KAPOSI'S SARCOMA IN TWO PRIMARY LIVER ALLOGRAFT RECIPIENTS OCCURRING UNDER FK506 IMMUNOSUPPRESSION

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ABSTRACT:

Of 1463 liver allograft recipients receiving the combination of FK506 and steroids as their primary immunosuppressive regimen, two patients developed Kaposi's sarcoma. Although previously described as a complication of organ transplantation, this is the first case report of Kaposi's sarcoma occurring in association with the macrolide immunosuppressive agent FK506. A discussion of the clinical presentation and course of Kaposi's sarcoma in these two patients, as well as a review of the past literature on Kaposi's sarcoma in organ transplant recipients, emphasizes the therapeutic difficulties encountered. Kaposi's sarcoma is also compared to lymphoproliferative disorders, another well recognized complication of immunosuppression, highlighting the differences between these two entities.

INTRODUCTION:

Kaposi's sarcoma is a rare multicentric neoplasm of controversial origin known to occur in individuals who are immune deficient. It is a recognized complication of organ transplantation, accounting for 6% of post transplant malignancies.[1] From 1 March 1989 until 19 June 1992, a total of 1463 liver allograft recipients have received FK506 in combination with steroids as their primary immunosuppressive regimen at the University of Pittsburgh. Approximately 10% of this population are foreign nationals, mainly of middle eastern extraction, in whom there also appears to be a genetic predisposition for Kaposi's sarcoma.

The literature on Kaposi's sarcoma in organ transplant patients has focused mainly on renal allograft recipients in whom regression of the disease and patient survival do not necessarily equate with continued graft function (see Table I). Treatment of Kaposi's sarcoma has closely paralleled the approach used in post transplant lymphoproliferative disorders (PTLD) and the two entities are frequently compared. The overall prognosis for Kaposi's sarcoma in liver allograft recipients has, however, been poor with a 45% mortality rate in a series of such patients presented by Bismuth et al in 1991.[2] This contrasts markedly with the results of a recent review from the University of Pittsburgh of 15 patients with PTLD (13 liver and 2 renal allograft recipients) of whom 10 (67%) have survived with functional grafts.[3] The following case reports describe Kaposi's sarcoma occurring in

association with FK506 immunosuppression in two liver allograft recipients, and serve to illustrate the therapeutic difficulties encountered in its clinical management.

CASE 1

A 49 year old Saudi Arabian man was admitted on 24 January 1992, ten months after successful orthotopic liver transplantation for Laennec's cirrhosis, with a diagnosis of Kaposi's sarcoma. He presented with new onset dark raised purple lesions of his lower extremities which had recently been increasing in number. A biopsy of several of these lesions was performed on 17 January 1992 and confirmed a diagnosis of Kaposi's sarcoma.(Figure 1a, 1b) The patient's past history was significant for a portacaval shunt performed prior to his liver transplant, a biliary reconstruction performed in May 1991 for ampullary dysfunction, and chronic renal failure, requiring hemodialysis three times per week since August 1991, due to glomerulonephritis and hypertension. After transplantation, he had experienced two episodes of acute cellular rejection documented by liver biopsies which were treated with a steroid recycle, a pulse bolus of methylprednisolone and the institution of azathioprine. Medications on admission consisted of FK506, 4 mg po bid, Prednisone 20 mg po q/day and Acyclovir 200 mg po bid. The serum FK506 level was 0.5 ng/ml and azathioprine had been stopped soon after the skin biopsy documented the presence of Kaposi's sarcoma.

On admission, FK506 was reduced to 2 mg po bid and Prednisone

to 5 mg po qd; α interferon at a dose of 5 million units sq qd was started and was increased four days later to 10 million units sq qd; Acyclovir was discontinued. Investigations during the patient's hospitalization included a CT scan of the head, chest and abdomen which showed a large right pleural effusion, a small pericardial effusion without pulmonary parenchymal lesions or lymphadenopathy and scattered focal areas of small bowel thickening. An enteroclysis study revealed a generalized dilatation of the small bowel with a slightly prolonged transit time, but no evidence for Kaposi's sarcoma. On esophagogastroduodenoscopy, a moderately inflamed distal esophagus with normal stomach and duodenum were noted; biopsies of the esophagus showed acute and chronic inflammation. A limited colonoscopy was performed which showed no colonic lesions. The right pleural effusion was aspirated and cytologic examination of the fluid revealed no malignant cells.

