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Histopathologic Spectrum of AIDS-Associated Lesions in Maharaj Nakorn Chiang Mai Hospital

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SUMMARY **The histopathological alterations in various organs and the presence of AIDS-associated lesions were studied in 86 biopsy and 29 necropsy specimens of AIDS patients. The most common cancer seen in this study were malignant lymphomas (4% of cases) with development of extensive extranodal lymphomatous involvement from the outset. Although a preponderance of high grade B-cell pathologic subtypes is found in AIDS-associated lymphoma, we also report the first case of T-lymphoblastic lymphoma with a picture of acute lymphoblastic leukemia (T-ALL). Tuberculosis (34% of cases) was the most common opportunistic infection presented in tissue sections, and the majority of tissue biopsies revealed poorly organized granulomas and extensive necrosis with numerous bacilli. Penicilliosis (20% of cases) appeared to be the most common cutaneous lesion with multiple organ involvement. The involved organs showed a partially anergic tissue reaction characterized by poorly formed granulomas with diffuse infiltrate of fungi-laden macrophages and lymphoid cell depletion. This organism has to be distinguished from *Histoplasma capsulatum* and other yeast-form fungi. Co-existing cytomegalovirus and *P.carinii* infections were the predominant findings in lung necropsy specimens from pediatric patients who died from AIDS. A major pathologic feature in this group was diffuse alveolar damage stage II to III with heavy loads of organism and extensive lymphoplasmacytic infiltration.**

Human immunodeficiency virus infection resulting in acquired immuno-deficiency syndrome (AIDS) is a multisystemic disease. On the basis of the data currently available these numerous systemic lesions can be classified into three categories.[1] The primary lesions are due to HIV infection of tissues or organs. Associated lesions are those with direct or indirect sequelae of HIV infection or its treatment. The third category comprises lesions of undetermined pathogenesis, some of which may be related to more than one pathogenetic mechanism. HIV-associated lymphoma leukemia currently occurs in 5-10% of AIDS patients.[2,3] AIDS-related lymphomas are high-grade tumors with the morphologic characteristics of either small non-cleaved cell lymphomas of the Burkitt type or large cell centroblastic and immunoblastic lymphomas. Acute lymphoblastic leukemia has rarely been reported in association with HIV infection and was reported to be only B-cell phenotype.[4,5] An increased incidence of tuberculosis (TB) in HIV-afflicted patients has been widely observed.[6-8] The atypical features of TB in patients with AIDS indicate varying degrees of failure of the cellular immune response.

Penicilliosis is endemic to countries of Southeast Asia and the southern part of China.[9] Only one-fourth of those cases who are also infected with HIV have been reported in the English language literature.[10-12] In this article we describe histopathologic and immunopathologic characteristics of common AIDS-associated lesions in our hospital reflected by study of 9 biopsies of lymphomas-leukemia, 36 biopsies of tuberculosis and 41 biopsies of penicilliosis in adult AIDS cases. Opportunistic infection in pediatric AIDS patients was also studied in 29 necropsy specimens.

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MATERIALS AND METHODS

Patients

All AIDS patients records, as defined by the Thai AIDS criteria, from medical and pediatric files (200 cases) were reviewed for pathological information. The slides from every biopsy or necropsy performed were reviewed. Additional special staining was carried out if necessary. Eighty-six (86) biopsy specimens and 29 necropsy specimens were studied. The data revealed three interesting types of AIDS-associated lesions in biopsy specimens comprising malignant lymphoma (4% of cases), tuberculosis (34% of cases) and penicilliosis (20% of cases).

Histopathology

Our group of pathologists then reviewed sections including special and immunostains in 10 biopsies (9 cases) of lymphoma and leukemia; 36 biopsies of tuberculosis; 41 biopsies of penicilliosis and 29 lung necropsy specimens from pediatric AIDS patients. Patients with tuberculosis and penicilliosis were included if they had mycobacteriology records for positive cultures.

