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Trends and Survival in AIDS-associated Malignancies

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Data from 1569 AIDS cases reported to the population-based AIDS Registry of Catalonia have been analysed to describe the epidemiology and temporal evolution of both Kaposi's sarcoma (KS) and non-Hodgkin lymphoma (NHL). Of the 1569 cases reported, 53 (3.4%) presented with NHL and 135 (8.6%) with KS. KS cases were more frequent among homosexual/bisexual men and the age of KS cases was significantly higher than all others presenting diseases (38.22 years). NHL cases were more frequently among men but no significant age difference was found. The percentage of KS over time decreased significantly only among intravenous drug users. Cases presenting with a NHL had by far the worst prognosis (median survival time = 169 days). Biases affecting the measurement of AIDS associated malignancies (AAM) using surveillance data are analysed. The prevalence of AAM will increase during the next few years, and NHL may be one of the leading causes of death among AIDS patients in the near future.
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INTRODUCTION

THE ASSOCIATION between immunodeficiency and different types of cancer has been identified in several conditions. Lymphomas are the most common form of neoplasia encountered among congenital immunodeficiencies [1]. Non-Hodgkin lymphomas (NHL) are present in 15.4% of Wiskott–Aldrich's syndrome cases, and Hodgkin's lymphomas (HL) are reported in 11.7% of patients with ataxia-telangiectasia. Moreover, secondary neoplasias have also been reported among patients receiving polychemotherapy [2] or organ transplants, who tend to develop skin cancer (39%) and lymphomas (29%), particularly with high malignancy degree and B immunological phenotype [3]. Finally, a variety of cancers have also been described in patients with the acquired immunodeficiency syndrome (AIDS) [4–10].

Prior to the AIDS epidemic Kaposi's sarcoma (KS) was limited to iatrogenically immunosuppressed patients [11], to certain parts of central Africa where it is endemic [12, 13], and to elderly men from Mediterranean areas or of Azhkenazi Jewish descent [14, 15]. However, in 1981 the identification of an increased number of reported KS among young people without any known cause of immunodeficiency in the U.S.A. [16, 17] led to the description of a new syndrome caused by the human immunodeficiency virus (HIV) [18, 19]. Since then several opportunistic infections and malignancies have been linked to the underlying immunodeficiency of these patients.

Many risk factors have been associated with both KS and NHL [10, 21–23], but currently available data are not consistent enough to establish any causal relationship. Therefore, the study of the frequency and distribution of these cancers may contribute to the formulation of aetiological hypothesis.

The aims of the present study are: (a) to describe the demographic and epidemiological characteristics of AIDS patients presenting with KS or NHL; (b) to assess the temporal evolution of AIDS patients presenting with KS and NHL; and (c) to identify possible differences between these groups regarding their survival.

MATERIALS AND METHODS

Catalonia (an autonomous region in northeast Spain with six million inhabitants) has the highest standardised AIDS incidence rate in Spain (82.8 per year and per million inhabitants) [24]. The population-based registry of the Catalonian AIDS prevention programme systematically collects information on all AIDS patients diagnosed in the region, using an active surveillance system, following the 1987 AIDS definition criteria [25]. Both KS (ICD-9-CM 176.0-176-9) [26] and NHL are currently accepted as AIDS definition criteria when associated with a HIV positive subject. Definition criteria for NHL include Burkitt's lymphoma (ICD-9-CM 200.2), immunoblastic sarcoma (ICD-9-CM 200.8), lymphoma histiocytic or lymphoma large cell (ICD-9-CM 200.0) and primary lymphoma of the brain (ICD-9-CM 202.8) [26].

A confidential data collection instrument, common to all health administrations, was used to collect demographic, epidemiological and clinical information on an individual basis. These reports are sent to our programme where data are validated and completed, when appropriate. To avoid underestimation due to reporting delay, cases reported after January 1990 were not included in the analysis.

