Pathology of Acquired Immunodeficiency Syndrome

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PROLOGUE

Acquired immunodeficiency Syndrome (AIDS) was first reported in 1981 (1, 2). Human immunodeficiency virus (HIV) has since been shown to be the causative agent of AIDS, and is present in virtually every country (3). The number of HIV infected patients has reached over 18.5 million adults and 1.5 million children in the world.

Currently in the United States, practicing pathologists have to be abreast with the disease process and complications of AIDS and to provide adequate diagnostic services to the patients.

There is no effective measure to deter the spread of the disease at the present. According to the Center for Disease Control (CDC) data (3), the incidence will increase at an estimated rate of 6,000 new infections each day. It is only a matter of time before reaching a pandemic including Korea. Thus it is timely to introduce and review the pathology of AIDS for the Korean pathologists and I thank the editorial board of this journal for inviting me for the task.

PATHOLOGY

The pathological changes seen in patients can be classified in three categories.

Ⅰ. Pathological changes caused by the host reaction to HIV Infection
Ⅱ. Opportunistic infection
Ⅲ. Pathological changes caused by opportunistic Infection

The above classification is only for the better understanding and is not to imply that the pathologic changes occur independently or in the same chronological order. These changes can be seen in any combinations and/or permutation in a given patient.

I. Pathological changes of HIV infection

1. Early phase

HIV is introduced by means of unprotected sexual contacts or parenteral introduction of blood products including the transplacental route. After the introduction of HIV, viremia follows causing prodromal symptoms. These are usually composed of fever, malaise, and transient lymphadenopathy mild or silent in many individuals. In this stage major findings include decreased peripheral lymphocytes, particularly T-helper cells and generalized lymphadenopathy.

A. Changes in peripheral lymphocytes

There is progressive reduction in the number of peripheral helper T-cells in patients with HIV infection as the infection progresses and the number of peripheral helper T-cells serves a good parameter to classify HIV infected patients into clinical categories (4). According to the new AIDS surveillance guidelines published by CDC in 1993 (5), patients with peripheral helper T-cells, (CD 4+) less than 200/μl are defined as AIDS. The exact mechanism of CD-4+ lymphocyte reduction in HIV infected patients is not known and remains as a matter of debate although several theories have been advanced (6). With progressive reduction of CD-4+ lymphocytes, a few morphologic changes of lymphocytes and monocytes can be identified by electron microscopy: test tube shaped confronting membranes (TCM) (7), and tubuloreticular structures (TRS) (8).

Both TCM and TRS are not specific to HIV infection and can be seen in other viral infections (9). However the frequency and extent of occurrence of these structures in AIDS exceed any other clinical conditions. TRS are also commonly found in endothelial cells of patients with systemic lupus erythematosus (SLE) which we were the first to report in 1969 (10). Originally we postulated that they would be viral in nature. Now we know they occur frequently in individuals with elevated alpha-interferon in the blood and can be induced by the administration of alpha-interferon experimentally (11). Thus TRS appear to be the "foot-prints" of alpha-interferon which are markedly elevated in AIDS as well as in SLE, and less marked by in other collagen vascular diseases. At times TCM and TRS are seen together in lymphatic tissue and systemic

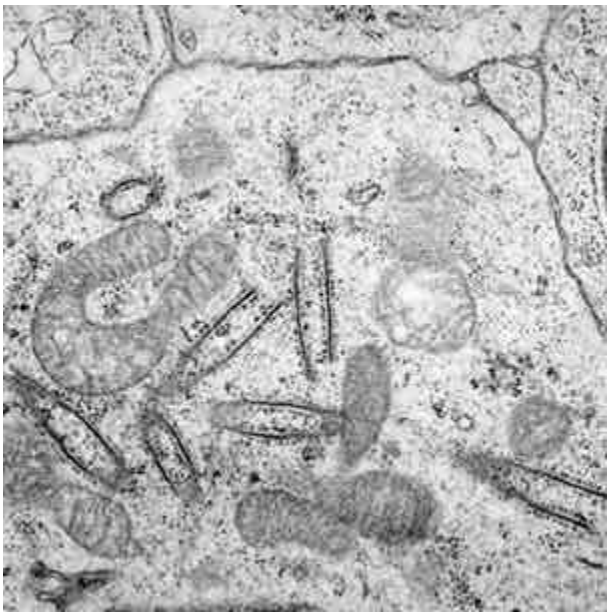

Fig. 1. Test-tube-shaped confronting membranes in the lymph node biopsy.

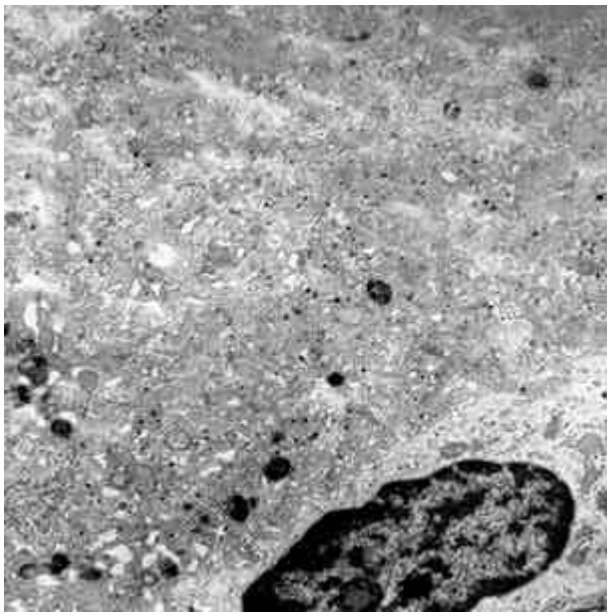

Fig. 2. Numerous HIV particles in the follicle undergoing folliculolysis.

endothelial cells (Fig. 1).

B. Lymphadenopathy

Some patients with HIV infection may present with transient or persistent generalized lymphadenopathy (PGL) (8,12~17). Transient lymphadenopathy is seen as a part of the prodome, and is rarely biopsied. The work-up for the etiology of PGL necessitates surgical biopsy. The common pathological changes seen in these lymph nodes are best characterized as florid follicular hyperplasia. Grossly, they are diffusely swollen and soft with prominent follicles at bulging cut surfaces. Microscopically, the nodal architecture is maintained with large prominent follicles often bizarre and dumbbell-shaped. The mantle zone is consistently attenuated and sometimes undetectable. The paracortex is often expanded and may contain scattered immunoblasts. In some cases, proliferations of monocytoid B-cells in the medullary sinuses, as seen in toxoplasmosis, can accompany reactive histiocytes in the paracortex. Occasionally multinucleated giant cells, as seen in measles, are present. These changes are typical enough to suggest a diagnosis of AIDS-associated lymphadenopathy for the experienced pathologist.

