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REVIEW ARTICLE

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Granuloma and cryptococcosis

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Abstract This review describes the general histopathological features of cryptococcosis in immunocompetent individuals, as well as in patients with acquired immunodeficiency syndrome (AIDS). Details of the histological examination of cryptococcal lesions are described, with the consideration of morphological modifications induced by treatment with highly active antiretroviral therapy (HAART). The essential histological features of cryptococcosis in individuals with impaired T-cell functioning are yeast-cell proliferation with a histiocytic response, but only minor lymphocytic and neutrophilic components. Several histological patterns of pulmonary cryptococcal lesions are introduced in this article, some of which could be graded with respect to the degree and type of inflammatory reaction. One pattern was a mild lesion consisting of scattered small foci of intraalveolar cryptococcal proliferation with a histiocytic response. Another pattern involved massive cryptococcal infection, which may have been simply more extensive than that in the mild lesion. Capillary involvement of alveolar septa should be understood as an important common finding in patients with AIDS who had not been treated with HAART. In those patients, the absence of T cells and a decreasing function of antigen-presenting activity in histiocytes were confirmed by immunohistological examination. These findings suggest that the lungs of AIDS patients without HAART offer little resistance to bloodstream dissemination by cryptococci. The unique histological feature demonstrated in patients treated with HAART is characterized by the presence of CD4+ cells, greater response of histiocytes and multinucleated giant-cell formation, and lack of massive capillary involvement.

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Inflammations, repair, and opportunistic fungal infection

Injury, inflammation, and repair are the hallmarks of pathology. Knowledge of the basic phenomena, as well as the consequences, complications, and nuances of these processes, constitutes the basis for understanding many diseases. Inflammation is the host-cell and tissue reaction to any injury. An injurious agent or a damaged cell, and normal inflammatory, homeostatic, and immune responses are the essential ingredients needed for inflammation to occur. Inflammatory responses may be provoked by many agents. The individual response to injury may vary widely for any given injurious agent, however, owing to the unique set of genetic, nutritional, physical, infectious, chemical, hormonal, and immune factors that make up that individual's internal and external milieu. Inflammatory and reparative processes are generally simultaneous, but one phase usually dominates when tissue is examined microscopically at any given time after injury. And the inflammatory response varies depending upon the particular agent, the tissue, and the individual host characteristics. Accordingly, an infectious disease can be recognized as an inflammatory response caused by a microorganism as an injurious agent.

The microscopic features of lesions demonstrated at the site of infection, and the altered structures, are generally epitomized by an extremely complicated interaction between the causative microbes and tissue response. In opportunistic infections, especially in those with invasive fungal infections, the tissue response to some pathogenic fungi may be impaired, but both the cause and degree of the decreasing function of defense mechanisms vary from case to case. Accordingly, the gross, microscopic, and ultrastructural features of the lesions produced by an invasion of pathogenic fungi can be understood as the phenotypical

expression that emerges from an interaction between the invasiveness of the causative fungi and variously impaired defense mechanisms of the host that are ubiquitously observed. We previously described the histopathology of invasive aspergillosis, with reference to variously impaired neutrophilic functions in hosts.[1,2] The inflammatory response to aspergillus can be essentially understood as an acute purulent inflammation that is characterized by necrosis and prominent neutrophilic infiltrate at the site of infection. Two types of necrosis, coagulation and liquefaction, are found in the lesions of invasive aspergillosis. When the disease occurs in patients with mildly impaired neutrophilic function, lobular consolidation develops at the focus of infection, and progressively enlarges. When the infection occurs in patients with severe neutrophilic dysfunction, the characteristic lesion is a discrete nodule with peripheral hemorrhage. If the patient has had continuous neutrophil dysfunction, the lesion consists of coagulation necrosis that can enlarge but does not change in morphology.[1] However, in previously neutropenic patients in whom neutrophil function has recovered, patent vessels around the discrete nodule will allow liquefaction necrosis to occur at the margins of the sequestered core of coagulation necrosis.[2] Cryptococcus, which is the main focus of discussion in the present review, is known as a fungus that causes a granulomatous response that is recognized as the phenotypical representation of the normal functioning of integrated cell immunity.[3] In these terms the defense mechanism against Cryptococci may be different from that against Aspergilli. In the present review, the histopathological features of the granulomatous response in several important forms of cryptococcal infection are described, and discussed, with reference to some particular mechanisms of the lowered functioning of immunity or defense mechanisms in the host, so that the pathogenesis as well as pathophysiology may be elucidated.

