Kaposi's Sarcoma: A Review and Recent Developments

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Introduction

Kaposi's Sarcoma (KS) is a potentially interesting model of a virus-associated human cancer. The special geographical distribution and the cluster occurrence associated with this disease indicate the possible involvement of genetic, environmental, and infectious factors. In view of the rarity of familial cases and the lack of consanguinity, its high incidence in endemic areas and in certain ethnic groups presents a challenging question to our understanding of the disease. While these observations mitigate against a simple Mendelian dominant or recessive inheritance, they do not negate the possibility that there may be a genetic predisposition to the disease.

The possible role of environmental factors in KS poses another intriguing question for investigators: are these likely to influence the development and course of the disease through the effects of nutrition, repeated infections, and other insults?

Kaposi's sarcoma is unique in that the lymphadenopathic type of the disease occurs only in African children; in other parts of the world, children—and adults—do not develop this form of KS.

Exciting new information has resulted from electron microscopic studies of KS in tissue cultures and seroepidemiologic analyses. These have revealed that a specific association exists between cytomegalovirus (CMV) and KS. This is interesting, given that the geographical distribution of KS in Equatorial Africa is similar to that of Burkitt's lymphoma—a malignancy closely linked to Epstein-Barr virus (EBV).

Our own observations and those of others clearly show a high incidence of second primary cancers, particularly lymphoreticular neoplasms in KS patients. This close association of lymphoreticular neoplasms and KS suggests that a tumor inducer or promoter continues to operate in these individuals, and that the etiopathogenic mechanisms of lymphomas and KS are either common to both or are closely linked in a similar manner.

That disturbed immunity plays a role in the pathogenesis of KS has been suggested by reports of patients who developed KS while on immunosuppressive therapies. Furthermore, a decreased immune responsiveness has also been observed in these patients.

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Historical Perspective

Kaposi's sarcoma was first described as "multiple idiopathic pigmented hemangiosarcoma" by the Hungarian physician, Moricz Kaposi, in 1872. He reported the disease to be a rare, chronic, cutaneous disorder of adult men which manifested as multiple vascular nodules. He was, however, aware of the multifocal nature of the disease, the occurrence of visceral involvement and the usually fatal outcome. All three men he described in his initial report died within three years of diagnosis.[1] Now considered to be a multicentric, malignant, neoplastic process, KS manifests as multiple vascular tumors which are composed of proliferating connective-tissue cells and capillary vessels.

Incidence

As recently as 1953, KS was considered a rare disease; at that time, the combined American and European literature contained less than 500 cases.[2] Most of these were in patients originating from Eastern Europe, Italy, or Russia. In 1960, Dutz and Stout reported over 1,200 cases, most of them in persons located in Central and South Africa.[3] Several other large series which have been reported on[4-8] indicate that KS is usually found in areas of endemic disease, including Equatorial Africa, Eastern Central Europe, Italy, and North America.[5,6,9-15]

The International Union Against Cancer Meeting on KS held in Kampala in 1962 concluded that KS constitutes nine percent of all cancers seen in Uganda,[16] indicating that the disease is most frequent in Equatorial Africa. The geographical distribution of KS among the native residents of Equatorial Africa is reminiscent of African Burkitt's lymphoma.[9,10,12,16] The annual incidence of KS in the United States is reported to be 0.021[5] to 0.061 per 100,000 population;[17] it is seen mostly in persons of European descent, but has been observed even in three patients of pure Eskimo heritage.[18]

A male predominance has been observed, with a ratio of approximately 10 to 15 men to one woman.[5,7,8,17] Kaposi's sarcoma usually occurs in adults, especially in later life. A high incidence is also observed among black children in Africa where the disease manifests as generalized lymph node involvement.[3,19]

The rarity of familial cases, even in the areas considered endemic, is of special interest.[5,7,11,20] Between 1908 and 1955, only six instances of families with multiple cases of KS had been found,[5] and since then only two other familial cases have been reported.[20,21] In a review of 96 documented cases of KS seen at this center between 1949 and 1975, only one instance of multiple cases in a family was noted. This was in two brothers (J. Digiovanna and B. Safai, unpublished material).

