Classic and immunodeficiency-associated Kaposi's sarcoma. Clinical, histologic and immunologic correlations.

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Classic and Immunodeficiency-Associated Kaposi's Sarcoma

Clinical, Histologic, and Immunologic Correlations

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• **The evolutionary modifications of the clinical, histomorphologic, and immunopathologic features of both classic and immunodeficiency (ID)–associated Kaposi's sarcoma (KS) were investigated in relation to the immune status of the patients. The histologic picture was similar in the classic and ID-associated forms of the tumor. In classic KS, a variably dense reactive infiltrate was present, and its amount was inversely related to the age of the lesions; conversely, a scarce reactive infiltrate, with the absence of CD4+ cells, was always evidenced in ID-associated KS lesions, even when the immune status of the patient showed no abnormalities. This evidence supports the hypothesis that a specific impairment of skin-associated lymphoid tissue may be crucial to the development of ID-associated KS.**

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Kaposi's sarcoma (KS) is, in its "classic" form, a quite rare disease,[1] with a higher incidence in people of Italian and Ashkenazic Jewish ancestry than one might expect from chance alone.[2] Classic KS mainly affects elderly men (age, >60 years), with the skin lesions being predominantly localized on the lower extremities. Extracutaneous involvement is rare, and the disease usually has a chronic, indolent course.

In the last few years, KS has been recognized with increasing frequency in patients who receive immunosuppressive treatment, including renal transplant recipients—who have a 400% to 500% greater incidence than the general population[3-7]—as well as patients with lymphoma, leukemia, and myeloma.[8-10]

Since 1979,[11] KS has been observed with continuously increasing frequency in patients with acquired immunodeficiency syndrome (AIDS) or AIDS-related complex. This "epidemic" form of KS mainly affects young male homosexuals and, less frequently, intravenous drug abusers or people with hemophilia who have received blood components. Kaposi's sarcoma affects 34% of patients with AIDS,[12] and it is reported as the initial clinical manifestation in about 30% of cases.[12-15]

Investigations of the immune status of patients with classic KS sometimes reveal functional abnormalities, such as hypergammaglobulinemia and diminished mitogen-stimulated lymphocyte proliferation.[4,16] In the large majority of patients with epidemic KS, various abnormalities are uncovered, such as elevated immunoglobulin levels, decreased mitogen-induced lymphocyte transformation, decreased reactivity in mixed lymphocyte cultures, and a marked decrease in CD4+ T cells, which are specific targets of human immunodeficiency virus (HIV), and, consequently, a decrease in the ratio of peripheral blood helper/inducer (CD4) to suppressor/cytotoxic (CD8) T lymphocytes. Recently, however, it has been reported that a laboratory-detectable impairment of the immune system is not a prerequisite for the development of KS in patients with AIDS or AIDS-related complex.[13,17]

It is generally stated that the histologic features of KS in the immunodeficiency (ID)–associated form are indistinguishable from those observed in the classic form[4,8,9,18-20]; the differences in the histologic picture have been related to the progression of lesions from patches to plaques and nodules.

The aim of this study was to com-

pare the clinical, histologic, and immunopathologic features of KS, both in its classic and ID-associated form, in relation to the age of the lesions and to the immunologic status of the patients. In particular, investigating the presence and the amount of T-cell subsets in situ in cutaneous lesions, we evidenced some peculiar differences between classic and ID-associated KS, ie, a strikingly less pronounced reactive infiltrate, with the virtual absence of CD4+ cells, in ID-associated KS lesions. A scanty reactive infiltrate was also found in KS lesions of a HIV-positive patient with normal immune cell function; this finding supports the concept that a specific impairment of skin-associated lymphoid tissue (SALT), even in the absence of any laboratory-detectable impairment of the immune system, may be crucial to the development of ID-associated KS.