The overall changes of lymph nodes in this stage of HIV infection are those of fulminant primary immune response to HIV. Electron microscopy and immunohistochemical stains using HIV-related proteins will show numerous HIV particles concentrating in the follicles, particularly between the dendritic reticulum cells (18~20) (Fig. 2). Similar viral particles are replicating in lymphoblastic culture of the activated CD4+ lymphocytes (Fig. 3). Lymphadenopathy resolves spontaneously in the majority of patients but may persist to produce persistent generalized lymphadenopathty (PGL) (15).

In PGL, there appears to be progressive histologic changes in the lymph nodes.

Florid follicular hyperplasia appears to be followed by stages of folliculolysis/folliculitis, changes similar to Castleman's disease, hyaline vascular type, and eventual disappearance of follicles with generalized lymphoid depletion. Folliculolysis is characterized by dissolution of follicles due to cellular degeneration and necrosis of follicular center cells as well as dendritic reticulum cells (Fig. 2). It was not pointed out by other authors but inflammation is also involved in this stage of follicular changes in my observation. In addition to lytic changes one often sees infiltration of small lymphocytes and plasma cells in the follicle. Following this stage, the follicles undergo atrophic changes characterized by depletion of centroblastic cells, prominent follicular vessels with hyalinization and compensatory prominence of follicular dendritic reticulum cells (features very similar to Castleman's disease, hyaline vascular type). This stage is followed by complete disappearance of follicles and marked depletion of lymphocytes in general. From the stages of folliculolysis, fully manifested AIDS may be apparent clinically and there may also additional histologic changes of known complications of AIDS, such

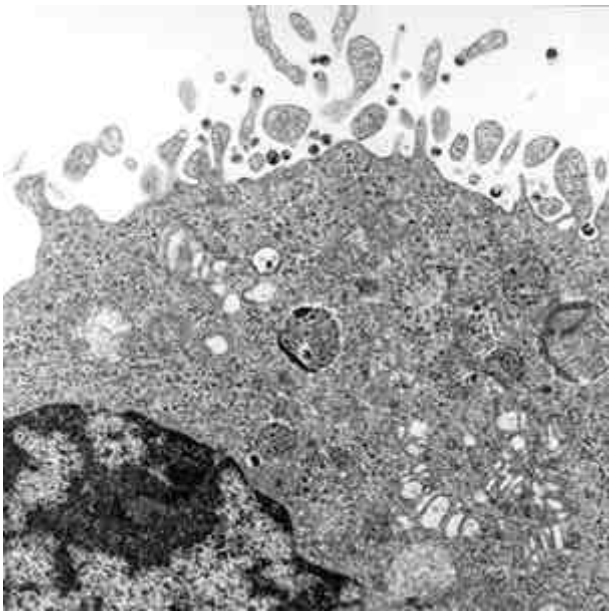

Fig. 3. HIV particles in lymphoblastic cultures.

as Kaposi's Sarcoma (KS) and opportunistic infections.

C. Lymphoepithelial cyst

Lymphoid hyperplasia in HIV-infected individuals is generalized involving tonsils and adenoids where changes are similar to those seen in lymph nodes (21). In salivary glands, lymphoid hyperplasia causes a lesion characterized as benign lymphoepithelial lesion with cyst formation. The incidence of lymphoepithelial cysts is high in AIDS patients and appears to be related to HIV infection (22).

D. Changes of other organs in HIV infection

HIV-encephalitis

Some patients with HIV infection develop encephalomyelitis without any evidence of identifiable opportunistic infectious agents or neoplasms (23). Microscopic changes are interesting in that aggregates of multinucleated giant cells are seen in perivascular areas of the brain with or without inflammatory infiltrates (24, 25). These giant cells are frequently shown to harbor HIV particles by electron microscopy, positive immunoreactivity for HIV-related proteins by immunocytochemical stains and HIV nucleoprotein sequences by in-situ hybridization (26) indicating the presence of infective HIV. These changes seem to be associated with progressive functional deficiencies of the central nervous system. No other etiologic agents have been isolated and HIV appears to be the causative agent, deserving a designation of HIV encephalitis (27). Production of giant cell formation is a known result of cytopathic effect of Human T-cell Lymphotropic Viruses (HTLV) in permissive human T-cell lines and multinucleated giant cells have been observed in lymph nodes and lymphatic tissue of HIV infected tonsils (21, 28) suggesting that HIV is directly responsible for this peculiar phenomenon.

II. Opportunistic infection

In AIDS cell-mediated immunity becomes gradually incompetent to a degree that any microbial agent of any degree of virulence may cause serious infection. Opportunistic infection by *Pneumocystis carinii* and cytomegaloviral infection were instrumental in the recognition and establishment of AIDS in 1981. Opportunistic infections may cause a great deal of diagnostic difficulties and provide daily challenges to pathologists. The author would like to offer three important "take-home" messages in dealing with opportunistic infections in AIDS.

a) Any microbial agents known or to-be-known can be etiologic agents in AIDS.
b) Recognized tissue reactions expected with certain known etiologic agents may be modified differently or may be totally absent.
c) Multiple infections are the rule rather than exception.

Thus one may have to include many unusual infectious agents in the differential diagnosis and perform special diagnostic procedures in dealing with tissue samples from AIDS patients. We should remember that we usually don't see what we don't think of ("out of mind, out of sight"). Although it is true that new etiologic agents and new manifestations of known etiologic agents are continuously found, they still occur in certain patterns which the experienced pathologist can sort out and pursue in order to arrive at the correct diagnosis without using wasteful shotgun techniques. For this reason, one has to be familiar with common and uncommon etiologic agents, and the pathologic changes they cause.

A partial list of etiologic agents in AIDS-associated infection is given below.

i. Bacterial
   a) *Mycobacterium tuberculosis* and *M. avium-intracellulare*
   b) *Salmonella*
   c) *Listeria*
   d) *Bartonella*
      Cat Scratch Disease
      Peliosis and angiomatosis
   e) Other common organisms

ii. Fungal
  a) *Candida*
  b) *Histoplasma*
  c) *Cryptococcus*
  d) Zygomycetes (*Mucor, Rhizopus, Absidia,* and *Cunninghamella*)
  e) *Aspergillus*
  f) Others
iii. Viral
  a) Herpes Group
  CMV, Simplex, EBV, Varicella HS-8
  b) JC virus (Progressive multifocal leukoencephalopathy)
  c) Human papilloma virus
  (Genital carcinomas)
  d) Others
iv. Parasites
  a) *Pneumocystis*
  b) *Toxoplasma*
  c) *Cryptosporidium*
  d) *Strongyloides*
  e) Others

For the interest of space the discussion will be limited to the most common, unusual or "new" pathogens.

