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Increased Frequency of Lymphocyte Depletion and Mixed Cellularity Subtypes of Hodgkin's Disease in HIV-infected Patients

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To assess whether the histological pattern of Hodgkin's disease (HD) in human immunodeficiency virus (HIV)-infected patients differs from that among HD patients without HIV infection, the observed (O) number of HD cases according to histological subtype [i.e. lymphocyte predominance (LP), nodular sclerosis (NS), mixed cellularity (MC) and lymphocyte depletion (LD)] among 92 Italian HIV-infected patients was compared with the expected (E) number derived from two case series of HD from Europe and the U.S.A. (14 315 cases of HD) and Italy (125 cases). After age standardisation, the O/E ratio was computed, along with its 95% confidence interval (CI). In comparison with 125 Italian HD patients not infected with HIV, a 4-fold higher frequency of the MC histological subtype (95% CI: 2.9–5.1) and an approximately 12-fold higher frequency of the LD subtype (95% CI: 7.0–18.0) emerged among HIV-infected patients. These results were substantially confirmed when the comparison was made with the case series from Europe and the U.S.A. These data show different histological patterns of HD between a group of HIV-infected patients and HD patients from the general population. Although caution is needed in their interpretation, the study results seem to indicate that HD of the MC or LD subtypes may be considered an AIDS-related malignancy.
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INTRODUCTION

A WIDE DEBATE exists on whether Hodgkin's disease (HD) should be considered a human immunodeficiency virus (HIV)-related malignancy [1–3]. Unlike Kaposi's sarcoma and B-cell high-grade non-Hodgkin's lymphoma (NHL), which are very uncommon in young adults, HD represents one of the most frequent malignancies in the age group of persons most at risk for HIV infection and acquired immunodeficiency syndrome (AIDS) [4, 5]. Therefore, the occurrence of HD among HIV-positive individuals may be compatible with chance, while a small or moderate increase in HD incidence due to the AIDS epidemic would be difficult to demonstrate.[3].

From a qualitative viewpoint, however, the clinical picture of HD in HIV-infected patients appears to differ from that in the general population. A substantial number of cases of HD associated with HIV infection has been reported, mostly based on homosexual males case series from the U.S.A. [6, 7] and intravenous drug users from Europe, in particular from Italy [8]. A higher frequency (more than 80%) of stage III and IV diseases and atypical patterns of disease spread have been described, with the majority of cases being of the mixed cellularity (MC) histological subtype [2, 6–8]. It has, therefore, been suggested that HIV-positive individuals with HD should be considered to have a diagnosis of AIDS [2, 3, 8].

In order to assess whether the histological patterns of HD in HIV-infected patients differ significantly from those of HD patients in the general population, we have compared the frequency distribution of HD subtypes in a series of 89 HIV-infected patients (91% males and 9% females, mean age: 29.6 years) (Table 1), out of 92 (97%) collected by the Italian Cooperative Group on AIDS and Tumours from 1984 to 1991 and described elsewhere (for a detailed description of such case series, see Tirelli *et al.* [8]), with that expected from the general population.

MATERIALS AND METHODS

The frequency distribution of HD subtypes in the HIV-positive patients was compared with two case series (Table 1). The first included 14 315 cases of HD (61% males and 39% females, mean age: 34.5 years) collected within a cooperative study of HD prognosis by 20 institutions in Europe and in the U.S.A. [9]. The cases were diagnosed from the early sixties to 1987, and for 13 903 of them (97%) the histological subtype was specified. No information was available on HIV serostatus, though it is likely that the prevalence of HIV infection was very low.

The second comparison group was drawn from a series of 125 cases of HD in patients without HIV infection (58% males and 42% females, mean age: 42.7 years), histologically diagnosed at the Centro di Riferimento Oncologico, Aviano, Italy, between 1984 and 1991. These patients were part of a case–control study on risk factors for HD in northeast Italy [10]. The histological subtype was defined for 115 of them (92%) (Table 1).

Such a single institution series was chosen for comparison with the HIV-positive group of HD patients since 22 out of 89 (25%) HD cases in HIV-infected patients collected by the Italian Cooperative Group on AIDS and Tumours were initially diagnosed, or histologically classified after review [11], by the Pathology Division of the Centro di Riferimento Oncologico,

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Table 1. Distribution of patients with Hodgkin's disease, according to histological subtype, case series and age

Case series	Age (years)	Histological subtype LP No. (%)	NS No. (%)	MC No. (%)	LD No. (%)
HIV positive					
	≤ 24	0 (0)	7 (37)	13 (27)	4 (20)
	25–34	0 (0)	11 (58)	27 (55)	13 (65)
	≥ 35	1 (100)	1 (5)	9 (18)	3 (15)
	All	1 (1)	19 (21)	49 (55)	20 (22)
Italy					
	≤ 24	1 (12)	14 (19)	5 (16)	0 (0)
	25–34	3 (38)	22 (30)	1 (3)	1 (100)
	≥ 35	4 (50)	38 (51)	26 (81)	0 (0)
	All	8 (7)	74 (64)	32 (28)	1 (1)
Europe–U.S.A.*					
	All	1012 (7)	8684 (62)	3778 (27)	429 (3)

LP, lymphocyte predominance; NS, nodular sclerosis; MC, mixed cellularity; LD, lymphocyte depletion. * The age distribution by histological subtype of Hodgkin's disease was not available.

a comprehensive National Cancer Centre where the Italian Cooperative Group on AIDS and Tumours was established in November 1986.