Table 1.—Monoclonal Antibodies Used

Monoclonal Antibody	Cluster of Differentiation (CD)	Commercial Source	Specificity
B1	CD20	Coulter Clone, United Kingdom	B cells[24]
T11	CD2	Coulter Clone	E rosette receptor[24]
T3	CD3	Coulter Clone	Mature T cells[24]
T4	CD4	Coulter Clone	T-helper cells[24]
T8	CD8	Coulter Clone	T-suppressor cells[24]
OKT6	CD1a	Ortho Diagnostics Systems Inc, Raritan, NJ	Thymocytes, Langerhans' cells, and related[24]
OKM1	CD11b	Ortho	Mononuclear phagocytes[24]
Leu M3	CD14	Becton Dickinson, Sunnyvale, Calif	...
Leu M5	CD11c	Becton Dickinson	...
Anti-HLA-DR	...	Becton Dickinson	Class II molecule[26]
Leu 14	CD22	Becton Dickinson	B cells[24]
Anti-IgG	...	Becton Dickinson	γ Heavy chains[24]
Anti-IgM	...	Becton Dickinson	μ Heavy chains[24]
Anti-IgD	...	Becton Dickinson	Δ Heavy chains[24]
Anti-κ	...	Becton Dickinson	κ Light chains[24]
anti-λ	...	Becton Dickinson	λ Light chains[24]

PATIENTS AND METHODS

We studied ten patients with classic KS and seven patients with ID-associated KS (four patients with AIDS, one renal transplant recipient, one patient with Hodgkin's disease, and one patient with chronic lymphocytic leukemia). The patients were selected according to the following criteria: (1) availability of HIV serology; (2) complete immunologic data, ie, total lymphocyte count, T-lymphocyte count, CD4/CD8 ratio, immunoglobulin quantitation, in vitro response to allogeneic cells and polyclonal activators, in vitro helper activity, and delayed-type cutaneous response to various antigens.

All patients' peripheral blood mononuclear cells were separated from heparinized blood by centrifugation on a Ficoll-Hypaque gradient,[21] processed as previously described,[22] and then incubated with T11 (CD2), T3 (CD3), T4 (CD4), and T8 (CD8) monoclonal antibodies (MoAbs) (Coulter Clone, Luton, United Kingdom). The percentage of mononuclear cells that bound MoAbs was determined by fluorescence-activated cell sorter analysis as previously described.[22,23] The in vitro response to polyclonal activators phytohemoagglutinin (Wellcome, Manchester, United Kingdom), concanavalin A (Pharmacia Laboratories, Piscataway, NJ), and pokeweed mitogen (Gibco, Grand Islands, NY), the response to allogeneic cells in the mixed-cell lymphocyte reaction, and the helper activity of the mononuclear cells of the patients who were studied were evaluated as previously described.[12]

A delayed-type cutaneous response to various antigens was measured by an intradermal skin test (Multitest IMC, Merieux, Milan, Italy).

In all patients, multiple biopsy specimens were taken from skin lesions of different ages (ranging between 1 and 11 months) and variable clinical morphologic features (patches, plaques, and nodules), either at presentation or on relapse after treatment. Biopsy specimens were, in part, fixed in formaldehyde solution, routinely processed, and paraffin embedded. The remainder of the specimens was snap frozen and stored in OCT compound at −70°C. Sections (thickness, 6 μm) of paraffin-embedded material were routinely stained with hematoxylin-eosin, Berlin blue (Perls' method), and van Gieson's trichromic stains. Cryostat sections (thickness, 5 μm) were processed according to a previously described indirect immunoperoxidase method.[22] The MoAbs used are listed in Table 1. Vascular structures were identified using *Ulex europaeus* agglutinin I (UEA-I) (Vector Laboratories, Burlingame, United Kingdom).

RESULTS

The clinical and follow-up data of the patients studied are summarized in Table 2.

In patients with classic KS (Nos. 1 through 10), the most commonly observed lesions at presentation consisted of thick angiomatoid plaques and nodules, usually present for several months. Young lesions (one to two months old) were more likely to be observed on relapse after treatment (excision and/or radiotherapy); such lesions consisted of small papules, thin plaques, or angiomatoid nodules (Fig 1). The lesions showed a striking predilection for the lower extremities. In some patients (Nos. 2 through 4 and 7), these lesions were also located in other acral sites (hands and auricles); in only patient 6, the lesions were limited to upper acral sites. In patients with ID-associated KS, conversely, the most commonly observed lesions were erythematous patches (Fig 2), slightly infiltrated plaques, and small angiomatoid nodules. The lesions were preferentially located on the upper half of the body (head and neck, lateral side of the trunk, and upper parts of the arms). In one patient (No. 17), however, the lesions were confined to the lower extremities, while thick plaques on the dorsum of the feet were associated with a nodule on the lower left eyelid in patient 15 and with erythematous patches and slightly infiltrated plaques on the lateral side of the trunk in patient 16. All the patients with ID-associated KS were observed