Mycobacteriosis

At the beginning of the AIDS era *Mycobacterium avium-intracellular* (MAI) enjoyed the interest of pathologists. As a matter of fact, AIDS was instrumental in bringing MAI to the forefront as an important pathogen. It provided good opportunity for pathologists to study the pathologic lesions caused by MAI (29).

These range from typical caseating granulomas to nonspecific foam cell infiltration/aggregation in involved sites. The "foam cells" actually represent histiocytes containing numerous intracellular acid-fast bacilli. Thus when a pathologist sees "foam cells" in tissues derived from HIV-infected individuals, acid-fast stain is essential for diagnosis. One has to be reminded of the previously mentioned caution that in spite of the numerous bacilli, there may be no inflammatory reaction as is expected in immunocompetent individuals. Another recently described lesion caused by MAI is spindle cell tumor-like reaction in lymph nodes and other parenchymal organs (30). The spindle cells contain multiple acid fast bacilli (Fig. 5). When one encounters spindle cell lesions of AIDS patients, MAI infection should be considered in the differential diagnosis.

Mycobacterium tuberculosis (MTB) is presently gaining more importance as a more prevalent mycobacterial infection in HIV-infected patients as well as in the general population (31). Recent resurgence of MTB, particularly chemoresistant variants, is becoming a national problem of great concern in United States (32, 33). The lesions caused by MTB in AIDS range from caseating granulomas to nonspecific chronic inflammatory reactions without necrosis, more frequently the latter. Thus it is again important to apply acid-fast staining in nonspecific inflammatory lesions to rule out *M. tuberculosis* infection.

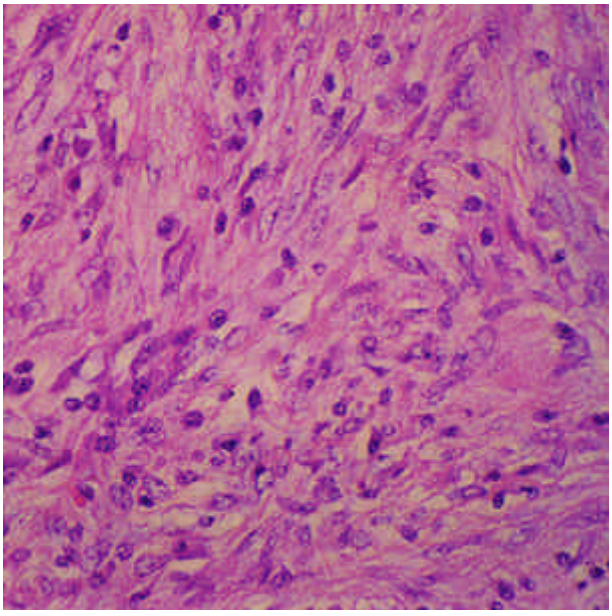

Fig. 4. MAI containing cells may appear spindly and lesions may simulate a spindle cell tumor.

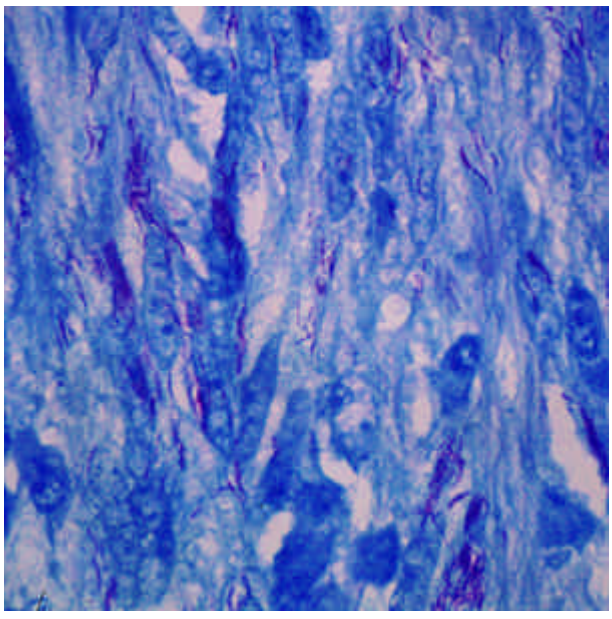

Fig. 5. Spindle cells contain numerous acid-fast bacilli.

Bartonella henselae

In 1983, an epoch-making case report by Stoler et al. appeared (34). They reported a patient with AIDS who developed multiple polypoid skin lesions with gross and microscopic appearance resembling Kaposi's sarcoma. The authors found tangled aggregates of bacillary organisms by Warthin-Starry stain. To the surprise of the authors, skin lesions disappeared by systemic antibiotic therapy. The authors equated the organism to those previously reported in cat scratch disease (CSD) (35). Subsequently, there appeared a plethora of reports of similar cases by many other investigators including our group. The lesion is now known as bacillary angiomatosis (36). Subsequently the bacilli causing bacillary angiomatosis, peliosis and CSD have been cultured (37) and found to be a fastidious organism, weakly gram-negative with biochemical and genetic characteristics similar to *Rochalimeae quintana* (the agent for trench fever) (38) and subsequently named *Rochalimaea henselae* (39). At the present this organism has the official designation of *Bartonella henselae*, because of microbiological and clinical similarities to *Bartonella bacilliformis*, the agent of verruga peruana (VP). *Bartonella henselae* infection in immunocompetent individuals causes a febrile disease often associated with a history of cat scratch and lymphadenopathy (CSD). Typical stellate granulomata with central abscess and geographic distribution in a lymph node biopsy clinches the diagnosis of CSD. In my laboratory Warthin-Starry stains were positive in 50% of cases studied (40).

B. henselae infection in HIV-infected patients may be widely disseminated, found in parenchymal organs and soft tissues. The lesions range from stellate abscesses to lesions designated as peliosis and angiomatosis. There is some controversy as to whether more than one organism, is involved in CSD as well as AIDS lesions. Our immunohistochemical studies using polyclonal goat and rabbit antisera raised against capsular proteins of *B. henselae* (after absorption with proteins) might be crossreacting with bacilli present in the lesions of immunocompetent immunocompromised individuals. These findings indicate that *B. henselae* is the responsible agent in the majority of cases, if not in all (41, 42).

