Original Report

Histopathology of Cryptococcosis and Other Fungal Infections in Patients with Acquired Immunodeficiency Syndrome

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ABSTRACT

Objective: To gain insight into the histopathologic characteristics of fungal infection in acquired immunodeficiency syndrome (AIDS).

Methods: A review was conducted of the histopathology for 162 patients with evident fungal infection.

Results: The microscopic appearance of esophageal candidiasis that was common in patients with single organ involvement revealed necrotic debris containing proliferating hyphae at the site of mucosal erosions without fungal invasion of underlying tissue. The incidence of oral and esophageal candidiasis was followed by that of pulmonary aspergillosis and *Candida* infection. Eighteen patients had generalized cryptococcosis, representing the commonest generalized fungal disease. The essential histologic features of the disease consisted of yeast cell proliferation with a histiocytic response, but only minor lymphocytic and neutrophilic components. This was different from the manifestations of both *Candida* and *Aspergillus* infections. The two histologic patterns recognized in the pulmonary cryptococcal lesions could be graded with respect to the degree and type of inflammatory reaction. The milder one consisted of small scattered foci of intra-alveolar cryptococcal proliferation with a histiocytic response. Another pattern involved massive cryptococcal infection, which might be simply more extensive than that in the former. Capillary involvement of alveolar septa was an important common finding in all 18 patients.

Conclusions: The absence of T cells and decreasing function of antigen-presenting activity in histiocytes were confirmed by immunohistologic examination. These findings suggest that the lungs in AIDS patients provide little resistance to blood stream dissemination by cryptococci.

Key Words: *acquired immunodeficiency syndrome, candidiasis,* Cryptococcosis, *CD4+ cells, histopathology*

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In the past, various factors have resulted in an increase in the number of immunocompromised patients. None of these, however, has had the impact of the dramatic worldwide epidemic of acquired immunodeficiency syndrome (AIDS). The pathologic and clinical features of AIDS, following infection by the human immunodeficiency virus (HIV), is associated with a progressive decrease of cell-mediated immunity, owing to defective functioning of CD4+ cells.[1,2] For this reason, certain mycoses have risen dramatically in frequency, particularly systemic cryptococcosis and oral or esophageal candidiasis. The incidence of opportunistic fungal infections, including any species of fungus, provoking both localized and generalized disease in AIDS patients, has been variously reported to be between 58% and 81%, of whom 10 to 20% of patients have died as a direct consequence of the fungal infection.[3,4] It is known that cryptococcal infection in AIDS patients often induces fatal disease.[3,5,6] The present article describes the histologic features of cryptococcosis and other fungal infections in patients with AIDS, focusing on the differences in inflammatory responses to the various fungal pathogens and details of pulmonary cryptococcal lesions, as determined at autopsy.

MATERIALS AND METHODS

The autopsy files of the UCLA Medical Center and the West Los Angeles Veterans Affairs Medical Center were searched for patients with AIDS who had either localized or generalized infection by any species of fungus. Here, the term generalized fungal disease is restricted to

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patients in whom more than two organs were involved by the fungal infection, excluding mucosal lesions.

The histopathologic examination to determine organ involvement by fungal pathogen and to determine details of tissue responses was carried out on routine hematoxylin and eosin (H&E) preparations, along with selective staining with the periodic acid-Schiff reactions (PAS) and Grocott methods.

To compare the histology of pulmonary cryptococcal infections, sections of pulmonary lesions obtained from two groups of non-AIDS patients with and without immunosuppressed condition were employed. The former consisted of five patients, ranging in age from 36 to 78 years (mean, 62.4 y). Four of them had carcinoma and one had been diagnosed with Evans syndrome. The latter comprised seven patients without any immunosuppressed condition, ranging in age from 21 to 73 years (mean, 43.7 y), who had a wedge biopsy or lobectomy for their incidental abnormal shadows on chest roentgenograms. In addition, a standard peroxidase-antiperoxidase technique was used for the antibodies to CD45RO, L26, human leukocyte antigen (HLA)-DR, and interleukin (IL)-1β, and the antigen-antibody complexes were visualized with diaminobenzidine. Sections of pulmonary cryptococcal lesions from both immunocompetent and AIDS patients were employed. The former, showing the typical features of peripheral pulmonary granulomas,[7] were chosen from the group of non-immunosuppressed patients as controls.

