

Kaposi's Sarcoma and HIV

E. PAPADOPULOS-ELEOPULOS, V. F. TURNER* and J. M. PAPADIMITRIOU†

*Department of Medical Physics and *Emergency Department, Royal Perth Hospital, Wellington St, Perth, Western Australia 6001, †Department of Pathology, University of Western Australia (Reprint requests to EPE)*

Abstract—Recently published informed debate affords strong indication that in patients with the Acquired Immune Deficiency Syndrome, HIV cannot, directly or indirectly, be the cause of Kaposi's sarcoma. This paper provides reasons for disallowing a current alternative theory that Kaposi's sarcoma is due to an unidentified sexually transmitted infectious agent and proposes instead that Kaposi's sarcoma is the result of prolonged and repeated exposure to nitrites and/or semen. If this alternative hypothesis is strengthened by confirmation of its predictions then the relationship of HIV to Kaposi's sarcoma, one of the principal AIDS-associated diseases, becomes somewhat remote. This may facilitate a shift of emphasis and encourage the development of alternative therapies.

A theory is a good theory if it satisfies two requirements: It must accurately describe a large class of observations on the basis of a model that contains only a few arbitrary elements, and it must make definite predictions about the results of future observations.
STEPHEN HAWKING

Introduction

In spite of the passage of more than a century since Kaposi's original description, Kaposi's sarcoma (KS) remains enigmatic with its precise nature in doubt. Recently even its classification as a malignant neoplasm has been questioned and John Brooks, a pathologist from the University of Pennsylvania, has argued that KS is a 'benign potentially reversible hyperplasia that may at times terminate in true malignancy' (1).

Summary of KS sub-types

Kaposi's sarcoma is classified on the basis of pathological, clinical and epidemiological descriptions (2). Epidemiologically Kaposi's sarcoma occurs as 'Sporadic', 'Endemic', 'Iatrogenic' and 'Epidemic' disease with obvious major differences between these sub-groups. The 'Sporadic' type has a predilection for Italian and Ashkenazy Jewish males over the age of 60 years (although in a series from the Armed Institute of Pathology published in 1959 22% of the patients were black (3)). This sub-type of KS is associated with a near normal life span. However, some cases exhibit the aggressive form and there are cases occurring in younger patients under the age of 45 years (4).

The 'Endemic' group, which constitutes the highest caseload in the world, occurs in eastern equatorial

Africa. Here KS affects young adults (25–45 years of age) and children between the ages of 2 and 15. Any of the clinical patterns may occur in this group and there is an appreciable incidence of the generalized variety in the young adults and children, most of whom die within 2 years of diagnosis (5). Prior to the AIDS era 'iatrogenic' KS accounted for approximately 15% of all cases enumerated in Europe and North America (2). These were associated with immunosuppressive agents administered to organ transplant recipients or to patients with other diseases. The incidence of post transplant KS in the United States is 0.18–0.3% of all transplant patients while interestingly the incidence in Saudi Arabia is considerably higher at 5.3% (2). Penn, who reported a series of 68 post organ transplant cases from the USA, considered that 72% were 'benign' (skin and mucosa involved) and 28% malignant (gastrointestinal and respiratory involvement) (2). The reason why KS and also lymphomas occur in these patients while there is no increased incidence of the common epithelial neoplasms is unclear. However, in a comprehensive review of this subject, published in 1982, Kinlen discounted failure of immune surveillance and argued the case for a specific viral-related effect in the pathogenesis (6).

In the early 1980s the Centre for Disease Control (CDC) in Atlanta, USA observed a high frequency, 26 cases by July 1981, of KS occurring in young homosexual men (4). Eight of these patients died within 24 months of diagnosis. Thus was ushered in 'Epidemic' KS, that associated with the Acquired Immune Deficiency Syndrome (AIDS). In addition to KS many of these original patients also had opportunistic infections and in four a diagnosis of *Pneumocystis carinii* pneumonia (PCP) was made by open lung biopsy. At this very early stage in the evolution of the syndrome, AIDS, for all practical purposes, consisted entirely of KS and PCP. In 1982 Robert Gallo, who had spent many years researching retroviruses and cancer at the National Cancer Institute, proposed that the cause of AIDS was a retrovirus (7). In 1983 Luc Montagnier and fellow researchers at the Pasteur Institute detected a retrovirus, presently known as Human Immunodeficiency Virus Type I (HIV-1), in the cultured T cells from a homosexual patient with lymphadenopathy (8). With few exceptions (9, 10), the hypothesis that the causative agent of AIDS is HIV has been universally accepted. However, as early as 1984 it became apparent that HIV does not exist in the cells from the lesions of KS and hence cannot cause KS directly (11). It was assumed then, that in AIDS patients, HIV indirectly caused KS and opportunistic in-