Clinical Features

Kaposi's sarcoma usually presents as dark blue to reddish-purple macules, plaques, or nodules. The lesions are commonly located on the extremities, most often on the feet, but may appear anywhere in the skin or even in the mucous membranes. Lymph nodes and internal organs may also be involved.[9,10,17,22] Edema of the lower extremities may precede or follow the appearance of the tumor, indicating infiltration of the tumor into the superficial and deep lymphatics. The lesions may coalesce to form large plaques or tumors which may become eroded, ulcerated, or fungating. New lesions may appear along the superficial veins. Regression of these tumors may occur; this is ascribed to either thrombosis of the lesions or to immunologic reactions.[8,11,22] The disease may appear initially in organs rather than in the skin, and metastatic dissemination has also been reported. Visceral involvement is the pattern most commonly seen in African children in whom lymphadenopathy is the main clinical feature.[3,19]

The natural course of the disease ranges from slow and indolent to rapid and fulminant, with metastatic dissemination. Average survival time in the American series is reported to be eight to 13 years; however, there are also a number of reports of spontaneous regressions and survival up to 50 years in the literature.[5-8,10,11,22]

TABLE 1
CLASSIFICATION OF
KAPOSI'S SARCOMA[10]

Clinical type	Behavior	Age	Bone involvement	Lymph node involvement	Predominant skin lesions
Nodular	Indolent	>25	Rare	Rare	Nodule, plaque
Florid	Locally aggressive	>25	Often	Rare	Fungating exophytic
Infiltrative	Locally aggressive	>25	Always	Rare	Diffuse infiltration
Lymphad-endopathic	Disseminated aggressive	<25	Rare	Always	Rare

Because of the diversity of the clinical and histopathologic manifestations of KS, it has been difficult to establish a reproducible classification. The one proposed by Taylor and colleagues in 1971 appears to be more comprehensive than the earlier ones[8,19] as it covers all aspects of the disease (Table 1). It accounts for clinical presentation, course and biological behavior of the disease, frequency of extracutaneous disease, and response to therapy. It also correlates well with the histopathology.

The four clinical types (Figs. 1–3), which have been well identified in African cases, are not as easily recognized in European and North American patients. Ulcerated and verrucous lesions are less frequent in cases reported by Rothman (1962)[6] as compared to those observed in Africans. Several other variations have been reported. There is an increased incidence of second malignancies in European and American cases,[8] a very high incidence of KS in Uganda,[5,10] and a reversal of sex ratio among KS cases in the white populations in South Africa and Algeria.[11,16,23]

Histopathology

The disease process is believed to start in the mid-dermis and extends upward toward the epidermis. Histopathologic features of KS (Fig. 4) consist of interweaving bands of spindle cells and vascular structures embedded in a network of reticular and collagen fibers. The vascular component may appear as cleftlike spaces between the spindle cells or as delicate capillaries. Lymphocytic infiltration may be present, especially in earlier lesions. Extravasated erythrocytes and hemosiderin-laden macrophages are commonly present. Spindle cells may show a wide range of

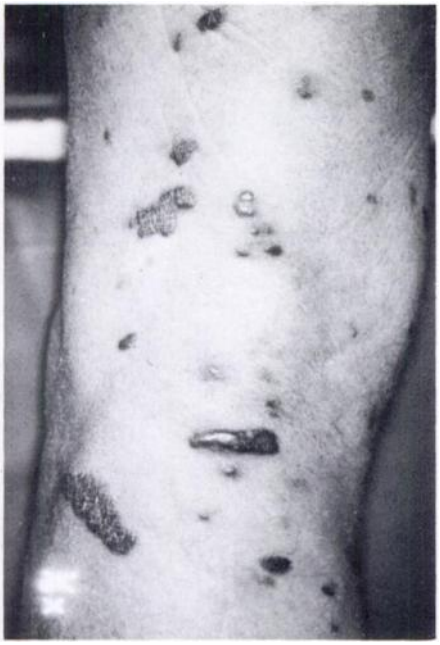

Fig. 1 Nodular lesions on the right upper extremity.