RESULTS

There were 162 autopsies on AIDS patients who had died during the period from 1983 to 1992 in the UCLA Medical Center, and from 1982 to 1991 in the West Los Angeles VA Medical Center.

Localized Disease

The prevalence of localized infection associated with oral candidiasis was 7.4%; esophageal candidiasis, 6.2%; pulmonary aspergillosis, 4.3%; candidal pneumonia, 3.1%; cryptococcal meningoencephalitis, 2.5%; and renal candidiasis (pyelonephritis), 0.6%, among the study group. The lesions of esophageal candidiasis were characterized by necrotic debris at the site of erosions with underlying infiltrates of chronic and a few acute inflammatory cells. Hyphae proliferated in the necrotic debris, but did not invade tissue in any patient.

Whereas most central nervous system (CNS) cryptococcal infections were found as a part of generalized disease, four patients had the infection localized to the CNS at the time of autopsy. One of them had a history of antifungal chemotherapy for generalized disease, but the remaining three patients had not been treated for any fungal infection. Lesions consisted of multiple small cysts containing many encapsulated yeasts, in cortical and subcortical areas, that were also present in the adjacent subarachnoidal space. There was a histiocytic response that varied from case to case, but necrosis and neutrophilic infiltrates were not encountered.

Localized lung disease was associated with two fungal species, *Aspergillus* and *Candida*. The essential feature of the pulmonary lesions with both fungi was purulent bronchopneumonia in which bronchioles and alveoli were filled with necrotic debris, neutrophils, and proliferating fungi. Alveolar septa often showed coagulative necrosis and disruption, but lymphocytes and fibrosis were not present. Bacteria were occasionally observed within necrotic debris. With *Aspergillus* infection, the mucosa was focally necrotic and eroded with readily visible hyphae.

Generalized Disease

Eighteen cases (11.1%) of generalized cryptococcosis were found to present the commonest generalized fungal infection among 162 autopsies. Much less commonly encountered were generalized histoplasmosis (1.9%), coccidioidomycosis (1.2%), and candidiasis (1.2%). Granulomatous lesions were demonstrated in the lungs of patients with generalized histoplasmosis and coccidioidomycosis, but were poorly formed in coccidioidomycosis (Figure 1). In addition, most of the affected patients with generalized cryptococcosis had widespread lesions. The lung was the commonest organ involved (94.4%). Lymph nodes, spleen, and the CNS were also frequently involved (Table 1). Yeast cell proliferation, a histiocyte response and minor lymphocytic infiltration but an absence of neutrophils and eosinophils were common findings. However, a minor neutrophilic infiltrate was infrequently observed in lung, liver, and kidney. The classic

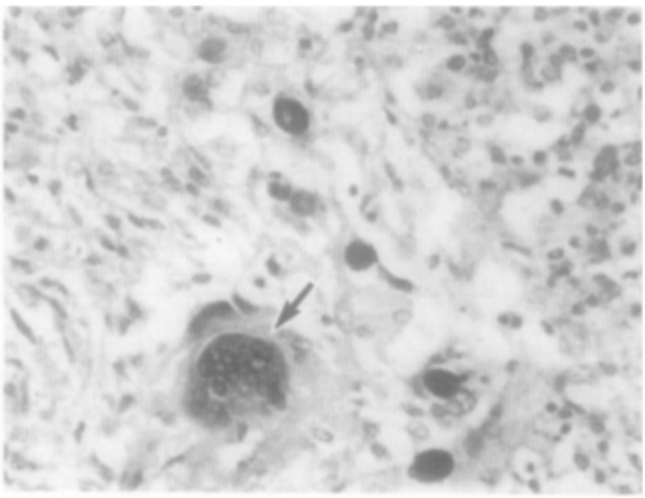

Figure 1. Pulmonary lesion of generalized coccidioidomycosis, showing spherules (*arrow*) and loosely aggregated macrophages (PAS reaction, original magnification ×400).

