Incidence and Management of Kaposi Sarcoma in Renal Transplant Recipients: The Greek Experience

G. Zavos, D. Moris*, S. Vernadakis, J. Bokos, S. Lionaki, G. Mamarelis, K. Panagiotellis, V. Zavvos, and I. Boletis

Transplantation Unit, "Laikon" General Hospital, Athens, Greece

ABSTRACT

Objective. One of the most common malignancies in kidney transplant recipients is Kaposi sarcoma. The incidence of Kaposi sarcoma, which develops after renal transplantation, is 400–500 times higher than that in the general population. The aims of this study were to review the experience with Kaposi sarcoma in the highest-volume transplantation Unit in Greece and to analyze clinical characteristics and response to treatment, with respect to both the patients' survival and the renal graft function.

Materials and Methods. The records of 2008 renal graft recipients between March 1983 and December 2012 were retrospectively reviewed. Kaposi sarcoma was diagnosed based on clinical, laboratory, radiological, endoscopic, and histopathologic examinations. The disease was staged according to the classification of Al-Khader et al.

Results. The prevalence of Kaposi sarcoma was 1.2% in our renal transplant population. Of these, 1006 recipients underwent living-donor renal transplantation, whereas 1002 received their graft from deceased donors. Post-transplantation malignancy developed in 153 patients, among which, Kaposi sarcoma has been found in 24 cases. Of the 24 cases of Kaposi sarcoma, lesions were mainly cutaneous in 14 cases, visceral and cutaneous in 8, and concomitant visceral and lymph node involvement was observed in 2 patients. With regard to the final outcome, 20 patients (83.3%) showed remission of the disease, whereas 4 patients with visceral involvement (16.6%) did not respond to chemotherapy and discontinuation of immunosuppression and died. Moreover, 8 deaths occurred due to apparently unrelated causes.

Conclusions. Kaposi sarcoma is an important part (15.7%) of all post-transplantation neoplasias in our series. Furthermore, our findings confirmed the previously described close association between human herpesvirus-8 and post-transplantation Kaposi sarcoma. Reduction of immunosuppression or discontinuation of calcineurin inhibitors results in remission of the disease in most of the cases. Prognosis in patients with Kaposi sarcoma limited to the skin is favorable, whereas visceral involvement is associated with high mortality.

FOR THOUSANDS of patients with end-stage renal failure, renal transplantation is a life-altering event. Since the early transplantation operations of the 1960s, there have been major advances in the field of transplantation leading to improved long-term survival. The overall 5-year survival rate for kidney transplant recipients reaches approximately 85% [1]. The major cause of death in these patients is malignancy [1,2]. One of the most common malignancies in kidney transplant recipients is Kaposi sarcoma (KS). KS was first described in 1872 by Kaposi, a Hungarian dermatologist, as a progressive sarcoma, even

G.Z. and D.M. equally contributed to this article.

*Address correspondence to Demetrios Moris, MD, Anastasiou Gennadiou 56, 11474, Athens, Greece. E-mail: dimmoris@yahoo.com

360 Park Avenue South, New York, NY 10010-1710

0041-1345/14
http://dx.doi.org/10.1016/j.transproceed.2014.09.165

though it resembles hyperplastic angioproliferative lesions with inflammatory changes rather than a true sarcoma [3]. The incidence of KS, which develops after renal transplantation, is 400–500 times higher than that in the general population [4] and mainly depends on the seropositivity of the population to human herpesvirus-8 (HHV-8) or recently known as Kaposi's sarcoma–associated herpesvirus (KSHV) and to the immunosuppression regimen [4]. The aims of this study were to review the experience with KS in the highest-volume transplantation unit in Greece and to analyze clinical characteristics and response to treatment, with respect to both the patients' survival and the renal graft function.

MATERIALS AND METHODS

The records of 2008 renal graft recipients who had been followed up at our department between March 1983 and December 2012 were retrospectively reviewed. Of these, 1006 received their graft from living-related donors and the remaining 1002 from deceased donors. Post-transplantation malignancy developed in 153 patients, among which, KS was found in 24 cases. KS was diagnosed based on clinical, laboratory, radiological, endoscopic, and histopathologic examinations. The age, gender, post-transplantation duration, immunosuppressive regimens, graft functional status, and rejection episodes of the patients were also evaluated. The disease was staged according to the classification of Al-Khader et al [5]. The immunosuppression regimen during this period included azathioprine (AZA) + cyclosporine (CsA) + corticosteroids (methylprednisolone), mycophenolate mofetil (MMF) + CsA + MP, MMF + tacrolimus (Tac) + MP, CsA + MP, or AZA + MP. The detection of HHV8 was performed using nested polymerase chain reaction (PCR) [6].

