

Nodular Lymphocyte Predominant Hodgkin Lymphoma: A Rare Subtype with Distinct Clinicopathological Features

Abstract

Nodular lymphocyte predominant Hodgkin lymphoma (NLPHL) is a rare subtype of Hodgkin lymphoma (HL) characterized by a distinct morphology, an older median age at onset, less incidence of mediastinal involvement, more frequent relapse and better prognosis as compared to Classical-HL (CHL). In contrast to CHL, the tumor cell (LP cell) of NLPHL almost always retains its B cell phenotype and is a CD30 non-expresser. Due to its rarity, only a handful of studies on this entity are available in the literature. We present a short case series of 10 cases of NLPHL diagnosed in our institute over 10 years. A total of 10 cases of NLPHL were retrospectively accessed, re-evaluated and classified further, based on various morphological patterns and immunophenotypic expression. Morphological patterns were correlated with overall the prognosis. Our study showed peripheral lymph node localization and overall good outcome in these cases. We also came across two unique cases, one was of NLPHL with Rosai-Dorfman disease (RDD) and another was of composite lymphoma showing components of NLPHL and Diffuse Large B cell Lymphoma (DLBCL).

Keywords: NLPHL, Nodular lymphocyte predominant Hodgkin lymphoma, NLPHL with special cases, NLPHL case series, NLPHL case series with special cases

Introduction

Nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL) is recognized as a distinct entity in the World Health Organization (WHO) classification of haematolymphoid tumors because of its unique clinical, histological and immunophenotypical features, which sets it apart from Classical Hodgkin lymphoma (CHL) and makes it suitable to be categorized separately.^[1-3] CHL accounts for approximately 95% of all Hodgkin lymphoma (HL) cases, while NLPHL accounts for the remaining 5%.^[4] Both CHL and NLPHL show sparse neoplastic cells in a reactive background. In CHL, mononuclear Hodgkin cells and bi/multinucleated Reed-Sternberg (RS) cells are seen in a cellular background, which is rich in lymphocytes, histiocytes, plasma cells, and/or eosinophils or neutrophils. In contrast, NLPHL has a distinct nodular pattern which is characterized by the presence of large neoplastic B cells set in a background of non-neoplastic small reactive B cells. The neoplastic cells were formerly called “popcorn cells” or “L&H (lymphocytic and histiocytic) cells”, but they are now referred

to as lymphocyte-predominant cells (LP cells). These are derived from germinal centre B cells, show somatic hypermutation and express B cells markers at varying intensities.^[5] These LP cells are characteristically surrounded by collarette of T-cells, which is frequently CD57 positive.

Clinically, NLPHL has a predilection for peripheral nodes and patients are mostly present in the early stages. In comparison to CHL, NLPHL cases show a slightly older median age at presentation (30-40 years), greater male predominance (3:1), less mediastinal involvement (15%), and lower occurrence of HL risk factors.^[6]

The RS cells of all the subtypes of CHL share common immunophenotypic features, and show reduced expression of pan B-cell antigens (CD20 & CD79a) and positive staining for CD30 and CD15 in most cases. PAX 5 (a B-cell antigen) typically shows weak positivity in nearly all cases. In contrast, the LP cells of NLPHL almost always retain their B cell phenotype and are CD30 non-expressers. These cells also variably express EMA and BCL6. In typical cases, the LP cells reside in the large

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nodular meshwork of follicular dendritic cell (FDC) processes that are filled with non-neoplastic reactive lymphocytes (mainly B cells) and histiocytes. Several other morphological variants are also described, although seen much infrequently.

Fan *et al.*,^[7] identified six distinct patterns of NLPHL based on morphology, which have also been included in the current WHO blue book. These patterns are classified as classic B-cell rich nodular pattern, serpiginous /interconnected nodular pattern, nodular with prominent extra nodular LP cells pattern, T-cell rich nodular pattern, diffuse T-cell rich pattern [T-cell rich B cell lymphoma like (TCRBCL-like)], and a (diffuse) moth-eaten B-cell rich pattern; designated as - type A, B, C, D, E, and F respectively. They also observed a mixture of different patterns being present in the same lymph nodes. Moreover, the presence of mixed patterns outnumbered pure patterns. In addition, the author described the hybrid pattern in which two or more patterns were superimposed on each other. They also documented the presence of diffuse (TCRBCL-like) pattern to be an independent predictor of recurrent disease.

