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Disseminated Kaposi's Sarcoma in Homosexual Men

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Nineteen cases from an epidemic of disseminated Kaposi's sarcoma in homosexual men were studied by clinical, virologic, immunologic, and genetic methods. The patients were all male homosexuals ranging in age from 29 to 52 years, with histories of multiple sexually transmitted diseases and exposure to both prescription and recreational drugs. Sites of disease included skin (16 of 19 patients), lymph nodes (13 patients), gastrointestinal tract (12 patients), spleen (three patients), and lung (one patient). Most patients had elevated levels of serum immunoglobins, positive antibody titers to hepatitis A and B virus, cytomegalovirus and Epstein-Barr virus, and impairment of cell-mediated immunologic reactions. The frequency of HLA-DR5 in these patients was significantly elevated. Two of the 19 patients died. Although the precise cause of this epidemic is unknown, it is likely that a genetic predisposition, an acquired immunoregulatory defect, and one or more infectious agents and drugs may be involved.

UNTIL RECENTLY, Kaposi's sarcoma was a tumor rarely seen in North America or Europe, with a reported annual incidence of 0.02 to 0.06 per 100 000 (1, 2). The disease occurred most often in persons aged 50 years and older with a man to woman ratio of 10 to 1 (3). The classic form of the disease, first reported in 1872 by Kaposi (4), presents with a localized, nodular tumor, ranging in color from blue to purple, on a lower extremity. The tumor is relatively sensitive to radiation or chemotherapy and survival has been in the range of 8 to 13 years (3). A more disseminated, lymphadenopathic, and rapidly fatal form of Kaposi's sarcoma occurs in equatorial Africa, primarily in black boys and young men and, less frequently, in women (5, 6). Kaposi's sarcoma accounts for approximately 9% of all cancers in that region (3). Kaposi's sarcoma has also been reported in patients having renal transplants, in patients with lupus erythematosis receiving immunosuppressive therapy, and in patients treated with corticosteroids for other diseases (7-11).

In the 2-year period before January 1981, an epidemic involving 73 homosexual men with a disseminated type of Kaposi's sarcoma had been reported to the Centers for Disease Control. These patients had been seen primarily in New York and California (12, 13); the 19 patients we describe here were in this group. The clinical features, natural history, and mortality of the disease in homosexuals are similar to the lymphadenopathic form of Kaposi's sarcoma seen in Africa and in immunosuppressed renal transplant patients (14-16).

We report our findings, including clinical features, virologic, immunologic, and genetic studies on 19 previously undescribed cases of disseminated Kaposi's sarcoma in homosexual men. All of these patients were evaluated prospectively at New York University Medical Center between 1 May 1981 and 1 September 1981.

Materials and Methods

Complement fixing antibody titers for cytomegalovirus were ascertained using patients' sera as previously described (17); cytomegalovirus strain AD 169 was used. Serum antibodies to Epstein-Barr viral capsid antigens were quantitatively tested by the indirect immunofluorescence technique. Eight-well microscope slides containing the acetone-fixed Epstein-Barr viral capsid antigen positive T 3 HR 1K Burkitt's lymphoma cell line were used (Litton Bionetics Inc., Kensington, Maryland) (18-19). Hepatitis B surface antigen (HBsAg), hepatitis B IgG antibody (anti-HBs), and hepatitis A IgG antibody (anti-HAV) measurements were done by radioimmunoassay (20, 21). For comparison, the sera of non-homosexual patients with the classic, indolent form of Kaposi's sarcoma were used for cytomegalovirus and Epstein-Barr viral antibody studies.

Complement (C3 and C4) and immunologlobulin levels were measured using radial immunodiffusion kits (Kalestad Labs, Inc., Chaska, Minnesota; and Meloy Labs, Springfield, Virginia, respectively). Measurements of rheumatoid factor were done