Table 1. Number of Organs Involved in Cases of Generalized Cryptococcosis

Organs Involved	*Number of Cases n = 18 (%)*
Lung	17 (94.4)
Lymph node	14 (77.8)
Spleen	13 (72.2)
CNS	13 (72.2)
Liver	8 (66.7)
Kidney	8 (66.7)
Bone marrow	6 (33.3)
Adrenal gland	5 (27.8)
Pituitary gland	3 (16.7)
Heart	3 (16.7)
Pancreas	1 (5.6)

CNS = central nervous system.

granulomas, usually present in primary cryptococcosis in immunocompetent patients, were not observed in these cases (Figure 2). Histologic findings of cryptococcal lesions in various organs are summarized in Table 2.

Histopathology of Pulmonary Cryptococcosis

To gain insight into the histopathologic characteristics of cryptococcal lesions in patients with AIDS, histopathologic examination of pulmonary lesions was performed in more detail.

Patients with AIDS

Two histologic patterns emerged from the study. In 15 patients, lesions were small, consisting of intra-alveolar proliferations of cryptococci with a histiocytic response. The architecture was unaltered, but involved alveoli were mildly expanded by both proliferating cryptococci and reacting histiocytes. Cryptococci were present in capillaries in all 15 cases. However, the number of intra-alveolar lesions varied from case to case. In five patients, lesions were scarce. In 10 patients, there was focal proliferation of cryptococci with a major histiocytic response. Cryptococci were widely distributed in the lung, involving many alveoli, and were accompanied by histiocytes and multinucleated giant cells, which were loosely aggregated. Most of the giant cells were of foreign body type with less than 10 nuclei per cell. Typical

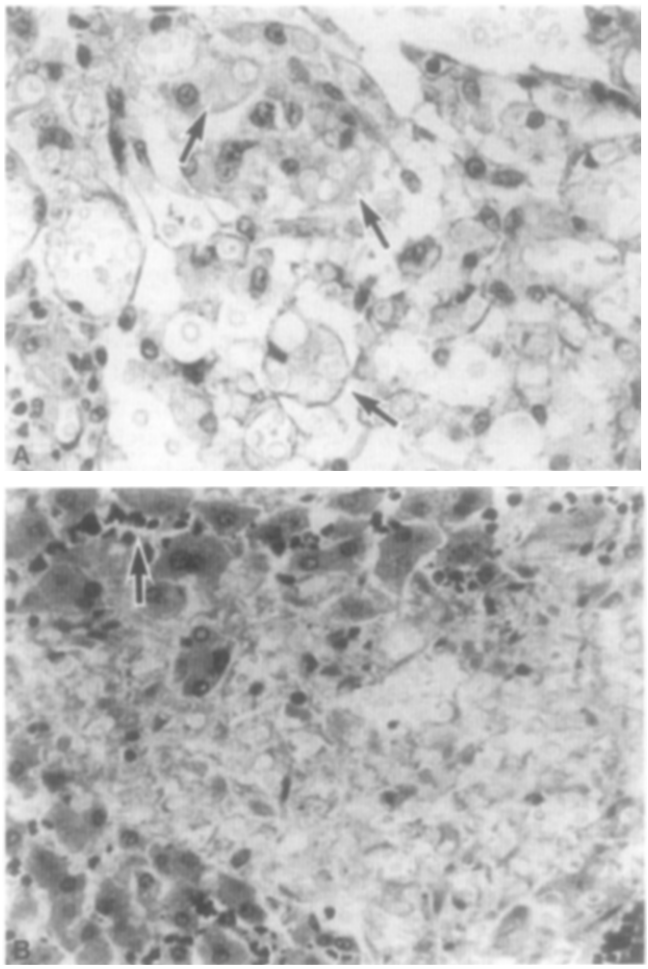

Figure 2. Generalized cryptococcal infection. *A*, The pulmonary lesion consists of proliferating cryptococci and reactive macrophages (*arrows*) with minor lymphocytic infiltrate (H&E, original magnification ×400). *B*, Confluent nodules of proliferating cryptococci with minor inflammatory cell response in liver. In the lesion, a few neutrophils are present in the sinusoid (*arrow*). (H&E stain, original magnification ×400).

