Abstract This observational cohort study of 4,160 AIDS patients hospitalised in a single institution in northern Italy between January 1985 and December 1999 was carried out in order to assess the natural history of cryptococcosis, the epidemiological trend of this opportunistic infection, the risk factors predictive of death at 10 weeks, the response to therapy, and autopsy findings. Cryptococcosis was diagnosed in 177 (4.2%) patients and was the AIDS-defining disease in 2.8% of cases. Its prevalence decreased significantly over time (from 6.4% in the period 1985–1989 to 5.7% in 1990–1993, 3.1% in 1994–1996, and 1.9% in 1997–1999, \( P < 0.0001 \)). Although neurologic disease was the most frequent clinical picture, a significant proportion of the patients (24.2%) presented with extraneural cryptococcosis. In a Cox multivariate analysis, high titres of cerebrospinal fluid antigen (>5000) and drug addiction were predictive of death at 10 weeks. A complete clinical and mycological response was achieved in 60.8% of the treated patients, with the highest response rate being observed in those treated with amphotericin plus flucytosine (66.6%). Cryptococcosis relapsed in 12.8% of patients on secondary prophylaxis. Autopsy findings demonstrated that cryptococcosis is a disseminated disease, but long-term antifungal treatment may be able to eradicate it in a subgroup of patients.

Introduction

Cryptococcosis is the most common life-threatening fungal disease affecting patients infected with the human immunodeficiency virus (HIV) [1, 2], and extrapulmonary cryptococcosis is one of the AIDS-defining diseases according to the classification of the Centers for Diseases Control and Prevention [3, 4]. The prevalence of cryptococcosis among HIV-positive patients is reported to be about 2–10% in Western Europe and the USA [5, 6, 7, 8] and more than 15% in some countries of sub-Saharan Africa [9]; however, there is some evidence that the incidence was declining in Western countries even before the introduction of highly active antiretroviral therapy (HAART) [6, 10, 11]. Although most patients (75–90%) present with a clinical picture of meningitis or meningoencephalitis, much of the natural history of cryptococcosis is still undefined.

We describe here the characteristics and clinical course of cryptococcosis associated with AIDS in a large Italian cohort, and we attempt to identify the factors that might affect early mortality (i.e., mortality at 10 weeks, the period currently indicated for completing the induction phase of antifungal treatment) [12]. We also evaluate the rate of clinical and mycological response to the different treatments used in a clinical setting, and we describe the autopsy findings of all of the patients who died in our hospital with a diagnosis of cryptococcosis during life.

Patients and Methods

All of the patients with AIDS consecutively diagnosed between January 1985 and December 1999 at the Department of Infectious Diseases of L. Sacco Hospital, Milan, Italy, were included in the
The clinical features of cryptococcosis at presentation were fever (93.3%), headache (68.5%), neck stiffness (28.5%), altered mental status (21.2%), vomiting (21.2%), and diarrhea (11.2%). The median time from the onset of symptoms to diagnosis was 14.5 days (range, 1–80 days).

Results
Over the 15-year study period, 4,160 patients were diagnosed as having AIDS in our hospital; cryptococcosis was diagnosed in 177 (4.2%) of them, and it was the first manifestation of AIDS in 120 (2.8%). Of these 177 patients, 154 were male and 23 were female; the median age was 32 years (range, 20–66 years). The HIV-transmission categories were as follows: previous or active intravenous drug use (117, 66.1%); homosexual contact (36, 20.3%); heterosexual contact (18, 10.2%); transfusion of blood products (4, 2.2%); and not determined (2, 1.1%). Cryptococcosis was diagnosed during life in all but two patients, both of whom died on the day of admission before culture results were available.

As shown in Fig. 1, the incidence of cryptococcosis at our hospital decreased significantly over the years, from 6.1% in 1985–1989 to 5.7% in 1990–1993, 3.1% in 1994–1996, and 1.9% in 1997–1999 (P < 0.0001). The median CD4+ lymphocyte count at the time of cryptococcosis diagnosis was 25/µl (range, 0–651/µl); 72% of the patients had <50 CD4+ lymphocytes/µl and 17.6% had 50–100 CD4+ lymphocytes/µl; 1.2% had more than 400 CD4+ lymphocytes/µl.

Cryptococcosis was diagnosed by the following means: (i) isolation of Cryptococcus neoformans in 164 (92.6%) episodes; (ii) detection of serum cryptococcal antigen in 9 cases; and (iii) histologic examination in 2 cases (1 with pulmonary and 1 with lymph node disease). Table 1 shows the different clinical pictures of cryptococcosis recognised at the time of diagnosis. The infection presented with neurologic involvement in 134 (75.7%) patients and as extraneural disease in 43 (24.2%).

No difference in the CD4+ cell counts at the time of cryptococcal diagnosis was found between the patients with and those without neural involvement (27 cells/µl [range, 0–651] vs. 24 cells/µl [range, 1–110]; P = not significant). The median time from the onset of symptoms to diagnosis was 14.5 days (range, 1–80 days).

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