Architecture of granuloma induced by cryptococcal infection

In an immunocompetent individual, typical granuloma is usually encountered at the site of cryptococcal infection and is recognized as a compact aggregate of macrophages with epithelioid features and multinucleated giant cells, of both foreign-body and Langhans type, containing numerous intracytoplasmic yeasts (Figs. 1, 2, and 3). These cells are strongly positive for both HLA-DR and interleukin (IL)-1 beta. CD45RO-positive small round cells, corresponding to CD4+ lymphocytes, are visible in such typical granulomas.[4] When we observe experimentally induced cryptococcal lesions in athymic mice, the response of macrophages is confirmed, but they are not aggregated, and cryptococci are seen as both intra- and extracytoplasmic yeasts (Figs. 4 and 5). Although necrosis is rarely seen at the center of the granuloma, lesions with necrosis are essentially large. Thus, necrosis can be understood as a result of an ischemic state that is produced by an enlargement of the granuloma, and the proliferation of cryptococci itself does not causes necrosis.

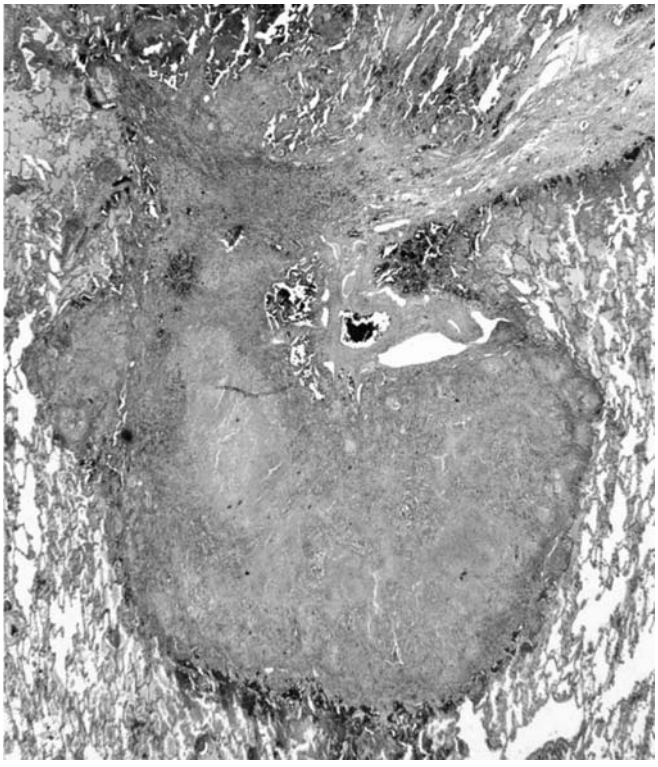

Fig. 1. Typical granuloma of cryptococcal infection in lung. H&E, ×4

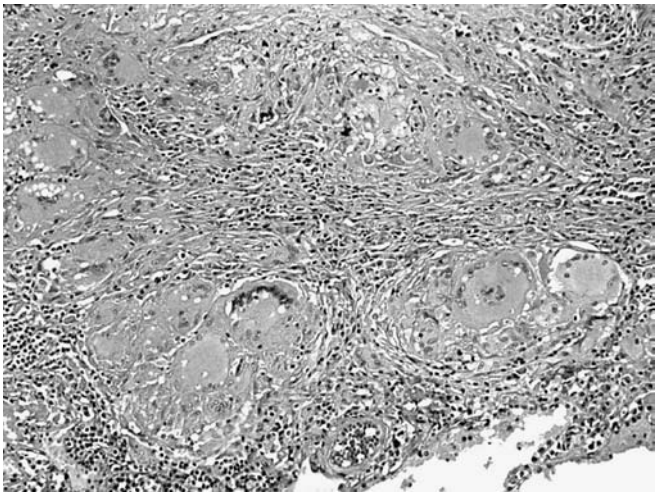

Fig. 2. Detail of the granuloma. The granuloma is composed of a compact aggregate of histiocytes with epithelioid features and multinucleated giant cells, of both foreign-body type and Langhans type. Periodic acid Schiff (PAS), ×200

Cryptococcosis and acquired immune deficiency syndrome (AIDS)

In the worldwide epidemic of AIDS, the pathological and clinical features, following infection by the human immuno-