The diagnoses were made based on routinely stained sections prepared from formalin-fixed, paraffin-embedded surgical biopsies or necropsy tissue samples. Penicilliosis patients were diagnosed based on Gomori-Methenamine-Silver (GMS) stain.[13] The histochemical stain for identification of acid fast bacilli (AFB) on sections was performed by the Ziehl-Neelsen method.[14] We determined whether granulomatous inflammation (defined as a focal aggregate of epithelioid histiocytes) was present and described the inflammatory cell population, including multinucleated giant cells. Semiquantitative scores were assigned to the percentage of granuloma area occupied by necrosis and to the number of AFB per high-power ($\times 400$) field in the most heavily infected area. Semiquantitative scores (1^+-$5^+ = 20\%$-100%) for fungus count on GMS stain were estimated by percentage of area of fungus load in each organ sample. Finally, the pathologists gave an overall impression as to whether granulomata were well or poorly formed, based on criteria modified from Ridley and Jopling.[15] A cohesive collection of epithelioid histiocytes in an overall nodular configuration was taken as well-formed, regardless of whether giant cells central necrosis, or a peripheral mantle of small lymphocytes was present. Patients with non-Hodgkin's lymphoma (NHL) were classified according to the Working Formulation.[16]

Immunophenotypic Analysis

The expression of B- and T-cell associated antigens, CSw75 (LN-1 from Dr Epstein) and CD45 RO (UCHL-1 from dakopatts) were determined on deparaffinized tissue sections prepared from formalin-fixed, paraffin-embedded tissue samples using an avidin-biotin immunoperoxidase technique.[17] CD_3, CD_4 and CD_8 (Leu 4, Leu 2a and Leu 3a from Becton-Dickinson) expression, markers of pan T; helper and suppressor T-cells, respectively, were also determined on cytospin from bone marrow aspiration using the same technique.

RESULTS

Histopathologic and immunologic features of AIDS-associated lymphoma and leukemia

This lymphoma-leukemia series in AIDS patients was classified according to the Working Formulation.[16] The results of the histopathologic and immuno-phenotypic classification of these lymphomas are shown in Table 1. Among the four NHL cases in the small non-cleaved cell category of the Working Formulation, two different morphologic subsets were noticed. In three cases, the lymphomas fulfilled the diagnostic histologic criteria proposed for Burkitt's lymphoma.[18] In another case, the lymphoma corresponded to the variant of Burkitt's lymphoma, designated as Burkitt's lymphoma-like lymphoma with plasmablastic differentiation.[19] The other four NHL cases fulfilled the dignostic histologic criteria of intermediate grade malignant lymphomas, diffuse mixed, small and large cell (3 cases), and large non-cleaved cell (1 case) in the Working Formulation. The last case first presented with the picture of ALL-L2 (Fig. 1) according to FAB classification.[20] Later, we received a lymph node biopsy showing the typical morphologic findings of malignant lymphoma, lymphoblastic convoluted cell type (Fig. 2).[21] We confirmed the lineage of these lymphomas by performing the ABC immunoperoxidase technique using T- and B-cell markers.

The expression of the B-cell associated marker, CDw75, was found in 8 of the 9 evaluated cases (Table I). The last case revealed positive staining with CD_3 and CD_8 on cytospin from bone marrow aspiration and the paraffin sections of lymph node from this patient also demonstrated positive results with CD45RO, a T-cell marker.[22]

Histopathologic features of AIDS-associated tuberculosis

Tissue biopsies (Table 2) from 36 patients were considered diagnosis if they contained either granulomatous inflammation (present in 83%) or AFB (present in 64%). Histologically, necrosis was usually of the central, amorphous type classically associated with caseation, but karyorrhexis was prominent in 40% of cases and a combination in 13% of cases. Granulomatous architecture was judged as poorly formed (Fig. 3) in 58% while well-

Table 1. Histopathologic and immunologic features of AIDS-associated lymphoma and leukemia.

