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HISTOPATHOLOGY OF CRYPTOCOCCOSIS IN PATIENTS WITH ACQUIRED IMMUNE DEFICIENCY SYNDROME

Pathology

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ABSTRACT

BACKGROUND: Autopsy studies of AIDS form an important database for evaluation of pattern of lesions of the opportunistic infection and its association with other opportunistic infections. There is paucity of such autopsy studies in Indian literature.

AIMS AND OBJECTIVES: This study was undertaken

- To observe variations in the histomorphological patterns such as spectrum of lesions, distribution and variations in the tissue responses in Cryptococcal infection in AIDS.
- To study different organs of the same patient and patient to patient variations.
- To note other concurrent opportunistic infections with Cryptococcosis in AIDS.

MATERIAL AND METHODS: The data for retrospective study was retrieved from the autopsy files of the department of pathology, B.J. Medical College, Pune between Jan 1993 to Dec 2001. Cases with documented serological diagnosis of HIV and/or patients with evidence of 1995 CDC (A) criteria for AIDS case definition, were followed and amongst these cases histopathological analysis of multiple sections from various organs were studied with H & E stain first and then special stains like mucicarmine, Gomori's silver methanamine (GMS), Periodic Acid Schiff, Masson's Fontana and Zeil Nelson stain were employed whenever necessary.

RESULTS : Out of total 42 cases of AIDS autopsies, 12 (28.6%) cases of Cryptococci infection were documented. Of these 12 cases, 8 were complete autopsies, 3 were partial autopsies and in one case necropsy material was obtained from multiple organs.

CONCLUSION:

1) The findings in this study indicated that cryptococcosis is a significant opportunistic infection in AIDS (28.57%) in India like western countries.
2) Marked variability was observed in histopathological reaction and features of Cryptococci from case to case and also in different organs of the same case.
3) Concurrent occurrence of other infections like candidiasis, PCP, Tuberculosis, Cytomegalovirus infection etc need to be ruled out even after confirmed diagnosis of Cryptococci as it has important bearing in comprehensive management of AIDS patients.

KEYWORDS

AIDS, Cryptococcosis, Histopathology

INTRODUCTION:

India has the third largest HIV epidemic in the world. In 2017, HIV prevalence among adults (aged 15-49) was an estimated 0.2%. This figure is small compared to most other middle-income countries but because of India's huge population (1.3 billion people) this equates to 2.1 million people living with HIV. It is considered as modern Pandemic. The united Nations AIDS Programme (UNAIDS) and WHO estimated that in 2005,about 40.3 million people globally were living with AIDS. The AIDS epidemic claimed 3.8 million lives and 4.9 million people acquired the HIV virus in the year 2005.[1]

Opportunistic infections are responsible for a great majority of the morbidity and mortality in AIDS patients. In Indian literature,many opportunistic infections have been reported in AIDS patients at autopsy, viz pneumocystis carinii pneumonia[2], disseminated tuberculosis[3],cryptococcosis[4], toxoplasma[5] etc. Cryptococcus neoformans is one of the foremost life threatening fungal infections that affects patients with AIDS[4][6][7].

Autopsy studies of AIDS form an important database for evaluation of pattern of lesions of the opportunistic infection and its association with other opportunistic infections. There is paucity of such autopsy studies in Indian literature.

AIM

This study was undertaken

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MATERIAL AND METHODS

The data for retrospective study was retrieved from the autopsy files of the department of pathology, B.J. Medical College, Pune, Between Jan 1993 to Dec 2001. Cases with documented serological diagnosis of HIV and/or patients with evidence of 1995 CDC (A) criteria for AIDS case definition were followed and amongst these cases histopathological analysis of multiple sections from various organs were studied with H & E stain first and then special stains like mucicarmine, Gomori's silver methanamine (GMS), Periodic Acid Schiff, Masson's Fontana and Zeil Nelson stain were employed whenever necessary.All the sections were independently studied under microscope.

RESULTS

Out of total 42 cases of AIDS autopsies 12 (28.6%) of Cryptococci infection were documented. Of these 12 cases, 8 were complete autopsies, 3 were partial autopsies and in one case necropsy material was obtained from multiple organs.

Out of the 12 cases, 11 were males and 1 was female. Age ranged from 25 to 58 years.

Table 1. Shows age/Sex, Organ/System involvement and associated infections in patients with AIDS with cryptococcosis.