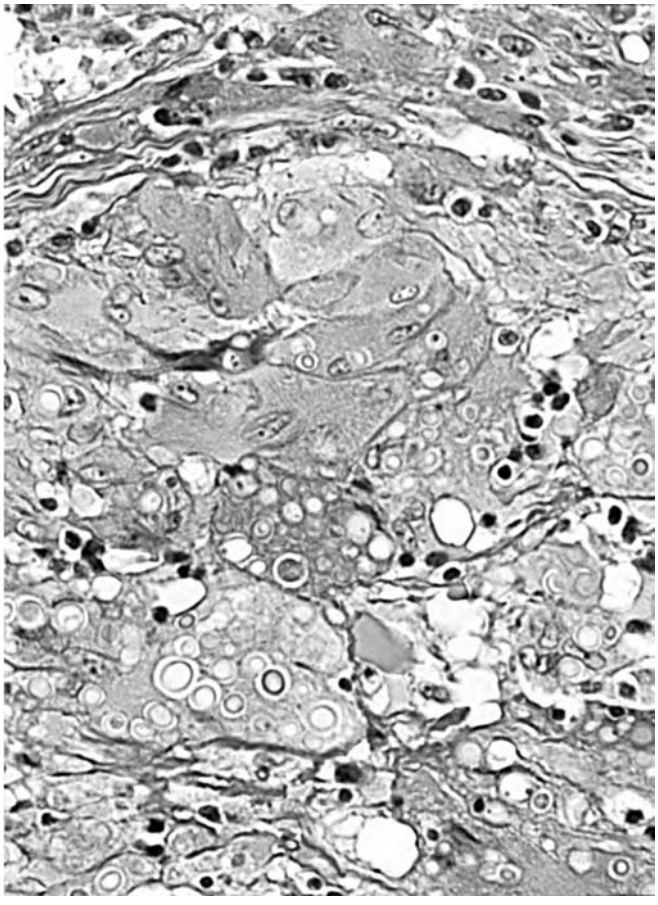

Fig. 3. Aggregate of multinucleated giant cells containing numerous phagocytozed yeasts. PAS, ×400

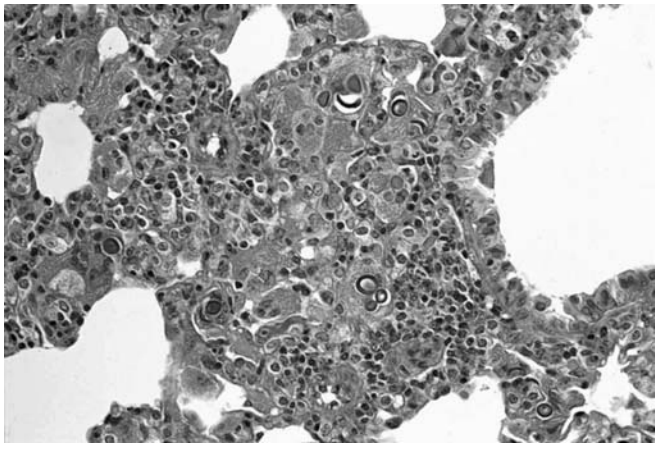

Fig. 4. Granulomatous lesion experimentally induced by an infection of cryptococci in nu/+ mouse. PAS, ×400

deficiency virus (HIV), are associated with a progressive decrease of cell-mediated immunity, due to defective functioning of CD4+ cells.[5,6] Because of this decrease in immunity, certain mycoses have risen dramatically in frequency, particularly systemic cryptococcosis. In AIDS patients, the incidence of opportunistic fungal infections, including any

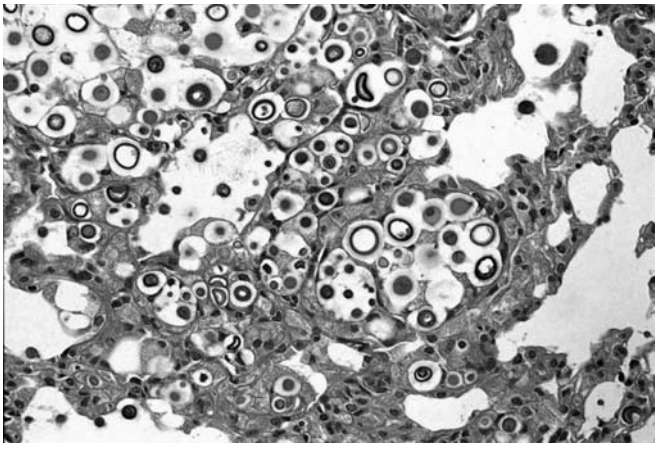

Fig. 5. Lack of granulomatous lesion in athymic mouse. PAS, ×400

species of fungus which provokes both localized and generalized disease, has been variously reported as 58%–81%, with 10%–20% of these patients having died as a direct consequence of the fungal infection.[7,8] It is well recognized that cryptococcal infection in AIDS patients often induces a fatal disease.[7,9,10] However, the acceptance of recent antiretroviral therapy in patients with AIDS has also had a dramatic impact on the epidemiology and clinical characteristics of many opportunistic infections associated with HIV.

Histopathology of cryptococcosis in patients with AIDS

Three patterns of pulmonary lesion have been reported.[11] The first pattern is small, consisting of intraalveolar proliferations of cryptococci with a histiocytic response. The architecture of the lung is unaltered, but involved alveoli are mildly expanded by both proliferating *cryptococci* and reacting histiocytes (Fig. 6). *Cryptococci* are prominent in capillaries (Fig. 7). However, the number of intraalveolar lesions varies from patient to patient. In the second pattern, foci are scarce, and there is focal proliferation of *cryptococci* with a major histiocytic response. *Cryptococci* are widely distributed in the lung, involving many alveoli, and are accompanied by histiocytes and multinucleated giant cells, which are loosely aggregated (Fig. 8). Most of the giant cells are of foreign-body type with fewer than ten nuclei per cell. Typical Langhans giant cells are not seen. *Cryptococci* are seen as extra- and intracellular yeast cells, with budding forms in both locations (Fig. 9). In the third pattern, there is a massive proliferation of cryptococci in both expanded alveoli and the capillary/interstitium, and septae are destroyed. A histiocyte and giant-cell response is present, as well as focal hemorrhage. Neither CD45RO-positive cells nor L26-positive cells are seen in the lesions of AIDS patients without highly active antiretroviral therapy (HAART), and the expression of HLA-DR and IL-1 beta is very weak, and rarely present in regenerated pneumocytes.

