Original Study

Non-Hodgkin Lymphomas Presenting as Soft Tissue Masses: A Single Center Experience and Meta-Analysis of the Published Series

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Abstract

Lymphomas with involvement of soft tissues are very rare. We describe our experience with soft tissue non-Hodgkin lymphomas diagnosed and treated in our institution over a 15-year period. Moreover, we systematically review the available data from the literature, showing that Diffuse Large B-cell lymphoma is the most common histologic subtype and is characterized by a dismal prognosis with current treatment strategies.

Background: Lymphomas with involvement of soft tissues as a primary event are very rare. The published studies have a small sample size, most of them being reported as case reports. **Patients and Methods:** In this article we describe our experience with soft tissue non-Hodgkin lymphomas (NHL) diagnosed and treated in our institution over a 15-year period. Moreover, we systematically review the available data from the literature in the past 2 decades, considering all the published series and case reports available from 1990 to 2011 using a PubMed access. **Results:** In the monocentric analysis, 16 consecutive patients treated at our Institution from 1996 to 2011 were considered. In the literature search, we selected 16 case reports (18 patients) and 5 case series (49 patients), including a total of 67 patients. Eighty-three patients were finally considered in the combined analysis. The most common histologic subtype was diffuse large B cell lymphoma (DLBCL) (>50% of cases in both groups). In both analyses we observed an inferior outcome for DLBCL compared with indolent B-cell NHL (5-year progression free survival: 34% vs. 64%, respectively, in the combined analysis; $P = .01$). Furthermore, the prognosis in the DLBCL group appears to be worse compared with the historical data of DLBCL patients treated with chemoimmunotherapy. **Conclusions:** Though indolent soft tissue B-cell NHLs appear to have a good outcome, soft tissue DLBCLs represent an anatomic-clinical entity with aggressive features, and dismal prognosis. Strategies of first-line therapy intensification could be considered. Studies aiming to a better biologic characterization of this peculiar entity are warranted.

Clinical Lymphoma, Myeloma & Leukemia, Vol. 13, No. 3, 258-65
Keywords: Diffuse large B-cell lymphoma, Follicular lymphoma, Indolent non-Hodgkin lymphoma, Soft tissue lymphoma, T-cell lymphoma

Introduction

Non-Hodgkin lymphomas (NHL) usually present with multiple lymphadenopathies but might also involve any extranodal site containing lymphoid tissue, and the bone marrow. Involvement of the soft tissue (defined as tissue that connects, supports, or surrounds other structures such as adipose tissue, connective tissue, and skeletal muscle) as a primary event is very rare, being estimated to occur in 0.1% of all lymphomas.[1,2] Most of the time the soft tissue is involved by direct spreading from affected lymph nodes and/or metastatic hematogenous dissemination.[3]

From a clinical point of view these lymphomas usually manifest with a soft tissue mass, swelling, and pain. The most common histology is Diffuse Large B cell lymphoma (DLBCL), but almost all types of NHL have been described. Hodgkin lymphoma of the soft tissue is very rare.[1,3,4] The main sites commonly involved are thigh, trunk, and lower limbs.[3,5] It is important to differentiate soft tissue lymphomas from soft tissue sarcomas.[5–8] Some peculiar imaging characteristics when using magnetic resonance imaging (MRI)

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Submitted: Aug 19, 2012; Revised: Sep 30, 2012; Accepted: Oct 1, 2012; Epub: Dec 14, 2012

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2152-2650/$ - see frontmatter
http://dx.doi.org/10.1016/j.clml.2012.10.003

might help to differentiate soft tissue lymphomas from soft tissue sarcomas.[9,10]

Because of the rarity of soft tissue presentation, the published studies on this topic have a small sample size; most of them have been reported as case reports, so it is difficult to draw conclusions about the best treatment approach, prognostic factors, and outcome of different histologic subtypes.

In this report we describe our experience with NHLs initially presenting as soft tissue masses, diagnosed in our institution over a 15-year period, with particular attention to the clinical presentations, treatment modalities, and outcomes. Moreover, we systematically reviewed the available data from the literature in the past 20 years, considering all the published series and case reports about lymphomas of the soft tissue available in the MEDLINE database from 1990 to 2011.

The rationale of this study was to systematically analyze the available data about soft tissue lymphomas in the past two decades, and critically evaluate the effect of different histologies, clinical presentations, and treatment modalities on the outcome.