For each of the four histological subtypes, according to the Rye modification of the Lukes and Butler classification [i.e. lymphocyte predominance (LP), nodular sclerosis (NS), lymphocyte depletion (LD) and MC] [12], the expected number of HD was computed (Table 2). The difference in the age distribution between the HIV-infected and the non-HIV-infected groups was taken into account, in the comparison with the Italian series, by standardisation for age [13] in six groups (< 19, 20–24, 25–29, 30–34, 35–39 and 40 or more years). Unfortunately, because of the small number of HIV-infected females with HD, it was not possible to adjust for the difference in the sex distribution across the histological subtypes.

Finally, the ratio between the observed and the expected number of HD in each of the histological subtypes among the HIV-infected subjects, along with its 95% confidence interval (CI) [13], was computed.

RESULTS

As shown in Table 2, the observed number of LD and MC subtypes of HD in the series of HIV-infected patients was significantly higher than expected, with respect to both series of HD from the general population.

In comparison with the Italian series of HIV-negative patients from a single institution, and after standardisation for age, the HIV-infected subjects had a 4-fold higher [95% CI: 2.9–5.1] frequency of MC subtype and an approximately 12-fold higher frequency (95% CI: 7.0–18.0) of LD subtype (Table 2). These findings were substantially confirmed when the comparison was made with the HD case series from Europe and the U.S.A., where age standardisation could not be applied (Table 2). As a result of such differences among the histological subtypes of HD, the ratio between NS and MC plus LD histological subtypes was 0.3 among the HIV-positive subjects and 2.1 and 4.9 in the case series from Europe and the U.S.A. and Italy, respectively.

DISCUSSION

Although HD is considered a single disease and a distinct clinicopathological entity, in the general population three HD groups may be identified, based on conventional light microscopy analysis [14]: (1) a major subset including the NS subtype; (2) a second subset encompassing almost the entire spectrum of the non-NS subtype. This second subset mainly includes the MC subtype along with a smaller group of related

Table 2. Number of observed and expected cases of Hodgkin's disease according to histological subtype among 89 patients with HIV infection

		Case series from Europe and U.S.A.		Case series from Italy	
	Observed (O)	Expected (E)	O/E ratio (95% CI)	Expected (E)	O/E ratio (95% CI)
Histological subtypes					
Lymphocyte predominance	1	6.4	0.2 (0.0– 0.5)	7.0	0.1 (0.0– 0.4)
Nodular sclerosis	19	55.6	0.3 (0.2– 0.5)	68.2	0.3 (0.2– 0.4)
Mixed cellularity	49	24.2	2.0 (1.5– 2.6)	12.2	4.0 (2.9– 5.1)
Lymphocyte depletion	20	2.8	7.1 (4.0–10.3)	1.6	12.5 (7.0–18.0)

cases with features of the LD subtype. A high rate of misdiagnosis of LD subtype occurs because the precise border between LD and MC subtypes and some NHL is not always easily defined [15]; (3) a minor subset consisting of the LP subtype which, in its nodular variant, seems to be a phenotypically distinct and, possibly, an unrelated disease.

The present report documents a significant difference in the distribution of HD histological subtypes in HIV-infected patients, as compared to HD in the general population. We found that in HIV-infected patients the frequency of the two main subsets, i.e. the NS subtype and MC plus LD subtypes is reversed. HIV-infected patients with HD included in the present series were consecutive patients seen in 32 collaborating institutions, and they do not necessarily represent the population of HIV-infected patients with HD. In particular, a tendency to notify more frequently HD histological subtypes supposed to be associated with HIV infection may be hypothesised, and, as mentioned above, misclassification of NHL as HD may also have occurred.

However, it is unlikely that the differences reported here could be entirely explained by bias, since a lack of NS subtype has also been found among other groups of HD patients with naturally occurring immunodeficiency, in particular among paediatric patients [16]. Variations of HD risk patterns according to histological subtype have also been shown in the general population, suggesting that the histological subtypes of HD represent distinct entities with, at least partially, different aetiologies [17].

The findings of the present study are not *per se* indicative of a significant association between HIV infection and HD, but they support the hypothesis that HD in HIV-infected patients may have features distinctive from those seen in the general population. Furthermore, since the MC and LD subtypes account for approximately one third of all HD in the general population [9, 17], such findings may also help to explain part of the difficulty in demonstrating a significant excess of HD in the population of HIV-infected individuals.

Although utmost caution is needed in the interpretation of the study results, it seems conceivable that HD of the MC or LD subtypes in HIV-infected individuals, with atypical pattern of clinical presentation and advanced stage disease, may be considered an AIDS-related malignancy. The addition of certain subtypes of HD to high-grade NHL among the AIDS-related malignancies may be important not only from a clinical standpoint, but also in understanding the relationship between a non-negligible fraction of these two major types of lymphomas. This is particularly timely, in the light of the recognition of the increased risk of HD following NHL [18], and *vice versa* [19], and the occurrence of composite NHL and HD [20–21].

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