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BRIEF REPORT

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Disseminated angiosarcoma presenting as a hemophagocytic syndrome in a renal allograft recipient

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Abstract A case of angiosarcoma arising in the setting of transplantation is reported. This rare and malignant tumor of the endothelial system is seldom observed in allograft recipients, with only seven cases having been previously reported. What is interesting about the present observation is that the tumor is thought to have developed in the vicinity of a Dacron graft and that it showed prominent erythrophagocyte-like activity. This activity was associated with a particular clinical syndrome that shared some attributes with infection-associated hemophagocytic syndrome.

Key words Hemophagocytic syndrome, kidney transplantation · Kidney transplantation, hemophagocytic syndrome · Angiosarcoma, kidney transplantation

Introduction

Renal transplant recipients are prone to developing various neoplasms, the most prevalent being lymphoproliferative disorders, carcinomas of the skin, lip, and cervix, and Kaposi's sarcoma [14]. Angiosarcoma, a rare and highly malignant tumor of the endothelial system, has only been sporadically observed in renal allograft recipients, with a preferential occurrence at sites of altered vasculature or irradiation [1, 2, 4, 5, 8, 12, 13 and I. Penn, personal communication (1981)]. We report a kidney recipient who developed an angiosarcoma and presented with symptoms of hemophagocytic syndrome.

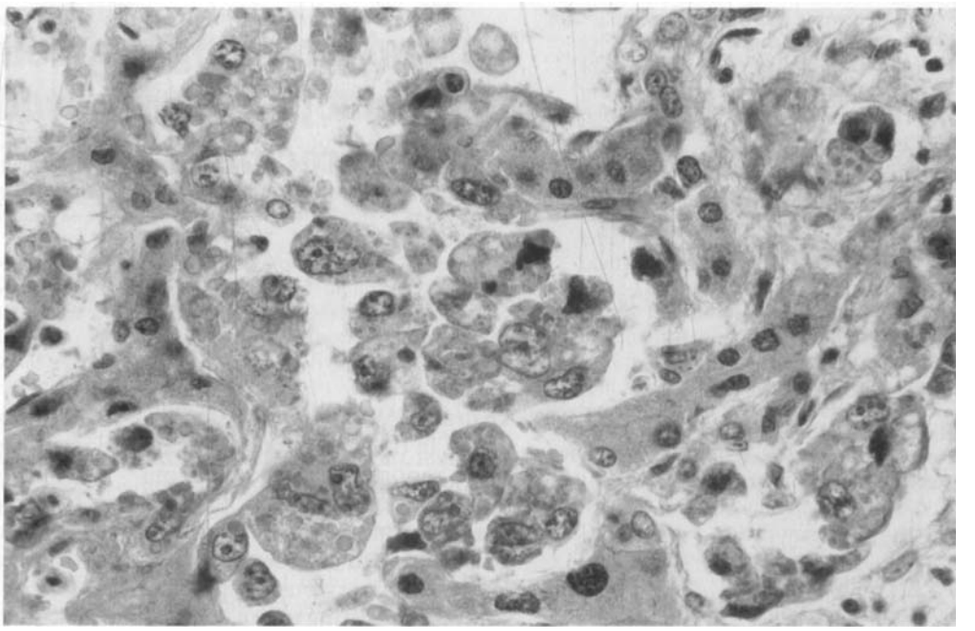

Fig. 1 Light microscopy of the liver: the architecture is disrupted by a malignant proliferation of large epithelioid cells that show erythrophagocytosis. These cells line newly formed vessels and are accompanied by reactive histiocytes. (H & E, × 400)

Case report

A 61-year-old male patient received a kidney transplant 3 years before his present admission because of an IgA nephropathy. His clinical history revealed hyperuricemia, arthrosis, and several surgical procedures, including a femorofemoral bypass with a Dacron graft for severe arteriosclerosis. The maintenance immunosuppression regimen consisted of azathioprine and prednisone. His general condition remained good until a few days before his present admission, when he developed arthralgias, myalgias, asthenia, and gastrointestinal tract symptoms. At the admission, clinical investigations revealed only symptoms of cardiovascular disease. During hospitalization, laboratory data showed a raised white cell count [21×10^9/l (normal values 4.5–11.0 × 10^9/l); neutrophils 80 %] with microangiopathic hemolytic anemia [hemoglobin level 9.2 g/dl (normal values 13.5–17.5 g/dl)], hematocrit value 29 % (normal values 41 %–53 %), haptoglobin 10 mg/dl (normal values 83–267 mg/dl), lactate dehydrogenase (LDH) 3980 U/l (normal values 210–420 U/l), total bilirubin 10.2 mg/dl (normal values 0.2–1 mg/dl), and thrombocytopenia 59×10^9/l (normal values 150–400 × 10^9/l). The Coombs test was negative, but schistocytes were present (1.8 %). The sedimentation rate was 15 mm in the 1st h. Abnormal biochemical indices included ferritin 2210 ng/ml (normal values 15–200 ng/ml), c-reactive protein (CRP) 11200 ng/ml (normal values 68–8200 ng/ml), and serum creatinine 1.52 mg/dl (normal values 0.6–1.2 mg/dl). The coagulation parameters and lysozyme were within the normal limits. Bone marrow aspirate and biopsy showed infiltration by poorly differentiated malignant cells with cytological features of hemophagocytosis. Extensive bacteriological and serological studies did not demonstrate any pathogen. Computed tomography (CT) scans showed that the liver, lungs, and brain were involved in a neoplasty like process. Nine days after admission, the patient died from multiple organ failure. An autopsy was performed.