Patients and Methods

Definition of Soft Tissue and Criteria for the Diagnosis of Soft Tissue Lymphoma

Soft tissue is defined as tissue that connects, supports, or surrounds other structures such as adipose tissue, connective tissue, and skeletal muscle, excluding bone. In this review only patients with soft tissue involvement at the moment of initial diagnosis were considered. The criteria for the definition of primary soft tissue lymphoma were originally described by Lanham et al[3], and are as follows: soft tissue involvement, no previous history of lymphoma, no more than 2 locations including nodes and extranodal sites, no masses in the thoracic or abdominal cavities or visceral organs, no groin, face, retroperitoneum, skin, bone, or axilla involvement, no lymph node structure observed in the biopsy specimen, and no evidence of disease spread after 3 months from initial diagnosis. In all cases the histologic material for the initial diagnosis originated from a soft tissue mass.

Single Center Experience

Sixteen consecutive patients with histologically confirmed soft tissue lymphomas of different histologies treated at our center between January 1996 and December 2011 were retrospectively reviewed in this study. Only patients with soft tissue involvement at disease onset were considered. All histologic materials were reviewed by a pathologist (SP) from our institution. All patients were evaluated by full clinical history, physical examination, total body computed tomography (CT) scan, complete blood cell count with leukocyte differential, and bone marrow biopsy as part of the initial staging. MRI scan was also employed in order to better evaluate soft tissue masses. All patients with DLBCL diagnosed after 2002 underwent fluorodeoxyglucose positron emission tomography (FDG-PET) as part of the initial staging workup. Additionally, patients were tested for blood chemistry (including creatinine, liver function tests, uric acid, and lactate dehydrogenase) and underwent urine analysis and electrocardiography.

Patients younger than 65 years of age were treated using CHOP-21 (cyclophosphamide, Adriamicin, vincristine, prednisone) or MACOP-B (methotrexate, Adriamicin, cyclophosphamide, vincristine, Bleomicin, prednisone) regimens (with or without rituximab). CHOP-21 and MACOP-B (with or without rituximab) regimens were given, respectively every 3 weeks and on a weekly basis, as previously described.[11–13] Elderly patients (65 years and older) were treated using the R-VNCOP-B (vincristine, mitoxantrone, cyclophosphamide, Bleomicin, vp-16, prednisone) regimen, as previously described.[14] All therapies were given on outpatient basis. Radiation therapy was given as initial therapy in patients with nonbulky stage IE soft tissue lymphoma, or 4 to 6 weeks after the completion of chemotherapy in patients with bulky presentation, with a tumor dose ranging from 30 to 36 Gy over 3 to 4 weeks using a schedule of 180 cGy per day for 5 days per week.

Restaging was done at least 4 weeks after the completion of the last chemotherapy cycle and 12 weeks after the last radiotherapy course with total body CT scan, MRI, bone marrow biopsy when positive at the disease onset, and FDG-PET scan when feasible. Responses were classified according to the International Workshop for Response Criteria for non-Hodgkin lymphomas[15] plus the FDG-PET implication data.[16]

Follow-up assessments were repeated every 3 months during the first year and every 6 months starting from the third to the fifth year, and every 12 to 18 months for further follow-up. All patients signed a written informed consent and the study was carried out according to the principles of the Declaration of Helsinki. The study was approved by the institutional review board.

Literature Meta-analysis

A systematic search of the available literature from 1990 to 2011 was conducted in the PubMed database. Keywords used for the literature search were soft tissue lymphoma, extranodal lymphoma, primary extranodal lymphoma, and skeletal muscle lymphoma. Because of the lack of published clinical trials on this issue, all studies describing patients affected by soft tissue lymphomas, with available information on patient characteristics, treatment strategies, and follow-up (at least 6 months), including case series and case reports, were included in this analysis. The accuracy of this meta-analysis was assessed using the checklist of items in accordance with the 'Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement.'[17]

Selection Criteria

We considered patients treated during the past 2 decades to have comparable data regarding both histologic classifications and treatment. For our single-center experience, we selected consecutive patients with histologically proven soft tissue lymphoma at the disease onset, diagnosed and subsequently treated in our institution, using the electronic archive of our hemolymphopathology unit (data available from 1996).

Statistical Analysis

The primary end points were progression free survival (PFS) and overall survival (OS). PFS was defined as the time from registration to the first observation of progressive disease or death as a result of disease progression. OS was defined as the time from registration to the observation of death as a result of any cause. The results of the study were analyzed statistically using the SPSS 8.0 software program (SPSS Inc, Chicago, IL). Differences between groups were evaluated by using the