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Pathology of AIDS-related lymphomas and other AIDS-defining neoplasms

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1. Introduction

In response to our steadily increasing understanding of the pathophysiology of HIV infection, the natural history of HIV-induced disease, and the recognition of new HIV-related illnesses and improved diagnostic methods, various systems designed to classify the clinical stages of HIV infection have been proposed and periodically revised throughout the AIDS epidemic [1–4]. In 1982, the Centers for Disease Control (CDC) Surveillance Definition of AIDS was "a disease, at least moderately predictive of a defect in cell-mediated immunity, occurring in a person with no known cause for diminished resistance to that disease" [5]. Two diseases that were included in this definition and thereby qualified a person for the diagnosis of AIDS were Kaposi's sarcoma (KS) and primary central nervous system lymphoma [5]. The CDC expanded the AIDS surveillance case definition in 1985 [6] and again in 1987 [7] to include laboratory test results for HIV infection and intermediate or high-grade lymphomas of B cell or indeterminate phenotype as qualifying diseases [6,7]. In 1993, the CDC proposed a further revised classification system for HIV infection and expanded the surveillance case definition for AIDS among adolescents and adults [8]. This system was proposed so as to simplify the classification of HIV infection, to more reliably categorise HIV-related morbidity, to emphasise the clinical importance of CD4 T lymphocyte counts, and to more accurately reflect the standard of care of HIV-positive individuals [8]. The 1993 system added three clinical conditions, one of which is invasive cervical carcinoma, to the previous list of 23 AIDS-defining illnesses to reflect their importance in the AIDS epidemic [8]. Thus, the CDC now recognises three neoplasms as defining criteria for the diagnosis of AIDS: KS, intermediate or high-grade non-Hodgkin's lymphoma (NHL) of B cell or indeterminate phenotype, and invasive cervical carcinoma.

2. Kaposi's sarcoma

2.1. Background

KS was initially described by Moritz Kaposi in 1872 [9]. For more than 100 years following its description, KS was considered a dermatological curiosity [10,11]. Recognition of its epidemic spread among homosexual men in the early 1980s [12–14] heralded the AIDS epidemic, focused worldwide attention on the clinical and biological features of this enigmatic disease and prompted many investigators to search for its aetiological basis.

Four clinical-epidemiological forms of KS are recognised. These are: classic Mediterranean KS which occurs rarely in elderly individuals, predominantly men, of Mediterranean and eastern European descent, in whom it usually exhibits benign, indolent clinical behaviour; endemic-African KS, which occurs frequently in non-HIV-infected individuals in Equatorial Africa, in whom it often exhibits aggressive clinical behaviour; iatrogenic KS, which occurs relatively frequently in solid organ transplant recipients in whom it often undergoes spontaneous regression following the withdrawal of immunosuppressive therapy [10,11]; and AIDS-epidemic KS, a defining condition for the diagnosis of AIDS [7,8], and the most common neoplasm occurring in HIV-infected individuals [15], in whom it often behaves aggressively [16]. The many special clinical, epidemiological and pathological peculiarities of KS have led to considerable debate concerning its cell of

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origin, its hyperplastic versus neoplastic nature, and its possibly infectious aetiology [10,11,17–19].

The most frequent site of involvement by KS is the skin [14,16], where the lesions are most frequently concentrated on the face, genitalia and lower extremities, although they can occur anywhere [16]. Extracutaneous spread of AIDS-epidemic KS is very common, however [19]. The oral cavity, especially the gingiva and palate, is involved frequently [16]. Pulmonary and gastrointestinal tract involvement are also quite common; the latter is highly associated with oral KS and is detectable in 40% of individuals who have KS at initial diagnosis and in as many as 80% at autopsy [16]. Both may occur in the absence of mucocutaneous disease [16]. Lymph node involvement by AIDS-epidemic KS is also common; it too may occur in the absence of mucocutaneous disease [16]. AIDS-epidemic KS may occur in benign lymph nodes exhibiting any of the histopathological patterns of HIV-associated lymphadenopathy, including florid follicular hyperplasia [20–22], as well as in lymph nodes that also contain malignant lymphoma [23]. Actually, no organ has been spared from involvement by AIDS-epidemic KS. Invasion by KS into solid organs such as the heart, liver, pancreas, testes and bone marrow has been described [19], as has metastases to the brain [24]. Extracutaneous involvement by AIDS-epidemic KS ranges from a solitary small nodule to multiple, variably sized nodules, to large confluent haemorrhagic masses of 10 cm or even greater in size [19].

2.2. Histopathology

In general, AIDS-epidemic KS is histopathologically indistinguishable from the other clinical-epidemiological forms of the disease [25]. KS is composed of a variable mixture of ectatic, irregularly shaped, round, capillary and slit-like endothelial-lined vascular spaces and spindle-shaped cells. The endothelial cells may be thin and elongate or oval to round. Generally, they lack cytological atypia and mitotic activity. The spindle cell component, thought to represent the 'tumour cell' population, is now generally believed to be of vascular endothelial cell origin [26,27]. These constituents are accompanied by a mixed mononuclear inflammatory cell infiltrate. Red blood cells and haemosiderin pigment are frequently present, often extravasated between the spindle cells. Refractile, eosinophilic, hyaline globules that stain positively with the periodic acid-Shiff stain, which represent the breakdown products of phagocytosed red blood cells, may be present within macrophages and extracellularly (Fig. 1). It may be very difficult to distinguish the earliest patch and plaque-stage KS lesions from granulation tissue. Over time, the spindle cells increasingly become the predominate cell population, forming fascicles that compress the vascular slits. This causes the individual KS lesions to form nodules and tumours which eventually consist primarily of interwoven fascicles of spindle cells, which may display prominent cytological atypia, numerous mitotic figures and even striking pleomorphism [20,25,28]. Extracutaneous Kaposi's sarcoma may differ slightly histologically from, and may exhibit a different developmental chronology than, cutaneous KS [25].

The earliest histopathological changes observed in lymph nodes involved by KS have been referred to as hypervascular follicular hyperplasia [29]. In these instances, vascular channels within the lymph node are prominent, are increased in number, and are associated with increased numbers of plasma cells [30]. Over time, these areas may develop the classical histopathological features of KS, including interwoven fascicles of spindle cells, vascular slits, and extravasated red blood cells [25,30]. KS involving lymph nodes generally extends along the sinusoids, infiltrates the interfollicular areas [20] and eventually replaces the entire lymph node [21].

