The diagnostic challenge and management of pulmonary Kaposi's sarcoma in renal transplant recipients

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ABSTRACT

Kaposi's sarcoma is a multicentric low grade tumor that usually begins with the development of violaceous skin lesions and is associated with the presence of human herpes virus 8. Kaposi's sarcoma has been described in immunocompromised patients, particularly following renal transplantation, with cutaneous involvement being the most salient finding. Infectious and non-infectious pulmonary disorders in immunocompromised patients can simulate the radiological manifestations of pulmonary Kaposi's sarcoma. This report highlights the dilemma in reaching an accurate diagnosis of pulmonary Kaposis sarcoma as a complication of immunosuppression post-renal transplant and reviews the management of immunosuppression related Kaposi's sarcoma.

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Moriz Kaposi in 1872 was the first to described 5 patients presenting with a condition he called "sarcoma idiopathicum multiple hemorrhagicum".1 Until the advent of organ transplantation, reports of Kaposi's sarcoma (KS) were rare. In the 1960's, KS was increasingly reported following organ transplantation and immunosuppressive therapy.2 After 1981, the epidemic form of KS associated with the acquired immunodeficiency syndrome (AIDS) was described.3,4

Kaposi's sarcoma is a multicentric low-grade tumor that usually begins with the development of violaceous skin lesion and is associated with infection with human herpes virus 8 (HHV-8).5,6 It is the most common malignancy associated with human immunodeficiency virus (HIV) infection. It occurs in approximately 6% to 20% of HIV-infected homosexual or bisexual men and a smaller number of HIV-infected patients from other risk groups.4 In patients with known cutaneous KS who present with a respiratory problem, up to 50% have parenchymal involvement.7 In decreasing order of frequency, the lung parenchyma, pleura, and endobronchial tree have been involved.8 Pulmonary KS has been described in immunocompromised patients following renal transplantation, with cutaneous involvement being the most salient finding.9-11 Infectious and other non-infectious pulmonary disorders in immunocompromised patients can simulate the radiological manifestations of KS. In this communication, we highlight the challenge in diagnosing such pulmonary complications and review the management of immunosuppression related KS.

Incidence. A marked increased incidence of malignancy in transplant recipients is well recognized. Tumors known to be associated with immunosuppression are KS, non-Hodgkin lymphoma and the common malignancies of the skin except melanomas.12 The incidence of post-transplantation KS has varied among

different reports, and ranged from 1% to 6%.10,13,14 In a review of 8724 denovo malignancies that occurred in 8191 organ transplant recipients, KS accounted for 6% and was most common in Arabs, Africans, Italians, Jewish and Greek patients.13 Qunibi et al from the Kingdom of Saudi Arabia,15 reported a similar incidence of 5%.

Kaposi's sarcoma is the most common tumor post renal transplantation in the Saudi population. In another study, Montagnino et al10 reported 820-kidney transplant recipients, 13 of which 2% developed KS. Approximately one 3rd of KS patients have clinically evident pulmonary disease and 50% have pulmonary involvement at autopsy.16,17 Among 350 recipients of renal transplants from the Kingdom of Saudi Arabia, 12 (3%) developed KS, of which, 2 (17%) presented primarily with lung involvement.18

Clinical presentation. The presenting symptoms of pulmonary KS are indistinguishable from those of opportunistic pathogens that cause pneumonia. Most of the affected patients present with shortness of breath, fever, cough, chest pain and hemoptysis while others may be asymptomatic but have an abnormal chest radiograph.7 Therefore, in a patient with known cutaneous KS who develops either changing symptoms or new roentgenographic findings, an attempt must be made to rule out an associated infectious process. However, the detection and documentation of extracutaneous sites of this disease can be difficult. This is particularly true of pulmonary involvement, due to radiographic findings varying from a normal chest radiograph to nodular opacities associated with hilar adenopathy, interstitial or alveolar opacity, and pleural effusion or both.19-21 In a series of 24 patients with autopsy-proved intrathoracic KS, Davis et al19 reported radiological findings with a high predictive value, which include parenchymal nodules, pleural effusions, mediastinal and hilar adenopathy. Furthermore, the presence of mucocutaneous KS can positively predict the pulmonary involvement of this malignancy.10

Computerized tomography scan in pulmonary Kaposi's sarcoma. The role of computerized tomography (CT) scan in diagnosing intrathoracic KS was evaluated in several studies20,22,23 and was found to be more specific than routine roentgenograms for identifying pulmonary KS. A retrospective study of 24 patients in the absence of infections pointed out that the peribronchovascular distribution of the disease is sufficiently characteristic, though not pathognomonic, to obviate more invasive diagnostic procedures.20 In another retrospective review, Khalil et al22 evaluated 53 CT scans of patients with intrathoracic KS, in the absence of concomitant infectious process. Numerous nodules 79%, bronchovascular thickening 66%, tumoral masses 53%, and pleural effusion 53% were the main signs. The association of more than one sign in 66% of patients was very characteristic but not diagnostic for intrathoracic KS. The perivascular, ill-defined, nodular interstitial pattern of this malignancy is considered to be the most common radiological finding reported in the literature. Although pulmonary KS does not usually cavitate, there is one report in the literature of such cavitation in a patient with AIDS.24 Therefore, searching for a concomitant pathology is essential in the presence of cavitary lesions. Lung biopsy is usually required to diagnose such pulmonary complications whenever the diagnosis is in doubt.