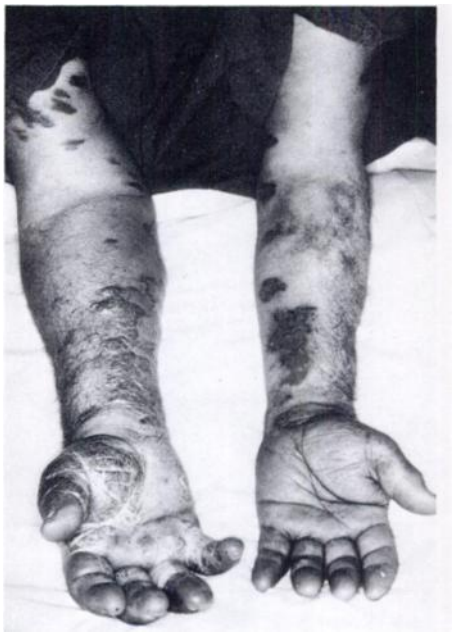

Fig. 2 Infiltrative tumor resulting in swelling of the hand and arm.

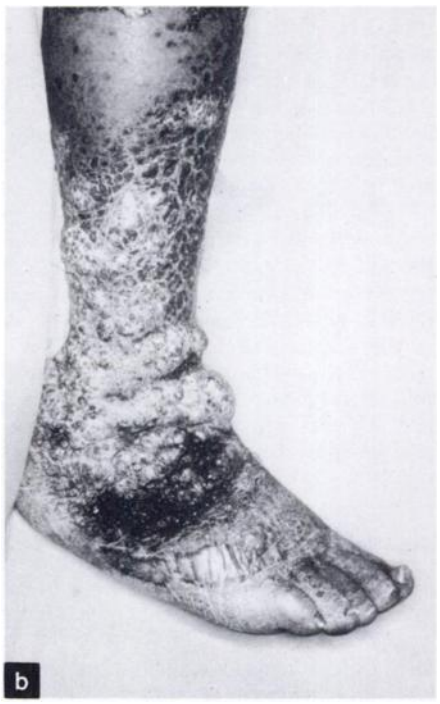

Fig. 3 a and b Florid tumor on the lower leg and dorsum of the foot.

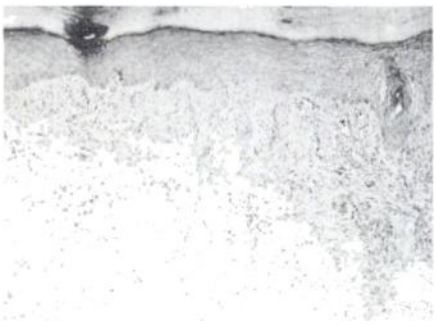

Fig. 4 Photomicrograph showing histopathologic features of Kaposi's sarcoma.

nuclear pleomorphism. The pathologic lesions are often found along the veins. The histopathology of KS in lymph nodes and viscera is similar to that seen in skin.

Based on the variations in the quantity of the vascular component, the presence of spindle cells, fibrosis, and nuclear pleomorphism in the tumor, three basic histologic patterns of KS have been described.[8,10] These include: (a) a mixed cell pattern consisting of equal proportions of spindle cells, vascular slits, and well-formed vascular channels; (b) a mononuclear pattern characterized by proliferation of one cell type, usually spindle; and (c) an anaplastic pattern featuring cellular pleomorphism and frequent mitosis. While the mixed cell pattern is seen in all four clinical types, it appears most frequently in the nodular, florid, and lymphadenopathic forms. The mononuclear pattern may also be seen in the nodular, florid, and infiltrative forms. The anaplastic pattern has only been observed in the florid type.