In patients who had been treated with HAART, consisting of zidovudine, lamivudine, and indinaver, however, a significant difference in histopathology, compared with findings in untreated patients, was recognized.[4] The pulmonary lesion was characterized by the presence of a lymphocytic infiltrate, a much greater response of histiocytes and multinucleated giant-cell formation, and the lack of massive capillary involvement. Although foci of dense cryptococcal proliferation were distributed throughout the lung, they were encompassed by fibroblasts and reacting histiocytes with considerable multinuclear giant-cell formation, but no giant cells of typical Langhans type were found (Fig. 10). In AIDS patients with HAART, CD45RO-positive cells are present at the periphery of each focus of dense cryptococcal proliferation. Both histiocytes and multinucleated giant cells are positive for HLA-DR as well as IL-1 beta, but their reactivity is relatively weak.

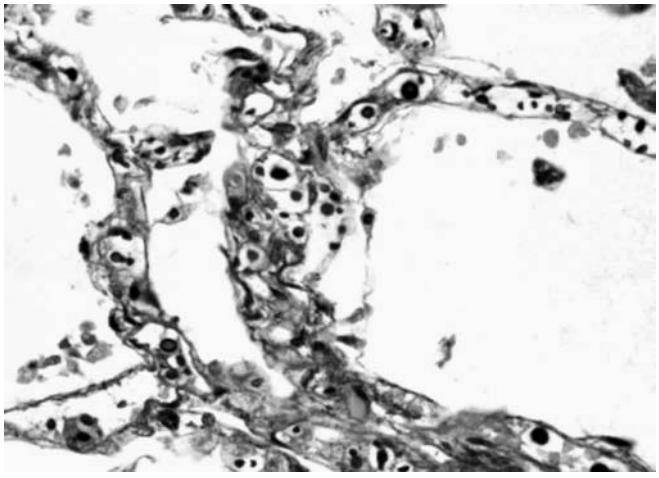

Fig. 6. Massive capillary involvement of cryptococci in a patient with AIDS without highly active antiretroviral therapy (HAART). PAS, ×400

Granulomatous response in AIDS patients with variously impaired T-cell function

Before the era of HAART, fatal opportunistic infections, such as cryptococcosis, mycobacterial infection, and pneumocystis pneumonia, usually developed in patients with AIDS. However, there were also very few patients with generalized candidiasis, and their pulmonary lesions showed prominent necrosis and neutrophilic infiltration. These facts support the idea that neutrophils play an important role in restricting candidal infection[6,16] in individuals with terminal HIV infection. Localized pulmonary aspergillosis also occurred in those with single-organ involvement, and also featured purulent bronchopneumonia with necrosis. Although it has been reported that the production