Tissue examined	No of cases	Histopathologic types/working formulation; FAB*	Immunologic expression
Lymph nodes	5	High grade ML, SNCC, Burkitt's (2); High grade ML, SNCC, Non-Burkitt's (1); Intermediate grade ML, large non-cleaved cell (1);	B cell ($CDw75^+$ $CD45RO^-$)
		†High grade ML, lymphoblastic, convoluted cell (1)	T cell ($CDw75^-CD45RO^+$)
Intestine (Ileum)	1	Intermediate grade ML, diffuse mixed small and large cell	B cell ($CDw75^+CD45RO^-$)
Liver	1	Intermediate grade ML, diffuse mixed small and large cell	B cell ($CDw75^+CD45RO^-$)
Nasal mass	1	Intermediate grade ML, diffuse mixed small and large cell	B cell ($CDw75^+CD45RO^-$)
Pericardium	1	High grade ML, SNCC, Burkitt's	B cell ($CDw75^+$ $CD45RO^-$)
Bone marrow	1	†$ALL\text{-}L_2$	T cell ($CD_3^+CD_8^+CD_4^-$)

*FAB = French-American-British classification for leukemia
†Same patient

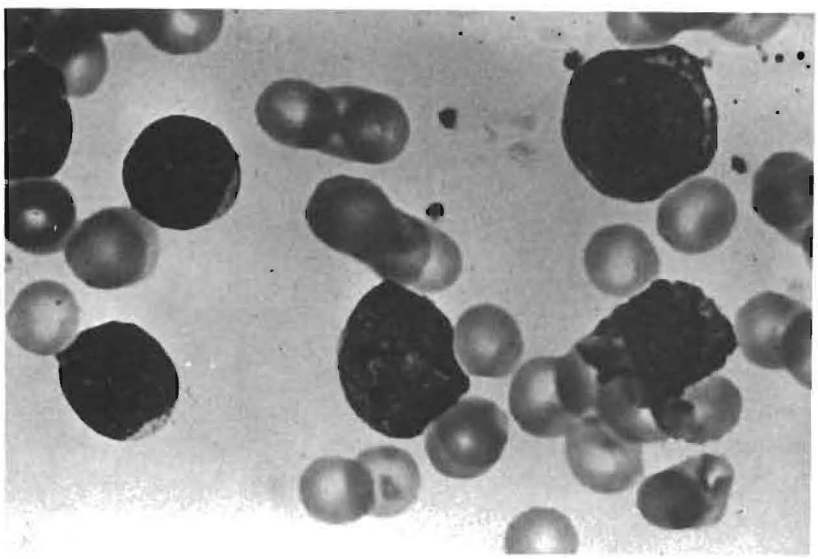

Fig. 1. Peripheral blood smear (×1000) showing a range in cell size, primitive chromatin, and marked nuclear irregularities and convolutions, identical to that seen in "T-cell ALL".

formed types (Fig. 4) were recognized in 25% of the cases. Multinucleated giant cells were notably present in only 19%; granulomas were absent in the the remaining cases (17%). AFB were seen in 23 of 36 specimens (64%) and were present in a higher proportion of biopsies. Most lesions harbored AFB in high density, exceeding 100 per field in 39% of all biopsies (Table 3) or 61% of positive cases.

Five of six cases without granulomas had miliary lesions, showing a relatively uniform histologic picture characterized by extensive central necrosis. The necrotic areas typically contained copious nuclear debris rather than acellular caseation. Moreover, cellular infiltration, consisting of histiocytes and lymphocytes, was observed at the periphery of the necrotic foci. Multi-

Table 2. Histopathology of AIDS-associated tuberculosis.