fections by its detrimental effects on the immune system. Alterations in T lymphocyte subsets (T4 and T8 cells) and a decrease in the T4/T8 ratio were believed to be the hallmark of AIDS and the immune deficit that defined this condition (7). However, in heterosexuals, evidence existed that many diverse causes could be associated with the same (and additional) laboratory abnormalities of immunodeficiency that were manifest in AIDS patients. These causes included a number of infections (12), blood transfusion (13), the intake of many drugs including antibiotics (14) and even solarium exposure (15). It is noteworthy that in none of these reports was there a single case of associated KS.

Conversely, some researchers at the time were of the opinion that KS could result from immunostimulation with angiogenesis-promoting factors formed as a result of alterations in immunoregulation, a mechanism that had been earlier suggested in patients receiving immunosuppressive therapy (16). As recently as 1988 researchers from the Walter Reed Army Institute of Research, disallowed KS from the definition of AIDS stating that, 'in our system the presence of opportunistic infection is a criterion for the diagnosis of AIDS, but the presence of Kaposi's sarcoma is omitted because the cancer is not caused by immune-suppression' (17). Most recently data has been published confirming the fact that in some homosexuals KS can occur in the complete absence of both immune deficiency and HIV (18). Thus neither HIV nor immune deficiency is a prerequisite for the development of this disease, at least in homosexuals.

Despite all this uncertainty, acceptance of HIV as the cause of Kaposi's sarcoma prevailed for over 6 years until early 1990 (19). In January of that year Valerie Beral and her colleagues from the CDC published a paper (20), in which they concluded that 'Kaposi's sarcoma in persons with AIDS may be caused by an as yet unidentified infectious agent transmitted by sexual contact'. This argument was based on the epidemiological spectrum of KS in different AIDS risk groups and the fact that in homosexuals KS may appear in the absence of HIV. This conclusion, to which we cannot accede, is based on the authors' assumptions that:

- a. 'The agent that causes Kaposi's sarcoma must be the same irrespective of whether there is any associated HIV infection'. (Implying that KS in all individuals, homosexual or heterosexual, African or European, black or white, is caused by one and the same agent.)
- b. The agent is infectious but is not HIV.

Before this theory becomes accepted and as a necessary overture to our own hypothesis, we will present evidence that:

- a. There is no need to assume that the same causative agent is responsible in all cases of KS regardless of age, race or geographic region.
- b. The assertions upon which Beral and her colleagues base their infectious theory are themselves only hypotheses which their various authors acknowledge as being largely unproven and have even suggested alternative explanations.
- c. There are plausible explanations for the apparent correlation between sexual activity and KS in homosexuals other than sexual transmission of an infectious agent.

Common aetiology

It is inconsistent with current knowledge of other neoplasms to assume that KS is exceptional by having a single cause in all individuals. At present it is well recognised that many neoplasms have multiple aetiologies. One may also argue that, since the precise cause of most if not all neoplasms is unknown, it is impossible to state with any certainty that a particular type has only one definite aetiology.

Infectious aetiology

Beral derives support for an infectious origin of KS from the following data:

1. The massive increase in KS in AIDS patients—'at least 20 000 times more common in persons with AIDS than in the general population and 300 times more common than in other immunosuppressed groups'.
2. The fact that 'few known human carcinogens increase the risk by more than 100 fold and, in the best documented example, hepatitis-B and hepatoma, the cause of the cancer is an infection'.
3. In immunosuppressed subjects such neoplasms 'may have an infectious cause' (20).

