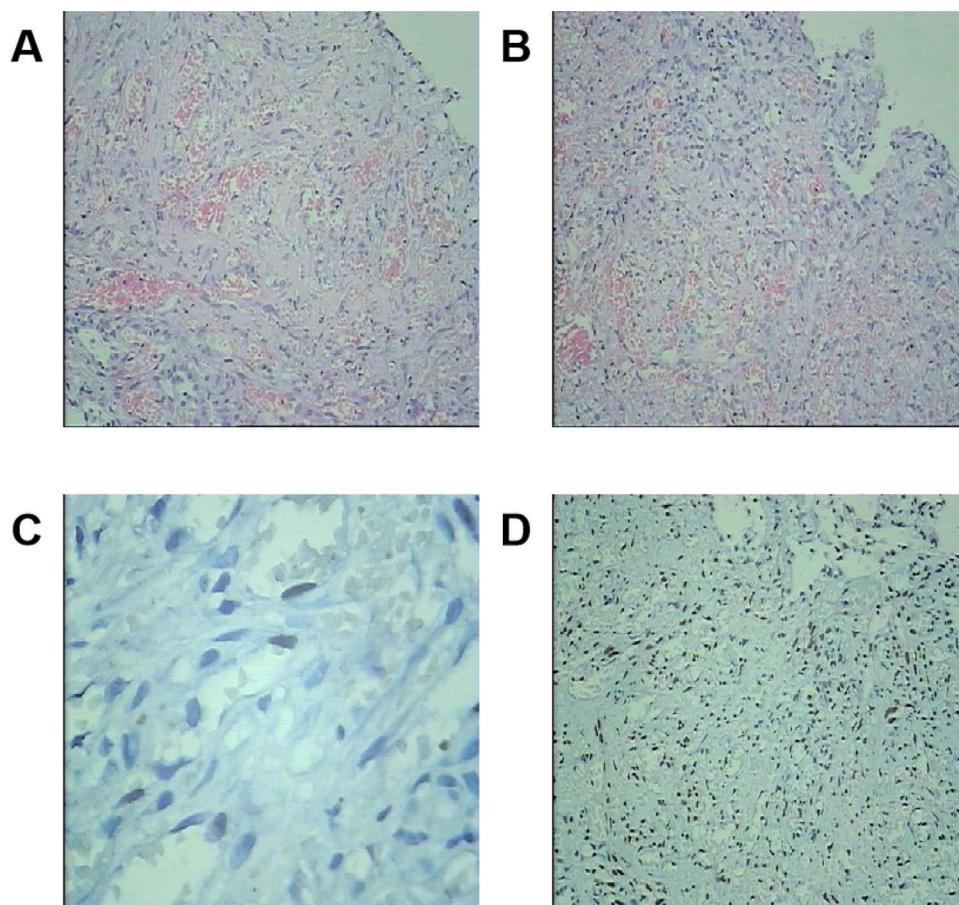


Figure 3 The histopathological examination. (A and B) Neovascularization with red blood cells of varying sizes can be seen in the alveolar stroma; Spindle cell hyperplasia with mild stroma atypia (Kaposi's sarcoma); (C and D) Immunohistochemical examination/specific stain of pathology: CD34(+) D2-40(+) Fli-1(+) HHV8(+) Ki-67(20%+) PAS (-) acid-fast staining (-) Silver hexamine staining (-).

five days. Recombinant thrombopoietin was given to promote platelets. 15000U was given for subcutaneous injection once daily for nine days.

Chest CT (8/12/2018) showed that multiple lesions were observed in both lungs, with a small amount of exudation and a small amount of fluid in both pleural cavities (Figure 4A). Finally, he was diagnosed with AIDS-KS, lung infection, and thrombocytopenia.