The role of nuclear medicine scanning. Several reports suggested the diagnosis of KS by the characteristic "thallium positive, gallium negative" scan patterns.25,26 Other reports revealed that infected areas of the chest are generally thallium negative but are gallium positive.27 Lee et al25 reported 3 cases of AIDS associated pulmonary KS that demonstrated this characteristic scan pattern. Abdel-dayem et al26 reported 19 patients with pulmonary KS in which opportunistic infections were excluded. Thallium-positive, gallium-negative scan pattern was described in 17 patients with a sensitivity of 89%. However, in the presence of KS associated with opportunistic infections in the same study, this pattern was only detected in 7 out of 19 patients resulting in a significantly lower sensitivity of 37%. In contrast to pulmonary KS, some pulmonary infections such as tuberculosis were reported to have the characteristics of thallium negative, gallium positive scan patterns.25,27 Therefore, in the absence of pulmonary infections, an abnormal chest radiograph, a positive thallium scan and a negative gallium scan is thought to be suggestive of pulmonary KS.28 However, the role of thallium and gallium scans in diagnosing intrathoracic KS is not universally accepted.

Pulmonary function testing. Pulmonary KS is associated with non-specific abnormalities in the pulmonary function testing. These include a low diffusing capacity as the most common finding and low forced expiratory volume in one second to vital capacity ratio. The finding of obstructive pattern may correlate with the presence of endobronchial KS.8 In general these abnormalities are not helpful in establishing the diagnosis of pulmonary KS.

Diagnosis. The diagnosis of parenchymal KS is considered clinically confirmed if characteristic endobronchial lesions of KS are seen at bronchoscopy. However, many patients with parenchymal involvement have no bronchoscopic evidence of KS. These endobronchial lesions are typically red or violaceous, flat or raised discrete plaques similar to cutaneous KS. They usually cause no symptoms but cough, hemoptysis, wheezing and upper air way obstruction can develop.8 Endobronchial and transbronchial biopsy of KS lesions is not indicated due to the very low diagnostic yield and the serious risk of hemorrhage.8,16 In addition, the detection of HHV8-deoxyribonucleic acid in bronchoalveolar lavage using polymerase chain reaction assay has been reported and was found to be highly sensitive (100%) and specific (99%) for pulmonary KS.29,30 This might be used to augment the diagnostic accuracy of bronchoscopy for pulmonary KS. However, in the absence of endobronchial lesion, lung biopsy is the definite diagnostic tool used to establish the diagnosis of pulmonary KS and to rule out other possible etiology.

Treatment and prognosis. The management of mucocutaneous and visceral KS in renal transplant recipients has been based on the reduction or cessation of immunosuppression, disease progression has been observed when immunosuppression was continued. Penn13 reported a complete remission following various treatment methods occurred in 53% of the mucocutaneous KS and 27% of the visceral type. In both groups, 32% and 60% of remissions, occurred when the only treatment was reduction or cessation of immunosuppression. However, 22 out of 34 kidney recipients had impaired function or allograft loss as a result of this approach. In another report of 13

patients with KS post renal transplant, Montagnino et al10 reported the complete remission in 9 and partial remission in 2 patients after reduction or withdrawal of immunosuppressive therapy. In this report, 69% of the patients remained dialysis free after follow up for a mean period of 35 months. In another study, Margolius et al11 reported 4 out of 5 patients who responded with complete tumor regression at all skin and visceral sites upon withdrawal of immunosuppressive drugs. One patient suffered disease progression, when his immunosuppression was continued. In such cases, KS usually responds to a variety of chemotherapeutic agents including vincristine, vinblastine, bleomycin, doxorubicin and paclitaxel. More recently, in randomized multicenter trials, liposomal anthracyclines were at least as effective or superior to conventional chemotherapy in treating AIDS-related KS and have a better toxicity profile.31 They have become the first line treatment for KS with a response rate range from 30% to 60%. In contrast to the poor prognostic features of KS in AIDS patients, many patients with organ transplant associated KS respond to the reduction or withdrawal of immunosuppression inspite of the extensive involvement of skin and internal organs or both. The cessation of immunosuppression however, does not always result in graft loss.10 This has been postulated to be related to the depletion of CD4 T lymphocytes, which results in immune tolerance to the allograft even with minimal immunosuppression.15

In conclusion, this review highlights the dilemma in establishing an accurate diagnosis of patients presenting with pulmonary KS as a complication of immunosuppression post-renal transplant in which the coexistence of another lung pathology is well recognized. Clinical and radiological manifestations of KS can only suggest, rather than diagnose, the pulmonary involvement of this malignancy. In this setting, the presence of an endobronchial lesion characteristic of KS confirms the suspected diagnosis. While many reports described a particular gallium and thallium scan pattern for pulmonary KS, this does not seem to be sensitive or specific enough to obviate the need for lung biopsy using CT guided, thoracoscopic or open lung procedures. The management of immunosuppression-related KS in renal transplant recipients depends primarily on the reduction or cessation of immunosuppresion that gradually improves cell-mediated immunity. However, this does not always lead to allograft loss.

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