2.3. Pathogenesis

Clinical observation and epidemiological data had suggested for many years that KS has an infectious aetiology and is spread primarily through sexual transmission of this infectious agent to immunocompromised hosts [10,11]. While the risk of developing KS is greatly

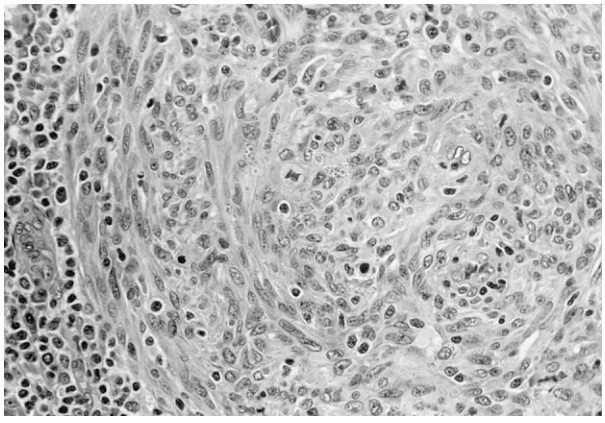

Fig. 1. Kaposi's sarcoma is comprised of a variable mixture of ectatic, irregularly shaped, round capillary and slit-like endothelial-lined vacular spaces and spindle-shaped cells accompanied by a variably mixed mononuclear inflammatory cell infiltrate. The endothelial cells may be thin and spindle-shaped or oval to round. They generally lack cytological atypia or mitotic activity. Erythrocytes and haemosiderin pigment are frequently present, often extravasated between the spindle cells. Small refractile, eosinophilic, hyaline globules, representing the breakdown products of phagocytosed erythrocytes, may be present within macrophages or extracellularly (Haematoxylin and eosin, X250) (from Knowles DM, Chadburn A. Lymphadenopathy and the lymphoid neoplasms associated with the immune deficiency syndrome. In Knowles DM, ed. *Neoplastic Hematopathology*, 2nd edn. New York, Lippincott-Williams & Wilkins, 2000, 987–1089, with permission) [115].

increased in all AIDS risk groups, the risk is astronomic in HIV-infected men who have sex with men [15]. It had been suggested that the higher risk in this AIDS risk group is because of enhanced transmission of an infectious agent due to certain sexual practices, especially those involving orofecal contact, in this population [31,32]. However, over the years, every infectious agent suspected of being the causal agent of KS had been eliminated from consideration upon careful study [10,11]. Then, in 1994, Chang, Moore, Cesarman, Knowles and their collaborators discovered unique non-human, herpesvirus-like DNA sequences in a KS lesion obtained from a patient who had died from AIDS by applying a newly described technique called "representational difference analysis" [33]. They demonstrated that these sequences belong to a novel, previously unrecognised herpesvirus that exhibits considerable homology with herpesvirus saimiri and Epstein–Barr virus (EBV) [34]. This agent was designated descriptively as the KS-associated herpesvirus (KSHV) (296); it also has been designated human herpesvirus-8 [34]. Considerable studies since then have shown that KSHV is a transmittable, B cell lymphotropic gamma herpesvirus belonging to the genus Rhadinovirus [35–37] (Fig. 2). In this regard, it is of considerable historical interest that herpes-type viral particles were identified by electron microscopy in cultured cells derived from KS lesions obtained from African patients in 1972 [38].

The KS-associated herpesvirus is detectable in virtually all KS lesions occurring in essentially all individuals who have any clinical-epidemiological form of the disease [34]. *In situ* hybridisation studies have visualised the virus in the nuclei of the spindle cells and the flat vascular lining cells of KS lesions [39,40]. In contrast, KSHV is absent from the large array of benign inflammatory lesions and benign and malignant vascular proliferations that resemble KS [33,34]. Considerable support for a causal relationship between KSHV and KS comes from multiple studies including those showing that the presence of KSHV DNA sequences in the peripheral blood antedates the development of KS [41], that seroconversion to positivity for antibodies against KSHV-related nuclear antigens occurs before the clinical appearance of KS [42] and that KSHV cellular gene homologues, which appear to represent viral oncogenes, are expressed in KS lesions [36]. There is little doubt that KSHV represents the long sought-after aetiological agent involved in the pathogenesis of KS. However, the development of KS is most likely a multi-step process that involves the interplay of KSHV with impaired immune surveillance, immune stimulation, and multiple genetic, environmental, behavioural and other factors. Interestingly and importantly, Knowles, Cesarman and colleagues further demonstrated that KSHV is consistently present in a distinct category of NHL, the primary effusion lymphomas, which they described [34]. This is discussed further below.

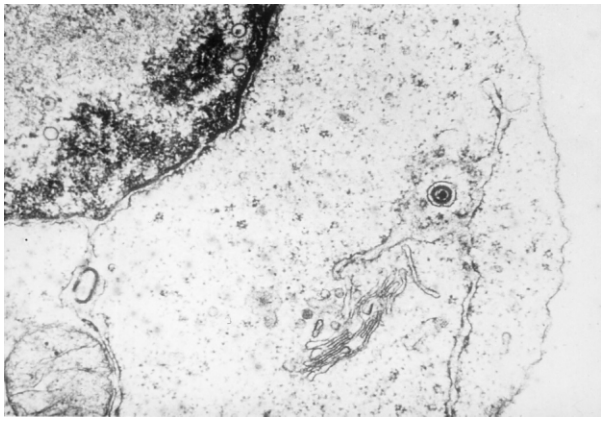

Fig. 2. A primary effusion lymphoma cell line containing Kaposi's sarcoma-associated herpesvirus (human herpesvirus-8) nuclear capsids and a cytoplasmic virion within the dilated endoplasmic reticulum (Uranyl acetate, lead acetate stain, X44,000). From Ref. [141] with the permission of W.B. Saunders Company.

3. Non-Hodgkin's lymphoma

3.1. Background

NHL is now widely recognised as the second most common neoplasm occurring among all HIV-infected individuals and the most common one occurring among HIV-infected injecting drug users and haemophiliacs [43]. The CDC has calculated the risk of NHL in the United States to be 60 times greater among individuals who have AIDS than among non-HIV infected individuals in the general population and the incidence of NHL in AIDS to be 2.9% [43]. These determinations are based on reports of NHL among AIDS patients in the United States reported to the CDC between 1981 and mid-1989 [43]. However, data collected from cohort studies and cancer registries suggest that the true incidence of AIDS-related NHL has been substantially underestimated by the CDC [44]. It is more likely that the incidence is approximately 200-fold in excess of expected rates [45] and that the overall incidence of NHL in AIDS is more likely between 4 and 10% [44,46–48]. It is thought that approximately 10% of all NHLs occurring in the United States currently are AIDS-related [47].

Men who have sex with men and injecting drug users represent the principal populations at risk for AIDS [49]. In the United States, the majority of the individuals who develop AIDS-related NHLs are men who have sex with men [49] while in western Europe the majority are injecting drug users [50,51]. These differences reflect the epidemiological variations in the spread of the AIDS

epidemic. In addition to these two major AIDS-risk groups, AIDS-related NHLs may develop in individuals of all ages who have been transfused with HIV-infected blood and blood products, children born to HIV-infected mothers, and the heterosexual partners of HIV-infected men [15,43,52,53]. The risk of developing NHL is relatively consistent among all AIDS-risk groups [15,53], without regard for geography [43,47], although it is highest in haemophiliacs [43]. Furthermore, the clinical and pathological characteristics of AIDS-related NHLs occurring in all AIDS-risk groups, regardless of geography, appear to be comparable [43,52,54–57]. One possible exception is primary oral and anorectal NHLs, which appear to occur preferentially in men who have sex with men [43,54–58].