The Cell of Origin

The origin and nature of the cell or cells involved in KS are as yet unknown. While several different origins have been postulated, histochemical staining, ultrastructural examinations, and cultural studies have yielded only controversial results so far. Based on histochemical and electron microscopic studies, Repler, in 1959, proposed a neural origin, and suggested that either Schwann cells or modified nerve cells from the glomus are proliferating malignantly in this disease.[24] Becker, in 1962, also suggested that the cell most likely involved in KS is the Schwann cell.[25] Also, on the basis of histochemical and electron microscopic studies, Hashimoto and Lever, in 1964, suggested that KS is derived from the malignant deviation of a vascular cell.[26] Mustakallio and his coworkers considered that the cell of origin in KS is a multipotent, primitive, mesenchymal cell.[27] There is also speculation that the KS cell may originate from the perithelial or endothelial cells of small vessels.[28] A reticuloendothelial origin for the KS cell was first considered by Dorfell in 1932.[29] Dayan and Lewis, using silver impregnation techniques, also concluded that KS is derived from reticuloendothelial tissue.[30]

The concept of the reticuloendothelial origin of KS is strongly supported by the increased association of KS with other lymphoreticular neoplasms as well as by the similarities between KS and Burkitt's lymphoma. Nevertheless, confirming evidence for this concept is still to come. The use of specific cellular markers in defining the cell of origin in KS will be crucial, as will efforts to cultivate the KS tumor in privileged sites such as the anterior chamber of the eye of the nude mouse or in cyclophosphamide-treated or splenectomized nude mice.

Etiology

The cluster distribution of KS in endemic areas suggests that hereditary, infectious, and environmental factors play a role in the etiology of the disease. The absence of consanguinity and the infrequency of familial KS argues against a simple Mendelian dominant or recessive inheritance. Studies of the genetic makeup in KS patients and their relatives using the major histocompatibility antigens may shed light on this. Environmental factors may play a role through the influence of nutrition,

infection, or other as yet unidentified factors. The incidence of KS among certain South African Bantus is reported as 10 times higher than that seen in the white population in the same geographic area.[5] The cultural differences that exist between the two populations may be of significance; however, this observation argues against environmental or geographic factors as sole etiologic agents.

The high incidence of KS in areas where the disease is endemic suggests a possible infectious etiology, but evidence for this was not available until the report by Giraldo and colleagues in 1972. Their electron microscopy studies demonstrated herpes type virus particles in tissue culture cell lines developed from African cases of KS.[31] Subsequently, they showed an apparent serologic association between CMV and KS in African and European[32] as well as in North American[33] patients. They observed the lack of such association between KS and herpes simplex virus types I and II or EBV. Although the serologic analyses suggest a close association between KS and CMV, they do not establish the role of CMV as an etiologic agent of the disease. They seem to indicate, however, that, as with EBV in nasopharyngeal carcinoma and Burkitt's lymphoma, continuing infection with CMV is a common concomitant of KS.

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In the light of the distribution of KS in Equatorial Africa, which is geographically similar to that of Burkitt's lymphoma—closely related to EBV—the serologic association of KS and CMV becomes especially interesting. Epstein Barr virus, which is closely associated with both Burkitt's lymphoma and nasopharyngeal carcinoma,[34-37] and CMV infections have much in common. Primary infection by either of these viruses may cause a self-limiting lymphoproliferative disease in adolescents and young adults.[38-40] Transforming capabilities have been demonstrated by both viruses.[41] However, EBV has a special cell tropism primarily affecting B lymphocytes and nasopharyngeal epithelial cells, both of which bear receptors for the virus; CMV has a much broader range of cell tropism affecting lymphocytes, granulocytes, phagocytes, as well as epithelial cells and fibroblasts.[42,43] It has been reported that Burkitt's lymphoma is associated with continuing acute infection with EBV, and that children with persistent EBV infection may develop this disease.[44] Similarly, evidence of continuing infection with EBV is present in patients with nasopharyngeal carcinoma, and evidence of a continuing infection with CMV fits the serologic observation in KS.