Subsequently, Hartmann S *et al.*,^[8] further showed prognostic impact of these morphological patterns of NLPHL. They documented that the patterns in which lymphoma cells are present outside the B-cell nodules {i.e. the cases presenting with at least one variant pattern (patterns C, D, E, and F) as a major or minor component}, showed a significant higher association with advanced stage and relapse rate.

The standard treatment for NLPHL is ‘involved field radiotherapy’- NLPHL typically has an indolent course as compared to HL; but tends frequent relapses. However, despite the frequent relapses, the prognosis of NLPHL is favorable as compared to HL and overall survival is also quite high.^[5]

NLPHL tends to transform into diffuse large B cell lymphoma (DLBCL). In different studies, the high-grade transformation rate of NLPHL to DLBCL varies from 3-10%.^[9, 10] According to WHO, the risk of transformation is 3-5%.^[4] In a large study by Kenderian S *et al.*,^[10] done over 40 years, 17 out of 222

patients (7.6%) were found to have transformed to DLBCL during their course. The median time of transformation was 35 months. This transformation was significantly associated with prior exposure to chemotherapy and splenic involvement at the time of diagnosis. Genomic studies on NLPHL indicate that the neoplastic LP cells infrequently carry monoclonal immunoglobulin gene rearrangements, which are, however, consistently present when the histologic transformation to DLBCL occurs.

We retrospectively analysed 10 cases of NLPHL diagnosed in our institute over the last 10 years and hereby present a short series of the same.

Materials and Methods

We retrospectively analyzed 10 cases of NLPHL diagnosed from 2010-2020, evaluated their morphological patterns and immunophenotypic expression, and tried to correlate the morphological patterns with the overall prognosis. Two senior pathologists reviewed the cases individually and categorized the cases into various morphologic patterns. The diagnostic criteria for these morphologic patterns were followed as proposed by Fan *et al.*^[7] Immunohistochemistry (IHC) was done and/ or repeated wherever needed. Clinical information regarding the initial date of diagnosis, type of therapy, recurrence (if any) of disease, and status of patients, at last follow-up were obtained from the patients/relatives and hospital records.

Results and Discussion

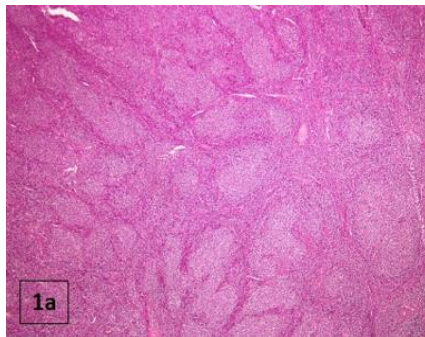
There were a total of 10 cases of NLPHL diagnosed for 10 yrs. All the details of these cases are mentioned in **Table 1**. The male: female ratio was 6:4. The age range was 8 to 80 yrs with a mean age of 35 yrs. In 9 of the 10 cases, peripheral groups of lymph nodes were involved, with cervical (3/9) being the most common. In one case, the mesenteric lymph node (central group) was involved.

Table 1. Clinical and histopathological features of cases

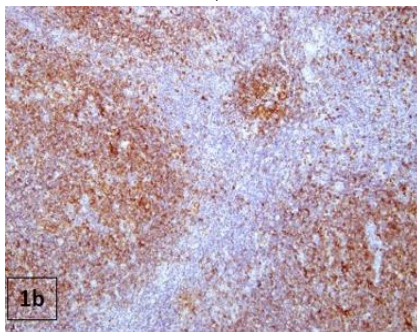
Case no	Age(yr)/sex	Lymph node	Pattern	Year of diagnosis and duration of follow-up (year)	Follow up
Case 1	12/M	Left cervical	C (85%) +E (15%)	2010	Not available
Case 2	16/M	Cervical	C (80%) +B (20%)	2013 (7)	Chemotherapy & well to date
Case 3	10/M	Right cervical	A	2017 (3)	Chemotherapy & well to date
Case 4	35/F	Axillary	A (45%) +B (30%) +D (25%)	2017 (2)	Chemotherapy & death in May 2019 (cause not known)
Case 5	80/M	Right Submandibular	C	2017 (2)	Only resection, no further treatment & well till 2019
Case 6	41/F	Left Submandibular	A	2017 (3)	Only resection, no further treatment & well to date
Case 7	55/M	Right Axillary	A	2018 (2)	Chemo and radiotherapy and well to date
Case 8	8/F	Right Inguinal	C	2018 (9 months)	Death due to septic shock in 9 months
Case 9	33/F	Mesenteric	C	2019	Not available