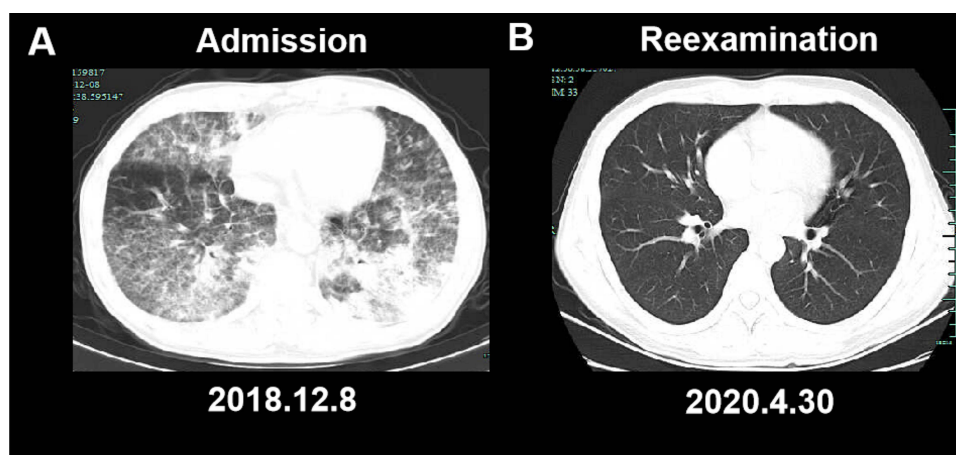


Figure 4 Chest CT image. **(A)** The chest CT in our hospital showed multiple lung lesions with exudation and fluid in both pleural cavities. **(B)** The reexamination of chest CT after discharge showed a marked improvement compared to the last examination; ground-glass attenuation was absorbed for both lungs.

According to the guideline of Clinical Pathways for AIDS and related diseases (second edition), ART started on 6/12/2018, and chemotherapy on 12/12/2018. ART was given for lamivudine 0.3g qd, tenofovir 0.3g qd and dolutegravir 0.05g qd. To reduce the potential adverse reactions of the drug, it was adjusted to lamivudine 0.3g qd and dolutegravir 0.05g qd on 11/9/2020. The first chemotherapy was administered with one liposomal doxorubicin treatment (20 mg/m², three times per week, seven times per course of treatment). New lesions on the right lower extremity after seven times of treatment, and pathologically diagnosed as KS. And pathological biopsy showed tumor recurrence. In general, if the effect of chemotherapy is not ideal, it is generally recommended to adjust the treatment plan according to the relevant literature, such as changing to paclitaxel liposome therapy. However, considering the drug was unavailable in our hospital, the second course of treatment of the original scheme (liposomal doxorubicin) was given after communicating with the patient. Surprisingly, the patient's condition was completely relieved after the second chemotherapy, and there has been no recurrence. During this period, no severe opportunistic infection occurred, the curative effect was significant, skin lesions gradually vanished, and lung lesions were absorbed.

A reexamination of chest CT (30/4/2020) showed a marked improvement compared with the last examination. The ground-glass attenuation was absorbed for both lungs (Figure 4B). No recurrence was observed after two years of follow-up. Reexamination results showed CD4+T 282/μL and HIV-1 RNA was not detected. Follow-up is still underway. The timeline of patient diagnosis and treatment is shown in Figure 5.

Discussion

HHV-8 could infect B cells latently and invade vascular endothelial cells when the immune system is compromised.^{4–6} HHV-8 was first identified from the case of KS in 1994 and then detected in all KS subtypes, thus referred to as Kaposi's sarcoma herpesvirus.⁷ The genome of HHV-8 encodes many genes, which include Bcl-2, Cyclin D1, interleukin-6 (IL-6), etc. It is worth noting that IL-6 enhances cell proliferation and angiogenesis of KS and causes joint pain and thrombocytopenia by mediating related systemic inflammatory syndrome.^{8–10} This case of disseminated AIDS-KS is characterized by thrombocytopenia and hemorrhagic purpura. The cause of thrombocytopenia is speculated to be related to the systemic inflammatory response and tumor invasion of bone marrow. Although this patient presented a systemic purple-brown maculopapular rash early on, the clinical diagnosis was easily missed when the characteristic lesions overlapped with hemorrhagic purple maculopapular caused by thrombocytopenia. AIDS with KS-related lung CT presents the bronchial enlargement of the blood vessel bundle, nodules distributed around the bronchovascular bundle, the edges of the nodules are marked by irregular flares, and ground glass image appears if KS invades the pulmonary alveolus. It is difficult to distinguish with interstitial pneumonia due to opportunistic infection when etiological evidence is absent.^{11,12} In this case, pneumonia-like exudation was the main sign for pulmonary imaging in the early course of the disease, and the typical flame sign was absent.

