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Testicular Lymphoma: a Population-based Study of Incidence, Clinicopathological Correlations and Prognosis

M.B. Møller, F. d'Amore and B.E. Christensen on behalf of the Danish Lymphoma Study Group, LYFO

In a Danish population-based non-Hodgkin's lymphoma registry, 2687 newly diagnosed patients were registered from 1983 to 1992. 39 had testicular involvement (TL) (incidence 0.26/10^5/year). Median age was 71 years. 24 cases had localised and 15 had disseminated disease. Histologically, all cases were diffuse (65% diffuse centroblastic type). Of the 27 tested, 11% were of T- and 89% of B-immunophenotype. In localised cases, where surgery was supplemented by combination chemotherapy (CCT), the relapse rate was 15.4%. The relapse rate for cases with localised disease treated with other regimens (orchiectomy and/or radiotherapy) was 63.6% ($P < 0.05$). Median relapse-free survival was 28 and 14 months, respectively. Overall 5-year survival for all cases was 17%. Adverse prognostic factors at the univariate level were stage IV, constitutional symptoms, serum lactic dehydrogenase elevation and performance score (WHO 3–4). It is suggested that the treatment of stage I_E/II_E TL should include early CCT and CNS prophylaxis.

Key words: non-Hodgkin's, lymphoma, testicular, surgery, therapy
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INTRODUCTION

SINCE THE first description of testicular lymphoma as a clinical entity in 1866 [1], a large number of publications have described the natural history of this lymphoma. Of these reports, only very few contain population-based data [2, 3].

Primary testicular non-Hodgkin's lymphoma (NHL), defined as testicular involvement at the time of diagnosis, is a rare disease, representing 1–8% of all testicular cancer [4]. It mainly affects older men, is histologically highly malignant (usually of centroblastic diffuse type), with a tendency to bilateral testicular involvement and an association with Waldeyer's ring, skin and CNS [4].

It is still debated whether truly (i.e. without microscopic spread) primary testicular NHL does exist as an independent entity, or whether it should be regarded as the first symptom of a more widespread disease. Rare cases have been reported where patients have achieved long-term disease-free survival after orchiectomy as the sole treatment.

This report is a clinicopathological analysis of 39 unselected cases based on the data from a Danish population-based lymphoma registry.

PATIENTS AND METHODS

The Danish population-based registry, LYFO registry, covering western Denmark (2.8 million inhabitants), was started on 1 January 1983, and is still ongoing. The organisation of the registry has been described elsewhere [5]. For this study, the data from 2687 consecutive cases of NHL, registered between 1 January 1983 and 30 September 1992, were analysed. 39 patients (1.4%), all with testicular involvement at the time of diagnosis, were included.

Clinical data

At the time of diagnosis, the registered parameters included date of birth, date of diagnosis, occupation, associated diseases,

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symptoms (including duration), histological type, clinical stage, site(s) of involvement and a number of biochemical parameters. Routine clinical staging procedure consisted of physical examination including ear, nose and throat examination, biopsy from involved tissue, bone marrow aspirate and biopsy (Islam needle), chest X-ray, abdominal CT scan and/or lymphangiography, and ultrasonic scan of liver and spleen. Staging laparotomy was not performed.

The Ann Arbor Classification [6] was used for staging.

At relapse, the following parameters were registered: site(s) of involvement, biochemical parameters, histology, treatment and response to treatment. Registration at death included date and cause of death, and clinical and/or pathological involvement of lymphoma.

Pathological assessment

The histological diagnosis and classification was reached by consensus among a panel of three haemopathologists. In the majority of cases, frozen sections were available for further immunohistochemical analysis. The updated Kiel classification [7] was used. The cases were also graded as low, intermediate or high, according to the National Cancer Institute Working Formulation for Clinical Usage (WF) [8]. NHL of diffuse centroblastic type was considered as high grade [9].

Primary treatment

Of the 24 cases with localised disease (stage I_E/II_E), 23 underwent orchidectomy. In 19 cases, orchidectomy was either supplemented with combination chemotherapy (CCT) alone (14 patients), radiotherapy (RT) alone (4 patients) or both (1 patient). One patient received RT as sole treatment, without orchidectomy.

