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Kaposi's Sarcoma Occurring During Short-Term Dialysis : Report of Two Cases

Kaposi's sarcoma (KS) appears to develop in association with kidney transplantation, but unlikely with dialysis. We report two cases of classic KS that occurred in patients receiving short-term (less than 3 yr) dialysis. They have been suffering from chronic renal failure due to tuberculosis and diabetes mellitus, respectively. Several to multiple, reddened-violaceous patches, plaques and nodules were found on the hand and the lower extremities. Laboratory studies showed no evidence suggesting immunosuppressed state and there was no history of taking immunosuppressive agents. The biopsies of the two cases revealed proliferation of spindle-shaped cells focally arranged in bundles and multiple dilated vascular spaces outlined by an attenuated endothelium with intravascular and extravasated erythrocytes. The specimens expressed positivity with CD34 antigen. Human herpesvirus 8 (Kaposi's sarcoma-associated herpesvirus) was detected in one case by polymerase chain reaction method.

Key Words: *Sarcoma, Kaposi's; Dialysis; Antigens, CD34; Herpesvirus, Kaposi's Sarcoma-Associated*

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INTRODUCTION

Skin manifestations such as pruritus, bullous dermatoses and perforating diseases have been reported in patients with chronic renal failure. Hemodialysis or peritoneal dialysis and kidney transplantation may lead to ensuing carcinomas of the various organs. In general, surveys demonstrated that frequencies of malignancy in the liver, colon, rectum, thyroid, kidney, bladder, lung and lymphoid organs were higher in those on dialysis than in control group (1, 2). However, it may be hard to determine yet whether short-term dialysis can induce Kaposi's sarcoma (KS).

We describe two male patients with KS that developed on the hand and the lower extremities during a relatively short period of dialysis, more precisely 18 months and 26 months after the start of dialysis, respectively. Immunosuppressed people who have chronically received glucocorticoids, cytotoxic drugs and/or cyclosporins can be more vulnerable to KS (3, 4), but the immune conditions of our cases were shown to be normal. We also reviewed the literature on the relation between occurrence of cancers including KS and dialysis.

CASE REPORTS

Case 1

A 65-yr-old Korean male patient has been taking hemodialysis two to three times a week for 21 months since he was diagnosed as chronic renal failure following tuberculosis of kidneys. He had a 3-month history of several nodules developing simultaneously and growing slowly on the palm (Fig. 1). On examination, three red to purple, non-tender, non-fluctuant subcutaneous nodules measuring 0.5×0.5 cm to 0.7×1 cm were noted. No lymphadenopathy was present. Shortly before each dialysis, 1,500 IU of heparin was administered and then 250-500 IU of heparin per hour was maintained during the dialysis.

In laboratory studies, complete blood count (CBC) with differential count, platelet and fibrinogen were normal. Prothrombin time (PT) (27.1%, reference range [70-140%]) was shortened and activated partial thromboplastin time (aPTT) (43.2 sec, [27.5-37.5 sec]) was prolonged. Results of serum electrolytic and chemical analyses were as follows: values of sodium, potassium, mag-

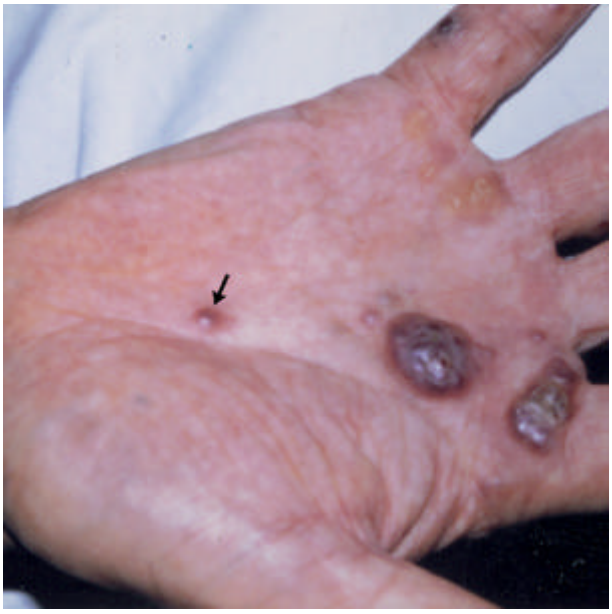

Fig. 1. Red to purple nodules on the palm (Case 1).

