**Case Report**

**Treatment of oral Kaposi sarcoma by sirolimus in renal transplanted children: case report and literature review**

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Kaposi Sarcoma is one of the most common neoplasia seen in patients after kidney transplantation. The mean occurrence time for malignant tumors after renal transplantation was reported as 61 months whereas for Kaposi’s sarcoma it was written as 20 months. The etiopathogenesis is poorly understood, mostly dependent on human herpesvirus type 8 (HHV-8) infection. In this study, we reported the occurrence of oral Kaposi’s sarcoma in a pediatric renal transplant patient on the 10th months after transplantation and complete regression of lesions with well functioning graft, via sirolimus therapy. A 13-year-old boy received a renal graft from a living unrelated donor. On the 10th months of transplantation, he admitted to hospital with a flat purple lesion of 17x11x3 mm in diameter on his left gum, presenting for 3 weeks. He also had a violaceous macular lesion on anterior one-third of the leg. The patient’s HIV antibody repeated twice was negative. The biopsy result of the lesion revealed the diagnosis of KS. Diagnosis of oral Kaposi sarcoma was made. The graft was functioning well and there was no systemic involvement. Cyclosporine A was stopped and sirolimus started. He has been on our follow up for a year without any recurrence and with well functioning graft. In the presented case, we wanted to emphasize importance of the switch to sirolimus in the treatment of Kaposi Sarcoma seen in the early post transplant period.

**Keywords:** Kaposi Sarcoma, kidney transplantation, sirolimus

**BACKGROUND**

Kaposi’s sarcoma (KS) is a rare neoplasm, defined by Moriz Kaposi in 1872 (Kaposi, 1872). Thereafter the increased risk of KS in immune compromised patients of acquired immunodeficiency syndrome or following organ transplantation was also defined and encouraged the studies on KS (Ahmadpoor, 2009; Biggar et al., 1985; Centers for Disease Control, 1987; Farge, 1993). After solid organ transplantation malignancies occurs with an increased incidence especially in developing countries (Bakr et al., 1997; Ecder et al., 1998). The prevalence of all malignancies in renal transplant patients ranges from 4% to 18% with a rising incidence of each year after transplantation (Darling et al., 2004). KS is one of the most common neoplasia seen after kidney transplantation (Sheil, 1996; Kyllonen et al., 1994). The mean occurrence time for malignant tumors after renal transplantation was reported as 61 months whereas for Kaposi’s sarcoma it was told as 20 months (Penn, 1990). Its etiology and pathogenesis was poorly understood,
Figure 1. A flat purple lesion on the left gum

mostly thought dependent on human herpes virus type 8 (HHV-8) infection (Moosa et al., 1998; Penn, 1997).
Clinical manifestations of KS are cutaneous nodules, blue or purplish color plaques. Lymph node enlargement seen in more than 90% of cases with signs and symptoms of less frequent visceral involvement (Lebbe et al., 2008). Treatment is controversial, mostly recommended as reduction of immunosuppression (Quinibi et al., 1993; Marsman et al., 1995). Stallone et al. reported complete regression of KS, after switching to sirolimus, from cyclosporine A (Stallone et al., 2005).

Here we reported the occurrence of oral Kaposi’s sarcoma in a pediatric renal transplant patient on the tenth months of transplantation and the complete regression of lesions with well-functioning graft, via sirolimus therapy.

THE CASE REPORT

A 13-year-old boy with an unremarkable past medical history, was diagnosed as having an end-stage renal disease and started to chronic hemodialysis. The primary cause of his renal disease was reflux nephropathy. He received a renal graft from a living unrelated donor on the 18th months of hemodialysis program. Cyclosporine A, mycophenolate sodium and prednisolone were given for immunosuppression. He was discharged from hospital with well-functioning graft on the second week of operation. During nine months of follow up period, he was fine without any complaint or transplant dysfunction. His medications were cyclosporine A, mycophenolate sodium and 15 mg/day prednisolone for immunosuppression and nystatin, trimethoprim for prophylaxis. Ten months after transplantation, he admitted to hospital with a flat purple lesion of 17x11x3 mm in diameter on his left gum, present for 3 weeks (Figure 1). He also had a violaceous 11x13 mm macular lesion on anterior one-third of leg. Skin adnexal structure and mucosae were normal. He did not have any lymphadenopathy. His physical examination was normal except left upper abdominal tenderness. The lesion on his left gum was excised and examined microscopically. His renal and liver function tests and CsA level were within normal ranges. All serological markers for Cytomegalovirus, hepatitis viruses and Epstein-Barr virus, HIV were negative. The patient’s HIV antibody was repeated twice, found negative. The biopsy result of lesion revealed diagnosis of KS. Dermally placed, vascular tumor with a polyploid appearance (Figure 2) and inflammatory cells around spindle shaped cells (Figure 3), elongated cells surrounded by many erythrocytes and cellular inflammatory infiltrate (Figure 4) were seen in histological sections. Immune staining with HHV-8 was strongly positive in the tumor cells (Figure 5). Abdominal and thoracic ultrasonographic examinations were normal.
Figure 2. Histological sections. Dermally placed, vascular tumor with a polyploid appearance

Figure 3. Histological sections. Dermally placed, inflammatory cells around spindle shaped cells
Figure 4. Histological sections. Dermally placed, elongated cells surrounded by many erythrocytes and cellular inflammatory infiltrate

Figure 5. Immune staining with HHV-8 was strongly positive in the tumor cells
Sometimes he has been suffering from abdominal and stomachache, therefore gastroduodenoscopy was made and signs of gastritis were seen. Pathological investigation of biopsy specimens from stomach and intestine weren’t compatible with KS. He had the diagnosis of oral Kaposi sarcoma without systemic involvement. The graft was functioning well. CsA was switched to sirolimus. It was started as 2 mg daily (blood levels – 7.2 ng/ml). The lesion on his leg was regressed within 10 days after sirolimus treatment. He has been on our follow up for a year without any recurrence of skin or mucosal lesion and with well-functioning graft. His serological exam for HIV was re-tested 11 months after diagnosis and found again negative.