3.2. Site of origin

AIDS-related NHLs are broadly divisible into three categories according to their anatomical site of origin: those arising systemically (either nodally or extranodally); those arising in the central nervous system; and those arising in the body cavities [59,60].

Approximately 80% of all AIDS-related NHLs non-Hodgkin's lymphomas arise systemically. The majority of these individuals have widely disseminated disease, including a high incidence of extranodal involvement at presentation; most of the remaining patients have large bulky stage IE disease [48,50–52,54]. The most common sites of extranodal involvement at presentation are the central nervous system, the gastrointestinal tract, the liver and the bone marrow [48,50,52,54,55,61]. In addition, certain locations, such as the anorectum and the heart, which only rarely serve as primary sites of lymphoma in the non-HIV-infected general population, have become recognised as frequent sites of origin for AIDS-related NHL [62–65]. Indeed, AIDS-related systemic NHLs may originate or present in virtually any extranodal site, irrespective of how isolated or obscure. They have been reported, for example, in the orbit, oropharynx, mandible, skin, heart, lungs, salivary glands, common bile duct, muscles, bones, kidneys, gonads, adrenal glands and even in the placenta and products of conception [50,52,54,65–69]. For these reasons, NHL should always be given diagnostic consideration in an AIDS-risk individual who presents with a tumour, regardless of the site or mode of presentation. Furthermore, the atypical presentation of diffuse aggressive NHL involving an unusual extranodal location should raise suspicion for HIV infection.

Primary central nervous system lymphomas comprise approximately 20% of all AIDS-related NHLs [48,51,54,70,71]. According to data collected by the CDC, primary central nervous system lymphomas occur approximately 1000 times more frequently in individuals who have AIDS than in the general population [43]; AIDS is now the most common risk factor for the development of primary central nervous system lymphoma. The majority of these patients are profoundly immunocompromised young men who have sex with men and who already have far-advanced HIV disease [62,63,70]; lymphoma is usually a secondary manifestation of AIDS in these individuals [54,63,70].

AIDS-related primary central nervous system lymphomas are intracranial parenchymal tumours. They are usually large, sometimes greater than 3 cm and frequently are multifocal [63,72]. Most commonly, they occur in the cerebrum, but they also occur frequently in the cerebellum, basal ganglia and brain stem [63,72,73]. Grossly, they are characterized by indistinct borders and a granular surface [63]. Frequently, they contain extensive areas of necrosis. The lymphoma cells tend to be distributed as perivascular cuffs along vascular channels [63,72,73]. The lymphomas display large cell and immunoblastic histologies and are of B cell origin [52,62,63,68,70,72,73].

In 1989, Knowles and colleagues described an uncommonly occurring subset of AIDS-related NHL that grow almost exclusively in the pleural, pericardial, and peritoneal cavities as lymphomatous effusions, usually without a contiguous tumour mass [74]. Knowles and colleagues also described several of the distinctive properties of these malignant lymphomas, including their immunoblastic cytology, indeterminate immunophenotype, B cell genotype, the presence of clonal EBV genome, and absence of *MYC* gene rearrangements [74]. Subsequently, other investigators described similar cases [75–77]. Since these lymphomas usually remain localised to the body cavity of origin and spread to lymph nodes or to distant sites only infrequently, they were referred to as body cavity-based lymphomas [59,60,76].

Following the discovery of the KS-associated herpesvirus [33], Cesarman, Knowles and coworkers identified the consistent presence of this viral agent in these AIDS-related body cavity-based lymphomas and the uniform absence of this virus from all other AIDS-related and conventional B cell and T cell derived NHLs and lymphoid leukaemias [78] (Fig. 3). Other investigators subsequently confirmed the unique association between KSHV and the AIDS-related NHLs arising as lymphomatous effusions in the body cavities [79–82]. Knowles and colleagues further showed the rare occurrence of such KSHV-containing lymphomas in non-HIV-infected men and women [83–85]. Cesarman, Knowles and coworkers proposed that the term primary effusion lymphoma replace the term body cavity-based lymphoma, since the former term describes these KSHV-containing lymphomas more accurately and avoids their confusion with other lymphomas arising in the body cavities [86], including the pyothorax-associated lymphomas [87].

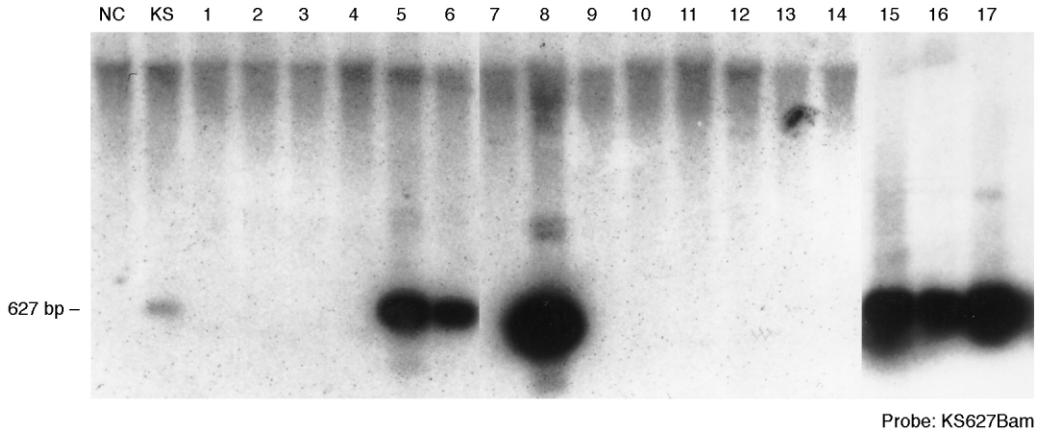

Fig. 3. Southern blot hybridisation analysis of AIDS-related non-Hodgkin's lymphomas for the Kaposi's sarcoma-associated herpesvirus (KSHV). The numbers above each lane indicate the number of the case. 'NC' refers to a negative control (HL60 cell line). The KSHV-positive control exhibits a weak, but definite, signal, indicative of the presence of KSHV within this AIDS-related Kaposi's sarcoma lesion. Lanes 5, 6, 8 and 15–17 exhibit very strong hybridisation signals, indicative of the presence of KSHV in these six examples. All six KSHV-positive samples represent cases of AIDS-related primary effusion lymphoma. The KSHV-negative samples represent examples of AIDS-related and non-AIDS-related non-Hodgkin's lymphomas. From Ref. [142] with permission.