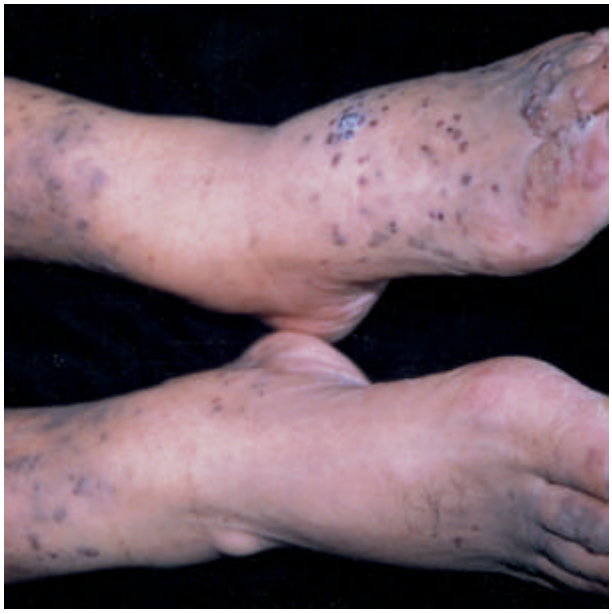

Fig. 2. Violaceous patches and plaques on the leg (Case 2).

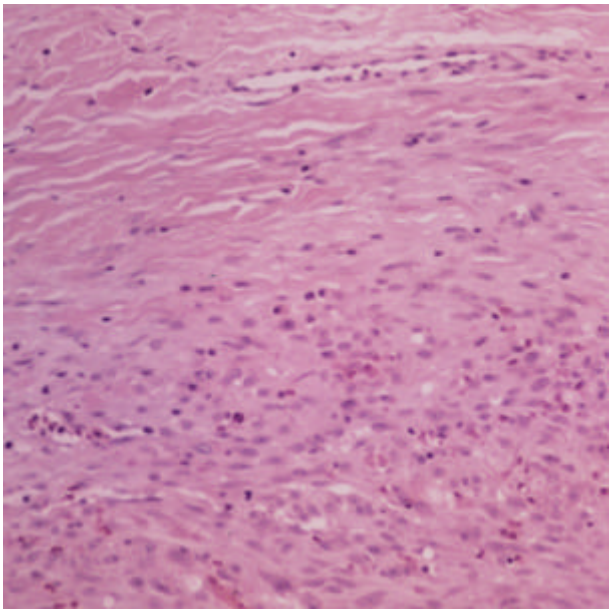

Fig. 3. Bland spindle cells with slit-like spaces and extravasated red blood cells (H&E, ×200, Case 1).

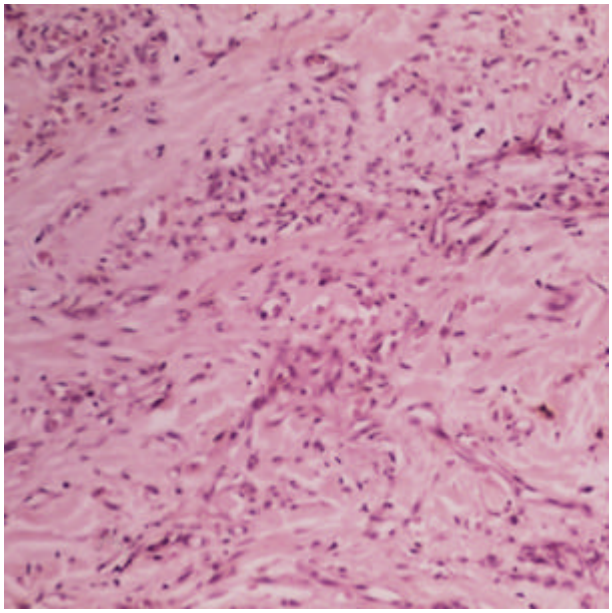

Fig. 4. Fascicles of spindle cells intermingled with numerous jagged vascular spaces filled with red blood cells (H&E, ×200, Case 2).

