Coexistence of Membranous Glomerulonephritis and Kaposi's Sarcoma: Case Report and Literature Review

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ABSTRACT

Kaposi's sarcoma (KS) is a malignant neoplasm of the vascular endothlium that closely related to human herpesvirus-8 (HHV-8) infection. Iatrogenic KS is associated with wide use of immunosuppressive therapy, which is well known in post-transplantation patient but only several cases reported in the literature associated with membranous glomerulonephritis. We herein report an unusual case of Kaposi's sarcoma in an HIV-negative patient with membranous glomerulonephritis from Sichuan, China. The 40-year-old male patient developed KS following treatment with long-term medium dose prednisolone, short-term cyclosporin and cyclophosphamide. The KS cases associated with glomerulonephritis are also reviewed.

Keywords: Glomerulonephritis, HHV-8, immunosuppressive therapy, Kaposi's sarcoma,

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INTRODUCTION

Kaposi’s sarcoma is a low-grade vascular tumour of endothelial origin that most commonly involves the skin. The extent and aggressiveness of KS tumours depends on the epidemiology (classic, African, AIDS-associated and iatrogenic KS) and host immunity (1). Kaposi’s sarcoma is well known in patients with acquired immunodeficiency syndrome (AIDS), iatrogenic KS mainly affecting recipients of solid organs (especially the kidneys), but rarely plaguing patients with glomerulonephritis under immunosuppressive therapy. To the best of our knowledge, the report of KS in patients with glomerulonephritis is only eight cases described in the literature (2–9). In this article, we are presenting another rare case of Kaposi sarcoma in a patient with membranous glomerulonephritis on immunosuppressive therapy.

CASE REPORT

A 40-year-old male patient presented with skin lesions that had appeared two months ago. There was no history of any opportunistic infection before the onset of skin nodules. His past medical history revealed that the patient was diagnosed with nephrotic syndrome one year earlier with a presentation of proteinuria. Clinical investigation at that time confirmed massive proteinuria (2.44 g/day), hypoalbuminaemia (28.1 g/L) and hyperlipidaemia.

The kidney function was within normal limits. Kidney biopsy was performed and showed atypical membranous glomerulonephritis. The patient was initially treated with prednisolone 65 mg/day orally (reduce 5 mg/month in the following four months). Then he had received additional immunosuppressive drugs during the last six months because of repeated colds and resistant proteinuria. First, six months ago, prednisolone 60 mg/day orally

(reduce 5 mg/month in the following six months) was given again. Then four months ago, intravenous cyclophosphamide 0.5 g/day (two days in a row in a month, increase 0.5 g/day in the following two months) was given. At last, one month ago, cyclosporine 125 mg/day orally had been added to steroid for about one month's duration.

Clinical examination showed multiple, dusky red nodules and plaques over the feet, soles, thighs, fingers and hands (Figure 1), majority of the lesions were painful and moderate edema on his lower limbs. His blood pressure was 97/51 mmHg. Laboratory tests disclosed the following values: haemoglobin: 87 g/L, white blood cell (WBC) count was 2.87 ($\times 10^9$/L), platelet: 114 ($\times 10^9$/L), serum creatinine: 115.7 umol/L, albumin: 26 g/L, triglycerides, 1.88 mmol/L; serology of hepatitis B and C was negative. Anti-nuclear antibody, anti-dsDNA, anti-SSA, anti-Rib, ANCA and anti-glomerular basement membrane antibodies were negative.

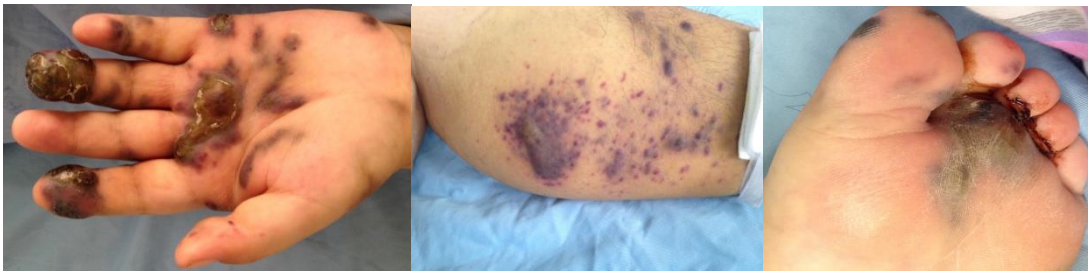

Figure 1, the lesions at the left fingers and palm, left thigh, left sole and toes.