Presence of necrosis	Number of cases	Percentage
Necrosis 0-10%	5	14
Necrosis 10-50%	10	28
Necrosis >50%	21	58
Presence of granulomatous formation	**Number of cases**	**Percentage**
Well formed	9	25
Poorly formed	21	58
Granuloma absent	6	17
Other findings	**Number of cases**	**Percentage**
Multinucleated giant cells-present	7	19
Multinucleated giant cells-absent	20	81
AFB-present	23	64
AFB-absent	13	36

Table 3. Acid-fast bacilli in tuberculous lesions.

No of AFB per HPF	No of cases	Percentage
None	13	36
<10	4	11
10-100	5	14
>100	14	39
Total	36	100

nucleated giant cells were always absent. All these five cases revealed numerous AFB, exceeding 100 per high-powered field.

Histopathologic features of AIDS-associated penicilliosis

Histopathologic features of AIDS-associated penicilliosis are shown in Table 4. The most common histopathologic feature of penicilliosis in lymph nodes was poorly formed granulomata, (Fig. 3) which were found in 18 of 21 lymph node samples. The area of necrosis was also identified and this was indistinguishable from the one observed in tuberculosis. In addition to these findings, we could recognize other patterns of histopathology in the same lymph nodes, such as sinus hyperplasia and clusters of epithelioid histiocytes. The latter were very similar to the histopathologic characteristics found in toxoplasmosis. Other organs of involvement included the liver, bone marrow and skin where the pattern of diffuse histiocytic reaction was predominant. This reaction was characterized by a diffuse infiltrate of fungi-laden macrophages and by lymphoid cell depletion.

Routine pathological sections with GMS and PAS stains revealed abundant spherical, oval, elliptical and also sausage-shaped or septate yeast cells in both intracellular and extracellular forms. *Penicillium marneffei* yeast cells varied in size from 3 to 8 μm in diameter. Semi-quantitative scores for fungus count in most cases revealed a high density of fungus load in 60% or more of the whole sample area (Table 4).

Histopathologic features of pediatric AIDS-associated opportunistic infection in lung necropsies

Histologic findings in tissue necropsies from 29 patients who died from AIDS are shown in Table 5. Co-infecting *Pneumocystis carinii* (PC) and cytomegalovirus (CMV) were the most common pathogens found in this study. Changes in lung parenchyma were the appearance of diffuse alveolar damage (DAD) which varies, depending upon stages of development. The early or acute stage of DAD (stage I) consisted of interstitial and intra-alveolar edema with varying degrees of intra-alveolar hemorrhage and fibrin deposition. Hyaline membranes, the histologic hallmark of this stage, were recognized in most cases. The late or organizing stage (stage III) of DAD was characterized by fibroblast proliferation mainly within the interstitium, but also focally within air spaces. Interstitial inflammation and alveolar lining cell hyperplasia remained prominent, but residual edema or hyaline membrane formation was minimal.

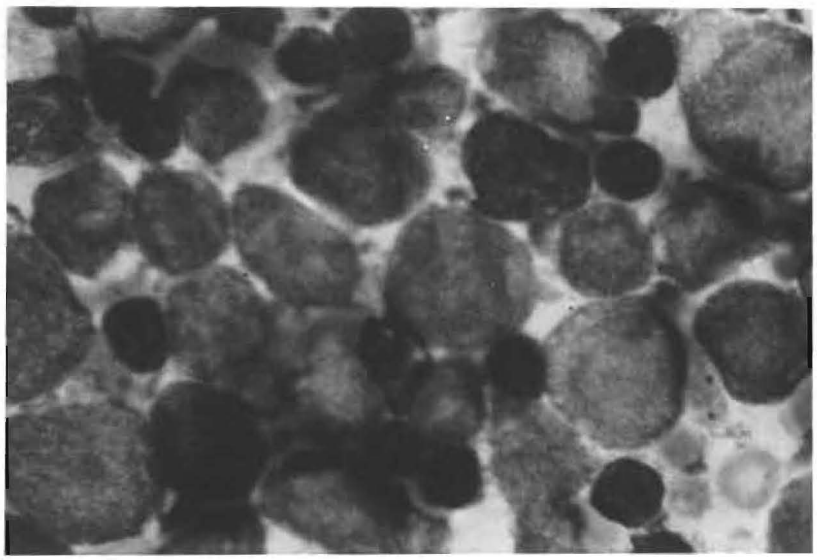

Fig. 2. Lymph node biopsy (×1000). The typical lymphoblastic T-cells with primitive dust-like grey chromatin, inconspicuous nucleoli, round to convoluted nuclei.