nesium, phosphorus, glucose, uric acid, SGOT, SGPT, bilirubin and cholesterol were normal, except for chloride (90 mEq/L), calcium (13.6 mg/dL), protein/albumin (5.7/2.4 g/dL), blood urea nitrogen (33.1 mg/dL), creatinine (6.4 mg/dL), alkaline phosphatase (296 IU/L). The serum complements (C_3, C_4) were normal, and immunoelectrophoresis demonstrated normal distribution. Red blood cells (3-5/HPF) and albumin (1+) were detected in urinalysis. He was experimentally sensitized with an allergen dinitrochlorobenzene (DNCB). Helper (T_H)/suppressor (T_S) ratio of peripheral blood was within normal limits. Serologic test for human immunodeficiency virus (HIV) was negative. In chest radiograph, a small nodular density was found on the left middle lobe. In EKG and echocardiogram, atrial fibrillation and left ventricular hypertrophy were noticed, respectively.

A biopsy specimen showed relatively well-defined nodules composed of spindle cells and vascular spaces inter-

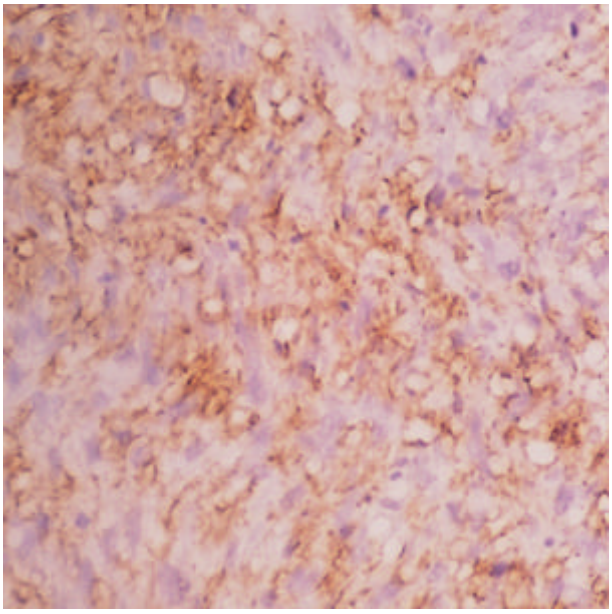

Fig. 5. Strongly positive staining of spindle-shaped and endothelial cells with CD34 (×400, Case 1).

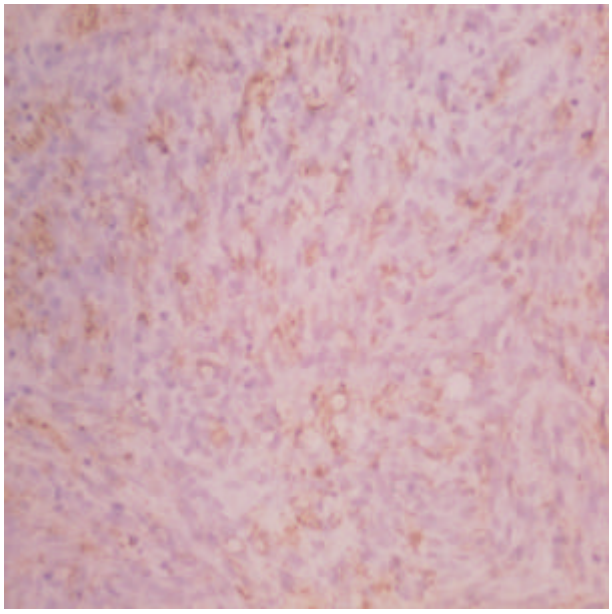

Fig. 6. Moderately positive staining of spindle-shaped and endothelial cells with CD34 (×400, Case 2).