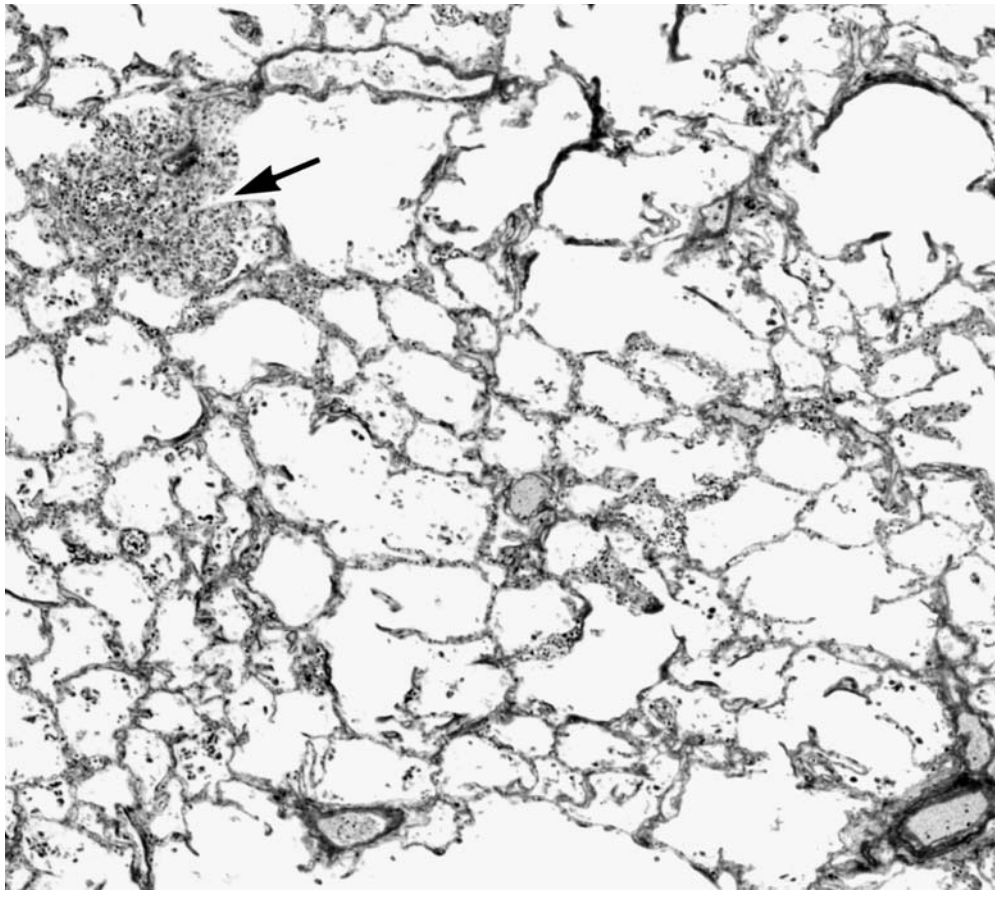

Fig. 7. A large part of the lung infected with cryptococci appears to have maintained air space, and there are a few minute intraalveolar foci (*arrow*) consisting of histiocytes. PAS, ×4

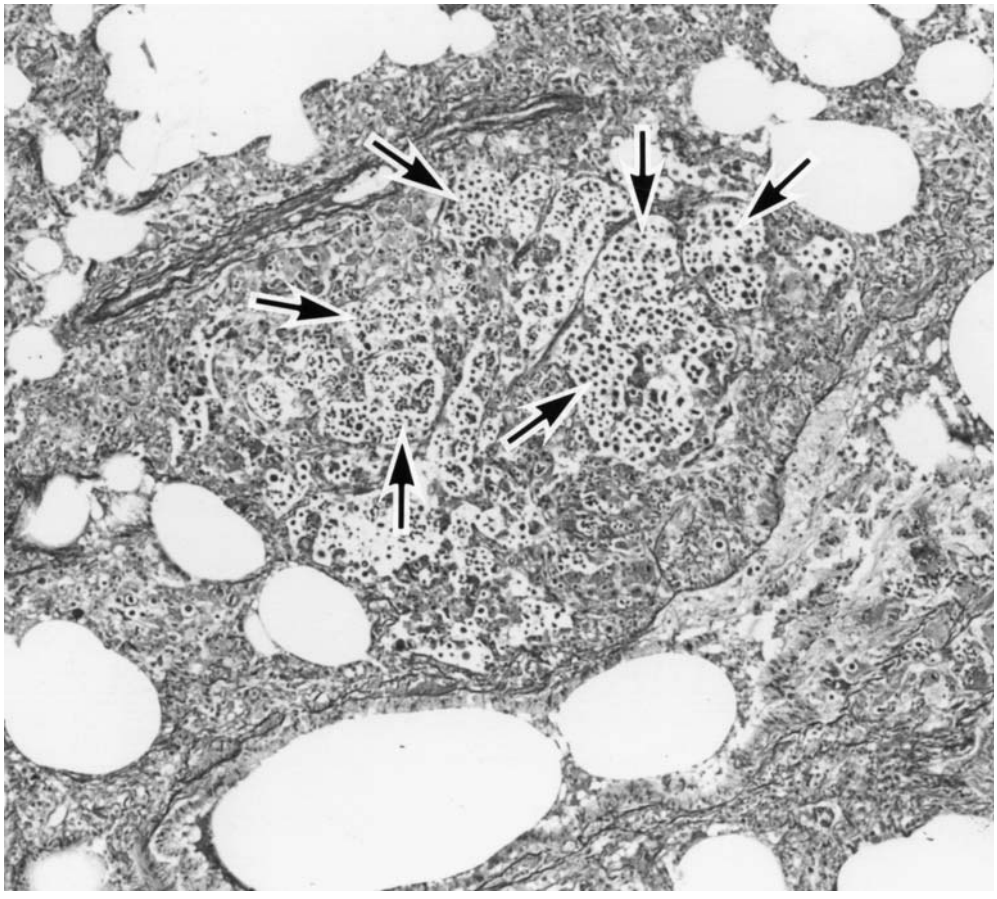

Fig. 8. Immature multinucleated giant cells of foreign-body type are present among histiocytes aggregated in alveoli; the cytoplasm in the histiocytes is markedly attenuated and enlarged by the intracytoplasmic proliferation of the yeast. (*arrows*). PAS, ×200