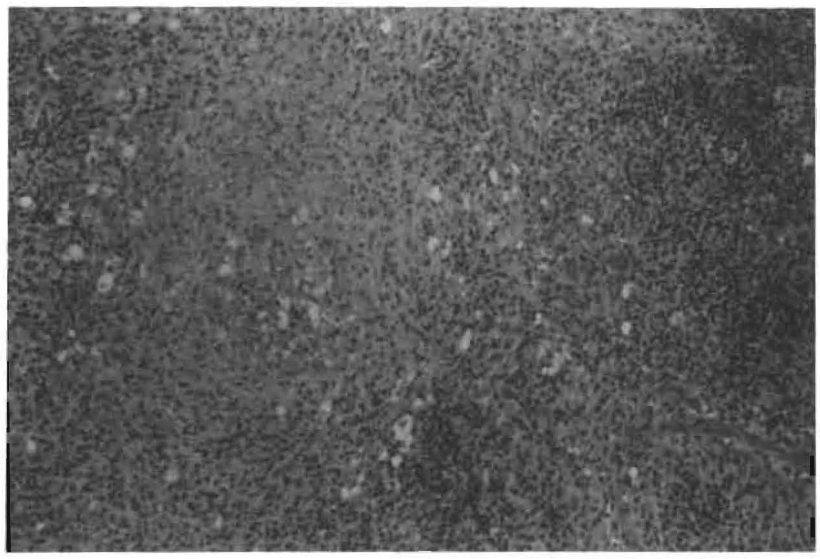

Fig. 3. Lymph node biopsy (×100). Poorly formed granuloma with scattered histiocytes.

Stage II of DAD demonstrated the histologic picture intermixed between stage I and stage III. *P.carinii* organisms were also present as the most common single pathogen characterized by foamy intra-alveolar material and septal infiltrate. Granulomatous reactions in *P.carinii* pneumonia (PCP) were observed in two cases. Diffuse alveolar damage grade I-II was also observed in all cases of PCP.On H&E stained sections, the nuclei of *Pneumocystis* were faintly shown, but GMS stains demonstrated the cyst wall clearly. The internal structure of the organism was not displayed, but the cyst walls were seen as round, ovoid, or collapsed cuplike structures, measuring 3.5 to 7 μm in diameter with a membrane of variable thickness. CMV alone was the third most common pathogen found in lung necropsy specimens with histologic features of DAD grade I-II. In this group (CMV alone), we occasionally noted that alveolar cells contained intranuclear or intracytoplasmic inclusion bodies which were different from numerous cells containing inclusions, as detected in co-infection with PCP specimens (Fig. 5). The cytomegalic intranuclear inclusion was amphophilic to eosinophilic, sharply demarcated and prominent. Other pathogens were found in only one or two cases and histologic features were summarized in Table 5.

DISCUSSION

The histopathologic presentations of AIDS-associated lesions in Thailand have not been previously reported in a complete article. In this study we describe common AIDS-associated lesions in which the diagnoses were made on biopsy and necropsy specimens. Lymphoma has been found to be the most common malignancy in our study (4% of AIDS cases). HIV-infected patients often develop B-cell lymphomas and occasionally other B-cell tumours or B-cell ALL.[23] Although high grade B-cell non-Hodgkin's lymphomas with small non-cleaved cells were predominant in this study, we also found a case of T-cell, lymphoblastic, convoluted lymphoma with the leukemic picture of T-ALL. To our knowledge, this is the first report of an AIDS patient affected by T-cell lymphoma-leuke-