The KSHV-containing primary effusion lymphomas account for approximately 3% or less of all AIDS-related NHLs and considerably less than 1% of all conventional NHLs [81]. Studies have shown that these KSHV-containing primary effusion lymphomas exhibit a unique constellation of features which render them a distinct clinical, pathological and biological entity. These features are: epidemiology similar to KS including a vast predominance in men, usually, but not always, HIV-positive, in whom homosexuality is a risk factor, and older age of presentation in non-HIV than in HIV-infected individuals; origination as a lymphomatous effusion in a body cavity, usually in the absence of a contiguous tumour mass and without lymphadenopathy or organomegaly; restriction to the body cavity of origin; cells with cytomorphological features bridging those of immunoblastic and anaplastic large cell lymphoma; CD45 and activation-associated antigen expression, usually in the absence of B cell lineage antigens; clonal immunoglobulin gene rearrangements indicating a B cell genotype; the uniform presence of KSHV and frequent presence of EBV; and the near uniform absence of *MYC* gene rearrangements [78,83–85,88]. Some of these features are discussed in more detail below.

3.3. Histopathology

In the first large clinical pathological study aimed at delineating the histopathological and correlative clinical features of AIDS-related NHLs, Knowles and colleagues reported that the vast majority of AIDS-related NHL belong to one of three diffuse aggressive histological categories, i.e. approximately 40% of cases are Burkitt's lymphoma and the remaining cases are equally divided between immunoblastic lymphoma and large cell lymphoma [52]. Knowles and colleagues further demonstrated that each of these major histopathological categories of AIDS-related NHL exhibit distinctive clinical features, including specific associations with clinical stage, sites of extranodal involvement, and perhaps even differences in prognosis and survival [52]. The French Study Group [68] and other investigators [50,54,56] have reported a virtually identical histopathological distribution and have confirmed the observation that certain significant clinical distinctions exist among AIDS-related NHLs according to their histopathology and anatomical site of origin [43,89,90]. Nonetheless, the morphological heterogeneity of AIDS-related NHLs renders the precise classification of some cases into one of these three categories difficult [48,68,91]. In addition, cases exhibiting transitional histopathological features have been described. This histopathological distribution contrasts sharply with that of conventional NHLs occurring in the non-HIV infected general population, where Burkitt's lymphoma and immunoblastic lymphoma comprise only approximately 10% of all cases in the United States [92]. Indeed, Burkitt's lymphoma appears to occur at least 1000 times more frequently in individuals who have AIDS than in the general population [43]. The histopathological distribution of AIDS-related NHLs also contrasts with that of other immunodeficiency-associated NHL since the vast majority of the latter exhibit large cell or immunoblastic morphology and only a small minority exhibit Burkitt's morphology [43].

AIDS-related NHLs display histological features similar to those exhibited by conventional NHL belonging to the corresponding histopathological categories. However, AIDS-related NHLs generally appear

to display a higher frequency of mitotic figures, increased cellular debris, and an enhanced tendency to undergo necrosis than conventional NHLs, suggesting a higher proliferation index and a more rapid growth rate, which is consistent with their natural history [59,60].

AIDS-related Burkitt's lymphomas include those cases displaying the histological features of classical endemic (African) Burkitt's lymphoma as originally defined by the World Health Organization [93] and the so-called Burkitt's-like lymphomas. The latter cases are those originally classified by Rappaport [94] as diffuse undifferentiated, non-Burkitt's lymphoma. These cases have been referred to as Burkitt's lymphoma with plasmablastic differentiation by Lennert and colleagues [95]. Burkitt's lymphoma characteristically has a prominent starry-sky pattern at low power magnification because of the presence of numerous, evenly distributed tingible body macrophages possessing abundant clear cytoplasm. These macrophages contain phagocytosed cellular debris from necrotic neoplastic cells, indicative of the extraordinarily high proliferation index of Burkitt's lymphoma. Mitotic figures are extremely abundant, as is scattered nuclear debris and there is a tendency for these lymphomas to undergo necrosis. A diffuse, monotonous proliferation of small to intermediate-sized neoplastic lymphoid cells containing moderately abundant basophilic cytoplasm and round, regular nuclei that possess two to five distinct nucleoli characterises Burkitt's lymphoma (Fig. 4a). Numerous well-defined cytoplasmic vacuoles staining with the oil red O stain can be observed in air-dried Romanowsky-stained imprints. The so-called Burkitt's-like lymphomas are histologically similar to Burkitt's lymphoma, with the exception that the neoplastic cells display more variability in size and shape. Some nuclei may be located more eccentrically and some nuclei may contain only one prominent, centrally placed nucleolus [59,60] (Fig. 4b).

Immunoblastic lymphomas often exhibit a starry-sky pattern as well, although usually less prominent than that of Burkitt's lymphoma. Mitotic figures are abundant, as is scattered nuclear debris, and these lympho-