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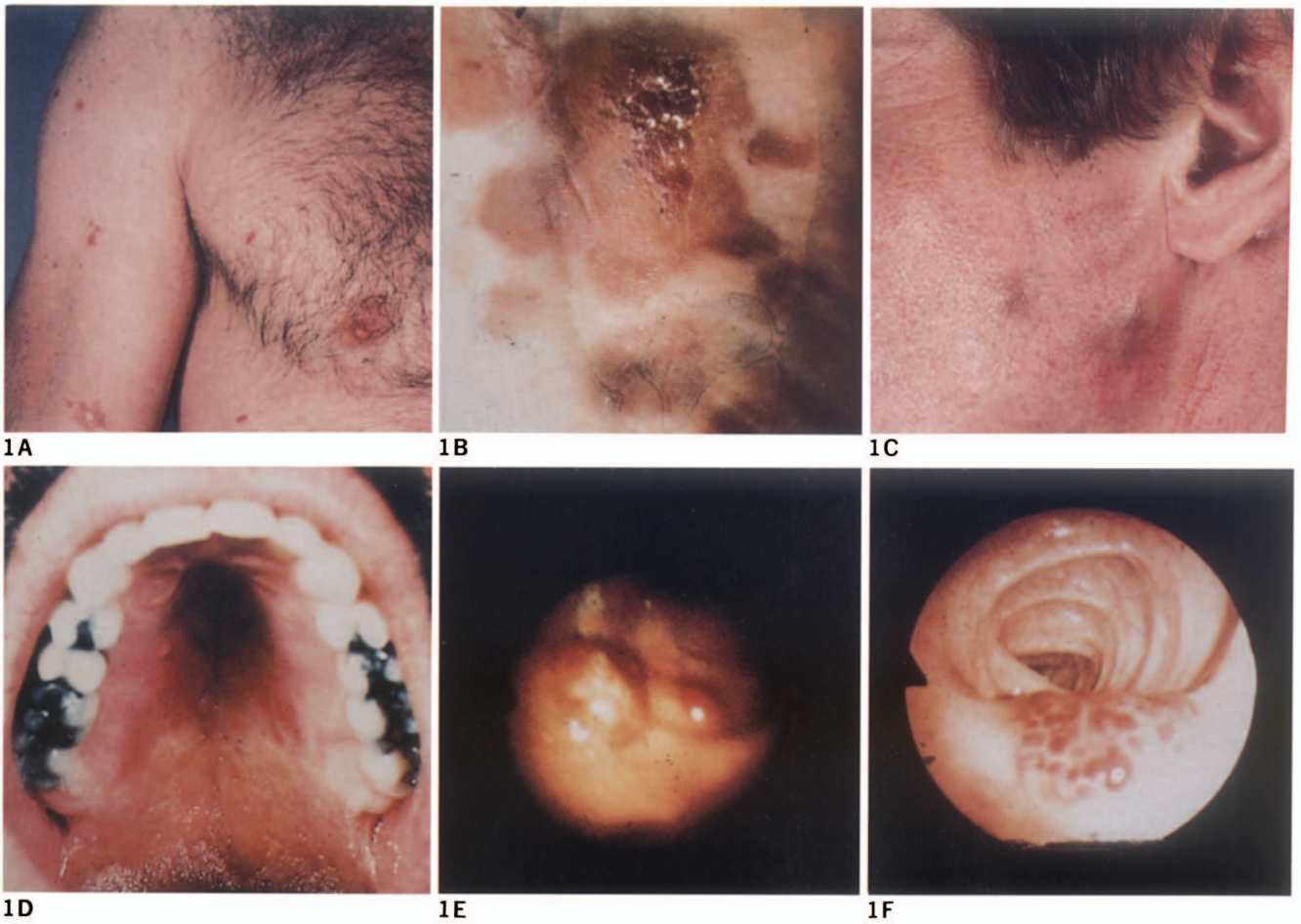

Figure 1A. Multiple flat and some elevated pink-red macules were spread over the skin of the entire body. The lesions varied from 2 mm to 1.5 cm in diameter. **B.** A slightly elevated red-brown plaque surrounded by an area of hyperpigmentation, localized on the sole of the foot. **C.** Nodular violaceous lesion, 6 mm to 8 mm in diameter, located on the left side of the face. **D.** A flat, deep purple submucosal lesion on the hard palate. Other similar lesions were on the gingiva, soft palate, and base of the tongue or posterior pharynx. **E.** A purple-red submucosal elevated nodule on the lining of the stomach, photographed during endoscopy. Nodules varied from 2 mm to 1 cm in diameter. **F.** Typical purple nodules in clusters, as seen on colonoscopy. Individual lesions varied in from 2 mm to 1.5 cm in diameter.

using the RA-test Reagent Kit (Hyland Diagnostics, Deerfield, Illinois) (22).