Viral serologic studies sent on admission included an HIV and a hepatitis C screen which were negative; a hepatitis B serology which was negative for hepatitis B surface antigen, positive for anti HBs, and negative for anti HBc. Other viral titers included cytomegalovirus (CMV) IgG >120 (ref. value <20), negative CMV IgM, Epstein Barr Virus (EBV) IgG >50, EBV IgM <10 and EBV nuclear antigen 2; herplex simplex IgG was >200 (ref. value <8) and herpes zoster IgM <20 (ref value <20). Immunoperoxidase, in-situ hybridization and polymerase chain reaction techniques failed to detect CMV particles within the lesions in the skin biopsy. The

HLA status of the patient was HLA - A2 A24 B35 B51 BW4 BW6 DR4 DR11 DQW3 DRW52 DRW53.

On a regimen of daily αinterferon therapy and reduced immunosuppression, the Kaposi lesions stabilized. Liver function however worsened, necessitating a liver biopsy on 3 February 1992, which showed a mixed portal inflammatory infiltrate with low grade lobular reactivity. The patient was given a one gram bolus of methylprednisolone intravenously, and his maintenance prednisone and FK506 were increased to 10 mg po qd and 2 mg po bid, respectively. The patient was discharged at his request on February 12, 1992. The serum FK506 level was 1.9 ng/ml and the Kaposi lesions of his lower extremities were unchanged. Medications on discharge consisted of αinterferon 10 million units sq daily, prednisone 10 mg once a day, and FK506 2 mg po bid.

Two days later, the patient was readmitted with complaints of increasing fatigue and muscular aches. His liver function tests on admission had deteriorated further with a total bilirubin of 3.5 mg/dl, a conjugated bilirubin of 3.1 mg/dl, an alkaline phosphatase level of 349 IU/dl, a gamma GTP of 1242 IU/dl, an SGOT (AST) of 1145 IU/dl and an SGPT (ALT) of 938 IU/dl; the FK506 level was reported as 2.1 ng/ml. A liver biopsy was performed on February 15, 1992, which revealed lobular reactivity, single cell necrosis and chronic bile duct injury. Immunoperoxidose staining for hepatitis B surface antigen was negative. Coxsackie virus titers were negative; autoimmune markers were negative and the erythrocyte sedimentation rate was 42 mm/hr.

On February 16, 1992, the patient developed coffee ground emesis and experienced a melanotic stool with a significant drop in his hematocrit. Esophagogastroduodenoscopy revealed prominent gastric varices along the greater curvature of the stomach and biopsies of the duodenal and gastric mucosa were negative for CMV. Repeat autoimmune markers were positive for thyroglobulin antibodies at 100 (Ref. value <100) and microsomal antibodies at 400 (Ref. value <100). With the continued deterioration in liver function, an acute autoimmune hepatitis precipitated by α interferon was suspected and the α interferon was discontinued.

A repeat endoscopy performed on February 20, 1992, for continued upper gastrointestinal bleeding demonstrated the continued presence of gastric varices. An arteriogram showed thrombosis of the midportion of the splenic vein with patent superior mesenteric and portal veins. An exploratory laparotomy, splenectomy and gastric devascularization was performed on February 21, 1992. In the immediate postoperative period, the patient was stable; he tolerated extubation well and was transferred out of the intensive care unit on postoperative day 3.

Ten days later, the patient redeveloped upper gastrointestinal bleeding necessitating endoscopy which revealed severe portal hypertensive gastropathy. His serum bilirubin level was markedly elevated at 26.3 mg/dl. On March 14, a liver biopsy was obtained which showed mild acute cellular rejection with marked duct damage and bile duct loss, as well as panlobular hepatocyte swelling and disarray. The patient was treated with one gram methylprednisolone

IV and FK506 was reinstituted at a dose of 2 mg po twice a day; prednisone was increased from 5 mg to 10 mg po daily. Repeat thyroglobulin and microsomal antibody titers were 400 and 1600 respectively. Hepatitis B serology and the hepatitis C screen continued to be negative. The Kaposi lesions of the lower extremities were essentially unchanged.

