Case
report

Kaposi's sarcoma in retrospect

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A historical overview of Kaposi's sarcoma is provided, scrutinising in particular past clinical and histological studies of the disease and the conclusions on aetiology and pathogenesis that were reached.

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Introduction

In 1997, it is 125 years since Moriz Kaposi (fig 1) described five patients with a peculiar tumour of the skin, mucous membranes, and internal organs which is nowadays referred to as Kaposi's sarcoma (KS).¹ At present, the cellular origin and pathogenesis of KS are still not fully understood.

This paper describes and clarifies the aetiological and pathogenic concepts of KS that have been contemplated in the past, starting with Kaposi's original description. The emphasis is on original studies that have used clinical and histopathological investigational tools trying to elucidate the nature of this enigmatic disease. Several distinct conceptions of KS can be differentiated and the studies have been grouped accordingly.

Neoplasm/sarcoma

Kaposi refers to the original work of Köbner, who in 1869 had discussed sarcomas of the skin

with special reference to their metastatic spread along lymph vessels.² Kaposi felt confident enough to distinguish the lesions of his five patients as a distinct entity among sarcomas of the skin, labelling them as "idiopathic multiple pigment sarcoma" (figs 2 and 3). The almost simultaneous eruption of the nodules on both feet followed by the appearance on both hands, without apparent spread along the lymph vessels, indicated, according to Kaposi, "a pre-existing systemic disease (dyscrasia)". There was no doubt in his mind that these lesions were "small cell sarcoma". The main reason for this classification he found in the microscopical characteristics of the sarcoma in two cases—namely, "nodular groups of small, round cells in the dermis, small haemorrhages in these nodules and an abundance of pigmentation".

De Amicis (cited by Ronchese, 1958) in 1882 added his own observations about the regression of individual nodules, and the prolonged course of KS which was thought to contradict the neoplastic nature of KS.³ However, Kaposi attributed the regression of individual nodules to reactions in the surrounding stroma when exposed to multiple haemorrhages. It was because of the latter that he proposed the term "sarcoma idiopathicum multiplex haemorrhagicum" instead of the adjective "pigmentosum" which had also created confusion with "melanosarcoma" (that is, melanoma).⁴

Funk gave an elegant description of the clinical forms of sarcomata of the skin.⁵ These consisted of a macula or a flat papule out of which later forms developed, such as nodules, tumours, diffuse infiltration of the skin, and subcutaneous nodules. This progression of lesions with increasing severity of skin involvement together with the observed infiltration of the dermis with "spindle-shaped cells" corroborated the true sarcomatous character of KS.

The simultaneous and sometimes acute eruption of skin nodules together with regression of older lesions were suggestive of a chronic infection. Bernard supported this by his observation that areas most distant to the heart, with diminished circulation, were always involved. He speculated further that this "chronic infection" induced vessel dilatation, extravasation of white blood cells, and neoplasia of perithelial cells which transformed into spindle cells and frank sarcoma.⁶

Pick saw the sequence of events in KS as an

Figure 1 Moriz Kaposi (1837-1902). (Kindly provided by Professor K Holubar, Institut für Geschichte der Universität Wien.)

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Figure 2 *Sarcoma melanodes*. (From Hebra F, Elfinger A, Heitzmann K. *Atlas der Hautkrankheiten*. Vienna, K-K Hof und Staatsdruckerei, 1856–1876.) Reprinted by permission. Watercolour painting.

initial dilatation of lymphatic vessels and a subsequent accumulation of plasma cells (that is, lymphocytic elements).⁷ Accordingly, he grouped KS with other lymphocytic malignancies such as mycosis fungoides and leukaemia. The plasma cells in this context were believed to be multipotential cells, able to transform into endothelial-like elements and eventually into fibrotic particles (spindle cells), thus accounting for all the cellular components of KS.

A more recent proponent of the malignant nature of KS argued that it was a neoplastic fibroblast tumour.⁸ The tumour cells (spindle cells) of KS were supposed to derive from dermal fibroblasts because of their structural similarities and the mature collagenous fibrils found among them. Since “no cell other than the fibroblast is known to produce collagenous fibrils . . . , it follows as a logical inference that the spindle cells in question are fibroblasts.”

Infectious hyperplasia

Steiner (1896) mentioned a male predominance in patients with KS, who were usually over 40

Figure 3 *Sarcoma melanodes*. (From Hebra F, Elfinger A, Heitzmann K. *Atlas der Hautkrankheiten*. Vienna, K-K Hof und Staatsdruckerei, 1856–1876.) Reprinted by permission. Watercolour painting.

years of age and otherwise remained healthy.⁹ He stated that “the clinical course of the disease gives the impression of a chronic infectious disease.” This paradigm soon gained support from other clinical and histological observations.