It is conceivable, therefore, that similar events in CMV-infected subjects may result in the development of KS. Some experimental work using CMV-infected adult mice supports this view.[45,46] Primary CMV infection has been shown to follow latency, and to be reactivated by allogeneic stimulation. Genetic susceptibility and immunologic responsiveness are among the factors influencing the progression of these events.

It has been postulated that in KS patients, most of whom are adults, heavy and persistent infection followed by frequent reactivation may occur as a consequence of repeated or continuous antigenic stimulation which, in turn, leads to an increased synthesis of defective viruses.[33] These events have been demonstrated in experimental systems by infecting cells *in vitro* at high virus multiplicity.[47] It has also been shown that defective herpesviruses (types I and II), as well as CMV, may maintain their transforming ability.[41,48-50] It is likely that under these circumstances, these viruses, even though they are defective, retain oncogenic potential in individuals with certain genetic and immunologic backgrounds. The high incidence of KS in some ethnic groups,[6,9,16] and the immunologic disorders observed in KS patients,[51-55] may be compatible with the view that both genetic and immunological perturbations can play a role in this disease.

The Immune System

Several recent reports have suggested that reduced immunity may play a role in the development and course of KS.[56-58] Klein and coworkers reported in 1974 on the occurrence of KS in a patient with systemic lupus erythematosus (SLE) during immunosuppresive therapy.[56] An increased incidence of KS has also been reported in patients with disorders of the immune system such as immunodeficiencies, plasma cell dyscrasia, thymoma, or polymyositis.[58-63] Also in 1974, Myers and coworkers observed two cases of renal transplant recipients who developed KS during the course of immunosuppressive therapy.[57] The KS nodules regressed when immunosuppressive therapy was tapered down or discontinued. Several other reports also emphasize this correlation between the immunodeficiency states and the development of KS.[64-67]

It has been speculated that activation of an oncogenic virus during periods when immunosurveillance mechanisms are suppressed may result in the development of KS.[58] Suppression or breakdown of the immunosurveillance mechanisms secondary to the natural course of the disease as a reflection of iatrogenic influences such as chemotherapy may allow a malignant clone of cells to emerge and multiply. The

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increased incidence of *de novo* cancers, particularly of the skin, uterus, cervix, and lymphoreticular system in renal transplant recipients, as well as the high occurrence of certain neoplasms in patients with immunodeficiency diseases,[68,69] may be taken as evidence for relating immunodeficiency with the pathogenesis of certain cancers.

The diversity of the clinical and histologic features observed in KS patients may represent interactions between host immune responsiveness and the degree of the antigenicity of the tumor. This concept is supported by the work of Master and coworkers (1970) which demonstrated severe impairment of delayed hypersensitivity reactions to dinitroclorobenzene (DNCB) in patients with the florid (malignant) type of KS. In contrast, normal responsiveness was observed in patients with the more benign nodular form of KS.[51] Similar correlations between cell-mediated immunity and the clinical morphology of the disease have been described by Taylor and his coworkers.[52,54,55] Using *in vitro* lymphocyte blastogenic responsiveness to stimulation by autologous tumor cells, they showed much stronger responses in patients with nodular and infiltrative types of KS than in patients with the florid type who often had either decreased or no responses to these stimuli. It has been postulated that the childhood form of KS (lymphadenopathic) may similarly reflect an unidentified impairment of the immune system. Other immunologic studies, such as assays of lymphocyte function measured by lymphocyte transformation in response to CMV, and assays of antibody-mediated cytotoxicity and natural killer cell activity, may be revealing.