The patient continued to have upper gastrointestinal bleeding which became refractory to all resuscitative efforts; comfort measures were instituted and the patient expired.

CASE 2

A 39 year old Saudi Arabian man was admitted to the Presbyterian University Hospital on February 10, 1992, 4.5 months after an orthotopic liver transplant for cirrhosis secondary to hepatitis B virus infection with increasing fatigue and extensive multiple nodular dark skin lesions which had started on his anterior abdominal wall approximately one month prior to admission and had rapidly disseminated to involve the rest of his body. On examination, these lesions had the typical appearance of Kaposi's sarcoma; there was no obvious oropharyngeal involvement and no palpable lymphadenopathy or edema. His past history was significant for excision of a hemangioendothelioma involving the right sixth and seventh ribs on December 23, 1991. Three biopsy documented rejection episodes had been treated with a pulse bolus of intravenous methylprednisolone and a steroid recycle; the patient was also receiving hepatitis B immunoglobulin every three

to four weeks as part of a research protocol. Medications on admission included FK 506 8 mg po bid, prednisone 2.5 mg po q day; acyclovir 800 mg po qid (CMV prophylaxis), Isoniazid 300 mg po q daily and Bactrim SS one tablet po on alternate days. The serum FK 506 level on admission was 1.7 ng/ml; the white cell count was 4.9 and liver parameters included a total bilirubin 0.8 mg/dl, an SGOT of 60 IU/dl, an SGPT of 50 IU/dl, an alkaline phosphatase of 83 IU/dl and a gamma GPT level of 95 IU/dl. The patient's HLA status was HLA A2 A30 B44 B51 BW4 DR1 DR11 DQW1 DQW3 DRW52.

In view of the diagnosis of Kaposi's sarcoma, FK506 was reduced to 2 mg po bid and α interferon therapy was started at 10 million units subcutaneously daily. Investigations obtained included: a CT scan of the head, chest and abdomen, which showed bilateral pleural effusions and no other evidence of disease; an enteroclysis study of the small bowel, which was normal; an esophagogastroduodenoscopy which showed multiple vascular lesions consistent with Kaposi's sarcoma involving the cardia, body and antrum of the stomach as well as the duodenum to the ligament of Treitz; colonoscopic examination was normal. A biopsy of the gastrointestinal lesions was not obtained due to a low platelet count of 33000/mm^3. Serologic studies performed on admission included a negative HIV antibody screen; a positive hepatitis C screen, a positive anti-HBc and anti-HBs and an anti-delta hepatitis screen which was positive. Other viral studies included a CMV IgG >120 (Ref. value <20) and EBV IgG 400, EBV IgM <10, EBV nuclear antigen >8 and an EBV early antigen of 10.

With the combination of a reduction in immunosuppression and continued α interferon therapy, the patient developed a progressive rise in his liver injury parameters ultimately requiring a liver biopsy on February 28, 1992, at which time the total bilirubin was 0.4 mg/dl, alkaline phosphatase 132 IU/dl, gamma GPT 258 IU/dl, SGOT 121 IU/dl and SGPT 147 IU/dl. The biopsy showed mild acute cellular rejection, and the FK506 dose was increased to 2 mg po bid having been previously reduced to 2 mg q d; FK506 levels had been ranging between 0.2 - 0.4 ng/ml.

Liver function, however continued to deteriorate despite the augmentation in immunosuppression. An analysis of the patient's T-cell subsets in peripheral blood showed a rise in the number of natural killer cells from 7% to 12%. Autoimmune markers were sent and were reported as negative. In view of the fact that α interferon can enhance T-cell mediated cytotoxicity and augment natural killer cell (NK) activity, and because the size and number of the patient's Kaposi skin lesions had diminished suggesting a partial response to therapy, it was opted to reduce the α interferon dose to 5 million units sq per day on March 5, 1992.