Tissue samples taken at autopsy were processed with standard histopathological procedures. For immunohistochemical studies, antibodies against the following antigens were used: vimentin, α_1 antitrypsin (α-AAT), α_1 antichymotrypsin (α-ACT), CD45 (LCA), CD68 (KPI), HLA-DR (TAL 1B5), L1 protein (Mac387) and lysozyme (Dako, Glostrup, Denmark); Von Willebrand Factor Antigen (FVIII-related antigen), CD34 (QBEnd/10), and S-100 protein (Biogenex, San Ramon, Calif., USA); and Ulex Europaeus Agglutinin-I (Sigma Chemical, St. Louis, Mo., USA). Ultrastructural studies were carried out with a Philips EM 400 Telectron microscope.

As previously described [9], a semiquantitative polymerase chain reaction (PCR) analysis of the Epstein-Barr virus (EBV) genome was performed with DNA extracted from tumoral tissue in the liver and spleen. We used primers specific to the EBV-Bam HI-W fragment. For each experiment, a similar amplification of a plasmid containing this fragment, at serial concentrations, produced a standard curve. This approach allows detection of the EBV genome in a range of 0.1 to 100000 copies per 1000 cells. In order to verify the amplification, the β globin gene of each sample was also amplified.

Results

Autopsy revealed a disseminated process involving the liver, spleen, lungs, retroperitoneal and mediastinal lymph nodes, and brain. There was a large aortic aneurysm and an extensive iliac thrombosis. A Dacron vascular prosthesis (from a surgical intervention) was found, as well as a femorofemoral bypass. The wall of the former appeared thickened and fibrotic. On inspection, it was considered inflammatory. It also showed postsurgical changes.

Light microscopy demonstrated infiltration of the brain, lungs, liver, spleen, lymph nodes, and bone marrow by malignant cells showing different growth patterns. Of these, the vasoformative aspect was the most prevalent and consisted of anastomosing vascular chan-

Table 1 Angiosarcomas occurring in kidney transplant recipients (*AZA* azathioprine, *STE* corticosteroids)

Case reported by	Age and sex	Immunosuppressive therapy	Underlying renal disease	Appearance after transplantation (months)	Site	Therapy	Outcome after diagnosis
Askari et al. [2]	24 M	STE	Obstructive uropathy-pyelonephritis	43	Periureteral involvement of allograft	En bloc excision	Death 4–5 months later; disseminated disease
Penn et al. [personal communication]	50 F	Immunosuppressive drugs, local irradiation	Unspecified	8	Unspecified	Unspecified	Disseminated disease
Alpers et al. [1]	31 M	STE, AZA	Lupus erythematosus	42	Muscles of the abdominal wall	Wide excision, radiotherapy	Unspecified
O'Connor et al. [12]	43 F	STE, AZA, radiotherapy	Analgesic nephropathy	80	Skin (vicinity of a skin graft), involvement of the allograft	Radiotherapy	Unspecified
Conlon et al. [5] Byers et al. [4][a]	40 M	STE, AZA	Membranous glomerulonephritis	84	Ligated elbow arteriovenous fistula	Wide excision, local radiotherapy	Death 5 months later; disseminated disease
Parrott et al. [13][a]	36 M	STE, AZA, cyclosporin	Unspecified	144	Right forearm, arteriovenous fistula	Amputation above the elbow	Death 17 months later; disseminated disease
Keane et al. [8]	41 M	STE, AZA	Glomerulonephritis	120	Defunctionalized arteriovenous fistula	Wide excision, local radiotherapy, combination chemotherapy	Death 8 months later; disseminated disease
Our case	61 M	OKT3, STE, AZA	IgA nephropathy	35	Unknown, probably vascular	None	Death within one month; disseminated disease

[a] These two publications report the same case

nels lined with atypical epithelioid cells, some of them showing prominent erythrophagocyte-like activity (Fig. 1). Some tumor cells also contained periodic acid-Schiff (PAS)-positive hyaline globules. A similar neoplastic process was also evident in the biopsies taken from the wall of the right iliac artery near the prosthesis. Associated with the neoplastic cells were numerous seemingly benign histiocytes, some of them also showing erythrophagocytosis.