Langhans giant cells were not represented. Cryptococci were seen as extra- and intracellular yeast cells with budding forms in both positions (Pattern I, Figure 3). In the remaining three patients, there was a massive proliferation of cryptococci in both expanded alveoli and the capillary-interstitium, and septa were destroyed. A histiocyte and giant cell response was present, as well as focal

Table 2. Summary of Histologic Findings of Organs Involved in Cases of Generalized Cryptococcosis

								Glands			
	Lung	*Lymph Node*	*Spleen*	*CNS*	*Liver*	*Kidney*	*Bone Marrow*	*Adrenal*	*Pituitary*	*Heart*	*Pancreas*
Histiocytic response	+/++	+	+	−/+	++	+	+/++	+	+	−	+
Neutrophilic infiltrate	−/+	−	−	−	−/+	−/+	−	−	−	−	−
Eosinophilic infiltrate	−	−	−	−	−	−	−	−	−	−	−
Proliferation of yeasts	++	++	++	++	+/++	+	+	+	+	+	+
Necrosis	−	−	−	−	−	−	−	−	−	−	−
Hemorrhage	−/+	−/+	−/+	−	−	−/+	−/+	−	−	−	−

CNS = central nervous system.
− = not demonstrated; + = mildly demonstrated; ++ = prominently demonstrated; −/+ = varied from case to case; +/++ = demonstrated, but the degree varied from case to case.

hemorrhage (Pattern II, Figure 4). On the assumption that these two patterns represented progressive severity, they were correlated with the number of organs involved in each patient. There was no particular association (Table 3).

Non-AIDS Patients with and without Immunologic Dysfunction

Five additional patients who were immunosuppressed but did not have AIDS were examined for comparison. In two patients, lesions of intra-alveolar proliferations of cryptococci with a minor histiocytic response were widely distributed in lungs, but the architecture was unaltered. Cryptococci were seen as extra- and intracellular yeasts. In none were neutrophils present, and lymphocytes were not prominent. In three patients, foci of cryptococcal infection were seen as circumscribed nodules, consisting of proliferating cryptococci and reacting histiocytes. There was proliferation of cryptococci in the capillary-interstitium. The histiocytic response was prominent in comparison to that in the former two patients. There were small multinucleated giant cells in lesions.

Circumscribed granulomas were seen in all seven patients without any history of immunologic dysfunction. The lesions were composed of compactly aggregated histiocytes and multinucleated giant cells, including both Langhans and foreign body type, with numerous intracytoplasmic organisms.

Comparative Immunohistologic Study

Lung sections showing cryptococcal proliferation with loosely aggregated reactive histiocytes and multinucleated giant cells, corresponding to Pattern I, and the typical granulomas developed in a 33-year-old male immunocompetent patient were used for this study. The presence of CD45RO-positive small round cells was visible in the typical granuloma. Histiocytes and foreign body giant cells with numerous intracytoplasmic organisms were strongly positive for both HLA-DR and IL-1β. There were a few and small aggregates of L26-positive cells in the lesion. In patients with AIDS, CD45RO-positive cells and L26-positive cells were not seen, and the expression of HLA-DR and IL-1β was weak, although present in regenerated pneumocytes (Table 4).