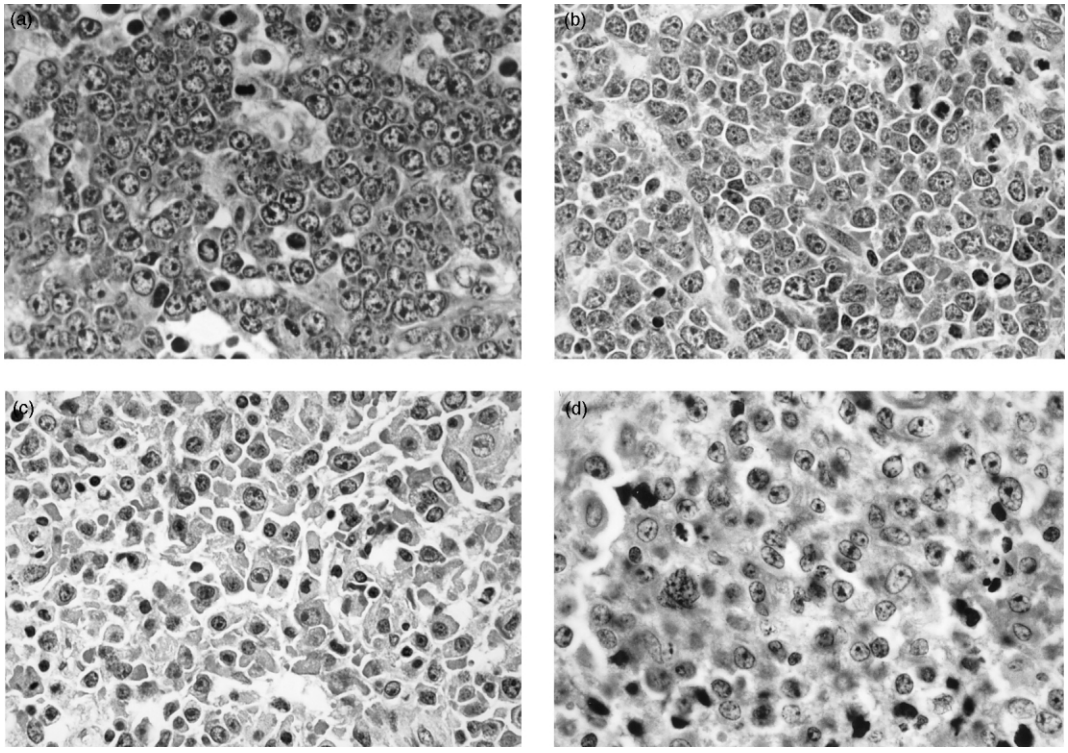

Fig. 4. AIDS-related non-Hodgkin's lymphomas. (a) Burkitt's lymphoma is characterised by a monotonous proliferation of uniformly sized neoplastic cells containing round, regular nuclei surrounded by a small rim of cytoplasm. The nuclei generally contain two to four nucleoli. Numerous tingible body macrophages impart a starry-sky pattern. (b) Burkitt's-like lymphoma is characterised by a neoplastic cell population which shows slightly more variability in nuclear size and shape than that of Burkitt's lymphoma. In addition, the nuclei may contain only one nucleolus. None the less, the cells display the characteristic squared-off or 'bathroom tile' appearance typical of Burkitt's lymphoma. (c) Immunoblastic lymphoma is comprised of a diffuse proliferation of large neoplastic lymphoid cells which exhibit considerably more variability in size and shape than those of Burkitt's and large cell lymphomas. The nuclei are often located eccentrically and are surrounded by abundant amphophilic cytoplasm and a perinuclear hof that imparts a plasmacytoid appearance to the malignant cells. (d) Large cell lymphoma is comprised of a diffuse proliferation of large neoplastic lymphoid cells that are intermediate in size between those of Burkitt's and immunoblastic lymphoma and usually are round to slightly oval. They generally possess scant to moderately abundant acidophilic cytoplasm without a paranuclear hof. The nuclei are usually round and regular and contain one or more small distinct nucleoli adjacent to the nuclear membrane (Haematoxylin and eosin, X630).

mas similarly have a tendency to undergo necrosis. The neoplastic cells of immunoblastic lymphoma are larger than those of Burkitt's or large cell lymphoma. The neoplastic cells may be round, oval or ovoid. They often contain abundant, deeply basophilic cytoplasm, sometimes with a paranuclear hof indicative of their plasmacytoid differentiation. The nuclei are round to ovoid and often contain a solitary prominent, centrally placed nucleolus. Binucleate and even multinucleate cells are often present [59,60] (Fig. 4c). Some immunoblastic lymphomas display marked cellular pleomorphism [74]; these cases are composed of large pleomorphic tumour cells containing abundant acidophilic to amphophilic cytoplasm and large, round and regular to highly irregular and hyperconvoluted nuclei containing one or more prominent nucleoli which may be reminiscent of Reed-Sternberg cells [52,74].

The large cell lymphomas contain far fewer tingible body macrophages than the Burkitt's and immunoblastic lymphomas and therefore usually lack the prominent starry-sky pattern seen in those lymphomas. Mitotic figures are less abundant, as is scattered nuclear debris, and necrosis occurs less frequently than in the Burkitt's and immunoblastic lymphomas as well. The neoplastic cells comprising large cell lymphomas are intermediate in size between those of Burkitt's and immunoblastic lymphoma and usually are round to slightly oval. They usually have scant to moderately abundant acidophilic cytoplasm, without a paranuclear hof or other evidence of plasmacytoid differentiation. The nuclei are usually round and regular and contain one or more small distinct nucleoli adjacent to the nuclear membrane [59,60] (Fig. 4d). Occasional large cell lymphomas contain variable proportions or are composed entirely of neoplastic cells containing cleaved or multilobated nuclei [68].

In Wright-Giemsa-stained air-dried cytocentrifuge preparations, the malignant cells of primary effusion lymphomas exhibit cytomorphological features that appear to bridge those of immunoblastic lymphoma and anaplastic large cell lymphoma. The majority of the malignant cells are large, sometimes very large, and are round or ovoid to polygonal. They contain moderate to abundant amphophilic to deeply basophilic cytoplasm and nuclei ranging from large, round and regular to highly irregular and pleomorphic. The nuclei contain coarsely reticular chromatin and from one to four large prominent nucleoli. Most cells display plasmacytoid or immunoblastic features. Some cells may be binucleated or multinucleated and resemble Reed-Sternberg cells. Mitotic figures, some of which are atypical, are numerous. The primary effusion lymphoma cells appear somewhat more uniform in size and shape in cell block sections than in haematoxylin and eosin-stained tissue sections. They possess moderate to lightly eosinophilic cytoplasm and round to slightly irregular nuclei that contain one or more prominent nucleoli. Occasional large pleomorphic cells, some of which resemble Reed-Sternberg cells and others which have wreath-like nuclei reminiscent of anaplastic large cell lymphoma cells, may be present [84,88] (Fig. 5).

Two other histopathological categories require mention; these are anaplastic large cell lymphoma and plasmablastic lymphoma. Carbone and colleagues have reported that as many as 15% of all AIDS-related systemic NHLs occurring in Italy represent CD30 positive anaplastic large cell lymphoma [51,96]. These cases exclusively express B cell or indeterminate immunophenotypes [97], and the majority contain EBV [96]. According to the Revised European-American Classification of Lymphoid Neoplasms proposed by the International Lymphoma Study Group [98], anaplastic large

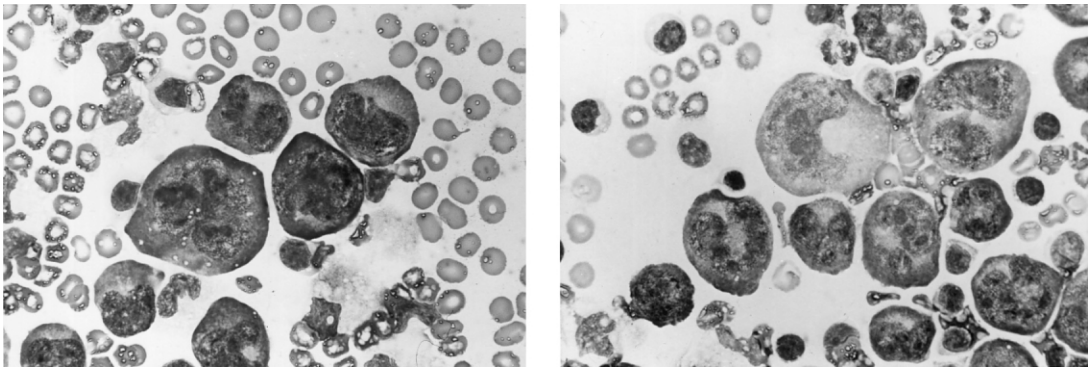

Fig. 5. Air-dried cytocentrifuge preparations of a primary effusion lymphoma containing Kaposi's sarcoma-associated herpesvirus. The cells are considerably larger than normal benign lymphocytes and red blood cells and exhibit cytological features that bridge immunoblastic lymphoma and anaplastic large cell lymphoma. The cells display variable polymorphism and generally possess moderately abundant amphophilic to deeply basophilic cytoplasm. A prominent clear perinuclear Golgi zone is frequently present. The nuclei vary from large and round to highly irregular, multilobated and pleomorphic and often contain one or more large prominent nucleoli (Wright stain, X630). From Ref. [84] with permission of W.B. Saunders Company.