Bacillary angiomatosis (BA) is characterized by nodular areas of prominent capillary proliferations with generous amounts of intervening connective tissue. The lining endothelial cells are prominent and often epithelioid (36) (Fig. 6). The morphologic variations of BA range from atypical granulation tissue to lesions mimicking Kaposi's sarcoma which (two main disease to be distinguished from BA). In BA one can appreciate more generous participation of stromal elements between the proliferating capillaries than in KS. There can be amorphous eosinophilic aggregates in the perivascular stroma, if one searches for them. These intercapillary aggregates are tangles of bacilli demonstrable by Warthin-Starry stain and electron microscopy (Fig. 7). The presence of bacilli is diagnostic.

The lesions of *bacillary peliosis* (BP) are most frequently found in the liver, and characterized by red

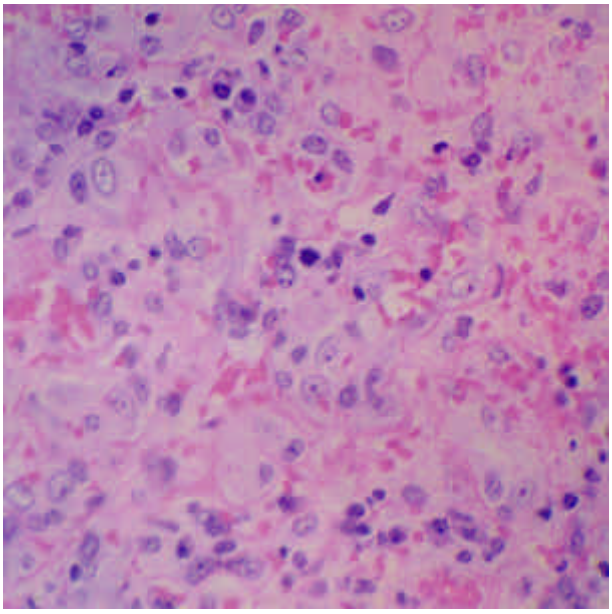

Fig. 6. Angiomatous proliferation of endothelial cells in bacillary angiomatosis. Note the epithelioid appearance of endothelial cells.

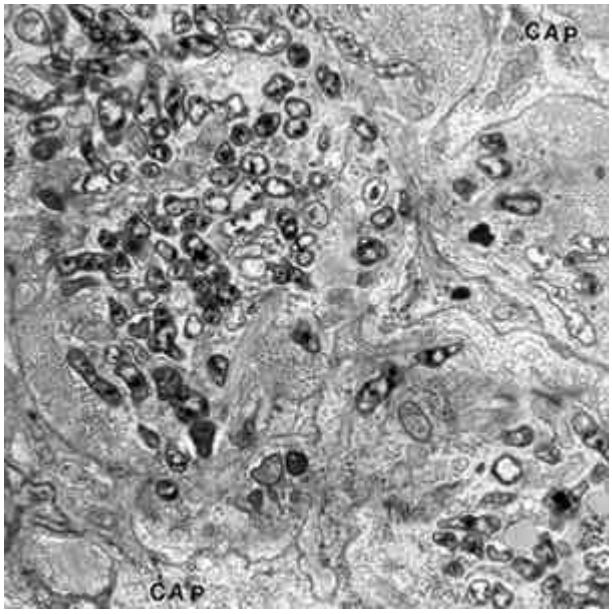

Fig. 7. Profiles of coiled bacilli in the stroma of BA lesions. CAP : capillary.

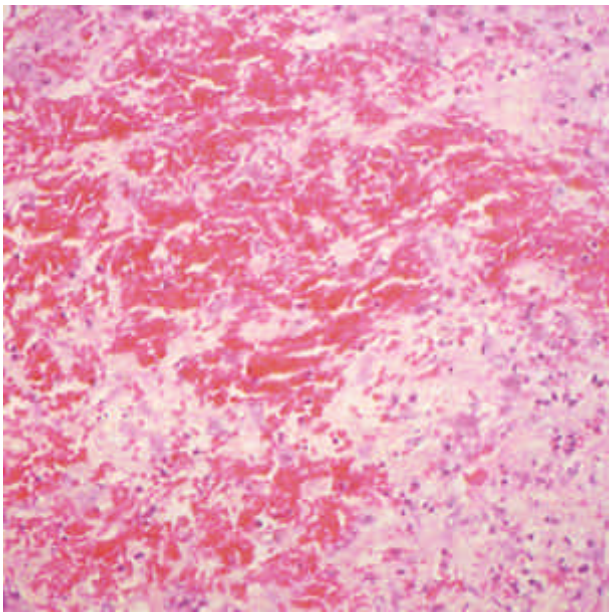

Fig. 8. A typical appearance of bacillary peliosis. Note dilated capillaries filled with red blood cells.

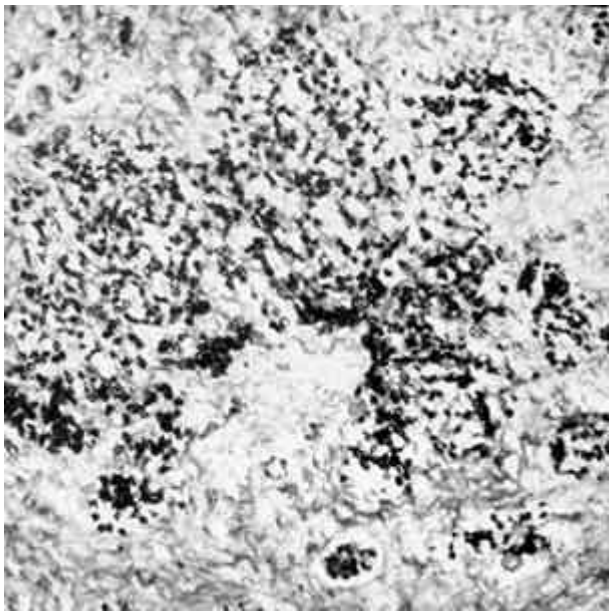

Fig. 9. Numerous *Pneumocystis carinii* organisms in the foamy fluid by silver-methenamine stain.

blood cell containing dilated endothelial-lined spaces forming nodules (Fig. 8). Occasionally there may be aggregates of polymorphonuclear neutrophils (PMN's) in the lesion. They are found within the lobules as well as in the portal tracts. The lining endothelial cells are usually indistinct and flattened compared to those of BA. BP is also associated with aggregation of Warthin-Starry positive bacilli in the stroma. In both BA and BP vascular proliferation and other changes are associated with numerous bacilli within the lesion suggesting that both lesions may result from angiogenic stimulation. Unabated proliferation of bacillary organisms in the immunodeficiency status of hosts might be the cause of vascular changes. In a related disease, verruga peruana (an endemic skin disease in Peru) due to *B. bacilliformis* shows similar histopathologic changes to *B. henselae* infection (43, 44). In VP, *B. bacilliformis* was found to produce angiogenic factors responsible for the histologic changes (45). Our preliminary findings indicate that the same is true for *B. henselae* infection.