Case 10 23/M Right supraclavicular E 2020 (6 months) Chemotherapy & well to date

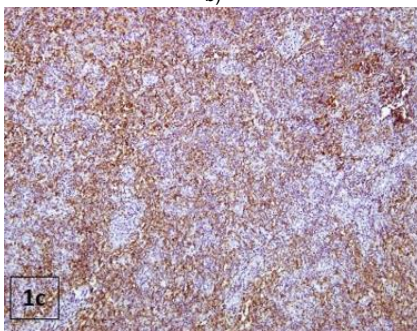
Seven cases showed pure morphologic patterns, including pattern A and pattern C in 3 cases each, and pattern E in 1 case (Figures 1a-1f). Three cases showed mixed patterns (Table 1), with pattern C being the predominant pattern in 2 cases and pattern A in 1 case.



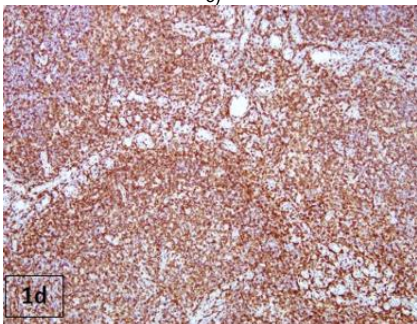
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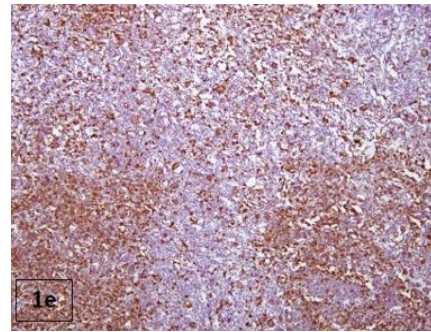
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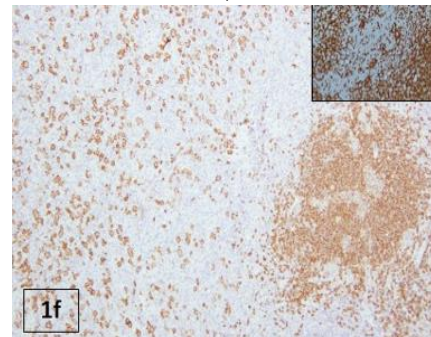
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e)



f)

Figure 1. a) Nodular pattern of NLPHL (H&E, 40X). b) Nodular pattern (CD20, 100X). c) Serpiginous pattern (CD20, 100X). d) T cell rich nodule (CD3, 100X) e) Nodules with prominent extra nodular L & H cells (CD20, 100X) f) Scattered large tumor cells in the diffuse background with preserved follicle at the periphery, pattern E (CD20, 100X), inset shows CD3 collar (200X).

On IHC, CD20 consistently highlighted the LP cells in all the cases (10/10). CD3 positive T-cells were forming collarette around the neoplastic LP cells and were consistently found in all cases. The majority of the cases were CD30 (8/10 cases) and CD15 (9/10 cases) negative. However, an occasional case showed few tumor cells expressing weak staining for CD30 and CD15. Other IHC markers (PAX5, EMA and BCL6) also proved to be contributing to the diagnosis of NLPHL. Thus the IHC profile in all the cases was consistent with the diagnosis of NLPHL. Details of the IHC used are mentioned in Table 2. Bone marrow biopsy report was available in 4 cases that didn't show any disease.