cell lymphoma is a distinct clinical pathological entity characterised by T cell derivation and a lack of Epstein Barr-virus association [98]. According to this scheme, B cell NHLs that exhibit anaplastic large cell morphology are included among the morphologic variants of diffuse large B cell lymphoma. This would appear to be the appropriate classification for the CD30-positive anaplastic large B cell lymphomas reported by Carbone and colleagues. Such cases generally have been included among the large cell and immunoblastic categories by other investigators. For example, the French Study Group designated only one case an anaplastic large cell lymphoma from among 113 AIDS-related NHLs that they investigated [68]. This conclusion is also supported by the fact that Carbone and colleagues have failed to identify any clinical differences, including AIDS-risk group, HIV disease stage, CD4 T cell counts, clinical presentation, clinical stage, disease distribution, performance status, eventual outcome, or cause of death between cases that they have classified as non-T cell anaplastic large cell lymphoma and other AIDS-related systemic B cell NHLs [97]. Legitimate examples of T cell anaplastic large cell lymphoma have been reported only very rarely in HIV-infected persons [99].

In 1997, Delecluse and colleagues described what they believe is a unique subset of NHLs which they have designated plasmablastic lymphoma [100]. In their experience, these lesions nearly always occur in HIV-infected individuals where they preferentially localise in the oral mucosa, usually in the gingiva. A majority of the patients present with localised disease, but the lymphoma may extend to involve the abdomen, retroperitoneum, soft tissues and the bone marrow; therefore, some patients have disseminated disease. These lymphomas grow diffusely and have a starry-sky appearance on low power magnification because of the presence of scattered tingible body macrophages, similar to Burkitt's lymphoma. The lymphoma cells are large and possess abundant, deeply basophilic cytoplasm, eccentrically placed nuclei and a paranuclear hof. The nuclei are round to ovoid and possess little chromatin and either a single prominent, centrally placed nucleolus or several peripherally located nucleoli. Abundant mitotic figures, apoptotic figures, and evidence of single cell necrosis are present, indicative of a very high proliferation index. The plasmablastic lymphomas exhibit a distinct immunophenotype characterised by: strong immunoreactivity with monoclonal anti-plasma cell antibody VS38c in all cases; complete absence of CD45 and CD20 in approximately one-half the cases and weak expression of CD45 or CD20 by variable proportions of the lymphoma cells in the remaining half of the cases; CD79a expression by a variable proportion of lymphoma cells; and intracytoplasmic IgG, but not other heavy chain isotypes, in approximately 50% of cases, which may be accompanied by monotypic light chain expression. The lymphoma cells exhibit clonal immunoglobulin heavy chain gene rearrangements and lack evidence of KSHV infection [100]. In summary, the blastoid morphology and immunophenotype of these lymphomas suggest that they most closely resemble plasmablasts, cells that retain the blastoid features of immunoblasts, but have acquired the antigen profile of plasma cells, hence the designation plasmablastic lymphoma [100]. They appear to represent a distinct clinical pathologic entity that is preferentially associated with AIDS. However, additional reports and studies of these lymphomas are necessary in order to understand their relationship to other AIDS-related and conventional NHLs.

3.4. Lineage and clonality

AIDS lymphomagenesis is a B cell phenomenon. Most investigators have found that the vast majority of AIDS-related systemic and primary central nervous system lymphomas displaying Burkitt's, immunoblastic, or large cell histology express monotypic surface immunoglobulin and/or B cell lineage-associated antigens [52,54,56,61,68,91,101–103]. Furthermore, AIDS-related B cell NHLs appear to express immunophenotypes similar to those expressed by conventional B cell NHLs of comparable histopathology occurring in the non-HIV-infected general population [52,59,60,91]. The primary effusion lymphomas comprise most of the small number of remaining AIDS-related NHLs lacking B cell immunophenotypes. The latter tumours usually express indeterminate immunophenotypes, i.e. presence of non-lineage-specific activation-associated antigens such as HLA-DR, CD30, CD38, CD71 and epithelial membrane antigen in the absence of surface immunoglobulin and B cell and T cell lineage-associated antigens [74,83–85,88,104]. Some investigators have, however, detected monotypic cytoplasmic immunoglobulin in some primary effusion lymphomas [81,82]. The relationship of the occasional T cell NHLs and lymphoid leukaemias occurring in HIV-infected persons to the AIDS epidemic is uncertain [48,59,60].

In addition, most investigators have found that the vast majority of AIDS-related NHLs, including the primary effusion lymphomas that express indeterminate immunophenotypes, exhibit clonal immunoglobulin gene rearrangements in the absence of clonal T cell receptor gene rearrangements, confirming their B cell lineage derivation and their monoclonal nature [52,74, 78,91,94,103,105–107]. The one conspicuous exception to the general literature experience are the studies by McGrath, Herndier and coworkers who have reported that as many as one-third of all AIDS-related NHLs occurring in the San Francisco Bay area are polyclonal [108–111]. These investigators have based this conclusion on their inability to detect clonal immunoglobulin

heavy chain gene rearrangements in biopsy specimens by Southern blot hybridisation or in some instances by reverse transcriptase-polymerase chain reaction [108–111]. These 'polyclonal lymphomas' have been described as exhibiting large cell morphology, containing a variable admixture of B cells, T cells and macrophages, displaying a spectrum of mixed immunophenotypes, and lacking EBV and *MYC* gene rearrangements [108–110]. It has been claimed that these lesions have a more favourable prognosis than other AIDS-related NHLs [111].

The explanation for these findings, which is discordant with the vast literature experience with AIDS-related NHLs as well as with the almost universally accepted concept of monoclonality in lymphomagenesis, is uncertain. We, as well as Raphael and colleagues, have found that only a few AIDS-related NHLs exhibit a germline immunoglobulin heavy chain gene configuration by Southern blot hybridisation [91,112]. In our experience, these occasional AIDS-related NHLs that appear to lack immunoglobulin heavy chain gene rearrangements usually exhibit clonal immunoglobulin light chain gene rearrangements or contain evidence of clonal Epstein–Barr virus infection [112] (Fig. 6). Thus, it is possible that tissue sampling or other technical factors may explain the findings of McGrath and colleagues since, for example, they often failed to analyse their cases for immunoglobulin light chain gene rearrangements [108–110]. Moreover, whether the rare apparently germline immunoglobulin gene cases are truly polyclonal or clonality is simply not detectable with the methods currently available remains to be determined. However, a number of scientific explanations other than polyclonality can be offered to account for the absence of clonal immunoglobulin heavy chain gene rearrangements by Southern blotting [113]. In addition, molecular genetic studies provide further support for the widely held belief that AIDS-related NHLs are monoclonal. For example, the fact that only one rearranged *MYC* gene or a solitary *TP53* gene mutation is detectable in an individual AIDS-related NHL strongly supports the concept that the lymphoma contains one predominant clone, i.e. is monoclonal [103,105,107,114]. Clearly, additional studies are necessary to confirm the significance of the observation that some AIDS-related NHLs apparently lack clonal immunoglobulin gene rearrangements, as well as to confirm the authenticity of the so-called 'polyclonal' AIDS-related lymphomas. However, we have failed to find evidence to support the contention that truly 'polyclonal lymphomas', those in which the neoplastic cell population is derived from multiple distinct clones, actually exist.