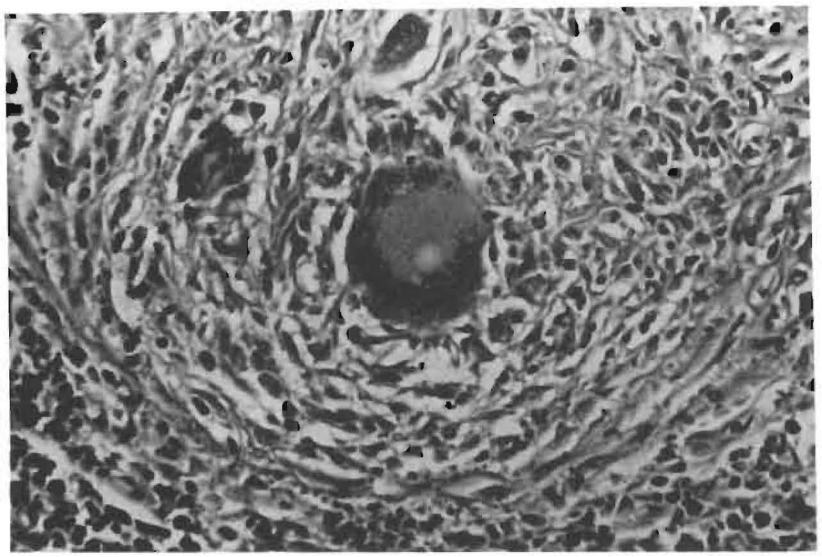

Fig. 4. Lymph node biopsy (×400). Well-formed, non-necrotizing granuloma demonstrating epithelioid histiocytes and giant cells.

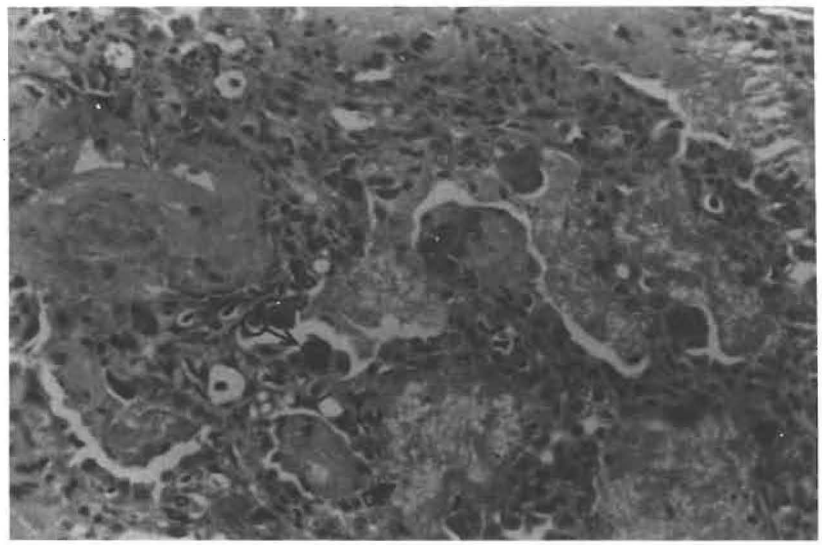

Fig. 5. Lung necropsy (×400). Co-infection of cytomegalovirus with intranuclear inclusion bodies (thin arrow) and *Pneumocystis carinii* showing the interstitial infiltrate and edema with honeycombed alveolar exudate (thick arrow) and prominent hyaline membranes.