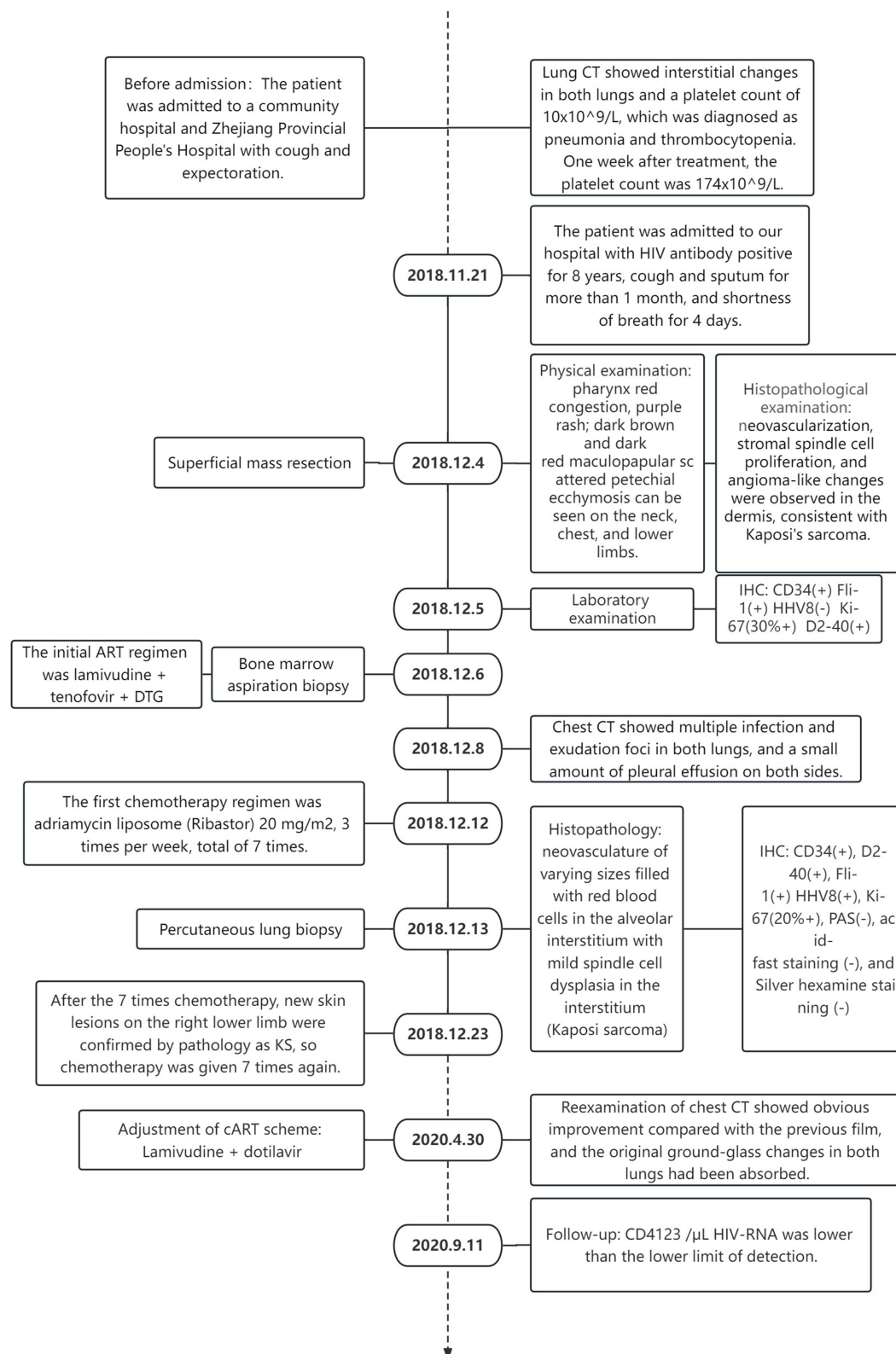


Figure 5 The timeline shows the entire diagnosis and treatment process of this case.

ART can inhibit the replication of HIV effectively and promote the body's immune reconstruction, thus is the most effective way to control AIDS.¹³ However, KS still occurs in persons living with HIV (PLHIV) who have received ART.¹⁴ It is speculated that it could be related to the failure of antiviral therapy or persistently low CD4⁺T cell count in

the first year after ART initiation.^{15,16} Some studies have also indicated that the lesions of KS can remain stationary for a long time or even fade spontaneously, so it is believed that the skin lesions of KS do not necessarily need treatment.^{17,18} However, for disseminated KS with multiple organ tissue invasion, chemotherapy with anthracycline or paclitaxel is still the first-line treatment for these patients, although it has some inherent drug toxicity.^{19,20} The effect of the immunomodulatory ability of HHV-8 may suggest the potential role of immunotherapy and immunomodulatory drugs.^{21–24} However, the efficacy of this new treatment needs to be determined by large-scale evidence-based medical evidence.

In our case, the patient was treated with ART for ten months and finally achieved remission after 14 rounds of chemotherapy with adriamycin liposome and no recurrence was observed after follow-up for more than two years. The patient is still being followed up.

KS is mainly characterized by HHV-8 infection, spindle cell proliferation, and abnormal neovascularization.²⁵ Typical skin lesions are commonly found in the nasal tip, oral mucosa, trunk, limbs, and other areas.²⁶ The skin lesions start with a pink macula, grow dark, form mauve or brown macula or plaques, and finally become hemorrhage skin lesions and nodules.²⁶ ART not only rebuilds immunity and improves immune activation but also significantly reduces the incidence and invasiveness of related tumors, such as KS.