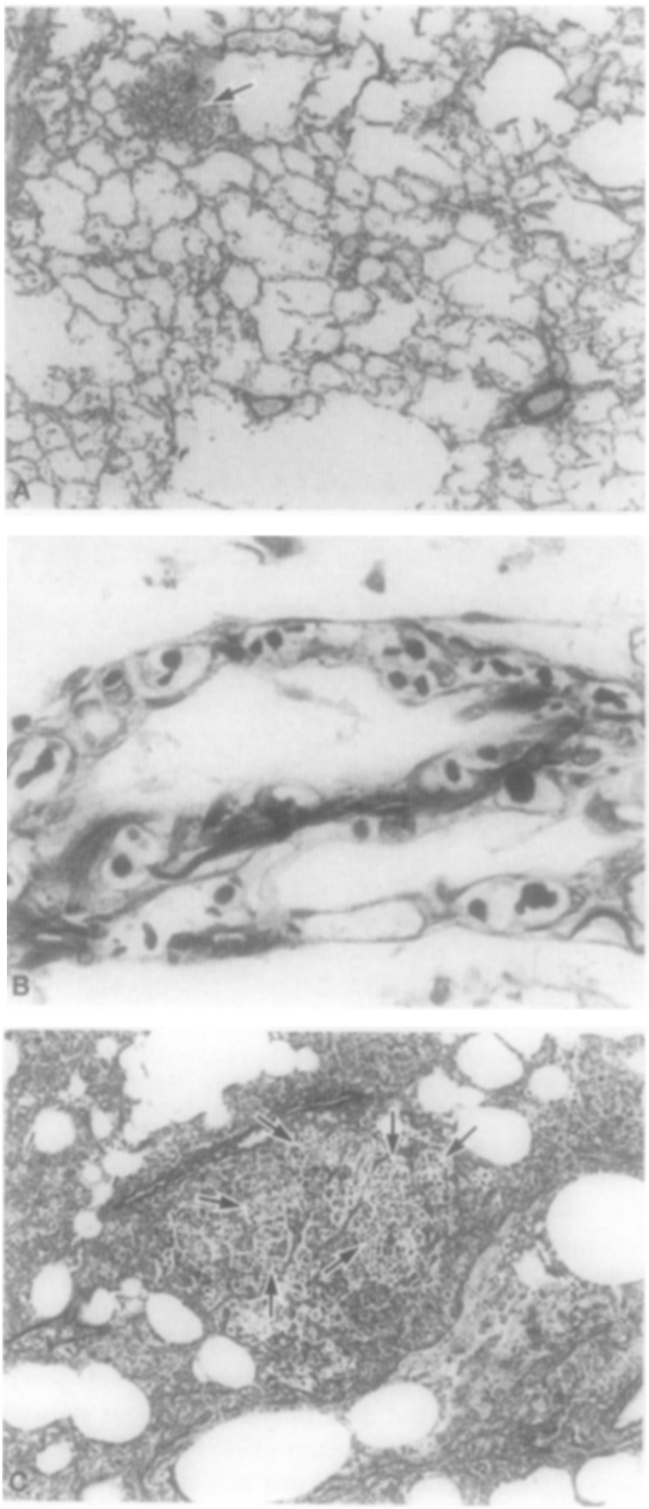

Figure 3. Pulmonary lesions of cryptococcal infection. Pattern I. In 5 of 15 patients, corresponding to Pattern I, lesions were small and extremely scarce, consisting of intra-alveolar proliferations of cryptococci with a histiocytic response. *A*, Pattern I: Intra-alveolar lesions (*arrow*), characterized by a collection of cells in alveolar space, were few in the lung (PAS-elastica stain, original magnification ×40). *B*, Cryptococci are widely spread among the septal capillaries (PAS-elastica stain, original magnification ×400). *C*, Cryptococcal proliferation with histiocytes involving many alveoli. Pattern I: Intra-alveolar lesions, characterized by aggregates of extracellular proliferation of yeasts (*arrows*) and reactive histiocytes (PAS-elastica stain, original magnification ×100).

DISCUSSION

Fatal opportunistic infections, such as cryptococcosis, mycobacterial infection, and *Pneumocystis* pneumonia, usually develop in patients with AIDS. Among them, oral and esophageal candidiasis and generalized cryptococcosis are regarded as the important complications of the disease.[1,3-6,8,9] The present autopsy study confirms this.