For cellular immune studies, mononuclear cells from 30 mL of heparinized or acid citrate dextrose peripheral blood were taken by centrifugation over Histopaque 1077 (Sigma Chemical Co., St. Louis, Missouri) (23). T and B lymphocytes were counted using the E rosette method and by direct immunofluorescence, respectively (24). T cell subtypes were distinguished by indirect immunofluorescence, microscopically, using the monoclonal antibodies OKT4 and OKT8 (Ortho Pharmaceuticals, Raritan, New Jersey) (25-29). The Mann-Whitney *U*-value test was used for statistical analysis of these data because of the apparently non-normal distribution of the results.

Leukocyte responses to pokeweed mitogen and phytohemagglutinin (Gibco, Grand Island, New York) were ascertained using 2×10^5 mononuclear cells suspended in 0.2 mL RPMI-1640 medium (Gibco) supplemented with 5% heat-inactivated human AB serum, 2 mmol glutamine, 200 U/mL penicillin and 50 μg/mL streptomycin. Cells were cultured with no mitogen, with 0.1 to 10 μg/well of phytohemagglutinin or with 0.1 to 0.5 μL/well of a 1 to 20 dilution of pokeweed mitogen stock solution prepared according to manufacturer's specifications. For mixed lymphocyte cultures, RPMI-1640 medium was supplemented with 10% heat-inactivated human AB serum, glutamine, HEPES (N-2-hydroxy-ethyl-piperazine-N'-2-ethane sulfonic acid), and antibiotics. Each patient's cells were tested as both responders and stimulators in unidirectional mixed lymphocyte culture with mononuclear cells from three DR-typed normal persons. Fifty thousand responder mononuclear cells were incubated for five days in round-bottomed wells of microtiter plates with 5×10^4 irradiated stimulator mononuclear cells in a total volume of 0.1 mL. At the end of incubation, tritiated thymidine, 0.5 μCi, was added; after an additional 12 hours, the contents were harvested with an automatic harvester and counted in a liquid scintillation counter. All tests were done in triplicate.

Tests for a total of 52 discrete human leukocyte antigens (HLA-A, B, C, and DR) were done using a set of 180 mono- or oligo-specific antisera. For HLA-DR, the serum set used was able to discern antigens 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 and the supertypic specificities MT1, MT2, and MT3. Also, a pattern of reactivity detecting the cross-reactive form of antigens DR4 and DR5 was used. All tests were done with a modified microcytotoxicity test of the National Institutes of Health using the contrast fluorescence test (30) and the two-color fluorescence test (31) for HLA-A,B,C, and DR typing, respectively. Other genetic marker phenotypes, Factor B of the alternative pathway of complement activation, glyoxalase 1, and the third component of the complement were ascertained by conventional techniques (32-34).

Results

CLINICAL FEATURES

Of the 19 patients studied, eighteen were exclusively homosexual, and one was bisexual. Their ages ranged be-