The statistical χ^2 test (significance ≤ 0.05) was used for categorical variables. To compare the percentages of cases presenting with the different indicative diseases by year of diagnosis, comparisons of proportions from independent groups were used. The Mantel–Haenzel test was applied to test for overall trends. Since trends were assessed using proportional data, they were subjected to possible changes in the transmission group distribution over time. Therefore, they have also been analysed within intravenous drug users (IVDU) and homosexual/bisexual men, independently. Mean comparisons between independent groups were used to assess age differences [27].

Finally, the patients' survival was compared according to their presenting disease. After the closing date, information from all

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Table 1. Presenting disease distribution by sex

	Men		Women		Overall	
	n	(%)	*n*	(%)	*n*	(%)
OI	1024	(76.8)	192	(81.4)	1216	(77.5)
NHL	52	(3.9)	1	(0.4)	53	(3.4)
KS	130	(9.8)	5	(2.1)	135	(8.6)
Other	127	(9.5)	38	(16.1)	165	(10.5)
Overall	1333	(100.0)	236	(100.0)	1569	(100.0)

OI = Opportunistic infection; NHL = non-Hodgkin lymphoma; KS = Kaposi's sarcoma; Other = HIV encephalopathy, wasting syndrome or chronic intersticial pneumonia.

Table 2. Mean age distribution by presenting disease and sex (in years)

Presenting disease	Men	Women	*P* value	Overall
OI	31.19	26.03	n.s.	30.38
NHL	31.38	33	n.s.	31.42
KS	38.68	26.40	<0.0001	38.22
Other	30.59	26.69	n.s.	29.69
Overall	32.87	26.18	$P < 0.0001$	31.01

OI = Opportunistic infection; NHL = non-Hodgkin lymphoma; KS = Kaposi's sarcoma; Other = HIV encephalopathy, wasting syndrome or chronic interstitial pneumonia; n.s. = non significant.

cases still registered as "alive" was verified using both hospital records and mortality data, in order to update patient status and to identify the date of either last contact with the physician or death. In addition, death certificates were analysed, and all suspected AIDS-related deaths were verified with the AIDS registry. The actuarial life method [28] was applied to assess long-term survival from date of diagnosis, and the D statistics was used to compare survival functions between groups, as provided by the SPSS-X package [29].

RESULTS

From 1981, when the first AIDS case was diagnosed in Catalonia [30], until the closing date of the study, 1569 cases were reported, of which 77.5% presented with an opportunistic infection (OI), 8.6% with KS, 3.4% with a NHL and 10.5% with other indicative diseases (HIV encephalopathy, wasting syndrome or chronic intersticial pneumonia). Only 5 (3.7%) cases of KS and 1 (1.9%) of NHL were female, both malignancies being more frequent among men ($P < 0.0001$) (Table 1).

While no age difference was found between NHL cases (mean age: 31.42 years) and all other patients (mean age: 31.01 years), KS cases were significantly older than other cases presenting diseases (mean age: 38.22 years) ($P < 0.001$) (Table 2). The fact that in our setting homosexual/bisexual men are older than other groups explains such a difference. For the overall cohort, men (mean age: 32.87 years) were older than women (mean age: 26.18 years) ($P < 0.0001$), but when stratifying by presenting disease the difference was significant only among KS cases ($P < 0.0001$) (Table 2).

Table 3 shows the distribution of the presenting disease only among IVDU and homosexual/bisexual men. Regardless of sex, the HIV transmission category affects only KS, which is more frequent among homosexual/bisexual men ($P < 0.001$).

The percentage of both cancers tends to decrease over time, but no significant difference was found for the overall cohort (Figs 1 and 2). Figure 1 shows the evolution of KS cases from 1985 to 1989 among IVDU and homosexual/bisexual men, as well as for the overall cohort. The percentage of KS decreased significantly only among IVDU ($P = 0.04$). Figure 2 shows the evolution of cases presenting with NHL for the same three groups; none shows a significant decrease or increase over time.