Table 2.—Clinical Data*

Patient/Age, y/Sex	Site of Lesions	HIV Serology	Associated Clinical Findings	Therapy	Follow-up, mo From Diagnosis
1/58/M	Lower limbs	–	–	RT	LWD, 77
2/74/M	Lower limbs, hands	–	–	RT	LWD, 66
3/72/M	Hands, feet	–	–	RT	LWD, 87
4/75/M	Lower limbs, left auricle	–	–	RT	LWD, 43
5/70/M	Lower limbs	–	–	RT	LWD, 48
6/63/M	Upper limbs, hands	–	–	RT	LWD, 14
7/57/M	Feet, right hand	–	–	RT	LWD, 46
8/64/M	Feet	–	–	RT	LWD, 43
9/56/M	Lower limbs	–	–	RT	LWD, 86
10/67/M	Lower limbs, left buttock	–	–	RT	LWD, 56
11/46/M	Lateral aspect of trunk	+	–	CT†	DOD, 16
12/43/M	Upper limbs, head and neck	+	*Pneumocystis carinii* pneumonia	CT	DOD, 2
13/37/M	Trunk, neck	+	Fever, weight loss	Interferon alfa, CT	DOD, 4
14/39/M	Trunk	+	Weight loss	Interferon alfa	LWD, 7
15/33/M	Lower limbs, left lower eyelid	–	Renal transplant (cyclosporine treatment)	–	NED, 15
16/55/M	Feet, trunk	–	Hodgkin's disease	CT	DOD, 5
17/76/M	Lower limbs	–	B-CLL	Interferon alfa, CT	LWD, 15

*HIV indicates human immunodeficiency virus; B-CLL, B-chronic lymphocytic leukemia; RT, radiotherapy; CT, chemotherapy; LWD, living with disease; DOD, died of disease; and NED, no evidence of disease at seven months from the stopping of immunosuppressive treatment.
†Performed at ten months from diagnosis.

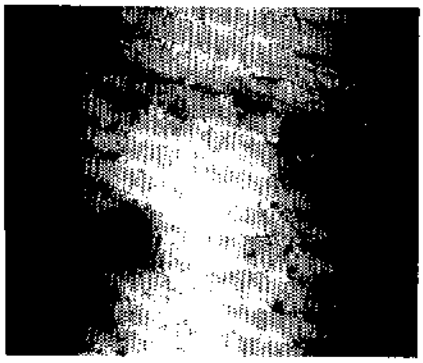
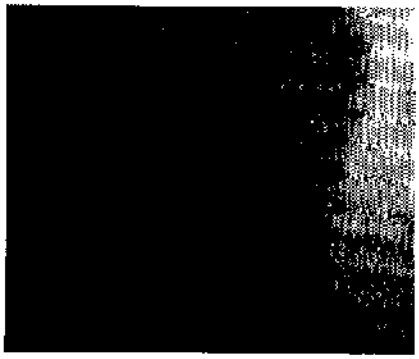


Fig 1.—Nodular angiomatoid lesions dating one month in classic Kaposi's sarcoma (patient 1).

Fig 2.—Erythematous patch on left lateral side of trunk in acquired immunodeficiency syndrome–associated Kaposi's sarcoma (patient 11).



within the third month from the onset of the lesions.

The immunologic parameters examined were within the normal range in all patients with classic KS (Nos. 1 through 10) and in patient 11 who was a young homosexual male with HIV-positive serology. Ten months after the first examination, this patient developed widespread cutaneous angiomatoid plaques, along with mucosal lesions and lymph nodal enlargement; at this moment, the patient showed, for the first time, impaired immunologic parameters, ie, lymphopenia, reduced CD4 subpopulations with an inverted CD4/CD8 ratio, a marked reduction of in vitro functional capacities, and cutaneous anergy to various antigens. In the other patients with ID-associated KS (Nos. 12 through 17), a clear-cut impairment of the investigated immunologic parameters was found at the time of the first clinical examination. The immunologic data of the patients at the time of presentation are shown in Table 3.

We did not find a strict relationship between the clinical morphologic characteristics of the lesions, ie, patches, plaques, and nodules, and their histologic features. In fact, substantial changes in the histologic features were seen even in relation to the aging of the lesions, irrespective of their clinical progression to more advanced ones. From the histologic point of view, the characterized lesions were represented by young, early patches on one side, and old, late nodules on the other.