The patient's liver function continued to deteriorate however, and a liver biopsy obtained on March 17 showed continued mild acute cellular rejection, with centrilobular cholestasis and a low grade hepatitis. Immunocytochemical stains for hepatitis B surface and core antigens were negative. Isoniazid was stopped, one gram of methylprednisolone IV was administered, and the daily prednisone dose was increased to 10 mg.

On March 24, α interferon was reduced further to 3 million units sq daily and an additional one gram of intravenous methylprednisolone was given for a total bilirubin of 15.4 mg/dl, alkaline phosphatase 1264 IU/dl, SGOT 436 IU/dl, SGPT 460 IU/dl and Gamma GPT 1706 IU/dl. An ultrasound of the liver was essentially normal.

A repeat liver biopsy obtained on March 28, showed evidence of chronic rejection as reflected by a paucity of bile ducts and prominent centrilobular cholestasis consistent with a vanishing bile duct syndrome. A lobular inflammatory infiltrate was present suggesting a low grade hepatitis. Immunocytochemical stains for hepatitis B surface and core antigens were again negative. All cytomegalovirus stains and cultures were negative. Liver injury parameters continued to be elevated with a total bilirubin of 17.3 mg/dl, an alkaline phosphatase of 1293 IU/dl, SGOT of 530 IU/dl, SGPT of 639 IU/dl, and a Gamma GPT of 2088 IU/dl. The serum FK 506 level was 0.9 ng/ml and a one gram intravenous bolus of methylprednisolone was given on April 1. The patient was discharged on April 4, 1992. He returned to Saudi Arabia on a regimen of FK506 2 mg po bid, prednisone 10 mg po q daily, and α interferon 3 million units sq q daily. The Kaposi skin lesions have continued to decrease in size and number, but have failed to completely resolve.

DISCUSSION:

Kaposi's sarcoma (KS) is a complex tumor of controversial

origin which was first described in 1872 by Moritz Kaposi.[4] It occurs in four different clinical settings, [5,6] each varying in its presentation and behavior. The original "classic" form of KS is a local indolent and slow growing disease of the lower extremities with a prevalence of 0.01 to 0.06 per 100,000 population in Europe and North America; it is found in greatest frequency in those of Mediterranean and Ashkanazi Jewish decent.[5,7] African or "endemic" KS usually presents with nodular lesions of the extremities which tend to become exophytic or ulcerative, with or without lymph node involvement. It forms 10% of all malignancies in Africa[7] and has a higher incidence in equatorial Africa.[6,7] "Epidemic" KS, associated with the acquired immune deficiency syndrome (AIDS) is more aggressive with widespread multiple purple brown macules, papules and nodules, as well as, visceral involvement in up to 75% of cases (5% have only visceral involvement); it frequently includes lymph node involvement resulting in a lymphadenopathic variant. The incidence of KS in the AIDS population is 20 - 30%.[7,8,9] Finally, KS can occur in immune deficiency states such as in organ transplant recipients and in disorders known to have a defect in T-lymphocyte function such as tuberculosis, leprosy, systemic lupus erythematosus, chronic lymphocytic leukemia, angioimmunoblastic lymphadenopathy and Hodgkin's disease.[4,7] KS in organ transplant recipients tends to be a mixture between the classic and epidemic forms: of 214 cases of KS listed in the Cincinnati Transplant Tumor Registry, 59% had local disease involving the skin, conjunctiva and oropharyngeal mucosa, and 41%

had visceral disease involving mainly the gastrointestinal tract and lungs.[1] Of the two patients presented in this report, case 2 had visceral involvement seen on endoscopy.

The incidence of KS appears to be higher in recipients of non-renal organs (4% vs. 2%)[1] probably reflecting the more aggressive immunosuppression used in such patients. An analysis of the type of immunosuppression used in organ transplant recipients with KS showed an incidence of 8% in those receiving the combination of Cyclosporine A (CsA) with steroids vs. 3% in those receiving conventional immunosuppressive therapy consisting of Azathioprine or Cyclophosphamide with Prednisone (Penn 1991).[1] To date, this is the first report of KS occurring in association with the use of the new macrolide immunosuppressive agent FK506, which has 100 times the immunosuppressive potency of CsA. From 1 March, 1989, until 19 June, 1992, a total of 1463 liver allograft recipients have received the combination of FK506 with steroids at the University of Pittsburgh; further follow-up will be needed to determine the long term incidence of KS within this population of patients.