Table 2. Panel of immunohistochemistry

Case no.	CD20	PAX5	EMA	BCL6	CD30	CD15	CD3 COLLAR
Case 1	+	+	+	+	-	-	+
Case 2	+	+S	-	-	-	-	+
Case 3	+	+W	-	+D	-	-	+
Case 4	+	+S	+	+D	+F	Few	+
Case 5	+	NA	-	NA	-	-	+

Case 6	+	+F	+S	+	-	-	+
Case 7	+	+S	+S	NA	-	-	+
Case 8	+	+S	-	NA	+W	-	+
Case 9	+	+S	+S	-	-	-	+
Case 10	+	+	+	+W	-	-	+

S= Strong, W=Weak, D=Diffuse, F=Focal, NA= Not Available

We also came across two interesting cases in our series. One case showed the presence of NLPHL in one axillary lymph node and DLBCL in another (ipsilateral) axillary lymph node (composite lymphoma). Another case showed coexistent NLPHL and Rosai-Dorfman disease (RDD) in the same (submandibular) lymph node. These two unique cases need special mention.

Follow-up information was available for 8 patients. Two of the patients had died. The remaining 6 patients were alive with no relapse at the time of follow-up (the range of follow up period was 9 months-7yrs with a mean follow up period of 21 months).

NLPHL is a distinct subtype of HL with unique clinical features, a different treatment paradigm, and better patient outcomes. NLPHL involves men more than women. In our study also, we found that there were marginally more male patients than female patients. However the small number of total cases available in the series precludes the assessment of real gender prevalence. NLPHL commonly involves a peripheral group of lymph nodes, which was also observed in our study with the majority of the cases (9/10) involving a cervical, submandibular, axillary, and supraclavicular group of lymph nodes.

On histomorphology, NLPHL is chiefly characterized by nodules that are well appreciated in low magnification. In a large study of 137 biopsy samples by Fan *et al.*, pattern A was documented to be the most common pattern, both as a pure pattern (54/137) as well as a predominant pattern (31/137); and mixed patterns were found to be more common than pure patterns.^[4] All the cases with pure patterns showed nodular morphology in our study as well. In addition, it was the predominant component in the lymph nodes showing mixed patterns. However, pure morphological patterns were more commonly observed than mixed ones in this study (7 cases vs 3 cases), contrary to the findings of Fan *et al.*

A multivariate analysis by Hartmann S *et al.* showed that histopathological variants of NLPHL were significantly associated with advanced diseases and higher relapse rates.^[8] The same study also concluded that variant histology is an independent prognostic factor for progression/relapse. We also came across a case (case no. 8), (Table 1), which showed pattern C (variant histology) with the higher frequency of LP cells within the background population. These LP cells showed

marked lobulation with prominent nucleoli as compared to the rest of the cases (Figures 2a-2c). The patient succumbed to death within 9 months due to septic shock.

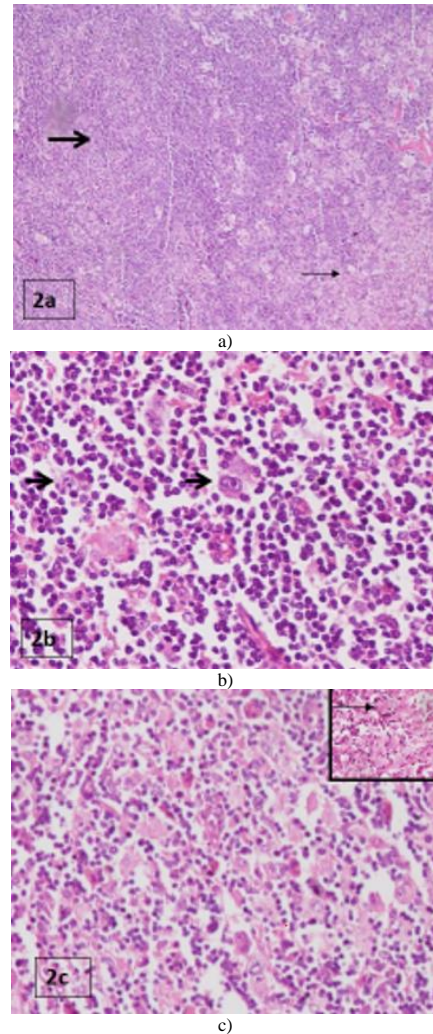


Figure 2. a) (case no. 8) LP cells showing marked lobulation with prominent nucleoli (H&E 400X). b) LP cells are positive for CD20 (400X). c) Collar of CD3 positive T cells surrounding LP cells (400X).