3.5. Molecular genetics

Structural alterations involving several protooncogenes and tumour suppressor genes occur non-randomly in association with specific histopathological categories of conventional NHLs occurring in the non-HIV infected general population and are believed to play a role in their pathogenesis [115]. Structural alterations of some of these genes, including *MYC*, *RAS*, *BCL-6* and *TP53*, as well as infection by EBV, variably occur among AIDS-related NHLs as well [116]. In a comprehensive analysis of the oncogene and tumour suppressor gene status and the viral content of 64 AIDS-related systemic NHLs, Knowles and colleagues detected *MYC* gene

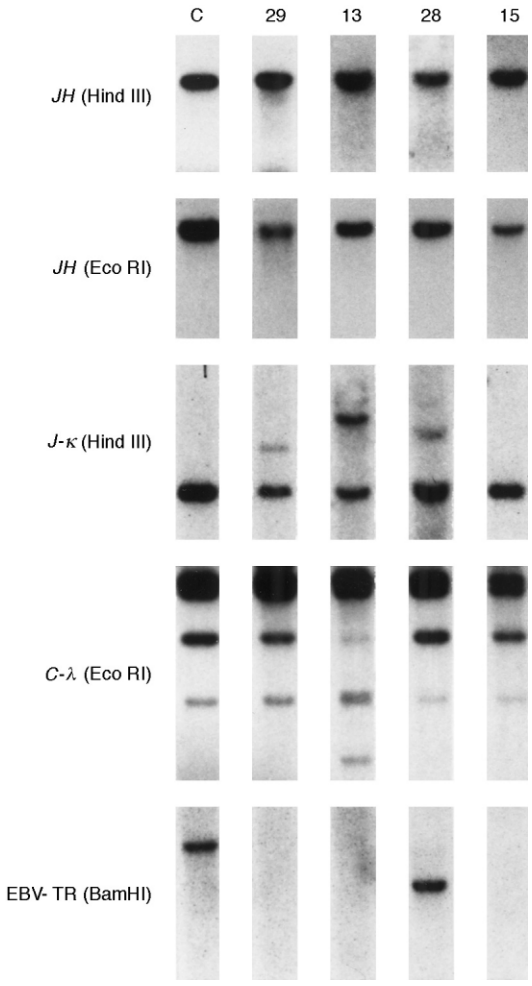

Fig. 6. Molecular genetic analysis of AIDS-related non-Hodgkin's lymphomas exhibiting a germline immunoglobulin heavy chain gene configuration by Southern blot hybridization. The number above each lane indicates the case number. 'C' indicates a control lane (HL60 cell line) except in the case of EBV-TR, in which an EBV-containing Burkitt's lymphoma cell line (Daudi) was used. Each of these four cases exhibited a germline immunoglobulin heavy chain gene configuration. However, cases 29, 13 and 28 exhibit clonal kappa light (*J–K*) gene rearrangement. Case 13 also exhibits clonal lambda light chain (*C–λ*) gene rearrangement. Case 28 contains evidence of clonal EBV infection. Case 15 apparently lacks clonal immunoglobulin (*JH*) heavy and light chain (*J–K*) and (*C–λ*) gene rearrangements as well as evidence of clonal EBV infection. From Ref. [143] with permission of W.B. Saunders Company.

rearrangements, clonal EBV, *TP53* gene mutations or deletions, *BCL-6* gene rearrangements, and *RAS* gene mutations in 44, 41, 30, 17 and 6% of the cases, respectively [112]. *BCL-1* and *BCL-2* gene rearrangements and retinoblastoma (*RB*) gene mutations/deletions were not detected [112]. However, these molecular genetic alterations do not apparently occur entirely randomly among AIDS-related systemic NHLs. Instead, they appear to vary among these tumours according to their histopathological category and anatomical site of origin. Among Burkitt's lymphomas, more than 80% have EBV and *MYC* gene rearrangements and approximately 50% have *TP53* gene mutations in the absence of *BCL-6* gene rearrangements and *RAS* gene mutations. The Burkitt's-like lymphomas display a comparable constellation of genetic alterations, except that a smaller proportion of cases have EBV, *MYC* gene rearrangements and *TP53* gene mutations and that *BCL-6* gene rearrangements occur in a smaller percentage of cases. Among the large cell lymphomas, only very few cases contain EBV, approximately 50% have *MYC* gene rearrangements, a small percentage have *TP53* gene mutations, and approximately 25% exhibit *BCL-6* gene rearrangements. The immunoblastic lymphomas display a constellation of molecular genetic alterations that closely resemble those of the Burkitt's-like lymphomas [112].

The molecular genetic characteristics of AIDS-related NHLs also vary according to anatomical site. In contrast with the AIDS-related systemic non-Hodgkin's lymphomas (described above) the primary central nervous system lymphomas uniformly contain EBV and lack *MYC* gene rearrangements [73,117]. Unfortunately, a more comprehensive molecular genetic analysis of AIDS-related primary central nervous system lymphomas has not been performed. The primary effusion lymphomas frequently contain EBV and nearly always lack *MYC* gene rearrangements. In addition, they nearly always lack *BCL-6* gene rearrangements and *RAS* and *TP53* gene mutations [34,78,84].

In summary, AIDS-related NHLs are characterised by the successive and rapid accumulation of multiple distinct genetic lesions involving viruses, protooncogenes, and tumour suppressor genes. Multiple molecular genetic pathways apparently operate in AIDS lymphomagenesis; some of these pathways may be associated preferentially with specific histopathological categories or anatomical sites of origin [116]. Consequently, future clinical studies, including therapeutic trials of AIDS-related NHLs should include a comprehensive correlative morphological and molecular genetic analysis. Such studies eventually may yield a classification based, at least in part, on genetic features that is clinically and prognostically more relevant than the current classification, which is based largely on histopathological evaluation alone.

3.6. Pathogenesis

AIDS lymphomagenesis involves multiple factors, including the state of HIV-induced immunosuppression, impaired immune surveillance, cytokine and growth factor release and deregulation, chronic B cell stimulation, differentiation and proliferation, and EBV infection. This milieu appears to be conducive to the occurrence of genetic alterations in critically important protooncogenes and/or tumour suppressor genes, leading, for example, to *MYC* gene activation and *TP53* gene inactivation, subsequent clonal selection, and the development of monoclonal B cell NHL [115]. Although multiple immunological and molecular genetic steps in this process have been elucidated, considerably more work needs to be done to acquire a complete understanding of AIDS lymphomagenesis.

