

# Indolent Lymphomas That Present With Clinically Aggressive Features: A Subset of Low-Grade Lymphomas With a Behavior Inconsistent With the Histologic Diagnosis

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## Abstract

**We have identified a subset of indolent lymphomas, the presentation of which differs from their expected indolent nature. This subset presents with aggressive features, such as high lactate dehydrogenase, high standardized uptake values, high Ki-67 (> 30%), B symptoms, and unusual areas of involvement (bone, pleura, lung). Although this subset histologically resembles typical indolent non-Hodgkin lymphomas, they functionally behave as aggressive non-Hodgkin lymphomas.**

**Background:** The expected presentation for low-grade lymphomas consists of disseminated lymphadenopathy with no constitutional symptoms, and with bone marrow involvement, normal lactate dehydrogenase (LDH), low proliferative rate as determined by Ki-67, and positron emission tomography (PET) scan with low standardized uptake values (SUVs) < 14. However, it is not unusual for some cases to present with 1 or more clinically aggressive features. Because the clinical behavior of such patients has not been investigated, there are no data regarding their expected outcome. **Patients and Methods:** For these cases, we use the term “clinically discordant indolent histology” (CDIH), which we define as any follicular grade 1-2, grade 3-A, or small lymphocytic lymphoma that meets at least 1 or more of the following conditions at the time of diagnosis: constitutional symptoms, LDH elevation, PET SUV > 14, unusual areas of involvement for indolent non-Hodgkin lymphoma (NHL) (bone, pleura, central nervous system, soft tissue, lung), Ki-67 > 30%, necrotic areas seen on computed tomography scan, or discrete space-occupying lesions in the liver or spleen. We have reviewed our NHL database with the objective of identifying such cases so we could compare them with those with the expected presentation of indolent NHLs. **Results:** Patients with CDIH have a less favorable overall survival and failure-free survival, and a higher rate of transformation to a higher-grade histology. **Conclusions:** CDIH functionally behaves as aggressive NHL despite the fact that under the microscope the lymphomas resemble typical indolent NHLs. These cases seem to fare better when treated with a regimen containing doxorubicin-rituximab.

*Clinical Lymphoma, Myeloma & Leukemia*, Vol. ■, No. ■, ■-■ © 2016 Elsevier Inc. All rights reserved.

**Keywords:** B symptoms, Indolent low-grade non-Hodgkin lymphoma, Ki-67, LDH, PET, Prognosis, SUV

## Introduction

The clinical presentation of patients with low-grade or indolent non-Hodgkin lymphoma (NHL) usually consists of asymptomatic

disseminated lymphadenopathy, absence of constitutional symptoms, and bone marrow involvement.<sup>1</sup> The disease usually is limited to the reticuloendothelial system (ie, lymph nodes, spleen, liver, and marrow). Other typical features at presentation include normal lactate dehydrogenase (LDH), low Ki-67 (10%-20%),<sup>2,3</sup> and positron emission tomography (PET) scan with low standardized uptake values (SUVs) (< 14).<sup>4,5</sup> Cases that do not fit this description can be considered as clinically discordant presentations. In clinical practice, it is not unusual to observe patients with low-grade lymphoma whose initial presentation deviates from the normal, and there are no data in the literature about their clinical behavior. We use the term “clinically discordant indolent

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Submitted: Apr 12, 2016; Revised: Jul 16, 2016; Accepted: Aug 2, 2016

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## Clinically Discordant Indolent Lymphomas

histology" (CDIH) for those cases who depart from the usual presentation.

### Materials and Methods

We define CDIH as any follicular grade 1-2, grade 3-A, or small lymphocytic lymphoma that meets at least 1 of the following conditions at the time of diagnosis: constitutional symptoms, unexplained LDH elevation, PET SUV  $\geq 14$ , unusual areas of involvement for indolent NHL (bone, pleura, central nervous system, soft tissue, lung), Ki-67  $\geq 30\%$ , necrotic areas seen on computed tomography scan, or discrete space occupying lesions in liver or spleen. This was based in part on our initial hypothesis, later shown to be erroneous, that patients with CDIH could have other areas with occult high-grade histology, or so-called divergent or transformed histologies. Because transformation has been described in the literature in association with many of the described features, we incorporated them into our definition of CDIH.<sup>6-11</sup> There are no available data in the literature regarding the frequency and prognosis of CDIH and no indication as to how these patients should be managed.