However a high incidence of a relatively rare disease in a confined population does not necessarily indicate an infectious origin. Malignant mesotheliomas are exceptionally rare in the general population, approximately one case per million (21). However, in a study published in 1988 of a cohort of individuals employed by the Australian Blue Asbestos Company that

operated in Wittenoom in Western Australia, there were 33 deaths from mesothelioma recorded. Even though this study grossly underestimates the incidence of mesothelioma, it still reveals a greater than 5000 fold risk of dying from this disease in these individuals (22). Asbestos, a non-infectious agent, has been accepted as the major causal factor in this condition. In another study of 2271 deaths of insulation workers who came into regular contact with asbestos the cause of death in 175 was mesothelioma, an incidence of 7706 in 100 000 (8%) (23). The risks quoted in these studies are considerably higher (50 and 800 times) than that associated with hepatitis-B referred to by Beral.

The data concerning hepatitis-B virus (HBV) and hepatoma were taken by Beral et al from a paper by Beasley et al (24). This paper describes a prospective study of 22 707 male civil servants from Taiwan where it was found that 'the incidence of primary hepatocellular carcinoma (PHC) among carriers of hepatitis-B surface antigen (HBsAg) was much higher than among non-carriers (1158/100 000 vs 5/100 000)'. These authors put forward the hypothesis that hepatitis-B virus has a primary role in the aetiology of PHC, an hypothesis that so far has not been conclusively proven. The authors themselves state:

'alternative explanations of the very high relative risk among HBsAg carriers are that HBV is a cofactor with another aetiological agent or is simply a risk factor. Case control studies have repeatedly shown that PHC does occur in HBsAg negative subjects. This finding can be taken to mean either that HBV is not sufficient to cause PHC or that there are several independent causes'.

The authors also refer to the geographical correlation between the amount of aflatoxin in food and the incidence of PHC that occurs in Africa. They postulate that a similar relationship may exist in Taiwan but also point out that, due to the eclectic nature of the Chinese diet, there are insurmountable difficulties in studying this particular factor. In support of their argument Beral et al also refer to a review paper published by Kinlen in 1982 (6). This paper is cited as showing that the increase in KS in immunosuppressed patients is caused by an infectious agent. However the substance of Kinlen's review is to:

1. Acknowledge the appreciable increased incidence of non-Hodgkins lymphomas, primary hepatocellular carcinoma, melanoma and KS in immunosuppressed individuals.
2. To refute the immune surveillance hypothesis of carcinogenesis by pointing to the fact that these

same individuals do not share an increased incidence in the common epithelial neoplasms.

3. To argue, without any convincing proof, a role for ultraviolet light in the skin cancers, HBV in hepatocellular carcinoma, Epstein-Barr virus (EBV) for lymphoma and cytomegalic inclusion virus (CMV) for Kaposi's sarcoma.
4. To speculate that antigenic stimulation or even the immunosuppressive agents themselves may directly cause some of these neoplasms.

Thus Beral and her colleagues base their infectious theory of KS either on an unproven hypothesis (HBV and hepatoma; lymphomas and EBV) or on a hypothesis (CMV and KS) which they (and many others) consider to be incorrect.

Sexual transmission

Beral and her co-authors reported several interesting and relevant findings concerning the incidence of KS in the various AIDS risk groups. 40% of homosexual and bisexual men in 1985 and approximately 21% in 1988 had KS compared with approximately 1% of haemophilic AIDS patients.

The next highest incidence, 6%, was from patients born in the Caribbean and African countries but living in the USA. There were 73 cases of KS in transfusion recipients. KS was most unusual in patients less than 15 years old, occurring in 1.6% of all children with AIDS, (13 cases). All but one of these US born children with KS were children of Haitian women, the other child was born in Central America and raised in the US.

These data were interpreted as evidence that:

- i. KS is 'caused by an as yet unidentified sexually transmitted infection'.
- ii. The appearance of the agents in transfused patients older than 15 years 'may be by routes other than blood'.
- iii. The agent in children younger than 15 may be perinatally transmitted.