²⁷ For disseminated KS with multiple organ tissue invasion, chemotherapy with liposome anthracyclines has significant efficacy and high safety.²⁸ In addition, the degree of immunosuppression is highly correlated to prognosis.²⁹ KS patients with poor immune reconfiguration are more challenging to treat for ART, the course of treatment is longer, and it is more prone to relapse. Thus, the reconstruction of immune function is significant for the treatment and prognosis of AIDS-KS.

Conclusion

This is the first case of AIDS with Kaposi's sarcoma, who was cured after ART and two consecutive chemotherapy with doxorubicin liposome without recurrence. This further validates the importance of reconstitution of immune function in treating KS. Last but not least, it is necessary to increase vigilance for the symptoms of thrombocytopenia and hemorrhagic purple papules and obtain the results of histopathological verification as soon as possible to timely diagnose and treat KS patients. This case may provide new ideas and methods for the clinical management of AIDS with Kaposi's sarcoma.

Ethics Approval and Informed Consent

The authors certify that the patient consent form has been obtained. Written informed consent was obtained from the patient for publication of this Case report and any accompanying images. All procedures performed in the study involving human participants were in accordance with the ethical standards of the Ethics Committee of the Hangzhou Xixi Hospital. The ethics committee approved the waiver in this case report, based on the ethical standards to publish the case details.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis, and interpretation, or all these areas; have drafted, revised, or critically reviewed the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

All authors report no conflicts of interest in this work.

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