mia. Acute lymphoblastic leukemia (ALL) has rarely been reported in association with HIV infection. A literature search revealed only Burkitt-type (B-cell) ALL associated with AIDS patients. In our reported case, the tumor cells showed positive results with pan T-cell and suppressor T-cell markers, but they were negative with the helper T cell marker. The CD_4^-/CD_8^+ absolute value has been reported to be significantly higher in HIV-infected patients than in patients with certain other pathological conditions.[24] HIV-1 infection may initiate an HLA-associated response designated the diffuse infiltrative lymphocytosis syndrome, characterized by increased numbers of circulating CD_8 T-cells that infiltrate various organs.[25] It was first believed that this response could either be an antigenically driven process induced by HIV-1 or a lympho-proliferation of cells with neoplastic or unusual features, but finally the syndrome was proven to be an antigenically driven process. Our CD_8^+ lymphoblastic lymphoma-leukemia could represent a lymphoproliferation of cells with neoplastic features. The most frequent pathologic site of AIDS-associated lymphoma was lymph nodes and the majority of cases revealed clinically stage IV with extensive extranodal involvement. Extranodal malignant lymphoma, including cardiac lymphoma are known to occur with increased frequency in patients with HIV infection.[23,29,32] Our case of cardiac lymphoma presented clinically as cardiac tamponade, and pathological examination of the patient's pericardial fluid and section revealed small non-cleaved Burkitt's lymphoma, the aggressive subtype similar to that in other reports.[30-34]

Infection with HIV (type I) is recognized as a leading risk factor for the development of mycobacterial diseases. In this study tuberculosis (TB) was found to be the most common opportunistic infection, and the majority of tissue biopsies revealed poorly organized granulomas, with extensive necrosis and numerous bacilli. AIDS patients are generally considered to have a deficient granulomatous response due to impaired helper T cell function. Despite several assertions in recent textbooks and reviews that

Table 4. Histopathologic features of AIDS-associated penicilliosis.

AIDS-associated lesions	Total No of cases studied	Organs studied (No of cases)	Histopathologic findings (No of cases)	Percentage of sample area loaded with fungi*
Penicilliosis	41	Lymph nodes (21)	Poorly formed granuloma (18) + diffuse histiocytic reaction with focal necrosis	GMS: 60-100%
			Well formed granuloma (3)	
		Spleen (1)	Diffuse histiocytic reaction (1)	GMS: 100%
		Liver (5)	Diffuse histiocytic reaction (3) and poorly formed granuloma (2)	GMS: 100%
		Bone marrow (2)	Scattering histiocytic reaction (2)	GMS: 20%
		Skin (12)	Diffuse histiocytic reaction (7)	GMS: 60-100%
			Diffuse histiocytic reaction + poorly formed granuloma (5)	

* Estimate from GMS staining sections.

Table 5. Histopathologic features of pediatric AIDS-associated opportunistic infection in lung necropsy.

Opportunistic infections	No of cases	Pathologic characteristics
CMV + PC	11	DAD gr II-III with extensive lymphoplasmacytic infiltrate, foamy exudate in alveoli loaded with PC and numerous CMV inclusions in alveolar lining cells
CMV alone	3	DAD gr I-II with few inflammatory response and few organisms detected
PC alone	8	DAD gr I-II with foamy exudate in alveoli loaded with PC
Candida	2	Abscess (2)*, co-infection with CMV (1)*
Actinomycosis	1	Diffuse suppuration
Zygomycosis (Mucormycosis)	1	Abscess
Nocardiosis	1	Abscess
Mycobacteriosis	1	Necrotizing granulomatous inflammation
Unclassified yeast formed fungus	1	Histiocytic reaction

PC = *Pneumocystis carinii*
CMV = Cytomegalovirus
DAD = Diffuse alveolar damage
* = Number of cases

granulomas are usually absent,[26] our data establish that granulomatous inflammation is the preponderant finding in biopsy specimens, a view supported by other series.[27,28] In addition, various degrees of necrosis were demonstrated in our cases.