The histomorphologic changes caused by *B. henselae* embrace a constellation of changes ranging from pyogranulomatous lesions with stellate abscesses in immunocompetent individuals to noninflammatory vascular proliferative lesions designated as BA and BP. This spectrum of disease may be a reflection of altered cell mediated immunity of the host. The number of organisms and the intensity of granulomatous inflammatory response with necrosis appear to be inversely related to the degree of preservation of T-cell function of the host.

In AIDS, *B. henselae* may grow to an uninhibited extent due to deficient cellular immunity permitting elaboration of sufficient angiogenic factor(s) to be produced by the organisms resulting in the vascular lesions of BA and BP.

Pneumocystis carinii (PC)

Before the era of AIDS, *Pneumocystis carinii* infection was rare and limited to those with severe immunosuppression due to extensive chemotherapy for advanced malignancy or subjects residing in the known endemic areas. PC pneumonia was one of the first clinical manifestations of AIDS instrumental in the establishment of the entity(1). Typically PC causes pneumonia characterized by accummulation of foamy fluid in the alveoli with interstitial inflammatory reaction. The foamy fluid contains aggregates of cysts which can be demonstrated by special stains. The most favored staining is Gomori's methenamine silver stain by which PC appear as cysts with smooth, rigid walls and small eccentric nucleoid. Cysts of PC can be easily recognized in the smears of bronchial lavage specimens. The cysts are often collapsed, forming a sickled appearance. The typical lesions are easy to recognize and usually limited to the lung. Organisms are found in the air spaces only without invading the interstitium. Therapy using aerosolized anti-PC medications was introduced in 1988, and brought a decline in the incidence of PC pneumonia. However the prophylactic use of aerosolized pentamidine caused atypical

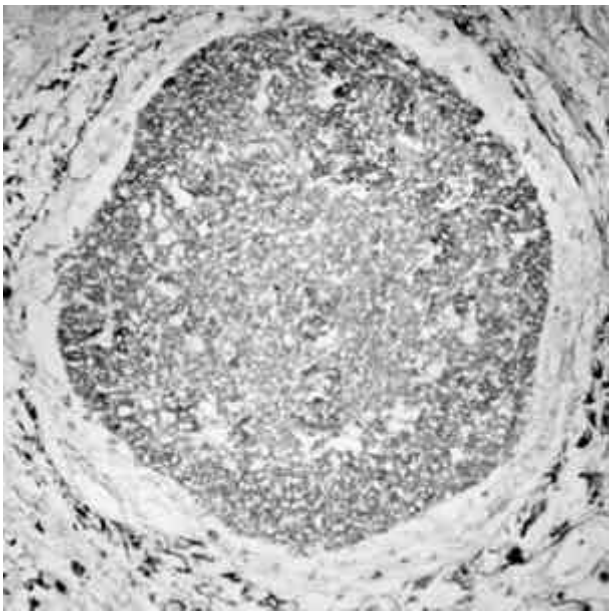

Fig. 10. A lung biopsy of a patient revealed invasive pneumocystis infection.

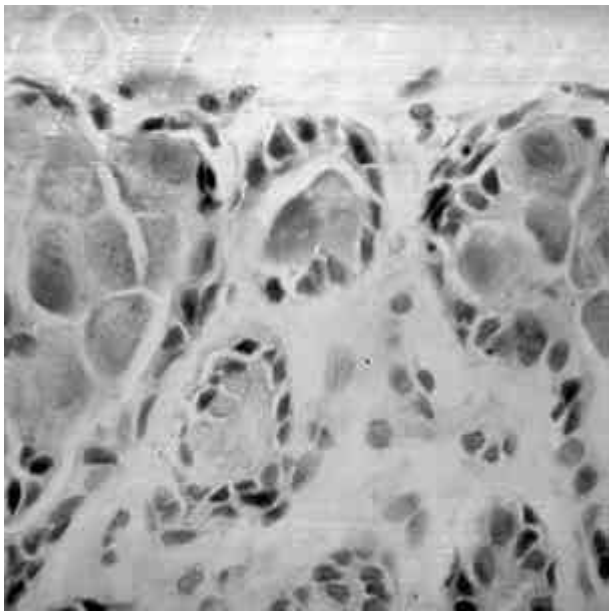

Fig. 11. Cytomegalic cells due to CMV infection in AIDS patients with colitis frequently appear atypical.

clinical and histopathologic presentations of PC infection (46, 47). Since then there have been frequent reports dealing with locally invasive and disseminated pneumocystosis in such patients. Ineffective control of organisms already spread beyond the reach of aerosolized pentamidine might explain this phenomenon (Fig. 10).

Cryptosporidiosis

Cryptosporidium sp. is another protozoan highlighted by AIDS. This intracellular coccidian parasite is implicated in persistent watery diarrhea in immunocompromised individuals, particularly humans with AIDS (48). The organisms have six major developmental forms which are usually found within extracytoplasmic parasitophorous host vacuoles formed by host membrane invagination and fusion. They are usually found along the luminal surfaces of the intestinal mucosa.

Cytomegalovirus (CMV) infection

Along with PC, CMV is the most frequent pathogen in HIV-infected individuals. The lung is the favorite site of involvement causing pneumonia and is often fatal (49). The gastrointestinal tract is another site of frequent CMV involvement of clinical importance (50). The epithelial cells are the favorite cells for CMV infestation closely followed by endothelial cells harboring typical intranuclear inclusions. The lesions are characterized by the scattered cytomegalic cells with typical owl-eyed Cowdry type A nuclear inclusions, presenting no serious diagnostic challenges, and usually not requiring additional diagnostic procedures such as immunohistochemistry or in-situ hybridization. In some patients seriously compromised individuals, however, cytomegalic cells can be atypical and nuclear inclusions may be smudgy, and appear less diagnostic (Fig. 11). In such instances adjunct techniques are required for the confirmation of the diagnosis (51, 52). A few additional points should be emphasized in the dealing with CMV infection. Firstly, CMV is frequently part of a compound infection requiring to be attentive of ruling out other pathogens such as fungi or parasites. Secondly, immunohistochemistry can be helpful to detect CMV-related protein when the CMV lesions are not fully formed, and are not diagnostic microscopically. When clinical presentation and tissue changes indicate a possibility of CMV infection, it is advisable to perform immunostains. I have seen a few cases of CMV infection diagnosed by immunostains only. Lastly, CMV can be disseminated and can produce surprising lesions at any body site.