Treatment of 11 patients with disseminated disease consisted of orchidectomy (10 patients) followed by CCT (3 patients), monodrug chemotherapy (3 patients), RT (1 patient) or a combination of CCT and RT (3 patients). One patient received CCT, total body irradiation and an autologous bone marrow transplant. 4 patients did not receive any form of cytoreductive treatment.

Follow-up

At the time of analysis the median follow-up time for patients with primary testicular NHL was 50 months. The maximum possible follow-up was 117 months. Patients were followed with 2-monthly post-treatment follow-ups within the first 6 months, 3-monthly follow-ups up to 2 years, and 6-monthly follow-ups from 2 to 5 years after treatment was discontinued; thereafter, once yearly up to a planned total post-treatment observation period of 10 years. Each follow-up consisted routinely of a physical examination and blood analysis (haematology, electrolytes, liver enzymes). At every second follow-up, a routine chest X-ray was taken.

Statistical analysis

Statistical differences between cross-tabulated values in frequency tables were evaluated by the Pearson χ^2 test. Time at risk began at the date of conclusive histological diagnosis, and ended at the date of last known status or at the date of death. Survival curves were plotted according to the actuarial method. Statistical differences at univariate level were evaluated by the Tarone–Ware test and Mann–Whitney test. The BMDP statistical programme package (Statistical Software, Los Angeles, U.S.A.) was used.

RESULTS

Demographic data

In the west Danish population of 2.8 million (1.39 million males) in the period 1 January 1983 to 30 September 1992, a total of 2687 newly diagnosed NHL cases was registered in the LFYO registry. This corresponded to an average annual NHL incidence rate (IR) for a Standard European Population (EP) of $9.5/10^5$ individuals (9.9 for males and 9.1 for females). Of all males, 39 (2.8%) had testicular involvement at the time of diagnosis, which corresponded to an IR (EP) of $0.26/10^5$ males. Patients with TL had a median age of 71 years, ranging from 10 to 89 years. Only 13% were under 50 years old, 15% were under 60 years of age.

Clinical features

Table 1 compares the clinicopathological characteristics of localised versus disseminated cases.

Enlargement of a testicle was the most common presenting symptom, present in 36 (92%) patients. Two of the remaining patients had a hard, globular testis. 28 patients initially contacted a physician because of testicular symptoms. In 1 case the testicular involvement was detected at autopsy. Other scrotal symptoms were tenderness (18%), pain (8%), feeling of heaviness (5%) and hydrocele (5%). 2 patients (5%) had bilateral testicular lymphoma (TL). Of the 28 cases where data on duration of symptoms were available, 11 (39%) had symptoms for more than 12 weeks.

12 patients had a family history of leukaemia. No patients had a disposition to NHL or testicular cancer.

The spectrum of disease associated with TL was not different from what could be expected in an older cohort, with inguinal hernias (6), ischaemic heart disease (5) and ulcers (4) being the most common. There was no association between the side of the hernia and the side of the affected testis. 2 patients had a history of testicular trauma, and 2 patients previously had orchitis and subacute epididymitis, respectively. Vasectomy was performed in 1 case. No patient had a history of cryptorchidism.

Other sites of involvement at diagnosis included paraaortic lymph nodes (8), skin (5), cervical lymph nodes (4), bone marrow (4), central nervous system (3), mediastinum (3), bones (3) and pelvic lymph nodes (3). The most common sites of involvement at relapse/progression were CNS (4), paraaortic nodes (3), skin (2) and gastrointestinal tract (2). One patient relapsed in the contralateral testis.

Pathological findings

Gross features. The largest diameter of affected testicles ranged from 3 to 9 cm with a mean of 6.8 cm. The cut surface of the tumour tissue was homogeneous, granulated or slightly lobulated. It was firm, grey-brown-white with small foci of haemorrhage and/or necrosis. In most cases, the tunica albuginea was distended and intact. In four specimens, there was macroscopic invasion.