mingled with some networks of blood filled slits (Fig. 3). Flattened endothelial cells were seen. Pigment-containing macrophages were occasionally noted. There were few mitotic figures. Immunohistochemical reactions with CD34 were identified as strongly positive to spindle cells and endothelial cells (Fig. 5). The results of immunohistochemical study were negative with S-100, SMA, vimentin, desmin and factor VIII-related antigen. Human herpesvirus 8 (HHV-8) was not detected at 233 bp by polymerase chain reaction (PCR) with the primers (Bioneer, Korea) of 5'-AGCCGAAAGGATTCCACCAT-3' and 5'-TCCGTGTTGTCTACGTCCAG-3'.

Case 2

A 62-yr-old Korean man with chronic renal failure related to uncontrolled diabetes mellitus has been taking peritoneal dialysis twice per week for 32 months. He had multiple red to violaceous patches, plaques and nodules on both legs and feet (Fig. 2). The lesions had developed in series, leading them to change from macules to papules to nodules during the past 6 months. The size of lesions ranged from 1 mm to 1 cm. Intermediate-acting insulin has been administered. Heparinization for dialysis was done the same way as in Case 1.

Laboratory investigation demonstrated normal CBC with differential counts and platelet, with the exception of increased monocyte (19.1%). Shortened PT (34%) and prolonged aPTT (41 sec) were checked. The values of serum electrolytes and chemistry were as follows: potassium, chloride, magnesium, phosphorus, fasting blood glucose, uric acid, alkaline phosphatase, SGOT and SGPT were normal, but sodium (129.5 mEq/dL), calcium (12.5 mg/dL), protein/albumin (5.9/2.9 g/dL), postprandial (2 hr) blood glucose (243 mg/dL), HB A1C (7.9%), blood urea nitrogen (32.0 mg/dL), creatinine (6.8 mg/dL), bilirubin (1.7 mg/dL) and cholesterol (280 mg/dL) were abnormal. Serum C_3, C_4 and immunoelectrophoresis were normal. Urinalysis showed one plus of albumin and a few red blood cells in high power field of microscope. Sensitization with DNCB was successfully obtained. T_H/T_S ratio of peripheral blood was within normal limits. Serologic test for HIV was negative. Chest roentgenogram and EKG revealed no abnormality.

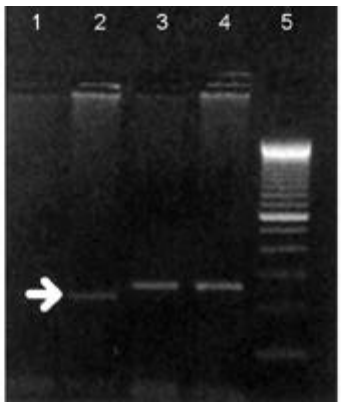

Fig. 7. Lane 1: negative (Case 1), Lane 2: positive (Case 2). Arrow marks amplification product for HHV-8 (233 bp). Lane 3 and 4: positive for beta globin (270 bp), Lane 5: molecular weight marker.

Histopathologic examination from a small papular lesion showed jagged vessels and thick-walled small vessels infiltrating through most parts of the dermis with red blood cells extravasation and some siderophages (Fig. 4). The vessels were characterized by various features including canalized cords, blood-containing vessels and lymphatic-like spaces. Spindle cells were distributed around blood vessels in a fascicle mode, which dissects collagen bundles. Immunohistochemical stainings for CD34, S-100, vimentin, desmin and factor VIII-related antigen were performed. Positivity of CD34 with spindle-shaped cells and focal endothelial cells was observed (Fig. 6). HHV-8 was detected at 233 bp by PCR (Fig. 7).