Trepoema pallidum antibody and HIV antigen-antibody complex were negative. Bone marrow puncture examination revealed that low proliferation of haematopoietic cell, particularly myeloid. Lower extremity arteriovenous ultrasound showed the soft-tissue of thighs was swelling. A biopsy of skin lesion revealed KS and immunohistochemical staining

showed positive expression of CD31, CD34, ERG and positive nuclear stains for HHV-8 and this confirmed the diagnosis of Kaposi sarcoma. Considering the bad condition of the patient, he was offered the oral chemotherapy drug VP-16, but the patient refused the therapy and went home.

Literature review

A Medline search (Pubmed and ovid) was performed to search for case reports published from 1966 to current. The keywords included *Kaposi's sarcoma, glomerulonephritis*. We finally identified eight cases without AIDS from the Medline search. Now there were a total of nine cases of coexistence of KS and glomerulonephritis without HIV infection including our case (Table 1). There are five men and four women, the age ranged from 30 to 78 years old.

There were four cases of MG, four of MPGN, one of FGS. Six patients (include two patients received an extra therapy of Mycophenolatemofetil) received a combination of corticosteroids and immunosuppressive drug therapy, which included cyclophosphamide, azathioprine, Tacrolimus and cyclosporine. Two patients received Prednisolone alone. One patient developed Kaposi's sarcoma simultaneously without the initiation of prednisone. The dose of corticosteroid ranging from 20 mg to 65 mg, the duration of drug therapy ranging from two months to seven years. The duration of KS presentation since diagnosed with glomerulonephritis ranging from one month to nine years. Kaposi's sarcoma lesions most involved extremities, other locations of involvement included eye, earlobe, axilla, face and tonsil, no inner organs were involved.

Table 1: Clinical features and outcome of Kaposi's Sarcoma associated with glomerulonephritis

Case: authors, year (reference)	Renal disease	Age/gender/ nationality	Immunosuppressive therapy	Time interval from diagnosis to KS	Location of involvement of KS	Antibodies to HHV-8	Treatment of KS	outcome
1.Current case,2015	MG	40M,Chinese	prednisolone 65 mg/day (reduce 5 mg/month in the following four months), prednisolone 60 mg/day (reduce 5 mg/month in the following six months), Cyclophosphamide 0.5 g/day (two days in a row in a month, increase 0.5 g/day in the following two months).cyclosporine 125 mg/day for 1 month	1 year	Fingers, palm, thigh, toes, sole	+	None	Light improvement
2.Rukasz D,2015,(2)	MG	78F, Poland	Steroids 40 mg/day for 2 month, Cyclosporine 125 mg/day for 2 month, Tacrolimus 2 mg/day for 3 months	5 months	Calves, shins, thighs, trunk, forearm, eye	+	Everolimus 0.75mg/day for 2 months	Regression of KS
3.Nabeel Al-Brahim, 2013, (3)	MG	30M, Kuwait	Prednisolone 60 mg/day for 6 months, cyclosporine 100 mg twice a day for 6 month, prednisolone was tapered gradually to 30 mg/day.	9 months	Tonsil	+	stop immunosuppressive therapy	Regression of KS
4.Yakup Sancar Baris,1998 (4)	MG	72M,Turkish	None	1month	Feet, hand, earlobe	NA	Local radiotherapy	Regression of KS
5Atasoyu,EM. 2009,(5)	MPGN	60F, Turkish	Deflazacort 42 mg/day for 6 weeks followed by gradual dose reduction (6 mg daily) for 4 years. Cyclophosphamide 1000 mg/month for 1 year. mycophenolate mofetil 2 g/day for 5 months.	6 years	Leg	-	Stop immunosuppressive therapy	Regression of KS
6.Kemal Agbaht,2007,(6)	MPGN	52F, Turkish	Prednisolone 20 mg/day for seven years, for short courses 60 mg/day, Azathioprine 125 mg/day for six months), Cyclosporine (two weeks), ,Mycophenolate mofetil (two weeks).	9 years	Leg	+	Local radiotherapy and Paclitaxel(weekly)	Regression of KS
7.Chim CS,1999,(7)	MPGN	38F, Chinese	Prednisolone 40 mg/day for three months	1 year	Axilla, face	NA	none	Not mentioned
8.Freuler CB,1994,(8)	MPGN	46M , Italian	Prednisolone	Months later	Toe	NA	Bleomycin and radiotherapy	extended
9.Zerbi S,2001,(9)	FsGS	59M, Italian	Prednisolone 25 mg twice a day for 15 months; then 1 mg/kg/day for 8 months; Cyclosporine 3 mg/kg/day for 10 months; Cyclophosphamide 100 mg/day 6 months.	2 years	leg	_	Vinblastine boli	Regression of KS