The main differential diagnosis of NLPHL is Tcell/ histiocyte-rich large B cell lymphoma (THRLBCL). In general, NLPHL has a favorable prognosis despite the tendency for disease recurrence. Studies showed that histopathological variants of NLPHL (pattern C, D, E &F) are associated with increased relapse and advanced stages.^[8] Bone marrow involvement is very uncommon in NLPHL.^[4] However, if stage 4 disease is present, the prognosis is poor.^[11]

NLPHL tends of transformation to DLBCL at the time of relapse and the rate of transformation ranges from 3-10%.^[9-12] Eyre TA *et al.* showed the median time for transformation to be 5 years and 33 days, and this time was greatly variable from case to case.^[11] The transformation was associated (although not significantly) with the presence of extranodal disease most notably liver, spleen and bone marrow involvement. Compared to the de novo DLBCL cohort, there was a higher rate of bone marrow involvement ($P = 0.013$) in the patients

where this transformation had occurred.^[11] Most studies have shown that transformation is associated with significantly poorer outcomes.^[7]

There is no clear treatment regimen that fits all cases of NLPHL. However, the consensus is, towards conservative management rather than aggressive curative intent. The NCCN recommends site-specific radiation therapy (ISRT) for early-stage favorable disease. An ABVD/CHOP regime with ISRT is recommended for early-stage unfavorable disease and advanced-stage disease. Rituximab may also be considered in combination with ABVD/CHOP. For refractory disease, maintenance rituximab may be considered.^[12] It is recommended that a biopsy should be done on relapse to detect transformation to aggressive B cell lymphoma, if present.

We came across two interesting cases, which require separate mention. One was (case no. 6), (**Table 1**) a unique case, where NLPHL was associated with RDD in the same lymph node. We observed both diseases (**Figures 3a-3c**) in adjacent areas. They were not overtly intermixed with each other and could be appreciated easily. In RDD areas, abnormal histiocytes were strongly positive for S-100 and negative for CD1a. The NLPHL component showed a classic nodular pattern (pattern A) and the typical IHC features of L&H cells. In literature, many case reports are available in which RDD is present along with lymphoma, but mostly involving different anatomic sites. Only a few case reports are available where RDD and lymphoma are simultaneously present in the same lymph node. Moreover, most of these cases showed non-Hodgkin lymphoma (NHL) component with RDD. An extensive literature search revealed only a few case reports describing the coexistence of RDD and HL.^[13] In our case, the patient underwent lymph node excision and we received an intact lymph node for diagnosis. The patient didn't receive any other therapy and is doing well to date (follow-up period of 3 years). Pathologists should be aware of this coexistence, as it may cause a problem in diagnosis by an inexperienced pathologist, especially in a small/ needle biopsy sample. Otherwise, it carries no prognostic or therapeutic implications and is to be managed in accordance with the type of lymphoma component being present.