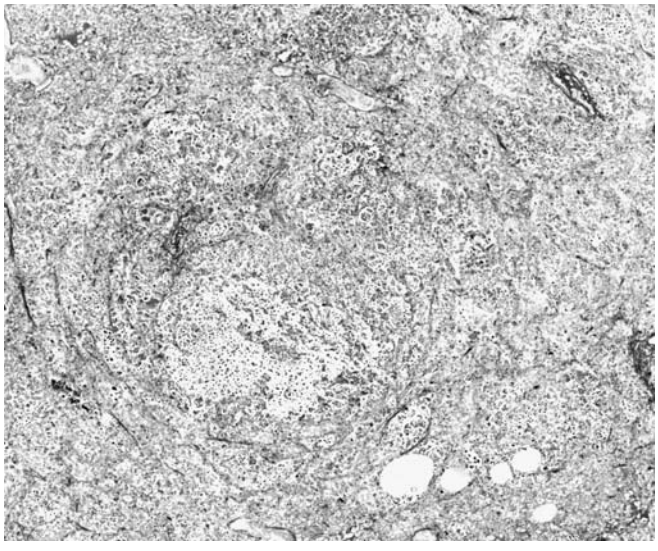

Fig. 9. Massive intraalveolar lesion of cryptococcal infection, consisting of proliferation *cryptococci* and reactive histiocytes (macrophages) without lymphocytic infiltrate. H&E, ×40

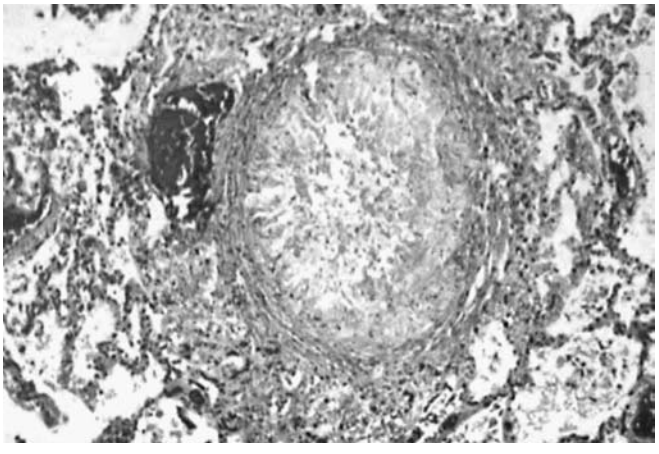

Fig. 10. Cryptococcal lesions that developed in a patient with AIDS treated with HAART. Scattered nodules are composed of dense proliferations of cryptococci, with the formation of marginal fibrosis, including histiocytes, multinucleated giant cells of foreign-body type, and an infiltrate of CD4+ cells. No capillary involvement is found in the septa, which are not involved by these nodular lesions. H&E, ×4

of IL-4 by CD4+ cells may be one major factor discriminating susceptibility and resistance to experimental *Aspergillus* infection,[16] few cases of generalized aspergillosis have been reported in AIDS patients. In patients with AIDS, the bloodstream dissemination of *Aspergillus* sp. appears to be prevented by the induction of a nonspecific purulent inflammation 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 functions of neutrophils and macrophages.[6,15] Thus, there is a striking histological difference between *Aspergillus* and candidial or cryptococcal infection in the lungs of patients with AIDS.

However, no purulent inflammatory responses were observed in the cryptococcal lesions of AIDS patients. This fact is supported by a previous investigation which concluded that cryptococcal polysaccharides, especially glucuronoxylomannan, can cause the shedding of L-selectin from the surfaces of neutrophils, and this may prevent neutrophils from attaching to the endothelial cell surface.[17] On the other hand, it has been reported recently that eosinophils may be one of the effector cells against *Cryptococcus neoformans*,[18] and tissue eosinophilia was experimentally induced in the lungs of mice infected with this organism.[19] In these animals, depletion of CD4+ cells ablated IL-5 production by lung leukocytes in vitro and eosinophil recruitment in vivo.[19] However, no cryptococcal lesions in humans have been associated with eosinophilic infiltration, and this is consistent with the depletion of CD4+ cells in HIV infection.