Toxoplasmosis

Toxoplasma gondii (TG) is an obligatory intracellular protozoan, another pathogen which came to its important status through AIDS (53, 54). TG is the most frequent cause of encephalitis in HIV-infected patients, but it can also disseminate throughout the body. The lesions are characterized by mixed inflammatory exudate with necrosis. TG-containing cells are usually found along the necrotic borders. One should pay particular attention to recognize trophozoites of TG aggregating within the

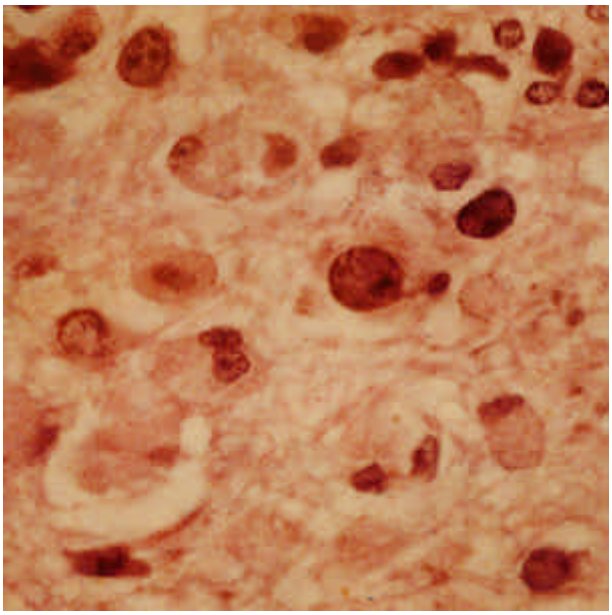

Fig. 12. Patchy areas of demyelinization and accumulations of foamy phagocytes are characteristic for PML. Note a nucleus containing an inclusion.

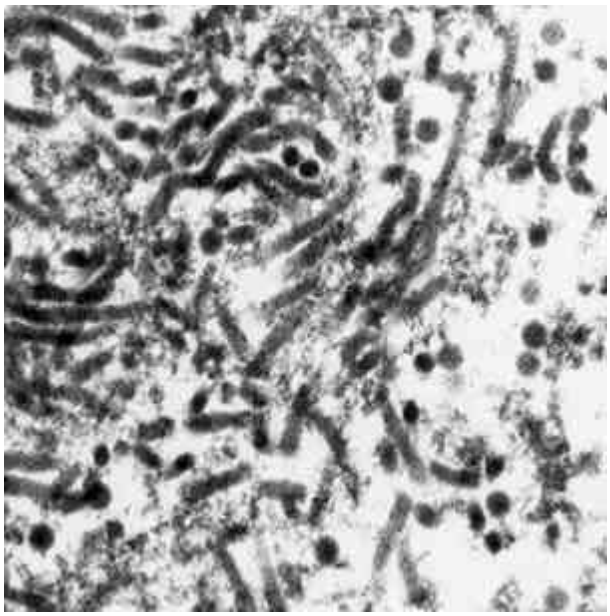

Fig. 13. J.C. virus are a DNA virus, usually round but occasionally may occur as solid curved tubes.

dying cells, mimicking cell debris. The organisms are seen in the routine H & E stain, are typical enough to be recognized on Giemsa stain, but are more easily identified by immunostains using commercially available anti-TG antisera.

JC virus infection

JC virus is not the agent for Jacob-Creutzfelt disease, a slow virus disease which became notorious because of "Mad Cow Disease" in England. JC virus is a DNA virus belonging to the papovavirus group, and is so named after the initials of the first patient yielding the isolate.

JC virus is the causative agent for progressive multifocal leukoencephalopathy (PML). PML is a primary demyelinating disease involving the white matter of the brain. PML is the most frequent encephalitis among HIV-infected patients (55, 56). Clinical presentation and imaging studies may give misleading findings of a neoplastic process, necessitating brain biopsy for definitive diagnosis. The lesions are characterized by patchy areas of demyelination, accumulations of foam cells, infiltration of mononuclear cells, and gliosis. On careful examination, some of the nuclei of these cells will appear smudged, representing JC virus inclusions (Fig. 12). On electron microscopic examination these inclusions are composed of round viral particles with frequent paracryastalline lattice arrangements and rare tubular forms (Fig. 13). Rarely viral particles are also found in the cytoplasm. Virus-containing cells have the features of oligodendrocytes. Rarely viruses can also be seen in astrocytes. The EM finding is quite diagnostic. Anti JC serum is available commercially for diagnostic application. DNA of JC virus has been sequenced, and specific oligonucleotide probes are also available for in-situ hybridization.

Epstein-Bar virus (EBV)

Epstein-Barr virus is a ubiquitous virus and belongs to the herpes group. EBV infection may be the most frequent infection in immunocompromised individuals. One of the peculiar lesions caused by EBV in AIDS patients is so-called hairy tongue condition of hyperkeratotic papillomatosis. The diagnosis of EBV infection has to depend on serological or molecular biological techniques, since it rarely produces cytolytic changes recognizable by the pathologist. The most important consequence of EBV infection is its latency which is associated with neoplastic transformation. This will be dealt with below.

Other infections

As previously stated, it is safe to assume that any kind of microbial agent known or unknown to man as a pathogen or saprophyte may become pathogenic in AIDS. Pathologists played an important role from the beginning of the AIDS era in recognition and identification of the pathogens is an etiology of AIDS. Challenges remain the same or greater today because of

emergence of new conditions, and modifications of existing ones by therapeutic interventions.

III. Seconary pathological changes as a consequence of opportunistic infection

From the very beginning of the AIDS era the occurrence of tumorous conditions was a well known complication of AIDS. Kaposi's sarcoma which used to be a rare tumor (except for certain endemic areas) became important in patients with AIDS, not only because of its frequency and morbidity, but also its role in establishing the syndrome of AIDS in 1981. Neoplasms have been common complications in immunocompromised individuals, even before the era of AIDS: and there have been several theories advanced to explain why. Among them was the infectious theory. AIDS patients have provided a fertile ground for observing the oncogenicity of any infectious agent. Recent technical refinement in molecular biologic techniques have been applied to uncover some mysteries surrounding infectious oncogenesis, and a vast amount of data have been accumulated to support the infectious theory of neoplasia. AIDS-related neoplasms and tumor-like conditions appear to be consequences of infection by various agents.