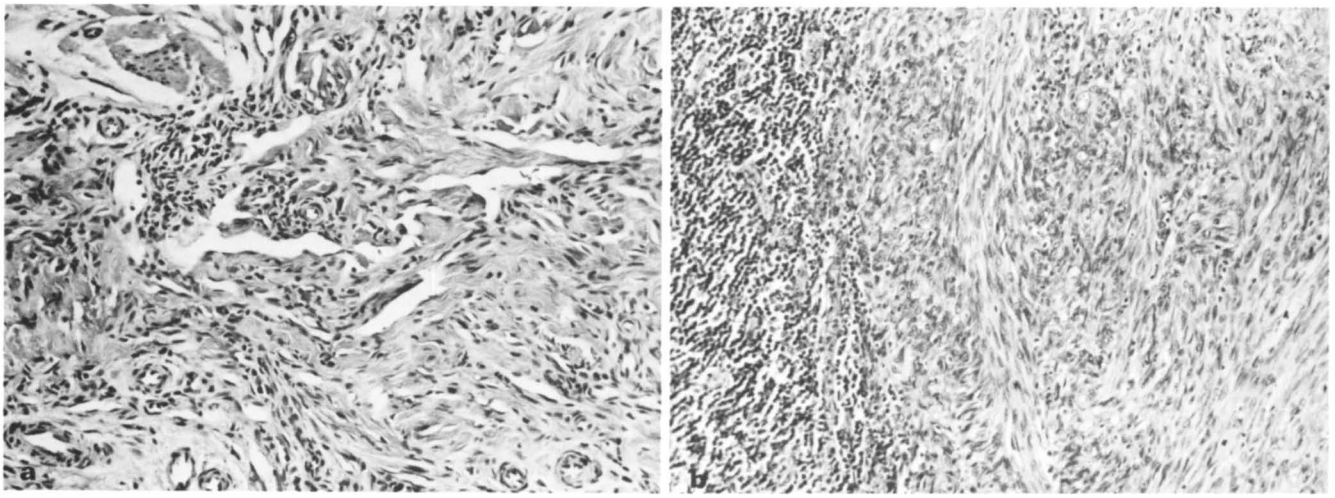

Figure 2a. A cutaneous plaque of Kaposi's sarcoma with irregular blood vessels. There were also increased numbers of spindle cells and a patchy mononuclear cell infiltrate containing plasma cells. Mitotic figures are absent, and nuclear atypia of the spindle cells and the endothelial cells lining the irregular spaces is minimal. (Hematoxylin and eosin; original magnification, × 172.) **b.** Kaposi's sarcoma in a lymph node. The normal lymph node architecture is largely effaced and replaced by a nodule composed of interweaving fascicles of spindle cells. This lesion is identical to the typical nodular cutaneous lesions of Kaposi's sarcoma. (Hematoxylin and eosin; original magnification × 180.)

tween 29 to 52 years (mean, 39.9 years). More than 50% of the patients were younger than 34 years at the time of diagnosis. The mean duration of symptoms was 6.6 months before diagnosis with a range of 1 to 24 months. The ethnic background of the patients was diverse: four of the patients were Italian, three were Jewish, one was black and American Indian, two were hispanic, and the remaining nine were of Northern European origin. Fever greater than 38 °C orally for 3 or more weeks, not associated with an identifiable, infectious agent, was present in 42% of the patients. In general, patients with constitutional symptoms had more extensive disease.

Skin lesions were the most frequent presenting complaint. They ranged from faint pink to red macules or papules only a few millimeters to 1.0 cm in size. Other lesions were slightly elevated plaques or nodules ranging in color from blue-purple to red-brown and differing in size from 4 mm to 2.5 cm (Figure 1A, B, C). Three patients had Kaposi's sarcoma in the lymph nodes without skin lesions. One patient had a single, violaceous 1.5 cm plaque on the left forearm as the only identifiable site of disease. The remaining 15 patients had different numbers and types of skin lesions widely distributed over their body. A representative histopathologic section of a plaque-type lesion is shown in Figure 2a.

Thirteen patients had generalized lymphadenopathy at presentation. Lymph nodes were not tender, firm or rubbery to palpation, usually discrete but sometimes matted together, and ranged in size from 0.5 cm to 4 cm in diameter. A representative histopathologic section of a lymph node involved with Kaposi's sarcoma is seen in Figure 2b.

In more than half the patients studied, Kaposi's sarcoma lesions were found in one or more sites along the gastrointestinal tract. In three patients, submucosal lesions ranging in color from red to purple were seen on the gingiva, hard palate, soft palate, base of the tongue, or posterior pharynx (Figure 1D). Endoscopy and colonoscopy showed small, telangiectatic, flat or slightly papular, red to blue lesions in the esophagus, stomach, duodenum, or colon. These lesions would not have been found with routine gastrointestinal contrast studies (Figures lE, F). Three patients had splenomegaly when first examined. One of these had a splenectomy confirming Kaposi's sarcoma involvement.

At the first examination, two patients had reticulonodular pulmonary infiltrates as shown by chest roentgenogram. One of these patients had Kaposi's sarcoma lesions in the lung that resolved after chemotherapy with doxorubicin, bleomycin, and vinblastine. The second patient with pulmonary disease was diagnosed by bronchoscopy and biopsy results to have *Pneumocystis carinii* pneumonia that improved after treatment with trimethoprim-sulfamethoxazole and pentamidine. This patient died of refractory amebic colitis several months later during chemotherapy with doxorubicin, bleomycin, and vinblastine. Three additional patients, also taking doxorubicin, bleomycin, and vinblastine, developed *P. carinii* pneumonia. The pneumonia resolved in two of these patients but one died. No evidence of residual Kaposi's sarcoma was found in the autopsy results. A detailed report on the results of chemotherapy trials in these patients and others is in preparation.

DRUG USAGE AND HISTORY OF SEXUALLY TRANSMITTED DISEASES

Patients reported the use of a wide variety of recreational drugs on an occasional or regular basis. All of the patients had used amyl or butyl nitrite inhalants, most had used cocaine, and all had smoked marijuana. Other drugs had been used with lesser frequency (Table 1).