The origin of KS is controversial, with theories ranging from a reticuloendothelial origin vs. that it may arise from vasoformative mesenchymal cells.[4,10] On the pathogenesis of KS, there is epidemiologic data suggesting a genetic pre-disposition as opposed to theories that it may be a tissue reaction to an infectious agent, such as a virus rather than an autonomous tumor.[10] In Sardinia, where there is a high incidence of classic non-HIV

related KS,[10] Contu, et al[11] reported a greater than expected incidence of the allele HLA DR5 in Sardinians with the disease ($p<0.001$). HLA DR5 has also been shown to be common in AIDS patients with KS.[24] Neither of the patients in this series had the HLA DR5 allele; both however, were Arab and were HLA A2 B51 BW4 DR 11 DQW3 and DRW52 positive. The A2 allele has been reported, by Qunibi et al, to be significantly increased in their population of Saudi Arabian patients with KS after renal transplantation.[9]

Arguments in favor of an infectious agent in the pathogenesis of KS include the fact that cutaneous anergy is frequently present in patients with classic KS, suggesting the possibility that a transmissible agent is facilitated in its colonization of dermal blood vessels.[4] In addition, in transplant recipients, Kaposi lesions may regress completely or at least improve with a reduction in immunosuppressive therapy.[2,9,12,13,14,15,16] Cytomegalovirus (CMV), herpes simplex types I and II (HSV I & II), polyoma virus and hepatitis B virus (HBV), have all been linked to KS.[2,16,17,18,19] Both of the patients in this report had evidence of a prior CMV infection with raised CMV IgG levels. There was however, no evidence for CMV reactivation, as demonstrated by the negative CMV IgM titers and CMV cultures. CMV nuclear antigen has been demonstrated in KS lesions of AIDS patients[16,19], and CMV DNA has been found by dot blot hybridization in cultures of KS cells from a renal transplant recipient.[16] Kaposi cells, however, have been shown to proliferate in tissue culture despite the disappearance of CMV-DNA, suggesting that CMV, in the setting of an immunosuppressed

state, may be required for the initiation of KS, but not its continued growth.[16] On the other hand, in AIDS patients with CMV infection, integrated CMV viral DNA has not been consistently detected, thus raising the question as to whether CMV exists in KS cells merely as a secondary invader.[19]

In 1991, Bismuth et al, reported 11 patients with KS after liver transplantation, of whom 7 were hepatitis B surface antigen positive.[2] This was from a population of 397 liver allograft recipients with an overall prevalence for KS of 5.2% in hepatitis B surface antigen positive liver recipients.[2] Hepatitis B virus DNA has also been isolated from tumor lesions and normal skin in an 80 year old man with KS, who was concomitantly seronegative for hepatitis B virus.[19,20] Both patients presented in this report were hepatitis B surface antigen negative, although case 2 was receiving hepatitis B immunoglobulin for an earlier hepatitis B virus infection.

Kaposi's sarcoma can be a ubiquitous tumor with a mode of spread which is multifocal and not dissimilar to that of a lymphoma. A parallel has been made in the past between KS and post-transplant lymphoproliferative disorders (PTLD).[13,21,22] Both occur in immunosuppressed individuals whose defense mechanisms against oncogenesis and/or a viral infection are impaired.[4,7,13] The incidence of PTLD in organ transplant recipients is increased relative to the general population by at least 10 fold[13], and the incidence of KS in transplant recipients is increased up to 400 to 500 times that of the general population.[7] The link between

cytomegalovirus infection and KS however, has not been as consistent as the association of Epstein Barr virus infection with PTLD.[13,16,19] Furthermore, although both conditions have been treated with a reduction in immunosuppression, unlike PTLD there appears to be a significant number of grafts lost to rejection in KS (See Table I). The course of PTLD associated with FK506 was recently reviewed at the University of Pittsburgh where a total of 15 patients (13 liver allograft and 2 renal allograft recipients) were treated by a reduction in immunosuppression and intravenous acyclovir therapy, 10 showed complete remission and all ten have retained their grafts.[3] This report stands in sharp contrast with the series of liver graft recipients presented by Bismuth et al, who were treated for KS with a reduction in their immunosuppression, and experienced an overall 45% mortality rate.[2]