**DISCUSSION**

Kaposi’s sarcoma is an extremely rare neoplasm in the general population, whereas the risk of its development is increased in immune compromised patients (Ahmadpoor, 2009). Acquired immune deficiency syndrome and solid organ transplantations are the major reasons, causing patients being immune compromised and susceptible for KS. Kaposi Sarcoma is responsible for 0.5-1% of de nova cancers in organ transplant patients (Sarikaya et al., 2001). The more intense immunosuppressive therapy was given and more time has been passed after transplantation were correlated with high risk KS (Penn, 1991). The frequency of malignant lesions in renal transplant patients is between 14 and 500 times higher than in general population (Penn, 1993). Incidence of KS in renal allograft recipients ranges from 0.5% to 5.3%. A little bit lower incidence (0.45%) was observed by Abbaszadeh et al. among the 2211 living kidney recipients (Euvrard et al., 2003; Abbaszadeh and Taheri, 2009). The cause of Kaposi’s sarcoma has been linked to human herpes virus, HHV-8 (Darling et al., 2004). The virus is mainly sexually transmitted and strongly associated with Kaposi’s sarcoma, lymphomas, Castleman’s disease, multiple myeloma and other non-neoplastic disorders (Leao et al., 2000; Sarid et al., 2002). Luppi et al. reported a case had KS on the 4th months of transplantation secondary to HHV-8 infection, and then experienced severe cytopenia with hemophagocytosis and normocellular bone marrow (Luppi et al., 2002). On the other hand, Sarid et al. mentioned about latent HHV-8 infection in donor kidneys, leading to KS development during post-transplantation immunosuppression (Sarid et al., 2001). Other case reports also described the development of Kaposi’s sarcoma from the seeding of donor-derived progenitors (Kapelushnik et al., 2001; Barozzi et al., 2003). There are four clinical types of Kaposi’s sarcoma defined in literature, shown in Table. Among these 4, the last one shown in table is the most common form. HHV-8 has been associated with all the forms of KS. Oral KS is a common finding in patients with HIV infection, but in the non-HIV-infected individual it is extremely rare (Gaber et al., 2013; Bottler, et al., 2007). For that reason he was tested for both antibodies HIV 1 + 2 and negative results were re-tested 11 months after in order to be able to rule out the HIV positivity.

There are few reported children with renal transplant and leading KS in literature (Ozen et al., 1996). We presented here a children had neoplastic differentiation after renal transplantation. The mean time reported in literature for Kaposi’s sarcoma was 20 months (2 weeks-18 years), whereas earlier occurrence (12 months) was seen related with the cyclosporine usage (Penn and Brunson, 1988). Our patient had been given to cyclosporine A and had the KS ten month after transplantation, supported to literature data. Additionally, it was reported that KS occurrence time is smaller in children than adults (Francés, 1998).

Recent studies showed the presence of HHV-8 on the mononuclear cells of peripheral blood and in almost all tissues of cases with KS (Noël et al., 1997; Pellet et al., 2002). Biopsy specimen of our case also revealed presence of HHV8 HHV-8 reactivation as a result of immunosuppressive treatment is probably the most relevant mechanism involved, but primary infection transmitted via organ transplantation has been also reported (Tessari et al., 2006; Marcelin et al., 2004).

Mucocutaneous lesions of KS seen in renal transplant patients, are characterized by macules, plaques, or nodules of different sizes, varying in color from deep red to bluish-purple (Zmonarski et al., 2005; Barete et al., 2000). Similarly, the oral lesion of our patient was a solitary pink-purple one, localized on the gum. Lower extremities may be initially affected, although lesions can also be found on the trunk and arms (Kolhe et al., 2006). Our patient had also a lesion on his leg.

Visceral organ involvement including the gastrointestinal tract, lymph nodes, liver and lungs may occur and is related with poor prognosis. Whereas involvement of the transplanted organ is veryrare (Duddridge et al., 2008). As having abdominal ache, our patient went on gastroduodenoscopy, and KS in gastrointestinal tract was excluded. The management of post-transplant KS often involves reduction of immunosuppressive therapy (Szajerka and Jablecki, 2007; Schwartz, 2004). Ferreira et al. reported complete remission of KS in most patients by reduction or withdrawal of immune suppressive drugs (Costa et al., 2005). However this reduction isa very high risk for graft loss. In recent studies, investigators have recommended switching the immunosuppressive drug from calcineurin inhibitors to mammalian targets of rapamycin (mTOR) inhibitors, such as sirolimus (osseini-Moghaddam et al.,
transplant recipients with KS, showed histologically proven remission by switch from CyA to sirolimus (Stallone et al., 2005). On the contrary, there are cases reported in literature, with the progression of KS during sirolimus therapy (Charfi et al., 2007). We discontinued the cyclosporine regime and started to sirolimus. In following upiscurrence and any decline of graft functions had not seen since a year. There were no any systemic involvement, thus we didn’t discuss to reduce mycofenolate sodium or prednisolone doses. In the presented case, we emphasized the importance of the switch from CyA to sirolimus in management of KS seen after early post transplant period.

REFERENCES