Young, early patches of KS always showed dilated, irregularly shaped, thin-walled, jagged vascular channels that were lined by flat endothelial cells. The newly formed vascular structures were mainly located in the upper half of the dermis and tended to be contiguous to the preexisting blood vessels. Extravasation of erythrocytes was noted with hemosiderin deposition in cells near the vascular walls. Old, late nodules were characterized by large aggregations of interweaving fascicles of spindle cells throughout the entire dermis and sometimes the subcutis, with erythrocytes scattered in the clefts between spindle cells. A focal presence of widely dilated blood vessels contiguous to one another, resembling a hemangioma, was frequently observed. Nuclear atypia, pleomorphism, and mitotic figures were present but usually not promi-

Table 3.—Immunologic Data at Time of Diagnosis*

Patient	Total Lymphocyte Count × 10^9/L	T Cell, %	CD4/CD8 Ratio	Ig Quantitation	Proliferative Response to Polyclonal Activators and Allogeneic Cells	Helper Activity	Skin Test Response
1	2.3	68	1:3	Normal	Normal	Normal	Normal
2	2.45	71	1:8	Normal	Normal	Normal	Normal
3	2.2	63	1:4	Normal	Slightly decreased	Normal	Normal
4	2.8	72	1:7	Normal	Normal	Normal	Normal
5	3.1	66	1:6	Normal	Normal	Normal	Normal
6	2.3	63	1:7	Normal	Normal	Normal	Normal
7	1.9	68	1:4	Normal	Normal	Normal	Normal
8	2.05	66	1:6	Normal	Normal	Normal	Normal
9	2.2	70	1:6	Normal	Normal	Normal	Normal
10	2.4	69	1:5	Normal	Normal	Normal	Normal
11	2.7	66	1:5	Normal	Normal	Normal	Normal
12	1.1	39	0:6	Increased	Greatly decreased	Decreased	Decreased
13	0.9	41	0:4	Increased	Greatly decreased	Decreased	Decreased
14	1.7	52	0:9	Normal	Decreased	Decreased	Slightly decreased
15	0.8	46	0:6	Decreased	Decreased	Decreased	Decreased
16	1.05	41	0:5	Increased	Decreased	Decreased	Decreased
17	16.0	21	0:8	Decreased	Decreased	Decreased	Decreased

*CD4/CD8 indicates the ratio of CD4+ cells to CD8+ cells in peripheral blood; Ig, immunoglobulin.

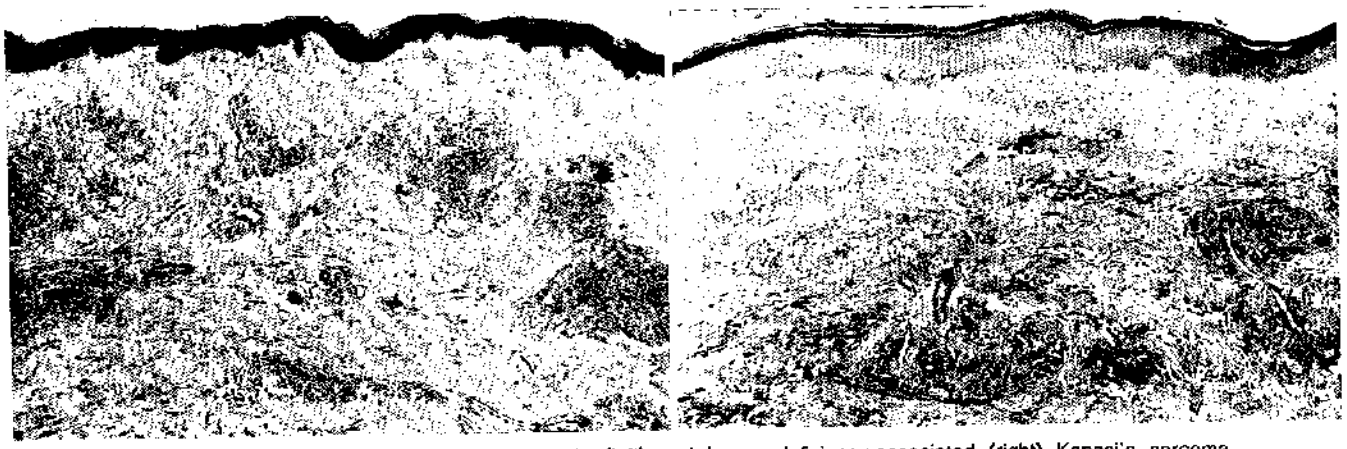


Fig 3.—One-month-old patchy lesions of classic (left) and immunodeficiency-associated (right) Kaposi's sarcoma. Moderately dense mononuclear reactive infiltrate is evident around newly formed vascular spaces in classic Kaposi's sarcoma lesion; note strikingly less pronounced reactive infiltrate and slightly increased number of spindle cells in immunodeficiency-associated lesion (hematoxylin-eosin, original magnification ×52).