Microscopic features. All neoplasms were histologically diffuse. The most common histological subtypes were centroblastic diffuse (65%), lymphoblastic (18%) and immunoblastic (8%), other histologies comprised 9%. Of 33 orchidectomy specimens, vascular invasion was found in 10 (30%); in 22 (67%) epididymis and/or spermatic cord invasion was found. Invasion of the tunica albuginea was prominent in 14 cases. The pattern of growth was usually infiltrative, disrupting the normal architecture of the testis, and, to judge from the smaller tumours, they originated

Table 1. Clinicopathological features in localised versus disseminated testicular lymphomas

Features	Stage I_E/II_E	Stage IV	*P* value
Number	24	15	
Median age (range)	73 (10–86)	69 (15–89)	
Testis-related primary symptoms	21 (88%)	7 (47%)	0.02
B symptoms	1 (4%)	9 (60%)	0.0004
Performance score > 1	1 (4%)	9 (60%)	0.0004
Histology grade			
Low	0	0	
Intermediate	1 (4%)	2 (13%)	
High	23 (96%)	13 (87%)	
Elevated s-LDH	2 (8%)	8 (53%)	0.006
Elevated s-urate	2 (8%)	3 (20%)	N.S.
Elevated s-IgM	4 (17%)	1 (7%)	N.S.
Elevated s-IgG	1 (4%)	0	N.S.
Elevated s-IgA	3 (13%)	0	N.S.
CR rate	96%	7%	< 0.00005
Relapse rate	40.9%	75%	N.S.
Median survival	28 months	3 months	< 0.00005
2-year survival	68%	14%	< 0.00005

N.S., non-significant; s-LDH, serum lactic dehydrogenase; CR, complete response.

centrally in the testis. The seminiferous tubuli were atrophic and dispersed in the lymphoma, and in 6 cases invaded by malignant cells. Twelve specimens showed areas of necrosis, although discrete. In 4 cases, there was a typically starry sky pattern. No cases with granulomatous reaction were seen.

Immunophenotyping. The majority of patients, 27 (69%), were immunophenotyped. Of those, 3 cases were of T- and 24 of B-phenotype. The 3 T-cell cases were lymphoblastic (2 cases) and peripheral T-helper cell lymphoma.

Laboratory findings

Elevated serum lactic dehydrogenase (s-LDH) and hyperuricaemia were correlated with advanced-stage disease (Table 1). Hyperimmunoglobulinaemia, with elevated s-IgM as the most frequent, was found in 23% of the cases. None of the patients, who were examined for α-fetoprotein and human choriongonadotropin, had pathological levels. No patients were known HIV-positive.

Treatment and mortality data

Median relapse-free survival for all patients, where complete response (CR) or partial response (PR) was achieved, was 19 months. Patients with localised disease had a relapse rate of 40.9% and a mean time to relapse of 13.2 months. More than half of the relapsing localised cases relapsed within 7 months. The 13 cases of localised disease treated with orchiectomy and CCT had a relapse rate of 15.4%, while the relapse rate for the remaining patients with stage I_E/II_E disease was 63.6% ($P < 0.05$). Median relapse-free survival was 28 and 14 months, respectively. Cases with stage I_E disease, where microscopic invasion of the epididymis and/or spermatic cord was found, had a relapse rate of 42% versus 25% for stage I_E cases without this feature. The difference was, however, not significant.

Disseminated disease treated with both CCT and RT had a remission rate of 75% (3/4), while remission was only induced in 9% (1/11) of patients treated with other regimens. In the 4 (27%) cases of stage IV disease where CR or PR was induced, 3 relapsed after a median period of 20 months (range 2–35).

At the time of analysis, 27 (69%) patients were dead. Of these, 15 (56%) were dead as a consequence of TL while 1 died of treatment complications (bleomycin pneumonitis). Autopsy was performed in 9 cases. Of the 12 patients alive, 11 were without clinical evidence of lymphoma with a median duration of remission of 34 months.

Survival and prognostic factors

The overall 2- and 5-year survival rates were 43 and 17%, respectively, belonging to the lowest values among extranodal sites (Figure 1). Survival of patients with disseminated disease differed significantly from stage I_E/II_E disease (Figure 2).