	Age/Sex	Organ/System involvement	Associated infection
1	30 M	CNS	-
2	35M	CNS, Liver, Kidney	-
3	58M	CNS,LN Adrenals	P. Carinii Pneumonia, CMV in Adrenal
4	32M	CNS	-

5	28F	CNS,Lungs,Spleen,Kidney, Adrenal,LN Bone Marrow	Oral Candidiasis, T.B GIT, Hbs Ag + Cirrhosis
6	32M	CNS	Oral Candidiasis
7	39M	CNS, Lungs, Adrenals	-
8	25M	CNS, Lungs, liver	-
9	40 M	CNS, Liver, Spleen, LN	P. Carinii Pneumonia
10	28M	CNS,	-
11	35M	CNS,Lung,Liver, Spleen, Kidney, LN, Adrenals	Oral Candidiasis
12	40 M	CNS,Lung, Liver.	-

As regards organs/system involvement 8 out of 12 cases showed disseminated cryptococcosis with involvement of more than one organ. It must be mentioned that in 3 case, only brain autopsies were advised because of CNS symptomatology and consent was given for only partial autopsy by the relatives of patients. In these cases, the possibility of involvement of other organs cannot be ruled out.

Histologically it was noted that in cryptococcosis inflammatory response varied from minimal to intense and from acute to Chronis. In chronic form there may be formation of granulomas with multinuclear giant cells.

Table 2. TYPES OF HISTOPATHOLOGICAL REACTION TO CRYPTOCOCCAL INFECTION (12 Cases)

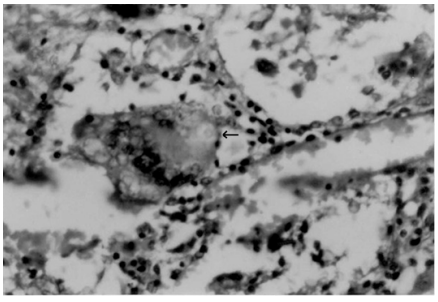
Organ	No. of Cases	Minimal to no reaction	Non granulomatous mononuclear cell reaction	Granulomatous Reaction
CNS	12	2	8	2
Lungs	5	1	2	2
Liver	5	1	1	3
Adrenal	4	1	3	-
Lymph nodes	4	3	1	-
Spleen	3	-	-	3
Kidney	3	1	2	-
Bone Marrow	1	1	-	-

CNS CRYOTOCOCCOSIS:

CNS was the most commonly involved organ system in all the 12 cases.

Histopathological examination with multiple sections from brain and meninges in all cases showed diffuse infiltration of leptomenings by encapsulated fungal bodies of Cryptococcus neoformans floating in pools of mucin. The Cryptococci were also seen extending into brain parenchyma along the perivascular Virchow robins spaces distending them, at times forming satellite perivascular clusters deeper in the parenchyma. There capsules were mucicarmine positive. It was observed that when the growth was florid admixed with capsule deficient strains they could be demonstrated well by Masson's Fontana stain (Fig-1). In 2 cases, granulomas with giant cells with engulfed Cryptococci were observed.

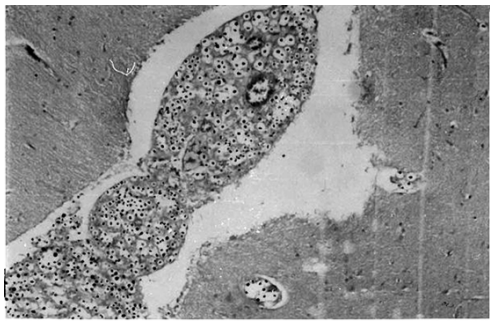
Fig.1. Cerebral cryptococcosis.Photomicrograph showing cryptococci in Virchow Robin space and forming satellite lesions in brain. (x100).H&E stain.



PULMONARY CRYPTOCOCCOSIS:

In cryptococcal pneumonia (5 cases) the common finding was interstitial septae with very minimal inflammatory response. When florid, pools of Cryptococci, with alveolar Lumina filled with them were also observed. In 2 cases macrophages and giant cells forming nodules mainly in subpleural zone were seen. Proliferation of organisms in pleural space was also seen in our case (Fig. 2)

Fig. 2. Giant cell reaction in cryptococcosis. Cryptococci engulfed by giant cell (arrow), from a case of pulmonary cryptococcosis. (x400).H&E stain.



LIVER CRYPTOCOCCOSIS

Total 5 cases were of hepatic cryptococcosis. Mulitple crytococcal granulomas were observed in 3 cases. These showed clusters of capsulated organisms with mild mononuclear cell infiltration .

One case was associated with changes of cirrhosis and had serological evidence of hepatitis B Viral infection.

LYMPHNODE: 4 Cases

Hilar and cervical lymph nodes were predominantly involved in four cases. Lose of architecture; Lymphoid depletion with clusters and pools of Cryptococci on mucinous background was a characteristic feature.

Renal Cryptococcosis:

The kidneys showed cryptococci in 3 cases.In disseminated cryptococcosis, kidney revealed Cryptococci in glomeruli, tubules and interstitium.