nent. Hemosiderin-laden macrophages were found in many lesions. Ulceration was often seen, and granulation tissue was then found beneath ulcers.

Between these two extremities, a spectrum of variable mixtures of the histologic features already described was observed. Nevertheless, a certain degree of relationship between the clinical morphologic characteristics of the lesions and their histologic features was evidenced, in the sense that as the early lesions grew old, became enlarged or well developed and elevated, the disease activity increasingly involved the entire reticular dermis and sometimes the subcutis, showing a progressive replacement of the angiomatous pattern by the spindle cell sarcomatous proliferation. Therefore, plaque lesions were highly heterogeneous, as a typical histologic picture was not identifiable.

We were not able to find significant differences in the histologic pattern between classic and ID-associated KS lesions. In ID-associated KS lesions, however, the number of spindle cells between dermal collagen bundles was found to be slightly to moderately increased in comparison with classic KS lesions of comparable age (Fig 3).

A variable dense reactive infiltrate of lymphocytes and plasma cells, surrounding the bizarre-shaped vascular spaces, between the interlacing fascicles of spindle cells or at the periphery of the tumorous nodules, was almost always observed. Interestingly, the reactive infiltrate showed a progressive and age-related reduction in quantity in lesions older than two months, irrespective of the clinical or histologic morphologic features of those lesions (Fig 4). A crucial difference was observed between classic and

ID-associated KS lesions, ie, the latter presented with a strikingly less pronounced reactive infiltrate in comparison with classic KS lesions of comparable age (Fig 3). This was observed even in the patient who presented with no impairment of the immunologic status at the time of diagnosis.

The immunohistochemical investigation in all young lesions (less than two months old) of classic KS showed, irrespective of the clinical morphologic features (patch, plaque, and nodule), a significant reactive infiltrate that consisted of CD2+ and CD3+ cells, with a CD4/CD8 ratio ranging within normal values, and CD20+, CD22+, and polytypic sIg+ cells. These cells were seen in the close neighborhood of UEA-I+ vascular structures (Fig 5). In long-standing lesions of classic KS, which were usually plaques or nodules, T and B cells were always scarce. In all lesions from patients with ID-associated KS, only sparse CD2+, CD3+, CD8+, CD20+, CD22+, and polytypic sIg+ cells were found; CD4+ cells were virtually absent (Fig 6).

COMMENT

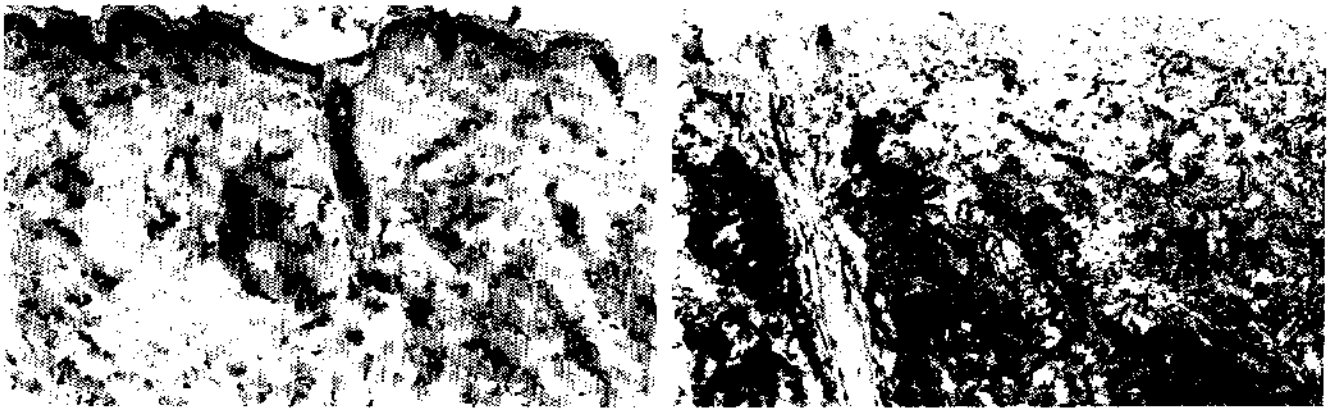
The dramatic change in the epidemiology and clinical course of KS, with its increasing incidence in ID-associated conditions, has aroused an intense interest on the part of not only dermatologists, but pathologists, oncologists, and physicians in general, as well; in particular, a heightening interest has been focused on the pathogenesis of this vascular tumor and on the similitudes and differences that exist between classic and epidemic forms.