The number of patients who had one or more episodes of the following sexually transmitted diseases within the past 10 years were as follows: gonorrhea, 16; hepatitis B, 15; syphilis, 14; amebiasis, 12; condyloma acuminata, eight; herpes simplex progenitalis, five; giardia lamblia,

Table 1. Reported Usage of Recreational Drugs

Drug	Patients
	n (%)
Alcohol	19 (100)
Marijuana	19 (100)
Nitrite (amyl, butyl, or both)	19 (100)
Cocaine	18 (95)
LSD	12 (63)
Amphetamines	10 (53)
Methaqualone	10 (53)
Tobacco	8 (42)
Ethyl chloride	7 (37)
Phencyclidine ("angel dust")	6 (32)
Mescaline	4 (21)
Tetrahydrocanabinol (THC)	2 (11)
Hashish	2 (11)

four; and lymphogranuloma venereum, one. The drugs reportedly taken for treatment of amebiasis included metronidazole, diiodohydroxyquin, paramycin sulfate, and quinacrine hydrochloride. A case-control epidemiologic study is currently in progress to delineate the significance of these data.

VIRAL AND RELATED SEROLOGIC STUDIES

Cytomegalovirus was cultured from the urine of three of 11 patients with Kaposi's sarcoma. Complement fixing antibody titers greater than or equal to 1:32 were found in 79% of the homosexual patients with disseminated Kaposi's sarcoma. None of the patients with classic Kaposi's sarcoma had complement fixing antibody titers greater than or equal to 1:32 (Table 2). The difference between the group of homosexual patients with Kaposi's sarcoma and the non-homosexual patients with the classic form of Kaposi's sarcoma is statistically significant ($p < 0.001$ using Fisher's exact test). As listed in Table 3, unusually high Epstein-Barr virus antibody titers (greater than or equal to 1:1280) were found in 16 of 18 homosexual patients with disseminated Kaposi's sarcoma. In patients with the classic type of Kaposi's sarcoma, titers of this level were seen in only two of eight patients. The difference between these groups was significant ($p < 0.003$ by Fisher's exact test). For hepatitis viruses, types A and B, 15 of 18 patients tested had antibodies against HBsAg. None of these patients were found to be HBs antigen positive. Thirteen of 15 patients had anti-HAV.

SEROLOGIC AND CELLULAR IMMUNE STUDIES

Serum immunoglobulin levels in all but one patient showed an elevated concentration of at least one class of immunoglobulins (Figure 3). Immunoelectrophoresis showed these increases to be polyclonal. Serum complement levels (C3 and C4) were found to be within normal limits (Table 4). Rheumatoid factor was absent. Sixteen of the 19 homosexual patients with Kaposi's sarcoma were anergic to all intradermal testing with antigens that included purified protein derivative of tuberculin, streptokinase-streptodornase, *Candida*, and *Trichophyton*. The other three patients did not react to tuberculin but had some reactivity to one or more of the other antigens.

The data in Table 4 indicate that homosexual patients with Kaposi's sarcoma had low-normal to normal levels of circulating leukocytes and lymphocytes. The percent of circulating B and T cells in all patients was normal. The absolute number as well as the percent of helper/inducer T lymphocytes (staining positively with the OKT4 monoclonal antibody) was decreased by 2.4 fold ($p < 0.001$ by two-tailed Mann-Whitney *U*-value test). The absolute number as well as the percent of suppressor/cytotoxic T lymphocytes (staining positively with the OKT8 monoclonal antibody) was increased two fold ($p < 0.001$ by two-tailed Mann-Whitney *U*-value test). Thus, the ratio of helper to suppressor lymphocytes was decreased by 4.8 fold ($p < 0.001$ by two-tailed Mann-Whitney *U*-value test).

In-vitro studies of pokeweed mitogen and phytohemagglutinin-induced lymphocyte proliferation showed a twofold to fivefold decrease in ^{3}H-thymidine incorporation by lymphocytes from Kaposi's sarcoma patients compared to lymphocytes from normal controls ($p < 0.001$ for both by two-tailed paired Student's *t*-test). When cells from homosexual patients with Kaposi's sarcoma were cultured as responder cells in mixed lymphocyte culture with irradiated stimulator cells from healthy persons in mixed lymphocyte culture, the response was decreased to 42% of control values ($p < 0.001$ by two-tailed paired Student's *t*-test). When patients' cells were used to stimulate cells from normal persons, a normal response was obtained ($p > 0.4$ by two-tailed paired Student's *t*-test).