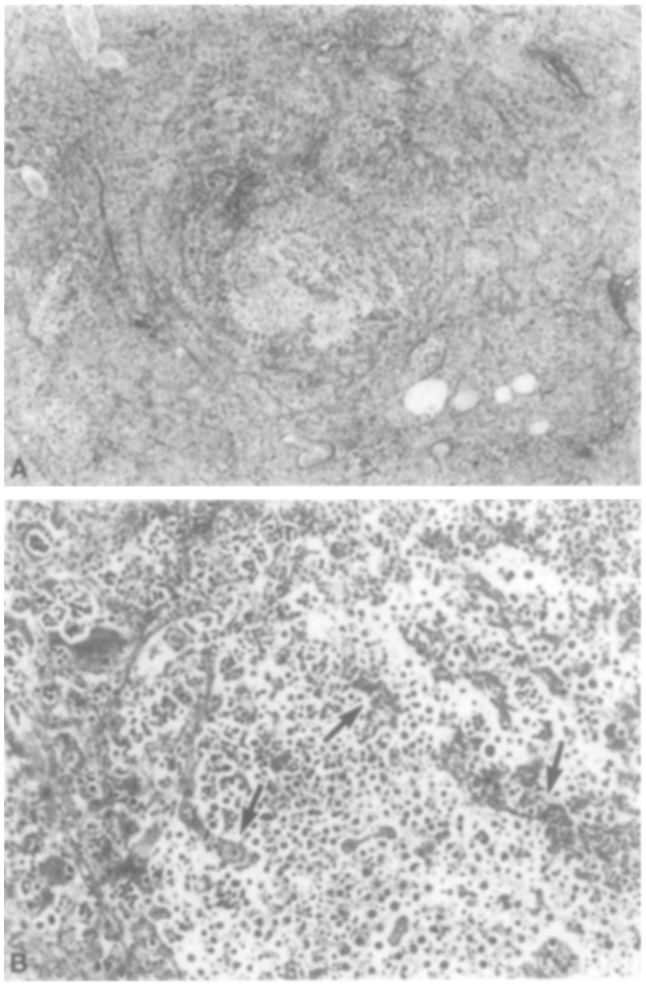

Figure 4. Pulmonary lesions of cryptococcal infection. Pattern II. *A*, Massive consolidation by cryptococci and histiocytes (PAS-elastica stain, original magnification ×10). *B*, High power magnification showing destruction of septa (*arrows*) (PAS-elastica stain, original magnification ×200).

Table 3. Summary of Autopsy Cases of the Present Study and Those Respective Histologic Patterns of Pulmonary Cryptococcosis

Case *		Age (y)	Race	Histologic Pattern†	Number of Organs Involved
1	U-1	38	C	Ia	10
2	U-2	41	A	Ib	8
3	U-3	29	C	Ib	4
4	U-4	45	C	Ib	6
5	U-5	54	C	Ia	6
6	U-6	26	C	Ib	2
7	U-7	48	C	Ia	8
8	U-8	35	A	II	10
9	U-9	48	C	II	4
10	VA-1	49	C	Ia	3
11	VA-2	29	B	II	8
12	VA-3	42	B	Ia	2
13	VA-4	40	H	Ib	3
14	VA-5	33	C	Ib	4
15	VA-6	56	C	Ib	2
16	VA-7	34	B	Ib	7
17	VA-8	36	C	Ib	2
18	VA-9	43	C	Ib	2

*Cases are arranged chronologically; all patients were male.
†Predominant histologic pattern demonstrated in lung of each case: I = characterized by foci of intra-alveolar cryptococcal proliferation with histiocytic response (Ia = lesions were scarce; Ib = lesions were widely distributed).
II = characterized by prominent cryptococcal proliferation with destruction of architecture and hemorrhage.
U = autopsy at UCLA; VA = autopsy at VA Medical Center; C = Caucasian; A = Asian; B = black; H = Hispanic.