Classic KS lesions confirmed, in this study, their highly preferential location on the lower extremities; conversely, the ID-associated lesions showed a preferential distribution on head and neck and trunk regions.[76] It is our belief that the presence of KS lesions on the upper half of the body in young adults has to be considered highly suspicious of AIDS, even in the absence of other clinical and/or laboratory signs of ID, as recently reported by Safai et al.[13]

Kaposi's sarcoma has been divided, as other cutaneous neoplasms, ie, mycosis fungoides, into patch, plaque, and nodular stages of the disease. These stages usually develop sequentially, although lesions representative of each of them can be seen simultaneously in any one patient. Plaquelike and nodular lesions, however, are more frequently observed in classic KS, probably due to its indolent course that does not alert the patient until the disease is advanced; conversely, patches represent the most like-

Fig 4.—Nodular lesions of classic Kaposi's sarcoma dating two months (left) and 11 months (right). Lymphoid infiltrate is remarkably less evident in older lesion (hematoxylin-eosin; left, original magnification ×62; right, original magnification ×50).

Fig 5.—*Ulex europaeus* agglutinin I+ vascular structures in a two-month-old classic Kaposi's sarcoma lesion (left). Numerous CD2+ T cells in same lesion (right) (immunoperoxidase, original magnification ×60).



ly lesions to be seen in ID-associated KS, due to the more rapid spread of early lesions in patients with AIDS and to the careful follow-up of pharmacologically immunosuppressed patients.

Patch, plaque, and nodular lesions have been considered expressions of the chronologic sequence of histologic appearances shown by KS; in fact, patches have been considered to represent early lesions, plaques fully developed lesions, and nodules late lesions.[27] In our opinion, KS actually represents a continuous histologic spectrum that is characterized by an early angiomatous and a late sarcomatous picture; the attempt to identify clear-cut histologic stages of the disease may be misleading, this even in light of the lack of a strict relationship between the clinical morphologic features of the lesions and their histologic aspect.[28]

In our cases, the histologic features were rather similar in classic and ID-associated KS, leaving aside the lymphoplasmacellular reactive infiltrate. In classic KS, its presence and amount could not be related to the clinical or histomorphologic features of the lesions, while it was related to their age, showing a progressive decrease after two months from the onset. In ID-associated KS, the reactive infiltrate was always strikingly less pronounced than in classic KS lesions of comparable age. Moreover, it was characterized by the virtual absence of CD4+ cells, even in patient 11 with no detectable impairment of the absolute number of circulating CD4+ cells, of the CD4/CD8 ratio, and of other immunologic parameters at the time of diagnosis.

We could not confirm the crucial importance of the presence of plasma cells around newly formed vessels as a subtle clue to the diagnosis of the early patch stage of KS[18,27,28]; in fact, in our experience, as in the experience of others,[22] they were a minor finding in ID-associated KS, which represents the instance in which young, early lesions are more likely to be observed.

Because our cases of AIDS-associated KS were always limited to the skin at the time of the investigation, we could not verify the observation of others[10] concerning a difference in the amount of lymphocytes identifiable in cutaneous lesions, according to the presence or absence of visceral dissemination of the disease, with a larger number of T lymphocytes having been observed to surround the tumor in skin-limited disease. However, we did not find a large number of T lymphocytes surrounding the tumor in any of our specimens; therefore, we are led to consider the presence of a consistent reactive infiltrate in specimens of AIDS-related KS limited to the skin as questionable.