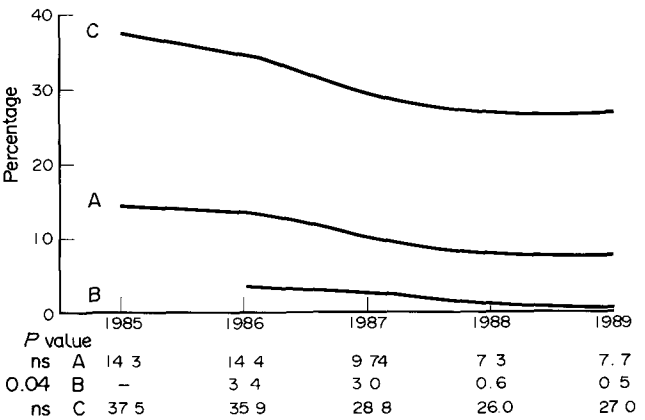

Fig. 1. Percentages of KS by year of diagnosis computed among several groups (a) KS among all AIDS cases; (b) KS among IVDU; (c) KS among homosexual/bisexual men; ns = non-significant overall trend.

Table 3. Distribution by presenting disease and transmission group

Presenting disease	IVDU		Ho/Bi			Overall	
	n	(%)	*n*	(%)	*P* value	*n*	(%)
OI	786	(84.0)	247	(60.5)	n.s.	1033	(76.9)
NHL	34	(3.6)	16	(3.9)	n.s.	50	(3.7)
KS	10	(1.1)	116	(28.4)	<0.001	126	(9.4)
Other	106	(11.3)	29	(7.1)	n.s.	135	(10.0)
Overall	936	(100.0)	408	(100.0)	$P < 0.001$	1344	(100.0)

OI = Opportunistic infection; NHL = non-Hodgkin lymphoma; KS = Kaposi's sarcoma; Other = HIV encephalopathy, wasting syndrome or chronic interstitial pneumonia; IVDU = intravenous drug users; Ho/Bi = homosexual/bisexual men; n.s. = non-significant.

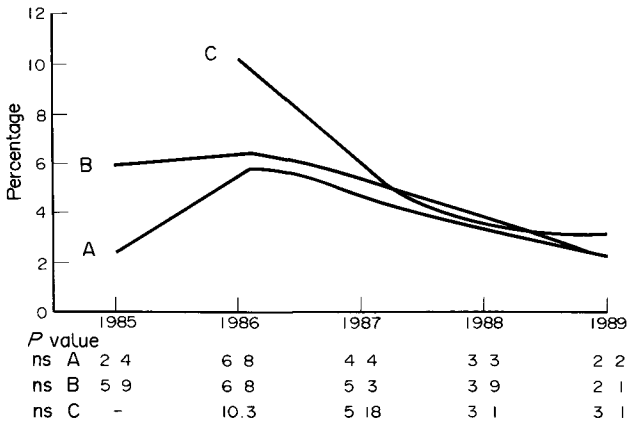

Fig. 2. Percentages of NHL by year of diagnosis computed among several groups. (a) NHL among all AIDS cases; (b) NHL among IVDU; (c) NHL homosexual/bisexual men; ns = non-significant overall trend.

The median survival time (MST) for the overall cohort was 625.5 days, and no significant sex difference was found. By transmission group, IVDU show the longest MST (804 days), followed by homosexual/bisexual men (484 days) and remaining transmission categories (329 days).

When analysed by presenting disease, patients presenting with a NHL have the poorest prognosis (MST: 169 days), patients presenting with an opportunistic infection or with a KS have the longest survival (656.7 and 423.6 days, respectively). Figure 3 shows the survival curve according to the present disease. While survival of KS cases did not differ from the rest of patients, NHL cases have a shorter survival time than any of the other presenting diseases ($P < 0.0001$).

DISCUSSION

According to our results the proportion of AIDS patients presenting with KS is lower in Catalonia than in Europe as a whole or the U.S.A. In our population, patients whose first indicative disease is KS account for only 8.6% of all AIDS cases, while in the U.S.A. [31] and Europe [32] this proportion is 15 and 16.9%, respectively. The fact that only 24% of all reported cases in Catalonia are homosexual men may explain this difference. On the other hand, in 3.4% of all AIDS patients in our setting the first AIDS-indicative disease is NHL, similar to the percentages found in the U.S.A. (2.9%) [33] and in Europe (3.3%) [32].