In AIDS-related esophageal candidiasis,[9] one important point provided by this study is that whereas necrotic debris was present at the site of mucosal erosions, the underlying tissue was not invaded by proliferating hyphae. In addition, there were few patients with generalized candidiasis, and their pulmonary lesions showed prominent necrosis and neutrophilic infiltration. These facts suggest that neutrophils may play an important role in restricting candidal infection in patients with terminal HIV infection.[2,10] Localized pulmonary aspergillosis also occurred in patients with single organ involvement, and also featured purulent bronchopneumonia with necrosis. Although it was reported recently that production of IL-4 by CD4+ cells may be one major factor discriminating susceptibility and resistance to experimental *Aspergillus* infection,[11] in the present study, no patient was observed to have generalized aspergillosis. In patients with AIDS, blood stream dissemination of inhaled conidiae of *Aspergillus* sp appears to be prevented by a non-specific purulent inflammation induced in the lung, the primary site of infection. This notion is supported by a previous report emphasizing that the defense mechanism against aspergilli is mainly dependent on the function of neutrophils and macrophages.[2,11] Thus, there was a striking histologic difference between *Aspergillus* or candidal and cryptococcal infection in lungs of patients with AIDS. No purulent inflammatory response was observed in cryptococcal lesions examined in the study. This result was supported by a previous investigation that concluded that cryptococcal polysaccharides, especially glucuronoxylomannan, can cause shedding of L-selectin from the surface of neutrophils, and this may prevent neutrophils from attaching to the endothelial cell surface.[12] On the other hand, it has been reported recently that eosinophils may be effecter cells against *Cryptococcus neoformans*,[13] and tissue eosinophilia was experimentally induced in lungs of infected mice.[14] In such a case, depletion of CD4+ cells ablates IL-5 production by lung leukocytes in vitro and eosinophil recruitment in vivo. The present study revealed that no cryptococcal lesions were associated with eosinophilic infiltration. This is consistent with depletion of CD4+ cells in HIV infection.

Cryptococcal infection has been recognized as a primary deep-seated fungal infection in immunocompetent hosts. The disease is usually asymptomatic,[15] and although typical granulomas develop in the lung, this type of infection is thought to be self-limiting and benign.[7] However, the incidence of opportunistic cryptococcal infection has been rising in recent years, owing in large part to increas-

Table 4. Immunohistologic Comparison of Pulmonary Lesions Between an AIDS Patient and an Immunocompetent Patient

Histology	*AIDS Patient*	*Immunocompetent Patient*
IL-1β		
Histiocyte		
Number	Few	Many
IR	Poor	Moderate
Giant cell		
Number	Few	Many
IR	Poor	Well
HLA-DR		
Histiocyte		
Number	Few	Many
IR	Poor	Moderate
Giant cell		
Number	Few	Many
IR	Poor	Well
CD45RO (lymphocyte)		
Number	None	Many
L26 (lymphocyte)		
Number	None	Few (focal)

ing numbers of immunocompromised patients.[1,3,16,17] Infection with *Cryptococcus neoformans* is now a life-threatening disease often occurring in patients with AIDS.[6,16-20] Many studies on cryptococcal infection in patients with AIDS have been reported, most of them concerned with clinical, microbiologic, and immunologic aspects,[1,3-6,18-22] but few with the histology of human disease.[5,17,23] In this report, histologic features are emphasized, focusing on the pulmonary lesions found in 18 patients who died with AIDS. Four distinct histologic types of pulmonary cryptococcosis were classified by McDonnell and Hutchins as peripheral pulmonary granuloma, granulomatous pneumonia, intracapillary-interstitial involvement, and massive pulmonary involvement, respectively, without reference to specific underlying disease.[7] Cryptococcal infection of the lungs in patients with AIDS took the form of intracapillary-interstitial or massive pulmonary involvement.[7,24] Peripheral granulomas and granulomatous pneumonia were not encountered in patients with AIDS. The majority of patients in the present study had lung lesions with Pattern I histology (i.e., alveoli containing proliferating cryptococci, reactive histiocytes, and multinucleated giant cells), and organisms were not seen proliferating within the bronchial mucosa. On the other hand, capillary involvement was prominent and even present in Pattern I lesions, where organisms were limited to relatively few alveoli. The lung is commonly considered to be the portal of infection and might be expected to reflect this by manifesting an intra-alveolar proliferation of inhaled yeasts without capillary involvement.[25,26] However, in this study, five patients had generalized disease, with histologic features that were characterized by a few lesions of intra-alveolar proliferation of cryptococci and widespread intracapillary involvement without fibrous thickening of involved septa. In such a case, the intracapillary form may represent hematogenous dissemination of inhaled yeasts to which an extremely weak inflammatory response might be induced in alveoli in patients with terminal HIV infection. However, there is still the possibility that the form reflects hematogenous dissemination from another organ in which primary infection was induced. This might explain the finding of patients with CNS cryptococcal infection without pulmonary lesions at the time of autopsy.