α Interferon was used in both patients in this case. There have been reports of improved results in the treatment of KS using α interferon (α IFN) in the AIDS population.[8,23,23,25,26] It's use has also been reported in a heart transplant[12] and a bone marrow recipient[15] with encouraging results. In AIDS patients, α IF has been shown to have anti-retroviral activity as demonstrated by a reduction in HIV antigen levels and a rise in the number of OKT4+ cells.[8,23,24,25] In KS, α IFN is thought to exert its effect by inhibiting angiogenesis either by a direct effect on endothelial cell proliferation[19,27,28] or by a direct inhibition of an angiogenesis factor[19] such as interleukin 6.[26] Most recently, it has been used with excellent results in cases of childhood angiomas.[28]

Improvement was seen with α IFN therapy in the Kaposi lesions of one of the two patients in this report. The immunomodulatory effects of α IFN however, presented a major problem in the setting of reduced immunosuppression in both patients[10,11,12] as manifested by a marked deterioration in liver function with documented cellular rejection by serial liver biopsies. In case 1, activation of a dormant autoimmune process may also have occurred and contributed to the liver dysfunction.

In conclusion, KS is a disease of unclear etiology to which there appears to be an underlying genetic predisposition. The therapeutic approach in KS has closely paralleled that of PTLD, but with a poorer end result. The use of antiangiogenesis and antiviral agents such as α IFN requires further evaluation. Early treatment of KS using chemotherapy and radiotherapy in association with reduced immunosuppression needs to be studied further.

KAPOSI'S SARCOMA IN RENAL TRANSPLANT RECIPIENTS: A REVIEW OF THE LITERATURE

Clinical course is subdivided into degree of regression of kaposi lesions, patient outcome and number of graft failures. Criteria for graft failure include patient death, graft rejection resulting in a return to dialysis and/or transplant nephrectomy. Immunosuppression received post transplant and therapy instituted for kaposi's sarcoma are included in the table.

AUTHOR	PATIENTS	IMMUNOSUPPRESSION	TREATMENT	KAPOSI LESIONS	PATIENT OUTCOME	RENAL FUNCTION
1. Siegel et al 1969	1	Aza + Steroids + RT + Actinomycin	None	Diagnosed at Autopsy	Death	Graft Failure
2. Halm et al 1972	1	Aza + Steroids + RT	↓ Immunos. + RT	Partial Remission	Alive	Functional Graft
3. Myers et al 1974	2	Aza + Steroids + RT --- Actinomycin Aza + Steroids + ALG	↓ Immunos. + 1 RT	-1 Remission	1 Death 1 Dialysis	2 Graft Failures
4. Birkeland et al 1975	1	?	?	?	Death	Graft Failure
5. Straehley et al 1975	1	Aza. + Steroids + Actinomycin	Gastrectomy	GI Hemmorrage due to KS	Death	Graft Failure
6. Farman et al 1975	1	Endoxan + Steroids	↓ Immunos. + RT + Excision	Remission	Death (Respiratory Arrest)	Graft Failure
7. Hardy et al 1976	1	Aza + Steroids	↓ Immunos. + RT + Chemo	Partial Remission	Alive 1 Year F/U	Functional Graft at 1 yr.
8. Meyers et al 1976	1	Aza + Steroids	↓ Immunos. + RT	Partial Remission	?	Unknown
9. Nissenkorn et al 1977	1	Aza + Steroids	Local Lesion Excision	Curative	Alive	Functional Graft