Other adverse prognostic factors at the univariate level were performance score ($P = 0.0002$), constitutional symptoms ($P = 0.0001$) and s-LDH elevation ($P = 0.00005$). Age and clinically assessed tumour burden (all cases) and local vascular

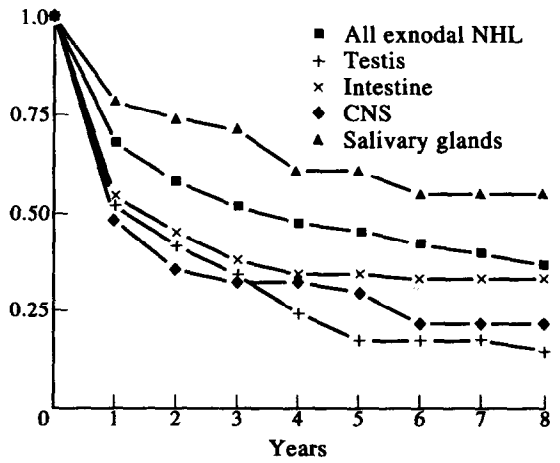

Figure 1. Survival of all extranodal NHL and selected locations.

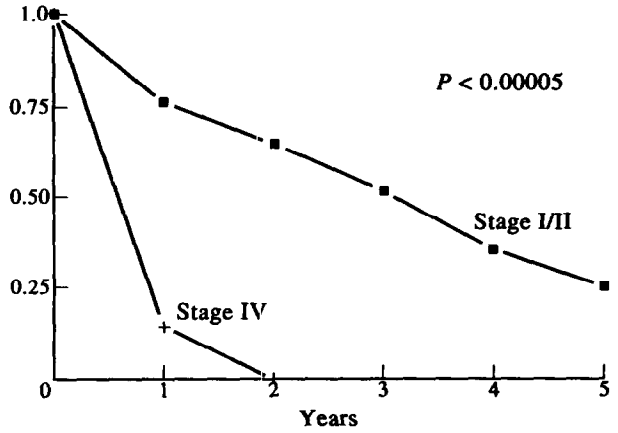

Figure 2. Survival of localised versus disseminated testicular lymphoma

invasion (localised cases) were without prognostic influence. Median survival after relapse was less than 2 months.

DISCUSSION

The literature on TL is extensive, but data derived from population-based studies are rare [2, 3]. By having a population-based registry, the bias due to differences in local referral policies have been avoided. Other limitations of earlier studies, describing larger series, is the fact that such cases have been collected over extensive time spans. This has resulted in non-uniform treatment, and often insufficient staging, when compared with modern diagnostic potential.

In the period 1983–1992, 2687 cases of newly diagnosed NHL were included in the LYFO registry. The frequency of TL in the LYFO material (1.4%) is comparable (0.83–1.6%) to that of other studies [10–12]. It corresponds to an annual incidence rate (Standard European Population) of $0.26/10^5$ males. A much higher incidence of subclinical testicular involvement is to be expected, according to existing data from autopsy studies [13].

This study further substantiates that primary testicular lymphoma is a disease primarily of older men, with the highest prevalence in the 7th to 9th decade. Eighty-five per cent of the patients are older than 60 years. In this particular age-group, testicular lymphoma is actually the most common testicular tumour [4, 14]. TL is also the most common synchronous bilateral testicular tumour [14, 15]. Synchronous bilaterality was 5% in this study, while metachronous involvement was not as common (2.6%). In other series, bilaterality occurred in 0–30%, with an average of 19% [4, 16]. The lower frequency of metachronous involvement in this study may be explained by the fact that stage I_E/II_E disease was treated with combination chemotherapy to a greater extent than in earlier studies.

In the literature, a uniformly poor prognosis (among the poorest of extranodal locations, see Figure 1) is reported [5, 12] with an overall mean survival of 9.5–12 months [4, 11, 17], and an overall median relapse-free survival of 7 months [3] to 19 months in the present series. Overall 2- and 5-year survival rates range between 4 and 30% (present study 43%) and 5–20%, respectively [18]. Advanced disease, constitutional symptoms, high performance score and elevated s-LDH were found to be associated with poor prognosis in this study.

Even if extensive staging procedures, including staging laparotomy, were performed, only very few patients with clinical stage I_E disease would remain long-term relapse-free after orchidectomy alone. Autopsy studies have revealed non-contiguous lung involvement in 86% of lethal cases, suggesting micrometastases by the haematogenous route, as a possible explanation [17].

Frequent sites of relapse seen in the present and earlier studies were CNS and the contralateral testis.