Other organ systems involved were adrenals (5 cases), one case associated with CMV adrenalitis, spleen (3 cases) showed singly scattered Cryptococci identified by mucicarmine stain based on strong suspicion.

DISCUSSION:

Infection by cryptococcus neoformans occurs following inhalation of yeast cells and remains as an asymptomatic pulmonary infection, which is dormant. It spreads to the other organs via hematogenous route following reactivation of pulmonary lesions in the immunosuppressive state[3,5]

The present study reports an account of 12(28.57%) autopsies with histopathologically confirmed cryptococcosis out of 42 HIV/AIDS autopsies. In Western literature, neuropathological studies of AIDS autopsy cases have reported the occurrence of cryptococcal meningoencephalitis in 2.6-8 % of cases[9,10]. In complete autopsy studies, the occurrence of disseminated cryptococcosis varied from 8.3% to 12.5%[11,12]. In a study conducted in India in Mumbai, cryptococcal meningoencephalitis was detected in 7 (8%) out of 85 cases on neuropathological examination[13]. A complete autopsy study by the same group revealed disseminated cryptococcosis in 5 (5.5%) out of 92 cases[5]. Another autopsy study conducted in Bangalore reported cryptococcal meningitis in 59% of cases[3].This high percentage of cases may be attributed to the study being conducted in a neurosciences institute.

Cryptococci were found to involve CNS along with multiple organ systems in 12 cases. This may be attributed to hematogenous spread of the organisms in terminally ill patients. The disseminated cryptococcosis thus leads to multiple organ/system infection. In a study from Bangalore[3], out of 23 cases showing cryptococcal meningoencephalitis, 5 had undergone a complete autopsy. In all these cases there was evidence of disseminated cryptococcosis involving organs like lungs, liver, spleen, lymph nodes and adrenals along with CNS cryptococcosis. It is interesting to note that on histopathological examination also the vascular lumina had showed cryptococci, a prelude to hematogenous spread.

Special stains like the mucicarmine stain and Masson's Fontana stain were helpful in demonstrating the organisms better. Carminophilia was less distinct when florid growth in the form of colonies was seen.

It is worth noting that other workers have also stated that particularly in AIDS, unencapsulated form of the organism may be seen, resulting in less intensity of capsular staining[3]. Cryptococcal infection can be diagnosed by India ink/Nigrossin wet preparation of CSF, CSF culture, CSF antigen in serum(which remains high inspite of therapy, as against CSF titres) and visual ELISA[8].

We encountered a number of opportunistic infections associated with cryptococcal meningoencephalitis, viz pneumocystis carinii pneumonia, oral candidiasis, cytomegalovirus, tuberculosis. Multiple opportunistic infections have also been reported by other authors[5] .

There are close similarities in the clinical features of pulmonary and meningeal infection secondary to cryptococcal infection and those due to tuberculosis[3]. As tuberculosis has been documented as the commonest opportunistic pathogen in HIV/AIDS patients in this part of the world, it tends to be overdiagnosed in these patients, possibly missing out infections like cryptococcosis[3] . It must be mentioned that in 2 of our cases , anti tubercular treatment was started empirically on clinical and radiological grounds but at autopsy, cryptococosis was found.

In the present series, the central nervous system was most commonly involved by cryptococcus infection.The histopathologial reaction to cryptococci was variable Granulomatous reaction with giant cells was found in 3 cases in the central nervous system, 2 cases in the lungs, 3 in the liver and 3 cases in the spleen. Such a granulomatous reaction has also been documented in the literature[7] .When cryptococcal meningitis is found, it warrants a search for cryptococci in other organs or other opportunistic infections. In view of similarity between tuberculosis and cryptococcal infection, a high index of suspicion must be kept for the latter.

None of our patients had received HAART therapy for their disease. HAART therapy has, until the recent past, been largely unavailable for the majority of Indian patients on account of its cost. Recent studies have highlighted the clinical and laboratory changes of HIV/AIDS related cryptococcosis, after the introduction of HAART therapy. Capillary involvement of alveolar septae has been described as an important finding in patients with AIDS who had not been treated with HAART, suggesting that the lungs of patients without HAART offer little resistance to bloodstream dissemination by cryptococci. In our study, intravascular cryptococci have been demonstrated in the lungs. The unique histological feature demonstrated in patients treated with HAART is characterized by the presence of CD4+ cells, greater response of histiocytes and multinucleate giant cell formation, and lack of massive capillary involvement.

CONCLUSIONS:-

1) The findings in this study indicated that cryptococcosis is a significant opportunistic infection in AIDS (28.6%) in India like western countries.
2) Marked variability was observed in histopathological reaction and features of Cryptococci from case to case and also in different organs of the same case.
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