It has been reported that the rate of acute-phase mortality from cryptococcosis among AIDS patients with pneumonia is 42%.[6] Thus, the pathogenesis of such a pattern is most likely explained by the rapidity of onset of vascular involvement, also leading to generalized disease. In addition, the histologic alteration of such a pattern might be expected to manifest a normal chest roentgenogram, which has been reported as a common finding in pulmonary or generalized cryptococcosis in patients with AIDS.[23]

A hallmark of infection with *Cryptococcus neoformans* is depression of the immune system characterized by poor inflammatory responses and loss of delayed hypersensitivity and antibody responses.[27] The authors found discrete granulomas consisting of compactly aggregated giant cells and histiocytes, strongly positive for HLA-DR as well as IL-1β, in all seven immunocompetent patients, most likely as a sequel to normal function of the considerable defense mechanisms against cryptococci. Development of a T cell-mediated pulmonary inflammatory response is critical for clearance of cryptococci,[28] and this has been demonstrated in murine cryptococcosis and supported by data from several human studies.[2,28,29] Although humoral immunity elicited by cryptococcal capsular polysaccharide has been discussed,[30,31] none of the histopathologic hallmarks of activated humoral immunity, such as reactive lymphadenitis and lymphoid follicular hyperplasia of bronchial mucosae, were represented in the patients in this study. Instead, the histology of pulmonary cryptococcosis in immunocompromised patients without AIDS varied from case to case. In three patients, the features of cryptococcal lesions were similar to that developed in patients with AIDS, but were focal. The remaining two immunocompromised patients revealed lesions of intra-alveolar proliferation of cryptococci with a minor histiocytic and lymphocytic response that were widely distributed in the lung. Decreased function of both lymphocytes and monocytes or macrophages, induced by administration of corticosteroids and other myelotoxic drugs, might have been expected in those two patients. This might also be the reason the histology of cryptococcal infection represented in such patients, especially the degree of histiocytic response, was different from that developed in patients with AIDS.

The present study showed an absence of CD4+ cells in pulmonary lesions, as per immunohistochemistry. Furthermore, the expression of IL-1β and HLA-DR was weak

in histiocytes and multinucleated giant cells, compared with granulomatous lesions in immunocompetent patients. Alveolar macrophages are recognized as a first line of defense against cryptococcal infection, and it has been reported that human alveolar macrophages from normal subjects play a significant role in antigen presentation to T cells, whereas their effecter function seems to be less relevant, at least in the afferent arm of the immune response to this yeast.[32] The results of the present study are consistent with decreased antigen-presenting activity of histiocytes in pulmonary cryptococcal infection in turn reducing the number of T cells in the lesion consequently induced by HIV infection.[33] However, the important finding from this study is that the phagocytic activity of histiocytes reacting toward cryptococci is unaffected in AIDS patients, and phagocytosis was commonly present. This histologic characteristic may be supported by a previous report that indicated that bronchoalveolar lavage cells from early-stage HIV-1-infected individuals did not have an intrinsic defect in fungistasis of cryptococci.[34] In addition to the lack of typical Langhans giant cells, the reactive histiocytes and multinucleated giant cells reveal that although there is mostly normal phagocytic function, there is a decrease in the ability to kill cryptococci. The essential feature of the pulmonary lesion in AIDS patients is the proliferation of cryptococci with reactive histiocytosis and a much lesser lymphocytic infiltration, possibly the morphologic response to cryptococcal infection in patients with apparent T-cell dysfunction. The absence of typical granuloma formation, the extended capillary involvement, and the minimal lymphocyte response in cryptococcal disease in AIDS patients are significant findings.

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