IMMUNOGENETIC STUDIES

Frequencies of HLA-DR antigens in patients with Kaposi's sarcoma and control subjects are summarized in Table 5. A significant increase in the frequency of DR5 was found in these patients when they were compared to 231 healthy, non-homosexual controls as well as to a group of 26 homosexual persons from the same community. Sixty-three percent of Kaposi's sarcoma homosexual patients and 62% of non-homosexuals with classic Kaposi's sarcoma had the DR5 allele. The increased incidence of DR5 in these patients over the normal population was significant even after correction for 52 antigens ($p < 0.01$) for patients with Kaposi's sarcoma, regardless of whether they were homosexual or not. These figures show a relative risk of 5.57 (method of Woolf) of

Table 2. Cytomegalovirus Antibody Titers in Homosexual Patients with Disseminated Kaposi's Sarcoma and in Non-Homosexual Patients with Classic Kaposi's Sarcoma

Cytomegalovirus Antibody Titers*	Homosexuals	Non-Homosexuals
	n (%)	*n* (%)
<1:4	1 (5)	1 (10)
1:4 to 1:16	3 (16)	9 (90)
1:32 to 1:128	9 (47)	0 (0)
1.256 to 1:1024	6 (32)	0 (0)
Mean titer†	1:112	1:11

* Detected by complement fixation.
† The difference between the two groups is $p < 0.001$, by Fisher's exact test.

Table 3. Epstein-Barr Virus Antibody Titers in Homosexual Patients with Disseminated Kaposi's Sarcoma and in Non-Homosexual Patients with Classic Kaposi's Sarcoma

Epstein-Barr Virus Antibody Titers*	Homosexuals	Non-Homosexuals
	n (%)	*n (%)*
1:160	0 (0)	4 (50)
1:320	0 (0)	2 (25)
1:640	2 (11)	0 (0)
1:1280	9 (49)	1 (12)
1:2560	5 (28)	0 (0)
1:5120	2 (11)	1 (12)
Mean titer†	1:1650	1:375

* Detected by indirect fluorescence against viral capsid antigen.
† The difference between the two groups is $p < 0.003$, by Fisher's exact text.

possessing the DR5 allele once the diagnosis of Kaposi's sarcoma has been made. The apparent reduction in the frequency of DR3, and the apparent increase of DR6 were not significant after statistical correction and will be verified by typing further patient samples. No significant differences were noted for HLA-A, B, or C alloantigens in either patient group. In the patients with Kaposi's sarcoma, factor B of the alternative pathway of complement activation, glyoxalase 1, and the third component of complement phenotypes did not show significant variations in frequencies or HLA association.

Discussion

This report describes our findings in 19 patients with an apparently new, epidemic form of widely disseminated and rapidly progressive Kaposi's sarcoma. In contrast, patients with the localized classic form of Kaposi's sarcoma seen in Europe and North America usually only have involvement of the skin on a lower extremity and the disease runs an indolent course. The aggressive form of Kaposi's sarcoma seen in our patients more closely resembles the disseminated form that has been described in equatorial Africa and in some renal transplant patients and other persons receiving immunosuppressive therapy.

Our patients shared a number of distinctive characteristics: they were all young homosexual men, highly sexually active, with histories of many sexually transmitted diseases and use of both prescription and recreational drugs. Although the patients appeared clinically to be immunosuppressed and had impaired cell-mediated immune reactions, their serum antibody titers reflected an active humoral immune response to various viruses. The frequency of HLA-DR5 was significantly increased in these patients. Four patients acquired *P. carinii* pneumonia during the course of their illness. One patient died as a result of this opportunistic infection. A second patient died of amebic colitis.

Because the cutaneous lesions of these homosexual patients with Kaposi's sarcoma look different from the skin lesions seen in classic Kaposi's sarcoma, they have sometimes been overlooked or misdiagnosed. The early skin lesions may be confused with bruises, ecchymoses, nevi, insect bites, dermatofibromata, secondary syphilis or lichen planus. Some early lesions, especially in dark-skinned persons, are hyperpigmented. In light-skinned patients, early lesions are violaceous and may become hyperpigmented after several months. In a few patients, no skin lesions are present at the initial examination but appear later in the course of the disease.