An example of the latter were the observed leucocytes and other inflammatory cells near areas of capillary proliferation. Philippson attributed the multifocal expression of the disease to multiple entries into the skin or haematogenous spread of the causative organism rather than metastasis of tumour cells.¹⁰

In an extensive study Dalla Favera denoted a geographical predisposition for KS from eastern Europe and Italy, rather than a racial predominance and to him this also confirmed an infectious origin.¹¹

Among those who favoured an infectious cause for KS there was still debate about the cellular origin and exact nature of KS. Steiner characterised KS by “a dilatation and neoplasia of lymph vessels”, whereas Philippson regarded the spindle cells as the actual tumour cells. He figured that they must be “connective tissue cells”, because the axis of these cells “runs parallel to connective tissue fibres in which they are imbedded”.¹⁰ A similar argument was used by Symmers when he described the spindle cells as fibroblasts.⁸

Steiner regarded KS as a benign process while others considered it to have malignant potential as well because of observed metastasis along lymphatic vessels.¹¹

In their histological study of KS, Dillard and Weidman found nodular accumulations of lymphocytes and stated that “a specific micro-organism is the irritant, [although] demonstration by current laboratory examinations of all kinds . . . has failed”.¹² This was controversial since Justus had claimed that his inoculation experiments with KS tissue had led to tumours in white mice at the inoculated area and also in internal organs.¹³ Becker and Thatcher repeated inoculation experiments whereby KS tissue was “injected into a patient with general paresis with only slight inflammatory reaction . . . A portion of a 6 day [KS] culture growth . . . was implanted under the skin of the patient... [and] at the site of the implantation...a bright red infiltrated plaque appeared, [which] showed features typical of very early KS”.¹⁴ These findings, however, were not confirmed by other investigators and the infectious origin of KS remained elusive.

Reticuloendothelial disease

The reticuloendothelial system was a concept that was proposed by Aschoff in 1924 and encompassed the phagocytic macrophages and specialised endothelia lining sinusoids in the liver, spleen, and bone marrow that were able to take up small dye particles in his experiments. This notion was soon applied to other tissues and seemed to provide a suitable origin for KS. From the onset the reticuloendothelial system was perceived as a flexible system in which a continuous dedifferentiation between different cells took place. Thus, vascular cells could change into reticulum cells and vice versa and

lymphocyte-like cells could form new vessels and were capable of phagocytosis.¹⁵ Considering KS as a reticuloendothelial disease seemed to resolve the variable histology and clinical course which were otherwise difficult to interpret.

This viewpoint is accurately depicted by the histological account in Bluefarb and Webster's report.¹⁶ "[T]here is evidence of hemorrhage; newly formed blood vessels, including proliferation of endothelium and adventitial connective tissue; spindle cells, and cellular infiltration, including early lymphoid elements and reticulum. What tissue other than that of reticuloendothelial system presents such a diversity of structures?"

In 1932 Dörffel published a much quoted study in which he proposed that "the hemorrhage is the initial pathologic feature of this disease", caused by vascular changes for example varicose veins, trauma, cold or arteriosclerosis.¹⁷ The observed cellular infiltrate which appeared at the same time was thought to be composed of cells arising from the reticuloendothelial system. Because these cells "are distributed almost entirely about the blood vessels; . . . they form a reticulum . . . [and] . . . there is a multiplicity of cell forms with many transitional changes". Tedeschi maintained that the pleomorphic nature of the lesions indicated an origin from the reticuloendothelial system.¹⁸

These claims, however, were difficult to test scientifically because of the inbuilt flexibility of the reticuloendothelial system.

Systemic vascular disease

Obviously the clinical characteristics of KS together with the microscopic vessel dilatation and proliferation suggested a relation with the vascular system. In this regard early 20th century investigators often focused on the spindle cells which were considered the true tumour cells of KS.

Sternberg implied that they were actually smooth muscle cells because of the "cellular and . . . nuclear form", the characteristics of the Gieson stain ("yellow . . . protoplasm") and the submucosal localisation in the ileum where the spindle cells could be compared with surrounding smooth muscle cells and appeared strikingly similar.¹⁹ Others attributed the origin of the spindle cells with the hyperaemic vascular slits to perivascular embryonic mesenchyme,²⁰ or interpreted them as transforming and regression steps in the vessel proliferation.²¹ Sachs *et al* doubted whether the spindle cells were a specific cell type, stating that "many different types of cells, even epithelial cells, may have spindle shapes".²²

Few authors regarded KS as a simple vascular malformation with no malignant potential,^{19,21} whereas most proponents of the systemic vascular disease concept pointed out that malignant degeneration of KS could and did occur.