In immunocompetent hosts, cryptococcal infection has been recognized as a primary deep-seated fungal infection. The disease is usually asymptomatic,[20] and, although typical granulomas develop in the lung, this type of infection is thought to be self-limiting and benign.[12] However, the incidence of opportunistic cryptococcal infection has been rising in recent years, due in large part to increasing numbers of immunocompromised patients.[5,7,21,22] Before the HAART era, infection with *Cryptococcus neoformans* was a life-threatening disease often occurring in patients with AIDS.[10,21–25] In the past, many studies of cryptococcal infection in patients with AIDS have been reported, most of them concerned with clinical, microbiological, and immunological aspects,[5,8–10,23–28] but few were concerned with the histology of the human diease.[9,22,29] Four distinct histological types of pulmonary cryptococcosis have been classified by McDonnell and Hutchins;[12] peripheral pulmonary granuloma, granulomatous pneumonia, intracapillary/interstitial involvement, and massive pulmonary involvement, without special reference to a specific underlying disease.[2] Cryptococcal infection of the lungs in patients with AIDS took the form of intracapillary/interstitial or massive pulmonary involvement.[12,30] Peripheral granulomas and granulomatous pneumonia were not encountered in patients with AIDS, in whom the majority had lung lesions characterized by 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 ubiquitously demonstrated in the lesions, whereas organisms were limited to relatively few alveoli. The lung is commonly considered as the portal of infection,[31,32] and might be expected to reflect this by manifesting an intraalveolar proliferation of inhaled yeasts without capillary involvement. However, we experienced five AIDS patients with generalized disease in whom the histological features were characterized by a few lesions showing the intraalveolar proliferation of *cryptococci* and widespread intracapillary involvement, without fibrous thickening of involved septae. In such patients, the intracapillary involvement may represent the hematogenous dissemination of inhaled yeasts, to which an extremely weak inflammatory response might be induced in alveoli in patients with terminal HIV infection. It has been reported that acute-phase mortality from cryptococcosis among AIDS patients with pneumonia was 42%.[10] Thus, the evidence of such a pattern is most likely explained by the rapidity of onset of vascular involvement, also leading to generalized disease. In addition, the histological alteration of such a pattern might be expected to manifest as a normal chest roentgenogram, and this has been reported as a common roentgenographic finding of pulmonary and/or generalized cryptococcosis in patients with AIDS.[28]

On the other hand, there is a striking difference in the histological features of cryptococcal lesions in AIDS patients with and without HAART. In those with HAART, these features can be summarized as: the presence of lymphocytic infiltrate, much greater response of histiocytes and multinucleated giant-cell formation, and lack of massive capillary involvement. This pattern may be transformed, from the massive capillary involvement that may have been previously produced in the patient by primary cryptococcal infection, as a sequel to the administration of HAART. In fact, in AIDS patients with HAART, Cd4+ cells were visible at the periphery of each nodule, consisting of dense cryptococcal proliferation. Accordingly, the recovery and reactivation of CD4+ cells induced by HAART can activate the histiocytic response to *cryptococci*, with prominent multinucleated giant-cell formation (Fig. 11). A hallmark of infection with *Cryptococcus neoformans* is depression of the immune system, characterized by poor inflammatory responses and loss of delayed-type hypersensitivity and antibody responses.[33] In all seven immunocompetent individuals that we examined, we found discrete granulomas, consisting of compactly aggregated giant cells and histiocytes that were strongly positive for HLA-DR as well as IL-1 beta, most likely as a sequel to the normal functioning of all considerable defense mechanisms against *cryptococci*. The development of a T-cell-mediated pulmonary inflammatory response is critical for the clearance of *cryptococci*,[34] and this has been demonstrated in murine cryptococcosis and is supported by data from several human studies.[6,34,35] Although it has been suggested that humoral immunity was elicited by a cryptococcal capsular polysaccharide,[36,37] none of the histopathological hallmarks of activated humoral immunity, e.g., reactive lymphadenitis and lymphoid follicular hyperplasia of the bronchial mucosae, have been shown in experimented studies.

The absence of CD4+ cells in pulmonary lesions has been confirmed, using immunohistochemistry, in patients with advanced HIV infection, and the recovery of these cells is the focus of HAART. Furthermore, the expression of IL-1 beta and HLA-DR was weak in histiocytes and multinucleated giant cells in immunocompromised individuals, when compared with granulomatous lesions in immunocompetent individuals. Alveolar macrophages are recognized as the first line of defense against cryptococcal