Kaposi's sarcoma

Kaposi's sarcoma (KS) was the first malignant tumor known to complicate HIV-infected individuals (2). The lesions are usually multifocal and undergo a few developmental stages from the lesions of inflammatory granulation to tumefaction similar to the ordinary KS seen in immunocompetant people (57). The similarity between ordinary KS and AIDS-associated KS stops at this level. AIDS-associated KS occurs at a younger age, is frequently multifocal, progresses and disseminate more rapidly, and can frequently be fatal.

The established lesions are characterized by spindle cell proliferation forming nodules with clear slit-like openings dissecting red blood cells. Their endothelial nature is not evident in some cases, but can be brought out by applying immunostains using antisera against endothelial cells or ultrastructural investigation (Fig. 14). There has been controversy as to whether the malignant endothelial cells are vascular or lymphatic in origin. Many investigators (including this author) believe they are lymphatic (58, 59). There have been several observations to support the claim, although immunohistochemical and other marker studies are inconclusive. The earliest change of KS in lymph nodes is always found in the capsule, and KS is rare in the anatomic sites in which lymphatic vessels are sparse such as liver and adrenals. There are several other interesting issues to consider. What is the real nature of KS? Neoplastic? Malignant? When Kaposi described his original cases, 2 of 5 patients died of the disease seemingly justifying the malignant designation. However, examining many KS lesions, one notes that in spite of the ominous appearance of the spindle cell proliferation, mitoses are rare, and usually not atypical. What about the widespread dissemination? Isn't it metastasis? It is true that AIDS-associated KS presents with widespread dissemination suggestive of metastasis (60). However, when the pattern of dissemination is closely scrutinized, one finds several discordant aspects. Numerous lesions of skin (exceeding a few hundred) can occur without metastatic lesions in any other organs (61). KS lesions are rare in the organs which are frequent sites for hematogenous spread. The pattern of pulmonary involvement of KS for example is peculiar in that lesions are found in the interstitium and submucosa of bronchi. There are hardly any grossly recognizable solid tumor nodules. These are not usual features of metastatic tumors in the lung. As previously mentioned, the earliest lesion of KS in lymph nodes is found in the capsule not in the marginal sinuses (which are the first site for any metastatic tumor). Furthermore the incidence of KS involving the liver is rare. Many case reports of KS in the liver represent confusion with bacillary angiomatosis. There are only a few cases of histologically well documented cases of liver involvement. In well documented cases the lesions are limited to the capsule or periportal connective tissue, hardly consistent with metastasis (62). Thus the claim that KS is a malignant tumor which can

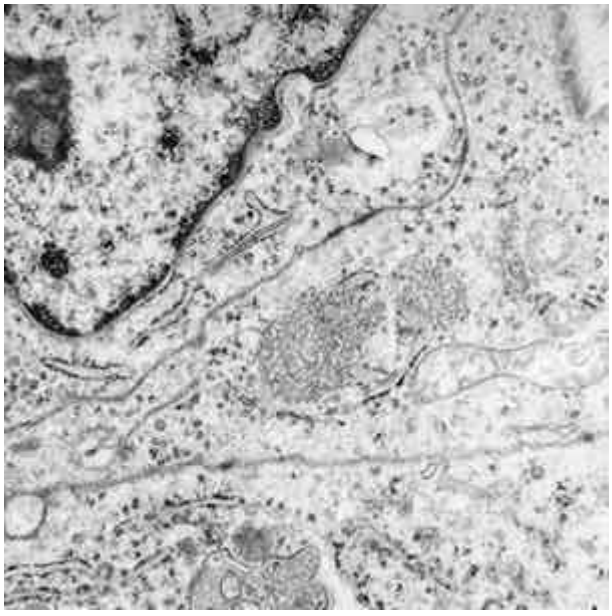

Fig. 14. A KS cell containing TRS in the endoplasmic reticulum.

metastasize is not based on a firm foundation (63, 64).

Alternatively, the above features can be nicely explained by a theory that KS represents a reactive proliferative process of lymphatic vessels and their endothelial cells as a response to certain cytokine(s) yet to be found. In this regard there are a few promising new developments (65~67). Chang et al. found a peculiar DNA sequence similar to HSV and EBV in the DNA of Kaposi cells in 1994. Chang's findings are now confirmed by many other investigators. They were found in AIDS-ssociated KS as well as endemic KS. It is designated as HSV-8. The etiological role of HSV-8 in KS is not yet known and requires further investigation. Proliferation marker CD-40 was found to be up-regulated in Kaposi cells, and alpha interferon seem to promote CD-40 indicating some cytokines are in operation. HIV tat gene was shown to cause dermal lesions in the transgenic mice suggesting a direct involvement of HIV in the pathogenesis of KS (68).

Lymphoma and Hodgkin's disease

The occurrence of lymphomas and Hodgkin's disease in immunocompromised individuals was also known even before the era of AIDS. Polyclonal B-cell proliferative disorders have also been documented in immunosuppressed patients with transplants. Since Doll and List (69) reported the occurrence of Burkitt's lymphoma in homosexual men, it soon became apparent that lymphomas were a frequent complication of AIDS, now they stand as the second most common malignancies in patients with AIDS following KS (70). The lymphomas in AIDS patients are characteristic in that they are intermediate to high grade, frequently extranodal, and progress rapidly (Fig. 15). Peculiarly they can be polyclonal (71). Even composite lymphomas of B and T-cells have been reported. Beside non-Hodgkin's lymphomas, Hodgkin's disease (72) and other lymphoproliferative disease such as plasma cell tumors, T-cell chronic lymphocytic leukemia, T-cell non-Hodgkin's lymphoma, B-cell acute lymphocytic leukemia, Sezary-like syndromes and angiocentric immunoblastic adenopathies have been documented in AIDS. Hodgkin's disease in patients with AIDS usually presents with advanced stage and exhibits aggressive behavior (73). The pathogenesis of lymphoproliferative processes in the immunocompromised individual in general, and AIDS in particular, are not clearly understood. However, data deriving from the investigations using advanced molecular techniques suggest that EBV plays an important role in this disease (74). Many investigators revealed EBV DNA sequences in the nuclei of lymphomatous cells in the majority of cases tested (Fig. 16). 40~60% positivity is too low in our judgement. Furthermore in a given case, EBV genome appears to be present in all tumor cells, indicating that EBV is involved in the earliest phase of clonal expansion (75, 76). These findings together with the proven role of EBV in African Burkitt's lymphoma present a strong arguement for the etiologic role of EBV in this disease.