The recent appearance of this disease may be associated with the changes that have occurred over the last 15 years in the lifestyle of homosexual men living in large urban centers. There has been a marked increase in gay bathhouses, bars, and meeting places where multiple, anonymous sexual encounters occur. This has been reflected in a marked increase in the incidence of sexually transmitted diseases: not only syphilis and gonorrhea but also amebiasis, giardiasis, Epstein-Barr virus, and cytomegalovirus infections. Use of multiple recreational drugs, especially the inhalation of amyl and butyl nitrite, available through nonprescription sources, is also an important aspect of this changing lifestyle.

The appearance of Kaposi's sarcoma in young homosexual men coincides with outbreaks of *P. carinii* pneumonia and other opportunistic infections in the same population (36-39). An interplay of factors is probably important in the occurrence of all of these diseases. From the available studies, the strongest link between homosexual patients with opportunistic infections and homosexuals with Kaposi's sarcoma is their abnormal immunologic status. This suggests that a factor or factors deregulating the immune response may be important in the development of these diseases. A clue to understanding the mechanism underlying the immune abnormalities may be provided by the type of immunologic impairment seen. Although these patients have impaired cell-mediated immune responses, they are able to produce high titers of anti-viral serum antibodies. Their immunologic profile, therefore, is characterized by suppression of the cellular arm of the immune response, although the function of the humoral arm of the immune response is unaffected or

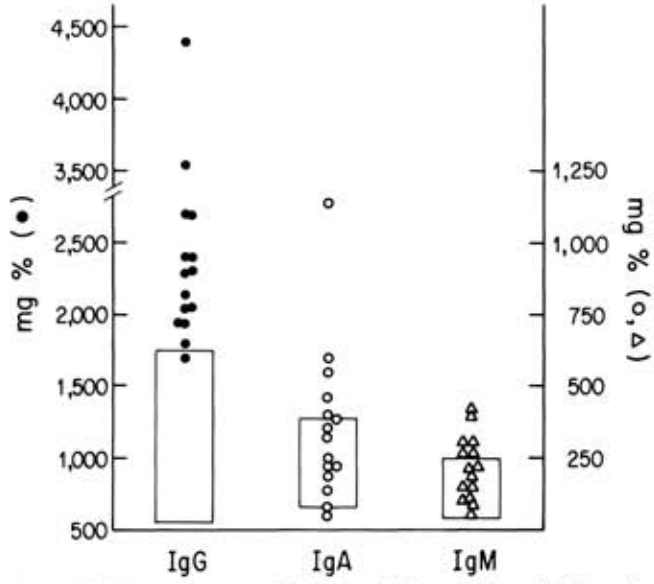

Figure 3. Serum immunoglobulin levels in patients with Kaposi's sarcoma. Levels of IgG, IgA, and IgM were measured by radial immunodiffusion. The boxes denote levels of these proteins in the serum of normal persons.

Table 4. Immunologic Findings on Homosexual Patients with Disseminated Kaposi's Sarcoma*

Test	Normal Control Subjects	Homosexuals with Kaposi's Sarcoma
Mean leukocyte count, *cells/mm³ ± SD*	6800 ± 3200†	5035 ± 1674 [*n* = 17]†
Mean peripheral blood lymphocyte count, *cells/mm³ (range)*	2100 (500-4700)†	1955(680-3976) [*n* = 17]
Serum complement levels, *mg/dL*		
C3	86-244†	133 (112-170) [*n* = 7]
C4	15-66†	28 (15-33) [*n* = 7]
T lymphocytes in peripheral blood, %	60 (38-75) [*n* = 10]	56 (37-70) [*n* = 17]
B lymphocytes in peripheral blood, %	9 (3-14) [*n* = 10]	8 (3-16) [*n* = 16]
OKT4 (T helper/inducer) lymphocytes in peripheral blood, %	48 (35-59) [*n* = 10]	20 (1-43)§ [*n* = 17]
OKT8 (T suppressor/cytotoxic) lymphocytes in peripheral blood, %	27 (19-39) [*n* = 10]	54 (34-71)§ [*n* = 17]
Ratio of OKT 4/OKT 8 cells in peripheral blood	1.9 (1.0-3.3) [*n* = 10]	0.4 (0.03-1.1)§ [*n* = 17]
Mitogen-induced transformation		
Phytohemagglutinin, *counts/min*	87 190 (40 150-169 460) [*n* = 9]	43 345 (4717-102 691)§ [*n* = 18]
Pokeweed mitogen, *counts/min*	43 253 (17 444-114 881) [*n* = 9]	9669 (1134-43 845)§ [*n* = 18]
Reactivity in mixed lymphocyte culture‖, %		
As responders	100	42 ± 39§, [*n* = 12]
As stimulators	100	84 ± 55§, [*n* = 12]