If the above conclusions are correct then because: (i) There is no cure for the disease; (ii) In non AIDS patients the disease is chronic, that is median survival is 8–13 years; (iii) Prostitutes have a higher frequency of all the sexually transmitted diseases especially in Africa where treatment is not readily available; one would expect a high incidence of KS in families (mother-child, husband-wife) and prostitutes. However, in Africa where it was known as far back as 1962 (5) that 'the disease occurs not uncommonly in African children in the first decade of life and is

probably much underdiagnosed', the incidence of KS in women (mothers) including prostitutes like elsewhere in the world is low, with a male to female ratio of 17:1. Among the many theories put forward before the AIDS era regarding aetiology of KS, the two most often mentioned were infectious and genetic. In order to test these theories many investigators searched for a familial incidence of KS. A very small number of cases with a familial distribution of KS were reported before the AIDS era but in none of these were sexual or mother-child relationships involved (25). Thus before AIDS there was no evidence to suggest that:

1. KS, at least in heterosexuals, is sexually transmitted,
2. The cause of KS is an infectious agent.

Even today with the exception of CMV and HIV, which are still considered by some as major aetiological factors, all the other factors considered possibly pathogenic are non-infectious (2).

Non-infectious aetiology

We hypothesize that in homosexual AIDS patients KS is caused by prolonged and repeated exposure to semen, nitrites or both agents which, under normal circumstances, in non-AIDS patients, are either absent or largely excluded from contact with endothelial targets in the vascular or lymphatic system. Both these agents are potent oxidising agents in biological systems (26, 27) and indeed oxidation is essential for many of their biological properties and effects. For example, sperm maturation (and thus fertilisation) is a process which requires the oxidation of sperm nuclear sulphhydryl groups to disulphides (28). All cells exhibit a thiol cycle and this cycle is a principal determinant of many cellular functions including mitotic rate (26). Thus nitrites and sperm, like all carcinogens and mitogens, by their oxidative nature may induce perturbation of the thiol cycle, and this effect may underlie the ample epidemiological evidence that semen and nitrites are alone the two factors highly correlated with the appearance of KS in homosexuals (29, 30).

Nitrites

Nitrites have as a major property a prominent effect on vasculature. Although the use of nitrites (poppers) is highly correlated with the appearance of KS in homosexuals, their causative role has been dismissed because of the belief that it is impossible to disentangle their use from sexual practices and also because they do not explain 'the occurrence of KS in children

and elderly people with parenterally transmitted HIV and in one-tenth of AIDS patients in Africa where nitrites cannot account for the pattern of occurrence of KS' (20). The only reason for preferring the explanation that an 'undefined' infectious factor relating to sexual behavior appears to be the cause, and not the alternative, seems to be a predisposition to favour a sexually transmitted infection. In fact in homosexuals evidence exists that the variable most strongly associated with KS is the consumption of more than four 'hits' of nitrites per night of use (30). The fact that the effects of nitrites and sexual practices are 'difficult to disentangle' does not negate the possibility that nitrites acting alone or in combination with another highly correlated variable may have a direct causal role. While it may be true that Africans do not use nitrites, it is also true that in Africans KS has existed independently of AIDS, probably for centuries and, although not disproven, an infectious origin of KS in Africa has been discounted as far back as 1962 (5). The common diagnosis of KS in African patients post 1983 as AIDS whilst 'legal' (19) is a semantic convenience with little, if any, scientific rationale, especially in relation to a putative common pathogen.

KS in children

Beral states that, in the 13 AIDS children with KS, the cases of KS were 'atypical' and admits that 'diagnostic biases might exist'. Also, because all children were from Florida where nitrite abuse is most prevalent and all but one were offspring of women born in Haiti, the possibility cannot be excluded that:

1. Some of these children may not have developed KS.
2. Children of Haitian women, most of whom are descendents of African slaves, may, like African children, have an appreciable incidence of KS that has existed independently for many decades.
3. The mothers of these children may have used nitrites.

KS in recipients of blood transfusion

A total of 73 cases of transfusion associated KS have been reported by the CDC up to 31st March 1989. In these patients not one of their sexual partners had KS. According to the CDC definition which 'accepts HIV as the cause of AIDS' KS occurring in anyone under the age of 60 years, even when laboratory evidence regarding HIV infection was either not obtained or

was inconclusive, indicates AIDS. Individuals with KS who are over the age of 60 and who have a positive antibody test are also considered AIDS patients. KS which develops in persons who received high doses or long term systemic corticosteroid or other immunosuppressive/cytotoxic therapy but which were discontinued 3 months before the appearance of the disease also indicates AIDS (19). In the US where approximately 3.8 million people are transfused annually, approximately 20% receive blood for treatment of malignant neoplasia (32).