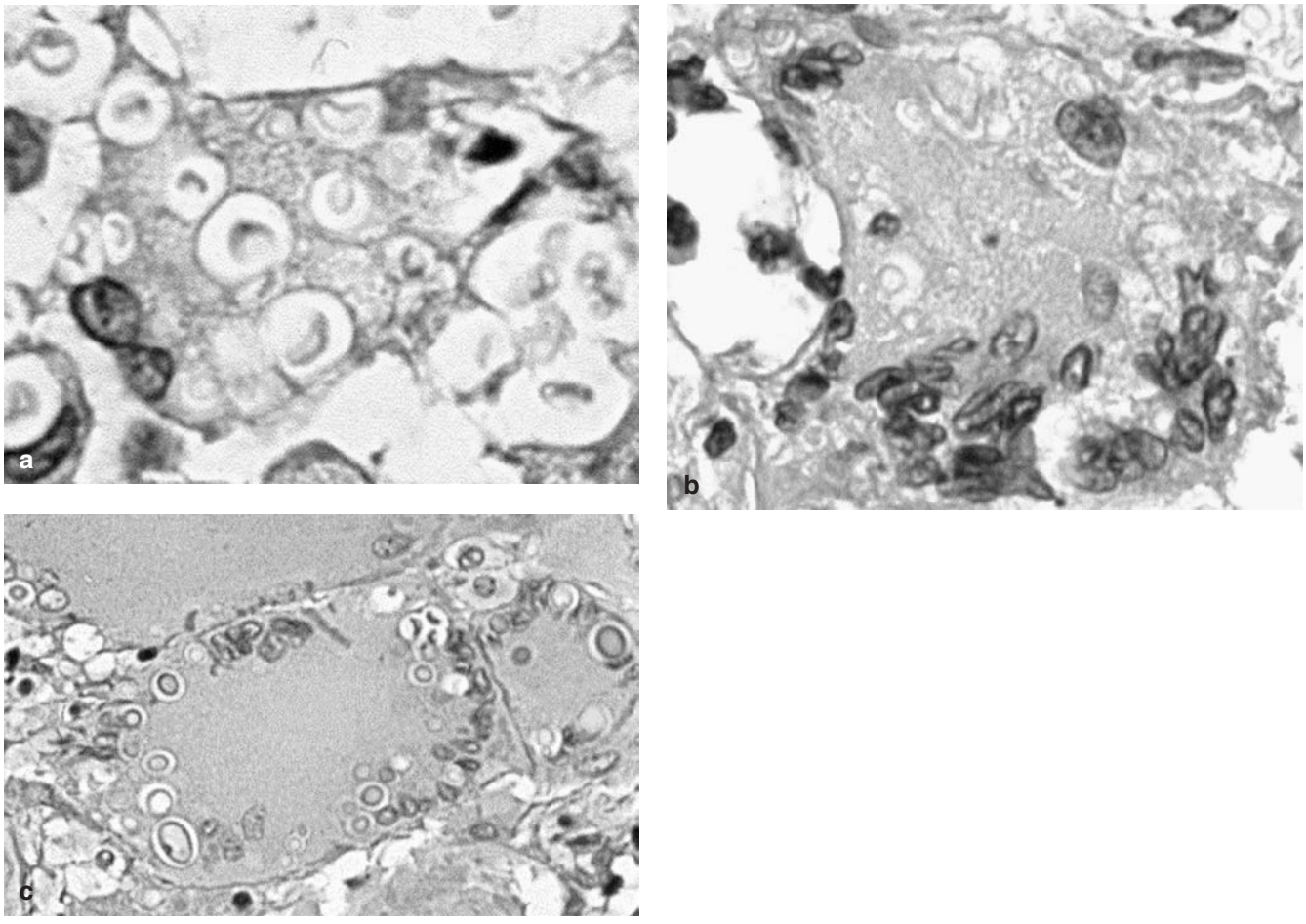

Fig. 11a–c. Comparison of features of multinucleated giant cells in patients with and without HAART, and a non-immunocompromised patient. **a** Giant cells in a patient with advanced HIV infection without HAART. There are many yeast cells in the cytoplasm of immature multinucleated giant cells of foreign-body type. **b** Giant cells in a patient with HIV infection with HAART. There is an increased number of nuclei in the cytoplasm of multinucleated giant cells of foreign-body type, which are more eosinophilic than those shown in **a**, and seem glassy. **c** Giant cells in a patient without any type of immunodeficiency. The multinucleated giant cell features are of the mature Langhans type, in which the nuclei are aligned in a single line at the periphery of the cytoplasm. **a**, **b**, **c** H&E, ×400

infection, and it has been reported, by Vecchiarelli et al.,[38] that human alveolar macrophages from normal subjects play a significant role in antigen presentation to T cells, while their effector function seems to be less relevant, at least in the afferent arm of the immune response to this yeast. That study was consistent with the decreased antigen-presenting activity of histiocytes in pulmonary cryptococcal infection (shown in their later study[39]), which in turn reduces the number of T cells in the lesion, consequently induced by HIV infection. The important event, however, from the findings of their later study,[39] is that the phagocytic activity of histiocytes reacting towards *cryptococci* was unaffected in AIDS patients, and phagocytosis was commonly present. This histological characteristic may be supported by a previous report indicating that bronchoalveolar lavage cells from early HIV-infected individuals did not have an intrinsic defect in fungistasis of *cryptococci*.[40] In addition to the lack of typical Langhans giant cells, the reactive histiocytes and multinucleated giant cells revealed that, while there was mostly normal phagocytic function, there was a decrease in the ability to kill *cryptococci*. The essential feature of the pulmonary lesions in patients with AIDS is the proliferation of *cryptococci* with reactive histiocytosis and a much lesser lymphocytic infiltration, which is, very possibly, the morphological response to cryptococcal infection in patients with manifest T-cell dysfunction. We wish to emphasize the absence of typical granuloma formation, the extensive capillary involvement, and the minimal lymphocytic response in cryptococcal disease in AIDS patients. Further, the reactivation of CD4+ cells induced by HAART can change the histological features of the cryptococcal lesions from predominant massive capillary involvement to granuloma-like formation in the presence of Cd4+ cells.

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