Immunohistochemical investigations demonstrated that the tumor cells expressed vimentin and Von Willebrand Factor antigen (F VIII-related antigen); they were stained by Ulex Europaeus Agglutinin-I. The neoplastic cells also displayed immunoreactivity with antibodies directed against α-AAT and α-ACT. In contrast, immunostaining of the CD34 antigen was negative.

The histiocytes were immunoreactive with antibodies respectively directed against CD45, CD68, HLA-DR, L1 protein, lysozyme, α-AAT, and α-ACT antigens, in accordance with their histiocytic nature. There was no immunoreactivity to S-100 protein.

Electron microscopy showed endothelial-type cells with abundant cytoplasm and intercellular junctions. The former contained homogeneous dense globules and "ingested" erythrocytes or other cells. In addition, some structures reminiscent of Weibel-Palade bodies were seen.

The semiquantitative PCR analysis demonstrated higher amounts of EBV genome in the hepatic and splenic tumoral tissues than in peripheral blood mononuclear cells (data not shown), but only with an estimated rate of 1–10 copies per 1000 cells. These results do not suggest an additional acute EBV infection responsible for a virus-associated hemophagocytic syndrome.

Based on these data, a diagnosis of angiosarcoma presenting with an hemophagocytic syndrome was made.

Discussion

Classical complications of kidney transplantation include acute and chronic graft rejections, opportunistic infections, and various neoplasms such as skin cancers, Kaposi's sarcoma, and post-transplant lymphoproliferative disorders (PTLDs) [14]. Unlike Kaposi's sarcoma, angiosarcoma, a rare and highly malignant tumor of the endothelial system, only occurs sporadically in the setting of transplantation [1, 2, 4, 5, 8, 12, 13 and I. Penn, personal communication]. Surprisingly, all reported cases involve renal allograft recipients. In these cases, the tumor occurs preferentially at sites of prior surgery [1], altered vasculature [4, 5, 8, 13], or irradiation [12] (Table 1). This tumor may show prominent erythrophagocytic activity [6, 11] and may be responsible for miscellaneous coagulation disorders [3, 6, 7, 11]. However, hemophagocytic syndrome encompasses a group of clinicopathological findings especially characterized by fever, pancytopenia, hypertriglyceridemia, hypofibrinogenemia, and a systemic proliferation of histiocytes showing hemophagocytosis [15]. This last characteristic is the hallmark of the syndrome. The majority of cases are reported to be associated with viruses, bacteria, fungi, parasites, and, on occasion, neoplasms, particularly of the hematopoietic types. Among viruses, EBV is known to be strongly implicated in a great number of cases [15].

In the present case, the histiocytic proliferation seemed to be related to the neoplastic process and not to have been induced by an infectious agent, EBV included. Moreover, it might have resulted from alterated peripheral blood cells circulating in tumoral vessels. The simultaneous hemophagocytic activities of both the reactive histiocytes and the malignant endothelial cells resulted in a particularly severe microangiopathic hemolytic anemia and thrombocytopenia in our patient. Although the tumor was disseminated at the time of diagnosis, it may have arisen at the vascular prosthesis, which was involved in the same malignant process. This would also explain the particularly rapid dissemination of the neoplasia. Indeed, angiosarcomas do occur in association with foreign body material [3, 7, 16] and may complicate vascular surgery [16]. In our patient, who was receiving immunosuppressive therapy, both conditions were present.

Table 1 summarizes the data on the seven previously reported cases of angiosarcoma arising in allograft recipients. In at least three cases, the tumor arose in the area of vascular surgery. All patients displayed a poor prognosis, independent of the treatment received.

In conclusion, the present case illustrates that immunosuppressed patients with vascular surgery are at risk of developing angiosarcoma. In addition, it shows that such a tumor might have an exuberant erythrophagocyte-like activity and may induce a particularly severe syndrome that clinically mimics the classical hemophagocytic syndrome.

Addendum

During the processing of this manuscript, an additional case of angiosarcoma arising from an arteriovenous fistula in a renal allograft recipient came to our attention [10]. This additional case highlights the assertion that renal allograft recipients are at higher risk of developing angiosarcoma at sites of altered vasculature.

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