Although exact data are unavailable it is certain that many of these patients will have received varying combinations of immunosuppressive therapy, radiation and chemotherapy, all agents known to be associated with the appearance of KS (6). It is reasonable to question whether the occurrence of 73 cases of transfusion associated KS over a period of 8 years, an average of 9 cases per year, represents a phenomenon peculiar either to the specific practice of blood transfusion or to the AIDS era. In the US the annual incidence of KS in the general population pre-AIDS is unknown but is estimated to be 0.2–0.6 cases per million (4). There are no data available on the incidence of KS in transfusion recipients pre-AIDS but these persons, 50% of whom die within 1 year of transfusion, are likely to have a higher incidence than the general population.

An incidence of 9 cases in nearly four million transfused therefore may not be significantly higher than expected since many of the post 1981 transfused group would be expected to be under the age of 60 years (and therefore fulfill the CDC AIDS definition), and/or suffering from malignancy. There has also been a well documented problem in establishing a definite diagnosis of KS in AIDS patients, a factor which relates both to diagnosis bias and histopathological interpretation (20, 32). In the absence of data to prove the contrary the low incidence of KS documented by Beral et al may simply reflect the presence, in this population, of other causes of KS which have previously operated and continue to operate independently of AIDS related factors. Also in the US there are 2.5 million exclusively homosexual males, and perhaps another 2.5–7.5 million who may have the occasional homosexual liaison (33). There are also at least 1.1 million IV drug users, 11% of whom use nitrites. Furthermore there are estimates that 1% of American students between the ages of 12–17 years of age use nitrites at least 10 times per month (34). The CDC publically accepts that this is likely to be an underestimate as not every person questioned would feel comfortable admitting to drug abuse or homo-

sexuality. We may therefore argue that since KS even post AIDS is so rarely reported in the non-homosexual non-drug abuser population that some, if not all, of the blood transfusion-associated KS cases may be related to one of the above mentioned mechanisms which include chemotherapeutic agents, radiation, semen and nitrite exposure—that is, to a cause which is not a sexually transmitted infectious agent. Even if it is true that not a single African, child or transfusion recipient is exposed to nitrites there is still no compelling evidence to exclude nitrites as a cause of KS in homosexuals since there is no proof that KS in all these groups is caused by the one and the same factor. However in the case of homosexuals with KS there is also other evidence which suggests that nitrites may be aetiological agents:

1. One of the only two factors which changed in the lifestyle of homosexuals in the late 1970s was increasing nitrite abuse (35).
2. In the early 1980s nitrite use became ubiquitous in California and New York—the two areas where the vast majority of patients with KS were found (35).
3. The latency period for the appearance of KS in patients treated with immunosuppressive drugs for organ transplantation is similar to that between homosexual exposure to nitrite and the appearance of the disease (36).
4. The decrease in the incidence of KS in homosexual men coincided with a decrease in nitrite abuse (37).
5. Nitrites and their metabolic products are mitogenic and carcinogenic (36).
6. Nitrites have major pharmacological effects on blood vessels—the site of the neoplasm—which is an unusual tissue for neoplastic transformation (38).

Sexual practices

A second factor directly relating to the development of KS is sexual intercourse. While this may suggest that the disease at least in homosexuals is caused by a sexually transmitted agent there are data available from numerous large, well designed studies that strongly support the hypotheses that semen itself has a direct causal role. All these studies have shown that in homosexuals, the only sexual act directly related to both the development of AIDS and Kaposi's sarcoma is passive anal intercourse (30, 39, 40). One can surmise from these data that if a large group of homosexuals could be studied where any individual

could be guaranteed to practise exclusively passive or active intercourse and not both, then one would observe that: (i) KS, like pregnancy, can only be acquired by the passive partner. (ii) KS, like pregnancy, cannot be sexually transmitted. As far as the cause is concerned at least two possibilities can be entertained:

1. In the passive partner KS could be caused by an infectious agent found in the ejaculate which is not bidirectionally sexually transmitted. The active partner would have to acquire the agent by other means.
2. In the passive partner KS could be caused by a non-infectious agent found in semen acting either alone or synergistically with nitrites. That this is the case is strongly supported by the following data: a) Apart from nitrite abuse the second factor which changed in the lifestyle of homosexuals in the mid 1970s was the high promiscuity rate (35). There are also many examples from clinical practice of homosexual men who admit to approximately 1000 partners per year. At 2–3ml per ejaculate this provides evidence that deposition of unusually large amounts of semen into the rectum of an individual can occur, and that as a consequence, semen may interact with and be absorbed by the intact or traumatised bowel. b) Unlike all the other sexually transmitted diseases, where the possibility of infection is directly related to the number of sexual partners, in homosexuals the number of sexual partners is only a risk in relation to the number of episodes of passive anal intercourse (40). c) Homosexuals have a relatively high incidence of gastrointestinal cancers other than KS and several researchers have implicated semen in the development of these neoplasms (41, 42). d) Reid and Coppelson described the relative high incidence of cervical cancers in promiscuous Australian women. Amongst other factors, this was attributed to semen (43). e) Spermatozoal penetration into the submucosa of the rat uterine epithelium can induce pre-cancerous changes in the cervix (44). f) In humans spermatozoa fulfil a well known mitogenic role in embryogenesis. There is also in vitro evidence that spermatozoa can penetrate somatic mammalian cells and that sperm DNA is incorporated into recipient nuclei (45). Permanent transformation occurs within a few days and this is associated with abnormalities in morphology and growth of recipient cells including the appearance of bi- and multi-nucleated cells (45, 46). g) Extracts of pooled human semen are potent promoters of

skin tumour production in the skin of mice previously treated with topical carcinogen (47). h) Injection of sperm suspensions directly into the anterior prostate of experimental rats can produce carcinoma of the prostate with metastases (48). i) Intratesticular injection of autologous spermatozoa in the rat can produce malignant testicular neoplasms (49). j) Seminal plasma is especially rich in polyamines, a group of positively charged substances which have a significant role in cellular proliferation (50, 51). Moreover in human semen the polyamine spermine is present in higher concentrations than in many other tissue or body fluid and it, like other seminal polyamines, is oxidized by enzymes derived from seminal vesicle secretion. The presence of polyamines in higher than normal concentration in malignant tissue has prompted their assay as a diagnostic aid in cancer patients and serial measurement has been suggested as a treatment marker during chemotherapy. (Interestingly it appears that polyamines are essential for optimal growth of most microorganisms and inhibitors of their biosynthesis have been successfully employed for the treatment of protozoal diseases including *Pneumocystis carinii* pneumonia (52).

Thus a mitogenic and carcinogenic effect of nitrites and semen (or their derivatives) may better account for the presently available epidemiological data on KS in homosexuals than a currently unspecified, unknown new, sexually transmitted infectious agent.

Conclusions and predictions

We present evidence that the oxidative effects of semen and/or nitrites play a pivotal role in the development of KS in homosexual AIDS patients. If anally deposited semen causes KS, we predict that case-controlled studies should show that:

1. In a group of exclusively passive homosexuals who also use nitrites, cessation of exposure to semen by the use of condoms should lead to a reduction in the frequency of KS.
2. Women who do not use drugs including nitrites but who practise anal intercourse should have a higher incidence of KS than those who do not.

If nitrites play an aetiological role in the development of KS then future observation will show that:

1. In groups of people who inhale nitrites and who have a high incidence of KS the frequency should diminish when all other factors are kept the same but nitrite inhalation is stopped.

2. In case control studies where the test population is identical in all aspects to the control population apart from inhaling high concentrations of nitrites, a high frequency of KS should be seen in the test cases but not in the controls. If anally deposited semen by itself cannot cause KS, but is an exacerbating factor when nitrites are used, then case-controlled studies should show an excess of KS in homosexuals who in addition to inhaling nitrites, practise exclusive passive anal intercourse.

Most importantly, this theory predicts that reducing agents may prevent or even ameliorate KS in homosexual AIDS patients. In this regard, the recent discovery of significant reductions in cellular reduced glutathione in AIDS patients lends strong support for contemplating such a therapeutic strategy (53, 54, 55).

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