AUTHOR	PATIENTS	IMMUNOSUPPRESSION	TREATMENT	KAPOSI LESIONS	PATIENT OUTCOME	RENAL FUNCTION
10. Stribling et al 1978	1	Aza + Steroids	Bowel Resection	GI Hemmorrage Due to KS	Death	Graft Failure
11. Penn I. 1979	20	-All Aza + Steroids -6 Also on Actinomycin -11 Also Graft RT -5 Also ALG	-6 None -2 Unknown -10 ↓ Immunos. -3 Aza changed to Cycloph. -7 Also RT -3 Also Chemo	-9 Regression -2 Unknown -2 Partial Remission -1 No Improvement -6 Diagnosis at autopsy	12 Dead	12 Graft Failures 1 Lost to F/U Rest Unknown
12. Harwood et al 1979	4	Aza + Steroids	- ↓ Immunos. 3 - 4 RT - 1 Also Intralesional Chemotherapy	- 3 Complete Remission - 1 Partial Remission	4 Alive	3 Functional Grafts 1 Unknown
13. Zisbrod et al 1980	1	Aza + Steroids + Graft RT	↓ Immunos. + Chemotherapy	- KS Regressed	Death	Graft Failure
14. Akhtar et al 1984	4	3 Aza + Steroids 1 CsA + Steroids	-All ↓Immunos. -2 Also RT	1 Dead 1 Complete Regression 2 Partial Regression	1 Dead	1 Graft Failure
15. Rodriguez et al 1986	2	Aza + Steroids	- ↓ Immunos. + 1 RT	1 Dead 1 Complete Regression	1 Dead 1 on Dialysis	2 Graft Failure

AUTHOR	PATIENTS	IMMUNOSUPPRESSION	TREATMENT	KAPOSI LESIONS	PATIENT OUTCOME	RENAL FUNCTION
16. Messina M. et al 1987	1	CsA + Steroids	↓ Immunos.	Partial Regression	Alive	Functional Graft
17. Wijnveen et al 1987	1	Aza + CsA + Steroids	↓ Immunos. + Foscarnat + αInterferon	Complete Regression	Alive (on dialysis)	Graft Failure
18. Al Suleiman et al 1987	12	7 Aza + CsA + Steroids 2 Aza + Steroids 3 CsA + Steroids	-5 ↓ Immunos. -6 No Immunos. -1 Chemo. + RT + No Immunos.	-3 Dead -5 Complete Regression -3 Partial Regression	3 Dead (3 on dialysis)	6 Graft Failures
19. Qunlbi et al 1988	14 (16 grafts)	9 CsA + Steroids 5 Aza + Steroids	- ↓ Immunos. in all -3 Also Chemo. -5 Also RT -3 Also Excision Lesions	-5 Dead -7 Complete Remission -2 Partial Remission	5 Dead (2 on dialysis)	7 Graft Failures
20. Butkus et al 1988	1	Aza + CsA + Steroids	Immunos. Stopped Transplant Nephrectomy	Complete Regression	Alive On Dialysis	Graft Failure
21. Riegler et al 1989	1	Aza + CsA + Steroids	↓ Immunos. + RT	Complete Regression	Alive (8 months F/U)	Stable Function
22. Hanid et al 1989	16	6 CsA + Steroids 2 Aza + Steroids 8 Aza + CsA + Steroids	- All ↓ Immunos. - 2 Also RT - 1 Also Cyclosphamide - 1 Also Local Excision	3 Dead 11 Regressed 2 Unchanged		10 Graft Failure 6 Functional Grafts

AUTHOR	PATIENTS	IMMUNOSUPPRESSION	TREATMENT	KAPOSI LESIONS	PATIENT OUTCOME	RENAL FUNCTION
23. Shmueli et al 1989	8	4 CsA + Steroids 4 Aza + Steroids	- All ↓ Immunos. - 7 Also RT - 4 Also Chemo Excision	- Remission in 3	5 Dead	5 Graft Failures

FIGURE LEGENDS

Figure 1a: Skin biopsy from patient number 1: The dermis is infiltrated by interlacing bundles of spindle shaped cells separated by dilated capillaries. (Haematoxylin and eosin x 100)

Figure 1b: Higher magnification of the skin biopsy of patient number 1: The spindle shaped cells are seen arranged in capillary channels and are admixed with extravasated erythrocytes and inflammatory cells. (Haematoxylin and eosin x 400)

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