4. Other haematological neoplasms

More than 400 cases of Hodgkin's disease (HD) occurring in HIV-infected individuals have been reported in the literature. However, these reports have not determined whether HIV infection truly promotes the development of HD or merely modifies its clinical course. Thus, the relationship between HIV infection, AIDS, and HD remains uncertain. It is true that HD occurring in association with HIV infection exhibits distinct clinical and histopathological features. In addition, the incidence of HD may be increased among injecting drug users. However, the incidence of HD does not appear to be increased among men who have sex with men or other AIDS populations at risk for acquiring AIDS. Consequently, the CDC has not accepted the occurrence of HD in HIV-positive individuals as an AIDS-defining condition (reviewed in [115]).

A variety of other haematological neoplasms occurring in HIV-infected individuals, some of whom have AIDS, have also have been reported in the literature. These include B cell acute lymphoblastic leukaemia, plasma cell neoplasms, histological low grade B cell leukaemias and NHLs, T cell neoplasms, angiocentric immunoproliferative lesions, and a variety of myeloproliferative disorders including acute myeloid leukaemia (reviewed in [115]). B cell acute lymphoblastic leukaemia represents Burkitt's lymphoma in leukaemic phase; the development of these lesions is most likely HIV-related and their occurrence in HIV-infected individuals is not coincidental. However, the other haematological neoplasms only appear to occur sporadically in HIV-infected individuals and there is no epidemiological evidence to suggest that their incidence has increased in parallel with the AIDS epidemic. Since the relationship between these haematological neoplasms, HIV

infection and AIDS is unclear, the CDC does not recognise them as meeting the criteria for the diagnosis of AIDS in HIV-infected individuals at the present time [115].

5. Invasive cervical carcinoma

5.1. Epidemiology and pathogenesis

Results of epidemiological, clinical, pathological and molecular studies have provided substantial evidence that cervical cancer is caused by infection with oncogenic types of human papillomavirus (HPV) (reviewed in [118,119]). Epidemiological risk factors for cervical carcinoma include those that correlate with the risk of acquiring HPV infection, such as early age at first sexual intercourse, multiple sexual partners, high parity rate and a partner with multiple sexual partners [118]. Furthermore, HPV DNA has been detected in 100% of squamous and adenosquamous cervical cancers and in over 90% of cervical adenocarcinomas [120–122]. In addition, results of *in vitro* transfection experiments indicate that HPV 16 and HPV 18 can immortalise both cervical squamous and endocervical glandular cells. However, although HPV is recognised as the single most important pathogenetic factor in cervical carcinoma, it has become clear that HPV infection alone, although necessary, is insufficient for complete malignant transformation of the infected cells. Anogenital HPV infections are the most common sexually transmitted diseases, with a prevalence of up to 60% in selected populations. However, only a proportion of these HPV-infected individuals develop mucosal or skin lesions, most of which are transient, and only a fraction of these lesions progress to cancer, if left untreated. The risk of progression correlates with the persistency of HPV infection, cigarette smoking and HIV infection. However, the events involved in the progression of premalignant lesions are not well understood (reviewed in [118,119]).

5.2. HPV and HIV infection

The prevalence of high oncogenic risk HPVs in cervical smears of HIV-positive women has been reported to be 1.5–3 times higher than in HIV-negative individuals [123–125]. In addition, persistent HPV infections were detected in 24% of HIV-positive women versus 4% of HIV-negative women [124]. Consequently, the incidence of premalignant squamous intraepithelial lesions (SIL) in HIV-infected women is increased 2- to 4-fold [126,127]. The lesions tend to be multifocal and involve the cervix, vulva and vagina as well as the perianal region, and have a greater tendency for persistence and progression from low to high grade, and to invasive cancer [128,129]. The standardised incidence ratio for invasive cervical cancer in HIV-infected women was reported to be increased from 2.5- to 15.5-fold, compared with the general population [130–132].

It has been proposed that the effect of HIV infection on the development of cervical cancer is related to two factors: immunosuppression, which results in an inefficient clearance of HPV infection, and a direct additive effect of HIV on HPV transforming properties. The latter interaction has not been supported thus far by conclusive evidence due to technical difficulties in human research and the lack of an animal model of HPV/HIV infection. Further, a co-infection of cervical epithelial cells by HIV and HPV remains to be fully ascertained. The promoting effect of immunosuppression on the development of HPV-related lesions has been well established in clinicopathological studies, and the risk for the development of SIL was observed to be inversely related to the CD4 count in HIV-positive women [126,133]. However, the exact molecular immunological mechanisms remain to be elucidated.

5.3. Histopathology

There are three main histopathological types of cervical carcinoma: squamous cell carcinoma (SCC), adenocarcinoma (ADC) and adenosquamous carcinoma (ADSQ). SCC is the most common tumour type, accounting for approximately 60–80% of cervical cancers. The histology is that of tongues and nests of malignant squamous epithelium infiltrating the stroma of the cervix. The malignant cells are polygonal with prominent cellular borders and intercellular bridges. SCCs are further subclassified as keratinising when they contain keratin pearls, and non-keratinising when they lack keratin pearls, but the latter may contain single keratinised cells. ADC of the cervix account for 15–20% of cervical cancers and are composed of malignant glands resembling endocervical type epithelium. Less frequently, ADCs may be composed of neoplastic glands resembling intestinal, endometrial or tubal type epithelium. ADSQ are composed of malignant squamous and glandular elements and account for 5–10% of cervical cancers. The cervical cancers observed in HIV-infected individuals have the same histological features as those occurring in non-infected individuals. The most common HPV types identified in SCCs are HPV 16 and HPV 18 with an approximate prevalence of 50–65% and 7–12%, respectively [120,121,134]. The results of HPV DNA detection in ADCs and ADSQs are more variable, as the study groups are smaller and subject to a statistical bias. However, the results from the largest series indicate that these cancers are associated with HPV 16 and HPV 18 in an approximately 1:1 ratio [122,134,135].

5.4. Clinical implications

Maintenance of the premalignant HPV-related lesions in HIV-positive women presents a significant challenge as the lesions tend to be multifocal and persistent, with a faster progression to malignancy [129] and a high recurrence rate after ablative or excisional therapy [128]. The invasive cervical cancers possess a higher rate of recurrence and higher mortality compared with those occurring in HIV-negative women [129,136].

According to current recommendations, HIV-positive women should undergo careful evaluation of the entire anogenital region every 6 months [137–139]. Immunocompromised women should be followed with a papanicolaou (Pap) smear and colposcopic examination of the cervix, vagina and vulva, while immunocompetent women may be followed with cytological examination alone. For women with high grade SIL, cervical LOOP excision and topical vaginal 5-fluorouracil (5-FU) is recommended [140]. The follow-up Pap smear and colposcopy should be performed in three-month intervals. The impact of HAART on the regression of cervical SILs is still under investigation. Therapeutic recommendations for invasive cervical carcinoma are the same as those for non-HIV infected women.

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