Our results confirm the classical distribution of AIDS patients, with KS being more frequent among homosexual/bisexual men

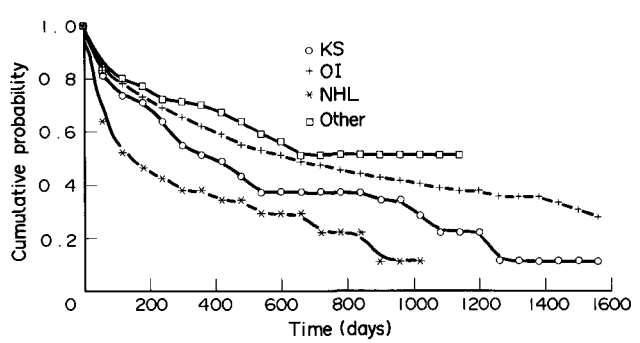

Fig. 3. Survival curve by presenting disease.

[8, 9, 34], even after adjusting for the use of intravenous drugs among homosexual men, supporting the hypothesis of a sexually transmitted aetiological agent [31, 35, 36]. Although there is a small number of women with KS or NHL, KS patients are the only group with age differences between sexes, male cases being older than female cases. This reflects the age distribution of homosexual men in our community [37], as well as the fact that IVDU are younger than in the U.S.A. [38].

Female KS cases have also been reported [39, 40]. In our study all 5 female KS cases were IVDU, and among this transmission group the proportion of KS in men and women was similar (1.5 and 2.7%, respectively; $P = 0.17$). Although heterosexual transmission of a possible putative agent for KS among these cases cannot be ruled out, parenteral transmission should also be explored further.

NHL was significantly more frequent among men than women, even after stratification by transmission group. Although some reports have suggested that haemophiliacs, blood transfusion recipients and IVDU have a greater probability of presenting with NHL [41], our results did not find any relationship between this cancer and the route by which the patient was infected. Only primary lymphoma of the brain has been found to be more frequent among IVDU in our community [42].

In the U.S.A. studies using population-based data have analysed the possible temporal trend of cancers among people thought to be at high risk for HIV, namely young, unmarried men [43–48]. Although these studies have used different methodological approaches, all agreed that the incidence of both KS and NHL is increasing in this population. On the other hand, studies done in the U.S.A. [31] and Europe [32, 49] using AIDS surveillance data, have confirmed a decrease in KS as a presenting disease over time, but no geographical difference between countries [32].

Nevertheless, using AIDS surveillance data to evaluate trends for AIDS associated malignancies (AAM) may lead to several biases. Most AIDS registries collect information on AIDS indicative diseases only as presenting diseases. Therefore, diseases which appear after the diagnosis are not recorded, and their incidence may be underestimated. Since KS appears early in the natural history of HIV infection, this effect is probably very small in comparison with NHL, which is usually a later diagnosis.

Other factors may also influence the distribution of the AIDS presenting disease. Since indicative diseases are a function of the underlying distribution of their associated factors, both the prevalence and distribution of the infectious agents, as well as the distribution of the transmission groups in the community, may affect them. Therefore, the quantification of AAM using proportional data is also affected by possible variations in the other indicative conditions. As an example, the introduction of the new AIDS definition criteria [21] in our setting in 1988 produced an increase of AIDS cases, mainly because of the introduction of extrapulmonary tuberculosis as a new indicative disease [50] and because of the simplification in the diagnosis criteria for toxoplasmosis [42]. Since both conditions are much more common among local IVDU than in other transmission groups like homosexuals, the decline found in KS among IVDU may be partly due to this factor.

Although a significant difference could be identified using a larger series, according to our results no temporal trend has been identified for the overall cohort for KS or NHL. In particular, the lack of a significant decrease in KS among homosexual/bisex-

ual men may indicate that if there is any environmental or behavioural risk factor, it has been constant over time in the homosexual community.