McCarthy and Pack reported on the typical histopathological evolution of KS, whereby the early "inflammation-like macule" is followed by a "granulomatous process", which ultimately progresses into the sarcoma stage.²³ They suggested

that "some systemic carcinogen acting upon the vascular tissues" might provoke KS. This notion was extended to the recently described lymphangiosarcoma in female patients with postmastectomy elephantiasis.²⁴ They implied that these lymphangiosarcomas "are truly identical with KS". In fact one of McCarthy's patients with KS was included in the original series of postmastectomy lymphangiosarcoma. Subsequently Stewart contradicted these findings because the vascular spaces in these angiosarcomas were often lined by atypical endothelial cells unlike the vascular slits in KS.²⁰

Cox and Helwig noticed enlargement of the nuclei and mitotic figures in spindle cells and also malignant KS tumour cells in pulmonary vessels.²⁰ They could hardly escape the conclusion that KS is a "neoplastic disease of the vascular system with multiple foci of origin", in which malignant transformation and metastasis can occur.

Understanding KS as a disease of the vascular system remained tempting but controversy reigned regarding the constituting elements and the precise nature of the lesions.²⁵

Neurovascular disease

Semenow in 1897 was one of the first authors to suggest that KS was linked to the nervous system when he found changes in trophic nerves leading to vessel dilatation and proliferation of the connective tissue.²⁶

The glomus body was first described by Masson in tips of fingers and toes whereafter it was soon found that an increase in size provoked radiating pain sensation. Neurological symptoms such as pain and cramps heralded the onset of hypodermic nodules of KS in a patient that was reported by Pautrier and Diss.²⁷ On histological examination they observed a proliferation of vessels with a neuromuscular sheath and a network of nerve fibrils, proliferation of Schwann's cells, and formation of touch corpuscles of Wagner-Meissner type. In their view this complex architecture of KS was akin to a neuromyoarterial glomus body.

Hudelo and Cailliau on the other hand postulated that "an inflammatory event (maybe infectious) leads to proliferation of nerve cells [sympathetic fibres (of Remak)] of the media and adventitia of normal vessels . . .".²⁸ Hence KS and the spindle cells were seen as hyperplastic nerve cell lesions. Yet most authors failed to confirm these findings.^{14,17}

Endemic (African) KS

In the second part of this century it became clear that apart from the "classic" form of KS which had been studied so far, a similar tumour, endemic KS, was prevalent in Africa and was found to be much more common. According to Thijs, KS accounted for 9% of the histologically confirmed malignant tumours in a central African region.²⁹ There was, however, marked variation with a lower prevalence being reported from western and southern Africa.³⁰ This geographical clustering of cases indicated either genetic susceptibility or environmental influ-

ences as aetiological factors in KS. So far there has been no evidence for either of these factors to influence endemic KS.^{31 32}

The male to female ratio of endemic KS, although showing marked regional differences again,^{30 33} was similar to that reported for classic KS.

The clinical presentation of endemic KS showed several distinct features. It occurred more often in young children who presented with lymph node involvement, and was associated with poor outcome.³⁴ Also in adults endemic KS could behave more aggressively with bone involvement and ulcerating skin lesions.³⁵

Relatively more female children presented with lymphadenopathic KS and the sex ratio of 3:1 was different from the adults. Sex hormones were suggested to provide some protection to post-pubertal females. When oestrogen treatment yielded no beneficial results and KS was described in pregnancy,^{35 36} this explanation seemed less convincing. Recent evidence that human chorionic gonadotrophin induces the regression of AIDS related KS, however, indicates some beneficial effects of female hormones.³⁷

Notwithstanding these clinical differences, endemic and classic KS appeared strikingly similar under the microscope.^{33 35 38} Several authors described distinct cellular patterns in endemic KS such as mixed group, spindle cell predominant or monocellular, and the anaplastic group.^{35 39} They conceded, however, that these probably indicated subsequent stages in the evolution of KS.³⁹

Most studies of endemic KS mentioned the spindle cell as the actual tumour cell of KS but opinions about its origin varied. Among the cells that were considered as likely candidates were reticulum cells, endothelial cells, mesenchymal cells (that is, "pericytes"), and Schwann cells.^{30 38 39} Doubt was expressed as to whether KS was a true sarcoma. Although the association of endemic KS and lymphoreticular malignancies was less commonly found than in other continents,^{30 39} several authors indicated that the reticuloendothelial system may be closely related to KS.^{30 31 33}

The era of relying solely on clinical and conventional histological examination is slowly coming to an end and numerous studies have appeared on the histochemical, electron microscopic, and molecular biological characteristics of KS. The relation between KS, immunodeficient states, and the recently described KS associated herpes virus have provided arguments for an infectious origin of KS which was first suggested more than 100 years ago.

This historical overview shows how past investigators with their modest investigational tools of astute clinical and histopathological observation have paved the way for our present interpretation of the nature and aetiology of KS.

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