Association with Other Cancers

An unusually high incidence of second primary cancers has been observed in patients with KS.[6,16,70,71] There is a particular increase of lymphomas and leukemias in these patients. In a retrospective study of 92 KS patients seen during the period of 1949 to 1975 at Memorial Hospital, we observed that 37 percent developed other primary malignancies.[71] We also noted a 20-fold increase in the incidence of lymphoreticular neoplasms in these patients as compared to the incidence expected in the general population. In an analysis of second primary cancers, we found only eight percent in our series of patients with double primaries (excluding KS) to have lymphoreticular malignancies, while the corresponding figure for KS patients was 58 percent. The underlying reason for this association is not yet well understood. It can be postulated that KS and lymphoreticular neoplasms coexist or occur in the

same patients because these two types of tumors share tumor inducers or tumor promoters. Our observations and those of others suggest a related etiopathogenic mechanism for KS and lymphoreticular malignancies.

Several reports indicate that transitional stages exist between KS and lymphoreticular cancers.[30,72-75] Confirmation of these observations using more recently available technology is needed. It has been suggested that the coexistence of KS and lymphoreticular malignancies in a given patient is not a true example of multiple primary cancers, but is rather an expression of the pleomorphism of a single malignant process involving the lymphoreticular system. If this is correct, the cell of origin in KS may arise from transformation of one of the cells of the lymphoreticular system. It is now commonly proposed that KS be considered, along with leukemia and lymphoma, as part of a spectrum of disease affecting the lymphoreticular system.

Certain similarities exist between KS and some of the lymphoreticular cancers. As was discussed earlier, Burkitt's lymphoma is strongly associated with EBV, while KS is shown to be related to CMV. The geographical distribution of KS in Equatorial Africa also closely simulates that of Burkitt's lymphoma. Both KS and Hodgkin's disease have variable clinical courses as well as pleomorphic, histologic pictures, and both are usually responsive to chemotherapy and radiation therapy. Although the basis for these similarities remains unclear, they suggest common characteristics and, perhaps, common pathogenesis.

Conclusions

Since it was first described in 1872, KS has presented challenging questions to physicians and investigators. The possible influence of infectious, genetic, or environmental factors in KS is suggested by the cluster distribution of the disease; this has been recognized only during the past two decades. The infrequency of familial KS and the lack of consanguinity noted argue against a genetic origin as the sole factor involved. Investigation of the role of major histocompatibility antigens in KS is needed and might reveal a genetic influence.

There are already strong indications for the seroepidemiologic association of CMV with KS. Further work is necessary to fully determine the roles of CMV and environmental factors in the pathogenesis of this disease. The rarity of familial cases suggests that even if the disease does involve an infectious agent, it is not contagious as such, but is a result of multiple factors at work. An appealing view is that a slow-growing virus infecting individuals with a particular genetic or immunologic makeup, or both, may lead to their developing KS.

Although the basic process underlying the close association of KS with other cancers is still unknown, this finding suggests related etiopathogenic mechanisms. The association of KS especially with lymphoreticular malignancies suggests that common factors may be operating in a susceptible host, and that there may be shared tumor inducers or promoters in each of these several diseases.

The nature and origin of the cell involved have not been established. Cultivation of KS tumors in immunodeficient laboratory animals seems to offer a logical approach to providing evidence of the neoplastic nature of the disease and for selecting out which is the actual malignant cell.

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Decreased immune functions and impaired immunosurveillance in individuals with a certain genetic makeup and exposure to certain environmental agents may trigger the process whereby KS cells develop and expand. Thus, further investigations into the possible participation of altered immune functions in the development of KS may help toward an understanding of this unusual disease.

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MEASURING THE COST OF BASIC RESEARCH

The political ambience of our time compels the scientific community to seek firm grounds for receiving a share of public resources. It might be far more realistic, however, as well as useful, for all parties to agree that, after all, we really can't measure these things with any precision and that the most difficult segment to measure, basic research, isn't so expensive that we can't afford to run on the principle that it should be kept reasonably plump.

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