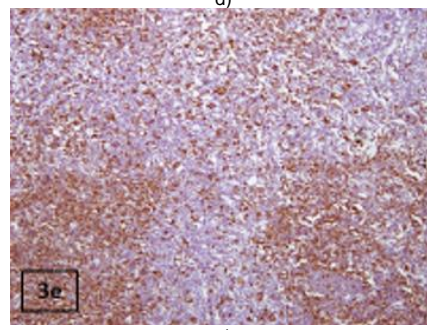
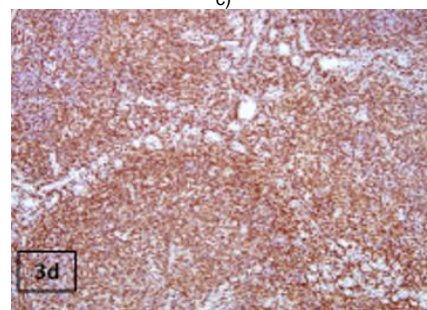
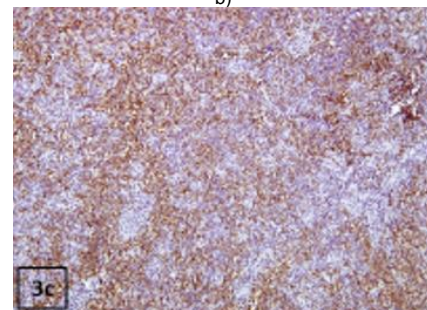
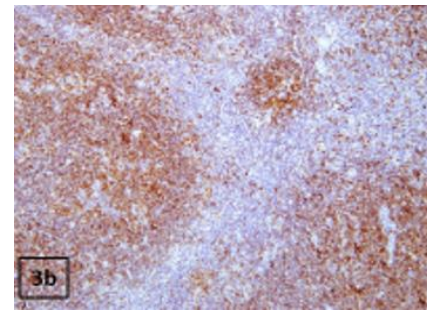
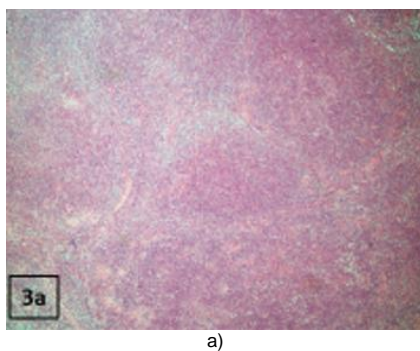


Figure 3. a) (case no. 6) Effacement of nodal architecture by a tumor (thick arrow) interspersed with paler histiocytic areas (thin arrow) (H&E 100X). b) Tumor comprising mononuclear LP cells with prominent nucleoli (arrows) (H&E 400X). c) In pale areas, cells were arranged in loose sheets and clusters with histiocytes showing emperipolesis (inset, arrows) (H&E 400X).

There was another interesting case (case no. 7), (**Table 1**) of composite lymphoma, where we received two different axillary lymph nodes at the same time and both showed different morphology. The larger lymph node was replaced by diffuse sheets of large-sized, atypical lymphoid cells, compatible with DLBCL. In the smaller lymph node, the characteristic histological features of NLPHL were present. The final diagnosis of composite lymphoma, comprising DLBCL and NLPHL, was given.

Composite lymphoma is defined as two distinct lymphomas which occur concurrently in a patient, and is a rare condition with the incidence varying from 1% to 4.7%.^[14] Most of the case reports in the literature are of CHL with NHL, usually of B-cell type. The combination of NLPHL with DLBCL is a rare occurrence. Although NLPHL tends to progress to DLBCL, in our case the two conditions were present simultaneously in two different lymph nodes and the patient didn't have any history of any type of lymphoma in the past. These cases are diagnostically challenging as sometimes one lymphoma component may mask the other component and also one of the components can be missed in a small biopsy sample. No definite treatment protocol is currently available for the treatment of composite lymphoma. Generally these are treated according to the high-grade component. Our patient received chemo and radiotherapy and is well to date (2 years follow-up).

NLPHL has a better prognosis than CHL. Follow-up was available in 8/10 cases in our study, where 75% (6/8) of cases were alive and didn't have any relapse. However 2 deaths were recorded; one was due to septic shock, while the cause of death in the second patient was not known.

Conclusion

NLPHL, due to its rarity and variable morphological patterns, can often be misdiagnosed (both over-diagnosed and underdiagnosed), especially in small biopsies. It has a better prognosis in comparison to CHL but with frequent relapses. Because of an indolent course and a conservative therapeutic approach, accurate diagnosis is crucial. Its morphological classification needs special mention by the pathologist as it carries some prognostic implications. It was recommended that a biopsy should be repeated if there is a relapse, to detect transformation to high-grade lymphoma, which needs to be treated aggressively with chemotherapy. NLPHL showing variant histology is a risk factor in itself for poor outcomes. In our study, two cases of deaths also showed variant histology (i.e. pattern A+B+D and pattern C), however exact prognosis and survival cannot be commented on in such a small study. Studies including larger numbers of variant histology cases are needed to define a definite impact on outcome and prognosis.

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Conflict of interest

None.

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None.

Ethics statement

None.

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