From our database of low-grade NHLs, we identified 97 patients who had Ann Arbor stage II-IV, of whom 86 had follicular grade 1, 2, or 3-A and 11 had small lymphocytic lymphoma. An additional 38 cases of marginal zone NHL were identified, and they are being reported separately in another article. Of these 97 cases, 46 met the criteria for our definition of CDIH. All of these cases were managed under the care of our staff. Institutional review board permission was obtained to retrospectively review their records to attempt to answer the questions raised in the representative cases described next.

All patients were treated initially with chemotherapy. Treatment was administered according to the attending physician's choice or existing protocol at the time the patient was treated. Because the concept of CDIH was not totally conceived or developed in the early part of this study, most patients were treated as having low-grade NHL using fludarabine combinations, and later during the study period those with CDIH were mostly treated with doxorubicin containing regimens consolidated with FND (fludarabine, mitoxantrone, dexamethasone)<sup>12</sup> and then maintained with rituximab every 6 months for 2 years.

### Results

We will present and discuss 3 illustrative patients who exemplify certain specific issues pertaining to CDIH. These cases are taken from our series of 97 patients.

#### Case Number 1

A 71-year-old woman underwent a surgical biopsy to diagnose a right groin node that measured 3 cm and that was associated with profuse night sweats. On physical examination, the patient had a palpable abdominal mass that was confirmed with a PET scan to have a necrotic center in the large mass. The highest SUV was 12.3 and corresponded to the large 10-cm abdominal mass. There were additional sites of uptake in the lymph nodes above and below the diaphragm with SUVs ranging from 4.3 to 8.7. Serum LDH equaled 341 IU/mL (normal < 225 IU/mL). The right groin biopsy revealed a diagnosis of CD20+, CD10+, and CD5-, grade 2

follicular NHL. Ki-67 was 25%. Bone marrow aspirate and biopsy were negative. This case presents with CDIH based on night sweats, high LDH, and an abdominal mass with a necrotic center, all 3 representing clinically discordant findings.

*Failure-Free Survival and Overall Survival.* The failure-free survival (FFS) of patients with and without CDIH is shown in Figure 1, and the overall survival (OS) is shown in Figure 2. At a median follow-up of 56 months, patients with CDIH have a less favorable outcome than nondiscordant cases for both FFS and OS. Those with nondiscordant histologies have an extremely favorable outlook because none of the 51 patients have died so far and only 2 patients have relapsed. These data suggest that patients with typical low-grade NHLs might represent a more benign clinical subset of low-grade NHLs, whereas those with CDIH correspond to a less favorable clinical subgroup.

*Number of Discordant Features and Correlation With Outcome.* We identified 46 (47%) of our 97 cases of low-grade NHLs in whom at least 1 discordant finding was observed at the time of diagnosis. Some of our patients with low-grade NHL presented with more than 1 feature of CDIH, as illustrated in case 1. When we analyzed the frequency of patients who presented with at least 1 discordant finding, we found that of our 97 cases of low-grade NHL, 23 (24%) presented with only 1 discordant feature and 23 presented with  $\geq 2$  discordant features.

We then analyzed the failure rate of cases according to the number of discordant findings. The results are depicted in Table 1. No trend was observed for relapses to increase or FFS to decrease with a larger number of discordant findings. No clear correlation between the reason for discrepancy and FFS was identified. In the 23 cases with a single discordant finding, there were 5 different reasons for discrepancy, which made it unfeasible to clearly pinpoint the influence of any particular discordant feature.

*Impact of Type of Treatment Administered.* In view of the aggressive clinical features of cases with CDIH, we started treating them with a doxorubicin-rituximab based R-CHOP (rituximab, cyclophosphamide, doxorubicin, oncovin, prednisone) regimen. Consequently, it is logical to raise the question as to how doxorubicin-treated patients with CDIH have fared. Of our 46 cases with CDIH, 31 received doxorubicin-rituximab based regimens and 15 did not. Figures 3 and 4 represent the FFS and OS of cases with CDIH according to whether they received doxorubicin containing combination therapy or not. The OS for patients treated with doxorubicin-containing regimens was significantly better statistically, whereas the FFS showed a nonstatistically significant trend for superiority. Two of our CDIH cases were treated with bendamustine, and the remaining 13 cases received mostly fludarabine-containing regimens. Of the 2 cases treated with bendamustine, 1 has relapsed.

*Transformation and Causes of Death.* We analyzed the risk of transformation to determine whether it correlated with CDIH. We found 5 patients with transformation, and all 5 were patients with CDIH. The rate of transformation of CDIH was 5 of 46 (11%) in contrast to 0 of 51 cases who did not have CDIH ( $P = .02$ ). All

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