DISCUSSION

The incidence of KS is very low and it has four distinctive variants: classic, African-endemic, immunosuppressive drug-associated and AIDS-associated KS (5). KS is known to occur mainly in immunosuppressed patients, who are infected with human immunodeficiency virus or who receive immunosuppressive agents after organ transplantation or for cancer treatment (3, 4, 6). However, there have still been some cases of KS which developed in non-immunosuppressive patients. In our cases of KS which we believe to be classic type, no immunosuppressed status and no use of immunosuppressive agents were found.

Currently, HHV-8 represents the putative causative agent of KS, meaning that KS is most likely derived from a cytokine-driven proliferative process characterized by the mutual stimulation of KS cells and leukocytes (7-9). We attempted to confirm a correlation between HHV-8 and KS by PCR method (7, 10); Case 1 gave a negative result and Case 2 gave a positive one. Gao et al. (11) recently hinted of molecular polymorphism of HHV-8 with a large repertoire of viral genotypes.

As increased incidence of malignancy in renal transplant recipients has already been admitted, it seems interesting that malignancy can develop rarely in patients on chronic dialysis (1, 2, 12-14). However, there is a difference between the two groups in that the dialysis group tends not to be in an immunosuppressed state, while the transplantation group tends to be an immunosuppressed state with administration of immunosuppressive agents to prevent graft-versus-host reactions. Tumors other than skin cancers were frequently observed in the dialysis group, whereas an excess of skin cancers were seen in the transplantation group (12). The time lapses between dialysis and onset of KS were 18 months and 26 months for Case 1 and Case 2, respectively. It is exceptional for cancers to occur for less than 3 yr on dialysis, not to mention KS. Malignant tumors in association with long-term dialysis for 3 yr or more, showing an incidence of 4.3% to 10.4% (12, 13), were listed as tumors of the urinary tract (kidney, bladder), malignancies of the digestive organs (liver, colon, rectum), vulval carcinoma, lymphoma, leukemia, breast cancer, lung cancer and thyroid cancer (1, 2, 12-14). Nampoory et al. (15) indicated occurrence of Castleman disease and KS in patients receiving dialysis. According to reports from Germany (12) and Spain (13), bladder cancer, accounting for up to 28.5% of all cancers, was most frequently observed in dialysis-undergoing people. On the other hand, according to a report from Japan (1), tumors of the liver, colon and rectum were expected to be higher, totaling 56%. In a report from Israel (16), classic KS as a second primary neoplasm with an incidence of 8.4% followed by Hodgkin's lymphoma, non-Hodgkin's lymphoma and leukemia. On the contrary, a report from U.S.A. (17) gave the view that no malignancy was detected in either the long-term or short-term dialysis patients whose population was 470. It is believed that an ethnic discrepancy may exist.

Among the disorders to be considered in the differential diagnosis of KS are angiosarcoma, targetoid hemosiderotic hemangioma, bacillary angiomatosis, lymphangioma, spindle cell hemangioendothelioma, acroangiodermatitis, histiocytoma, multinucleated cell angiohistiocytoma, fibrosarcoma, leiomyosarcoma, malignant cellular blue nevus and malignant melanoma (5, 18). KS can be distinguished from tumors that histologically resemble it with the help of tumor markers like CD31 and CD34 (19, 20). To rule out the possibility of being derived from melanocytic, neural, smooth muscular or fibrohistiocytic cells, various immunohistochemical stainings were carried out. As a result, positive expression for the CD34 antigen made the diagnosis of KS definite. Hodak et al. (21) claimed P53 immunoexpression is a marker of tumor progression in classic KS, but not in most cases of iatrogenic KS.

The treatment modalities of KS mainly comprise surgical excision, ionizing radiation, chemotherapy and interferon-alpha (5, 22-24). The patients wanted to undergo radiotherapy which was unavailable at our hospital, so they were transferred to other institution.

In conclusion, although it is uncertain whether our cases of KS might occur coincidentally during dialysis or not, we suggest that further study on the relation between dialysis and KS be needed.

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