RESULTS

The prevalence of KS was 1.2% (24/2008) in our renal transplant population. Male:female ratio was 5:1 and the mean age of patients at the time of diagnosis of KS was 47.7 years, ranging from 22 to 72 years. Of the 24 cases of KS, lesions were mainly cutaneous in 14 cases, visceral and cutaneous in 8, and concomitant visceral and lymph node involvement was observed in 2 patients. Nine patients had Stage 1 disease (localized skin lesions involving only 1 limb), 5 patients had Stage 2 (widespread skin lesions involving more than 1 limb), 10 patients had Stage 3 (involvement of viscera or lymph nodes), and none our patients had Stage 4 disease (Stage 1–3 plus life-threatening infection or other neoplasia). In all of our patients, the diagnosis of KS was verified based on histological examination. Fourteen KS patients had received their kidneys from living-related donors and 8 from deceased donors. Immunosuppressive therapy consisted of AZA + CsA + MP in 16 patients at the time of KS diagnosis. Four patients were on MMF + CsA + MP, 2 received MMF + Tac + MP, 1 patient was on CsA + MP, and another 1 was on AZA + MP. Eight patients had been treated with pulse MP and antithymocyte globulin (ATG) for an acute rejection episode before diagnosis of KS. The average time from transplantation to diagnosis of KS was 33.7 months (range, 3–138 months). Once KS diagnosis was made, calcineurin inhibitors (CNIs; CsA and Tac) were stopped in all patients on this treatment. In 6 patients, the immunosuppression was switched to mammalian target of rapamycin (mTOR) inhibitor. Chemotherapy was induced in 8 patients with Stage 2 disease and additional local radiotherapy in 1 of them. Applying these therapeutic approaches, complete remission of the lesions was observed in all patients with Stage 1and 2 disease, and in 6 of the 10 patients with Stage 3 disease. Thus, with regard to the final outcome, 20 patients (83.3%) showed remission of the disease, whereas 4 patients with visceral involvement (16.6%) did not respond to chemotherapy and discontinuation of immunosuppression and died. Moreover, 8 deaths occurred due to apparently unrelated causes. After the reduction or discontinuation of immunosuppression, graft loss due to rejection was noticed in 7 cases (29%). In the remaining 17 patients (71%), the renal allograft maintained adequate function (mean creatinine value of 1.43 mg/dL). In these patients, the immunosuppressive drugs were resumed in minimal doses after complete remission of KS. HHV-8 DNA was present in 95% of the renal recipients with KS, and only in 5% of the renal recipients without KS was identified in parallel. Table 1 summarizes the data presented in our study.

DISCUSSION

Increased incidence of cancer is a well-known complication of organ transplantation. Despite the fact that KS is an uncommon malignancy in the general population, is much more frequent among renal transplant recipients, especially in populations of Mediterranean, Arabic, Jewish, and black origin [7]. In Greece, as we have previously described, KS was thought as the second most frequent malignancy following renal transplantation reaching 24.32% of post-transplantation malignancies [6,8]. After meticulous analysis of our database, we reached the conclusion that the frequency of KS in our patients is 12.06% now, with skin cancers, visceral cancers, and post-tranplant lymphoproliferative disorders (PTLD) becoming much more common (37.7%, 37.2%, and 13.06%, respectively, unpublished data). Although the incidence of KS still remains high compared with Cincinnati transplant tumor registry (CTTR) where KS represents 5.7% of malignancies in kidney transplant recipients [9], we observed 3% in kidney recipients receiving AZA (9.4% in our data) and 10% in those with CsA-based immunosuppressive regimens (17% in our data) [9]. As far as the KSHV-8 status is concerned, a study by Mancuso et al found that subtype A KSHV was almost exclusively present in patients with fast progression of the disease, whereas subtype C was mainly seen in slow-progressing patients. Also, detection of subtype A was associated with higher blood viral loads [10]. In the Greek population, the positivity rate of 9.6% of HHV-8 was found. The data suggest that HHV8 is spread in Greece, but to a lesser extent than that observed in other Mediterranean countries [11], with a possible link of the C3 subtype of HHV-8 in renal transplant–related KS cases [12]. Many treatment procedures have been used for post-transplantation KS like surgical excision, radiation therapy, chemotherapy, reduction of immunosuppressive therapy, or a combination of