* Presented in part to National Cancer Institute workshop on Kaposi's sarcoma in homosexual men, 15 September 1981.
† Ascertained on 100 normal donors or normal values used at the New York Veterans Administration Medical Center.
‡ *n* = number of patients.
§ $p < 0.001$.
‖ Each patient was tested with three normal controls.

enhanced. A similar picture has been found in recent immunologic studies of apparently healthy homosexual men matched by age and race to our patients with Kaposi's sarcoma (40). Thus, there is strong evidence to indicate that defects in immunoregulation may predispose to the development of Kaposi's sarcoma and opportunistic infections in homosexual men. The reason for this finding is, as yet, undetermined; various infections and extensive drug use may be involved.

All patients described here had a history of multiple viral, bacterial, fungal, or parasitic diseases. It is possible that a single type of infection, a particular combination of infections, or the antigenic load presented by the multiple infectious agents may represent an immunologic insult that could overload or overstimulate the immune system. Other investigators have speculated about the immunosuppressive role of cytomegalovirus infections in these patients (37-39). Although cytomegalovirus infection causes transient immunosuppression during the acute and early convalescent phases of infection (41), 90% of homosexual men have positive antibody titers for cytomegalovirus (42), making the role of this agent difficult

Table 5. HLA-DR Antigenic Frequencies in Patients with Kaposi's Sarcoma

DR Antigen	Homosexuals with Kaposi's Sarcoma (*n* = 19)	Non-Homosexuals with Classic Kaposi's Sarcoma (*n* = 13)	Control A* (*n* = 26)	Control B† (*n* = 231)
	← % →			
1	16.6	31	8	10
2	16.6	31	35	25.1
3	5.4	8	12	20.3
4	22.2	8	23	23.4
5	63.0‡§	62‖¶	23	23.4
6	27.6	8	23	14.7
7	11.0	8	23	20
8	0	0	0	3.5

* Control A = randomly selected homosexual men from New York City.
† Control B = normal white population from New York City.
‡ $X^2 = 8.06$ versus Control A ($p < 0.005$).
§ $X^2 = 14.69$ versus Control B ($p < 0.001$).
‖ $X^2 = 9.85$ for all Kaposi's sarcoma patients versus Control A ($p < 0.005$).
¶ $X^2 = 21.72$ for all Kaposi's sarcoma patients versus Control B ($p < 0.001$); relative risk = 5.57 (method of Woolf).

to establish. Antibody titers to Epstein-Barr virus are also very high. Although an etiologic link has not been established, the levels of serum antibody to Epstein-Barr virus suggest, at the least, a reactivation of latent viral infection (43-44).

In addition to the development of Kaposi's sarcoma and opportunistic infections in previously healthy homosexual men, there is now a report of several cases of autoimmune thrombocytopenic purpura in this population (45). If immunoregulatory abnormalities are at least partially responsible for the development of these diseases, then the probability exists that an increased incidence of other autoimmune diseases and malignancies, particularly of the lymphoid system, may appear in this population.

The involvement of the HLA-DR5 allele is of special interest because we have found an increased incidence of this allele in both homosexual and non-homosexual patients with Kaposi's sarcoma (Table 5). It is also noteworthy that DR5 has its highest frequencies in blacks (18% to 50%), Italians (35.8%) and Jews (34% to 39%) (46), groups with the highest prevalence of classic Kaposi's sarcoma (1, 2). It is possible that genetically predisposed persons, who become immunosuppressed by any of several means, are particularly susceptible to the development of this malignancy.

Previous studies of HLA types in neoplastic diseases have been unrewarding. An association was reported between Burkitt's lymphoma and HLA-DR7 in studies of Ghanaian patients (47); however, it was barely significant ($p < 0.05$) after correction for seven antigens. A tenuous association was also found between the occurrence of testicular carcinoma and DR7 (48). With a $p < 0.01$ after correction for 52 comparisons, the association between Kaposi's sarcoma and DR5 appears to be the strongest evidence in humans for the involvement of the major histocompatibility system with susceptibility to a particular type of cancer. The possible participation of viruses in the pathogenesis of Kaposi's sarcoma and the evidence of immunoregulatory abnormalities in these patients suggest that specific immune response genes, in linkage disequilibrium with DR5, may be involved.

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