Abbreviations: MG, membranous glomerulonephritis; MPGN, membranoproliferative glomerulonephritis; FSGS, focal glomerulosclerosis; M, male; F, female; +, positive; -, negative; NA, not available

Antibody to HHV-8 was positive in four patients, negative in two patients, not mentioned in three patients. Treatment of Kaposi's sarcoma associated with immunosuppressive therapy included reduction or cessation of corticosteroids and immunosuppressive drugs, local radiation, administration of immunosuppressive drugs (bleomycin, Everolimus, Paclitaxel and vinblastine) and a combination of therapies. Seven of nine cases responded well to the therapy, they were all on the process of KS lesions regression. One patient became worse after Bleomycin and radiotherapy (Freuler *et al*). One case did not give valuable message (Chim *et al*).

DISCUSSION

Membranous glomerulonephritis (MG) is the most common cause of adult nephrotic syndrome and it accounts for about 25% of renal biopsies done for this syndrome. Most of the cases are primary or idiopathic in nature while only about one third of the cases are secondary to some known disease. Corticosteroid and cytotoxic drugs are the common treatments of MG based on the underlying cause of the disease process. Kaposi's sarcoma is an uncommon vascular tumour characterized by spindle cell proliferation and haemangioma-like structure that most commonly involves the skin. Kaposi's sarcoma includes four clinical varieties: classic, endemic or African, associated with HIV epidemic and iatrogenic. The latter is related to immunosuppressive therapies, mainly affecting not only recipients of solid organs (especially the kidneys), but also patients receiving immunosuppressive treatment due to other conditions, including rheumatic disease, leukemias and lymphomas, inflammatory bowel disease or asthmamunosuppressive therapy. In iatrogenic KS prognosis is variable, with an approximately 50% remission rate after the reduction or withdrawal of immunosuppressive therapy (1). There are some evidences indicates steroids have a direct role in stimulating

tumour development and growth. Previously study has shown that the glucocorticoid receptor is significantly increased in KS tissues, both in the cytoplasm and the nucleus (10). In addition, sustained application of corticoids could cause HHV8 antigen reactivation through various mechanisms (11). Kaposi sarcoma-associated herpesvirus (KSHV), also known as human herpesvirus8 (HHV-8), discovered in 1994, now known as the primary cause of KS, can be found in almost all forms of KS (12). Kaposi sarcoma-associated herpesvirus encodes a number of proteins and small RNAs that aid the virus in establishing a lifelong infection in the host and utilizes a number of mechanisms to dampen the immune response so that it can persist for the lifetime of the host (13). Atypical differentiation of endothelial cells induced by KSHV, inflammatory cytokines (includeIL-6, IL-2, IL-10, interferon and KSHV-encoded) and KSHV-induced alterations of angiogenesis work together to lead to the occurrence of KS (14). G Liu *et al* also found KSHV promotes tumorigenesis by modulating the Hippo pathway (15).

Although the association of corticoids, HHV-8 and KS has been well studied and many evidences support it, there are rare patients with glomerulonephritis under immunosuppressive therapy developed KS. Patients with chronic renal failure undergoing dialysis without application of immunosuppressive agents also developed KS (16). Additionally, in some patients with KS, HHV-8 was not detected (Table 1). These phenomena reminded us the development of iatrogenic KS may need other factors (like immune status, genetic, geographic and ethnic factors *etc*) other than immunosuppressive therapy and HHV-8.

Our patient received prednisolone, cyclophosphamide and cyclosporine because of glomerulonephritis, these immunosuppresive agents may deeply changed the immune status of patient, which provided opportunities for virus invasion or reactivation. The immune status may also directly leads to KS through some mechanisms.

In conclusion, as a rare complication of glomerulonephritis and other diseases under immunosuppressive therapy, KS is gradually drawing people's attention. Further studied and case report about patients with KS and glomerulonephritis are still needed. Immunosuppression treatment should be carefully applied in clinical treatment and avoided if they are not essentially necessary.

Conflict of Interest

The authors declare no conflict of interest.

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