Squamous Cell Carcinomas of the Anus in Homosexual Men

Anal carcinomas of homosexual men are frequently

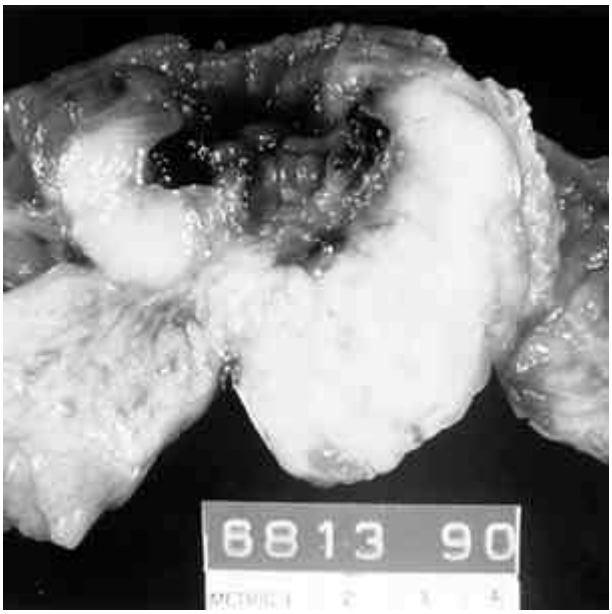

Fig. 15. A high grade lymphoma involving the intestine in an AIDS patient.

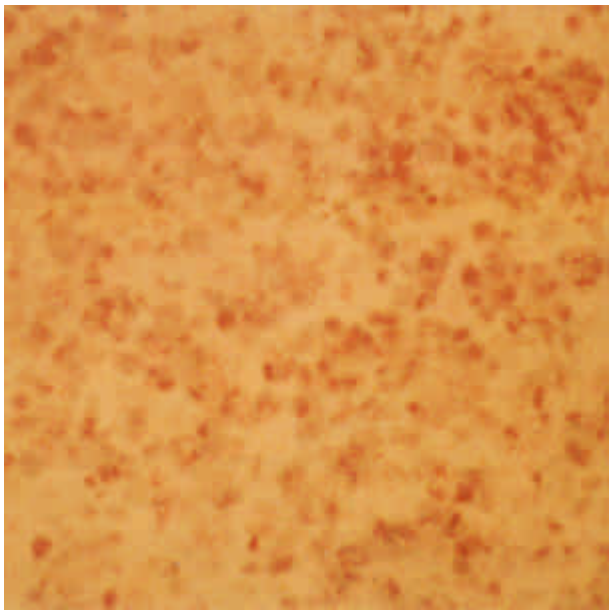

Fig. 16. EBER-1 expression of high grade lymphoma cells. In situ hybridization.

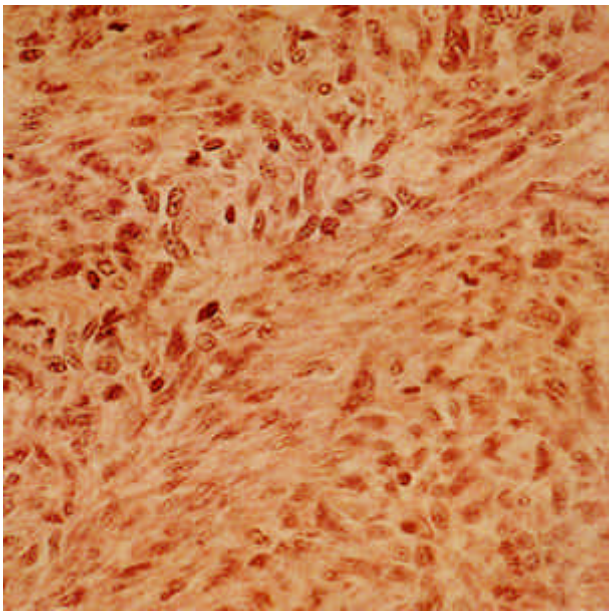

Fig. 17. A leiomyosarcoma of brain in a 14 year old patient with AIDS.

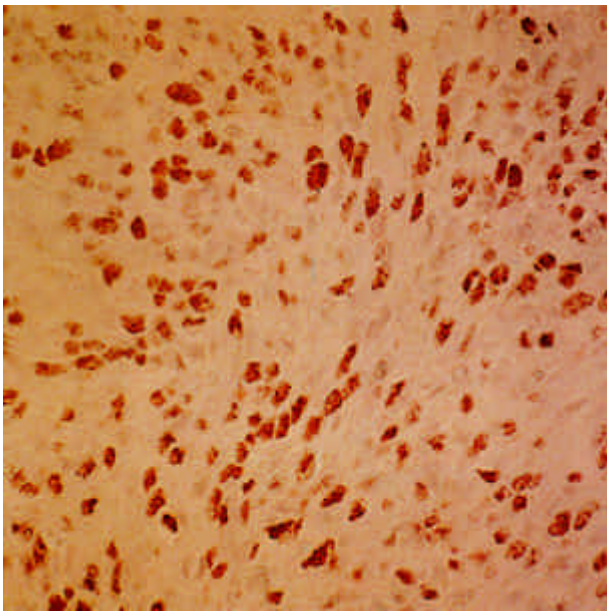

Fig. 18. The majority of tumor nuclei express EBER-1 EBV genome. In situ hybridization.

associated with human papilloma viruses (HPV) and HPV infection encouraged by the immunodeficient status in AIDS plays a role in this disease (77, 78).

Cervical carcinomas

Association of HPV and squamous carcinomas of the female genital tract is well established. Squamous cell carcinomas in females with HIV infection behave in a much more aggressive fashion (79) and the Gynecologic Oncologic Group made a special surveillance program for the management of such patients.

Smooth muscle tumors

Some HIV-infected patients particularly in the pediatric age group may develop benign as well as malignant smooth muscle tumors (80, 81) (Fig. 17). Interestingly the presence of EBV genome by in-situ hybridization was shown in the nuclei of these tumors (82, 83) (Fig. 18). The exact relationship and pathogenetic roles of EBV in these smooth muscle tumors are yet to be delineated by further studies.

Other constitutional changes

Patients infected by HIV develop a variety of diseases which do not belong to any categories heretofore presented. Chronic wasting syndrome similar to cachexia seen in advanced cancer patients (84), cardiomyopathy (85), peripheral neuropathy (86), nephropathy (87), marrow suppression and dysplasia, and dermatopathies of unexplained pathogenesis have been recorded.

EPILOGUE

It is apparent that HIV infection is a malady of immense magnitude and appears to present with bigger problems than any other malady mankind has faced, leading to helplessness and pessimism. Pathologists played an important role from the very beginning of the recognition of AIDS, and are expected to continue to play that role in the understanding of the disease process, and identification of etiologic and pathogenetic processes of infectious and neoplastic complications of AIDS. I am optimistic that we will face these challenges successfully.

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