A significant lower relapse rate of 15.4% was found in this series in cases with localised disease, where orchidectomy was supplemented with combination chemotherapy. The relapse rate of the remaining localised cases was 63.6%. Our data confirm the necessity of early combination chemotherapy for stage I_E/II_E disease. Conners and colleagues [19] found, by adding early, brief chemotherapy to orchidectomy and irradiation as treatment of stage I_E disease, an improved relapse-free and overall survival at 4 years of 93% versus 50%. In another study, treatment with brief doxorubicin-based chemotherapy resulted in an actuarial survival of 74% at 5 years [20]. It is not clear whether supplementing chemotherapy with radiotherapy is advantageous. However, there is some evidence for the efficacy of scrotal irradiation in preventing testicuar relapse [21].

In the present study, all of the 4 patients relapsing in the CNS did so in spite of having been treated with combination chemotherapy. Therefore, it seems appropriate to suggest the inclusion of routine CNS prophylaxis in the treatment of TL [10, 20].

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Response to Second-line Weekly Cisplatin Chemotherapy in Ovarian Cancer Previously Treated with a Cisplatin- or Carboplatin-based Regimen

G. Bolis, G. Scarfone, L. Luchini, C. Ferraris, F. Zanaboni, M. Presti, G. Giardina, A. Villa and F. Parazzini

Response to a second-line weekly cisplatin chemotherapy in ovarian cancer previously treated with cisplatin- or carboplatin-based regimens was analysed in a clinical series observed between 1984 and 1991. Women who achieved pathological complete response or pathological optimal partial remission after first-line cisplatin- or carboplatin-based regimens were treated at recurrence or progression, occurring at least 4 months after first-line treatment, with second-line chemotherapy. A total of 72 women were included in the analysis. Second-line chemotherapy regimens were: cisplatin 1 mg/kg weekly for seven courses plus epirubicin 70 mg/m^2 intravenously (i.v.) every 3 weeks for three courses (28 subjects), cisplatin 1 mg/kg plus etoposide 90 mg/m^2 i.v. weekly for a total of seven courses (11 subjects) and cisplatin 1mg/kg weekly for nine courses plus carboplatin 250 mg/m^2 every 3 weeks for three courses (33 subjects). Of the 72 women, 22 (31%, 14 clinical, 8 pathological) had a complete response and 28 (39%), a partial response (24 clinical, 4 pathological). The 24-month cumulative survival probability was 63% in women with complete response, 32% in those who had partial response, but all the 22 non-responders died within 24 months from diagnosis of recurrence (log rank test $P < 0.05$). The frequency of complete response and partial response increased with the interval between first diagnosis and recurrence: among the 33 women who had recurrent disease to < 18 months from first diagnosis, complete response or partial response was obtained in 20 (61%) subjects, this figure was 67% (14 out of 21 women) among subjects who had recurrent disease between 18 and < 36 months from first diagnosis and 89% (16/18) among those who had recurrence ≥ 36 months. In comparison with women who had recurrence 4–< 18 months from first diagnosis, the OR of response was 1.3 (95% CI 0.4–4.1) for those who had recurrence between 18 and < 36 and 5.2 (95% CI 1.1–24.3) for those who had recurrence ≥ 36 months from surgery (χ^2_1 trend p < 0.05). Survival rate after the end of second line chemotherapy for women who relapsed 4–< 18 months, 18–< 36 or 36 months or more after surgery were, respectively, 24, 20 and 67% (log rank test, $P < 0.05$). Age at first diagnosis, histology, stage, and grading of the disease at first diagnosis and site of recurrence were not associated with response to second-line therapy.

Key words: ovarian cancer, second-line treatment, prognostic factors, chemotherapy
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INTRODUCTION

REPORTED PERCENTAGES of response to second-line chemotherapy in relapsing ovarian cancer range from about 25 to 70 per cent [1–7]. These differences may be attributable to differences in the characteristics of treated populations [6–8]. Definition of the determinants of responses to second-line chemotherapy may help in comparing results from different series and, from a clinical point of view, may be useful in establishing the prognosis of recurrent ovarian cancer and identifying women who may benefit from treatment.

We have analysed the response to second-line chemotherapy in ovarian cancer cases with recurrent disease, previously treated with platinum-based regimens.