The occurrence of KS in recipients of renal transplants and patients who receive immunosuppressive therapy, and the regression of neoplasia when immunosuppressive therapy is stopped, suggest that defective immune regulatory circuits may be crucial to the development of this neoplasm.[1,4] The recent findings of Bencini et al[31] in a group of patients who received kidney transplant gave further support to this thesis, and the progressive reappearance of the inflammatory reaction that they found in resolving KS lesions after immunosuppressive therapy was stopped provides important supporting evidence for a certain role of SALT in the pathogenesis of this form of KS.

The results of our study confirmed the concept that a measurable loss of circulating T- and B-cell functions is not a prerequisite for the development of KS in HIV-positive patients, probably because the level of ID needed for this tumor to arise is not measurable with the current laboratory assays.[13,17]

In our experience, the cutaneous immune response to the tumor in ID-associated KS is modified and reduced at the very beginning of the disease, even before the onset of any laboratory sign of ID. This evidence, along with the reduction in the number of Langerhans' cells in the epidermis in HIV-positive patients,[32] is indicative of a specific impairment of SALT. In fact, Langerhans' cells, which could be one of the primary targets of HIV possibly due to their CD4 antigen

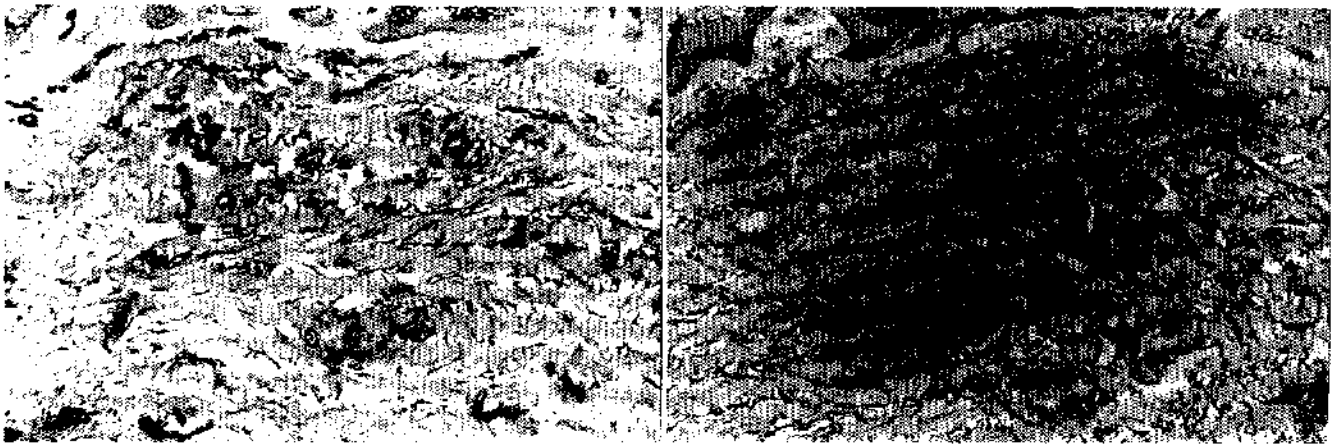


Fig 6.—Two-month-old acquired immunodeficiency syndrome-associated Kaposi's sarcoma lesion (patient 11). *Ulex europaeus* agglutinin I (UEA-I+) vascular structures (left) with absence of CD4+ cells (right) (immunoperoxidase, original magnification ×60).

expression,[33] are the antigen-presenting cells for the T lymphocytes that preferentially recirculate through the skin. Therefore, their decrease and their defective antigen presentation[34] could account for the absence of CD4+ T-cell proliferation, which, in turn, leads to further deficiency.[10]

A specific impairment of SALT may be a prerequisite for a viral-dependent endothelial proto-oncogen stimulation[35] and/or a release in tissues and circulation of some angioplastic factor(s)[20]; this release, in patients with AIDS, may represent a response to HIV viremia or HIV cell infection, with this speculation being at least, in part, supported by the discovery of endothelial cell growth-promoting activity in cell lines infected with human T-cell lymphotropic II.[36] The cellular proto-oncogen activation and/or the production of growth factor-like substances might lead to the onset of the multicentric angioproliferative process that progresses slowly until laboratory-detectable ID supervenes. In fact, the presence of normal absolute numbers of circulating lymphocytes, the CD4/CD8 ratio, and other immunologic parameters have prognostic value in AIDS-associated KS; these patients have a more stable and less aggressive disease.[13,17] However, this status has to be considered limited in time, and when a frank ID becomes detectable, a characteristic clinical evolution has to be expected.

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