Non-granulomatous lesions occurred mainly in overwhelming cases of miliary TB, in which acute, granular necrosis containing nuclear debris and numerous AFB were predominant. In these cases, epithelioid cells were sparse, even absent from some foci; surrounding lymphocytes were few to absent; and multinucleated giant cells and fibrosis were not seen. The poor cellular response probably reflects the immune suppression found in AIDS, although we cannot exclude suppressor activity induced by extensive TB itself. The pathologic specimen of *Mycobacterium avium-intracellulare* complex infection in AIDS shows some overlap with that of TB; but granulomas are typically

non-necrotizing, and the more characteristic picture of aggregations of foamy macrophages packed with AFB, has not been described in AIDS-associated TB.[35,36]

Penicillium marneffei was the most common pathogen present in skin biopsies of AIDS patients in our hospital. It is the only known penicillium species that is dimorphic and can cause systemic infection in healthy and compromised hosts.[37] Compromised hosts, especially those infected with human immunodeficiency virus, seem to be predisposed to this infection.[38-40] The involved organs included lymph nodes, liver, bone marrow and skin, and showed a partially anergic tissue reaction characterized by poorly formed granulomas with diffuse infiltrate of fungi-laden macrophages and lymphoid cell depletion. Since the morphology of penicilliosis can mimic that of tuberculosis and certain fungal infections, the identification of the organism is essential. On routine H&E stain, this organism has to be distinguished from *Histoplasma capsulatum* and other yeast-form fungi. The presence of septate yeast cells, characteristic of *P. marneffei,* as shown on GMS stain can help in making the diagnosis. For early diagnosis, GMS or Wright's stain can also be performed on touch smears of skin-biopsy specimens and bone marrow aspirate. Establishment of the diagnosis is important, not only because this infection is potentially curable, but also because it is a likely indicator disease of AIDS in Southeast Asia as supported by other series.[40]

The most common opportunistic infection and clinical cause of death in pediatric AIDS has been reported to be PCP.[41] Our studies on lung necropsy specimens revealed three unusual types of lesions associated with opportunistic infections, namely, (1) the presence of *P.carinii* and CMV organisms in the same specimen; (2) diffuse alveolar damage obscuring the features of PCP and CMV; and (3) granulomatous reaction in two cases of PCP. Lung biopsy specimens from patients presenting with acute PCP typically reveal scarce, if any, interstitial lymphocytic infiltration and occasional mild septal edema.[42] Co-infection with other pathogens may be of importance in establishing a sustained inflammatory response. Because CMV causes endothelial damage in the lungs,[43] co-existing CMV pneumonitis is probably a risk factor chronic or disseminated *P.carinii* infection. It has been recently shown that alveolar macrophage isolated from HIV-infected patients with PCP vigorously secrete tumor necrosis factor alpha (TNFα).[44] TNFα has been postulated to initiate interstitial fibrosis and granuloma formation through recruitment of inflammatory cells and stimulation of fibroblast proliferation.[45] Moreover, acute pneumocystosis will rapidly proceed to full blown respiratory distress unless promptly and appropriately treated.[46]

Therefore, TNFα may be an important factor in the induction of chronic productive or disseminated PCP with histologic features of granulomas and/or DAD with interstitial fibrosis, although the relationship between the level of pulmonary TNFα and the histologic picture and clinical course of the disease awaits investigation.

Histopathologic studies are limited in that, unlike the usual process with malignancy cases, the diagnosis of many opportunistic infections in AIDS patients can be made by scrapping or smearing from a superficial lesion and then staining the material to examine the organism, or alternatively, by sending the material for culture. In our study the pathological specimens we reviewed were from patients who may or may not have been preliminarily diagnosed by other means. Although not all lesions from AIDS patients taken from the medical or pediatric files were morphologically studied, the pathological changes available in pathology files were reviewed and analyzed. Interestingly, pathological changes found in AIDS patients caused by opportunistic infections vary and some are not usually found in normal hosts. An awareness that unsuspected organisms may be obtained from pathological specimens is an important finding. Moreover, this study showed that co-infections were not uncommon, especially in the lungs. These findings have implications for the accurate diagnosis, treatment and survival of AIDS patients.

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