The temporal pattern of KS may differ regionally and any comparison should take into account possible local differences in both underlying risk factors and in the characteristics and distribution of the transmission groups. Sources of information other than AIDS surveillance data should be used to analyse the occurrence and distribution of KS and NHL among AIDS cases, in particular both population-based cancer registries and cohorts of HIV infected people. It will also be necessary to assess the possible role of the introduction of zidovudine in the evolution of KS incidence among HIV infected patients.

Although as a whole the survival of AIDS patients is improving over time [51–53], this pattern is not homogeneous for all patients, varying according to the indicative disease present at the time of diagnosis [54]. While some studies from the U.S.A. have shown that KS cases have a better prognosis than cases presenting with an opportunistic infection [51], in others, cases presenting with an opportunistic infection have the longer survival time [55]. The high prevalence of tuberculosis infection in our community—particularly among IVDU—may explain such differences. In any case, it is clear from our results that patients presenting with NHL have the poorest prognosis, irrespective of age, sex or transmission group.

The future scope of AAM will depend not only on the prevalence and distribution of the risk factors which are yet to be identified, but also on the prevalence of the population at risk. The fact that for at least the next 5 years the prevalence of HIV infection will continue to increase in most European countries will lead to an important increase in the prevalence and incidence of AAM in the short term. Moreover, since patients with a more impaired immunological system, (CD 4 less than 200) are specially at risk [56], the continuous increment in the survival of AIDS patients due to the prevention and treatment of opportunistic infections and specific antiretroviral therapy, will particularly contribute to this increase.

According to our results, since NHL is the indicative disease with the poorest survival, in the future NHL may be one of the leading causes of death among patients with AIDS.

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Immunochemical Analysis of the p53 Oncoprotein in Matched Primary and Metastatic Human Tumours

Jirina Bartkova, Jiri Bartek, Borivoj Vojtesek, Jiri Lukas, Ales Rejthar, Jan Kovarik, Rosemary R. Millis, David P. Lane and Diana M. Barnes

There is much interest in the range of genetic aberrations which occur in human malignancies. An immunohistochemical study has been carried out to investigate the consistency of expression of abnormally accumulated p53 protein in paired samples of archival primary and metastatic carcinomas. The staining of methacarn-fixed tissue from 136 matched pairs of mammary carcinoma and 20 cancers from other sites was completed using antibody CM-1 and DO1 in a sensitive peroxidase-conjugated streptavidin-biotin technique. The majority of tumour cells were positive in 25% and the tumours were negative in 17% of the primary carcinomas; staining was heterogeneous in the remaining cases. Staining was identical in 180/186 (96%) metastatic lesions. An ELISA assay carried out on 12 matched pairs of the tumour specimens demonstrated that altered conformation of the aberrant p53 protein present in a primary lesion was maintained in its metastasis. These data indicate that alterations in the p53 gene result in a relatively stable phenotype and that progression of disease is not usually accompanied by either further mutation or loss of the mutant allele.
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INTRODUCTION

THERE IS compelling support for the notion that carcinogenesis represents a multistep process. Cancer statistics relating the tumour incidence with age indicated that some five or six steps or 'hits' are required for a common human tumour to reach a diagnosable stage [1]. More recently, the cytogenetic and molecular biology analyses have confirmed the long anticipated presence of a range of genetic aberrations in human malignancies [2, 3]. Among the most striking of such alterations are mutations in the p53 gene [4, 5]. At present, the p53 mutations are regarded as the most frequent genetic change so far identified in human cancer and the genetic and biological features of p53 show a puzzling combination of a tumour suppressor gene and a dominant oncogene [4, 5]. The p53 mutations are usually point missense mutations in the phylogenetically highly conserved central region of the molecule [5, 6]. They appear to be important both in the pathogenesis of a broad range of sporadic tumours [5, 7, 8], and as germline mutations representing the inherited basis