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Leiomyoma with Bizarre Nuclei: A Stagnant Precursor to Leiomyosarcoma?

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Abstract

Leiomyoma with bizarre nuclei (LM-BN) is a rare uterine smooth muscle tumor characterized by a remarkable nuclear atypia reminiscent of its malignant counterpart leiomyosarcoma (LMS). While it presents with an overall benign clinical course, the biological nature and pathogenesis of LM-BN remains largely unknown. The controversy about the relationship between LM-BN and benign and malignant uterine smooth muscle tumors remains unresolved. To date, the diagnosis of LM-BN relies mainly on morphological characteristics, and no effective molecular markers have been established. Here we describe and summarize recent progress in understanding this unique tumor entity, with a focus on new findings regarding molecular and genomic alterations and the potential relationship of LM-BN with LMS.

Keywords: Leiomyoma with bizarre nuclei; Leiomyosarcoma; Pathology; Gene mutation; Genomic alteration

Introduction

Leiomyoma with bizarre nuclei (LM-BN) is a rare variant of uterine smooth muscle tumor characterized by a remarkable nuclear atypia. LM-BN is histologically heterogeneous and usually identified inside of typical leiomyoma, with a wide range of cellularity, density, and distribution of nuclear atypia. Many different names have been used in the literature and pathology reports to describe LM-BN symplastic leiomyoma, atypical leiomyoma, atypical smooth muscle tumor, and leiomyoma with bizarre nuclei-reflecting how relatively little is known about this tumor type. Several large cohort studies [1-5] have provided in-depth analyses of LM-BN histology and clinical outcomes and report similar findings that this tumor type has a low risk of recurrence and rarely contributes to patients' death. These findings led to a consensus to classify LM-BN as a benign leiomyoma variant based on the WHO gynecological tumor classification (WHO 2014, 2020) [6]. However, in practice, the diagnosis of LM-BN remains a challenge due to its nuclear atypia and its histologic heterogeneity reminiscent of leiomyosarcoma (LMS). With the advent of molecular biology and next-generation sequencing (NGS), it is now possible to compare molecular differences between LM-BN and its benign and malignant counterparts and to explore the tumorigenesis and histogenesis of LM-BN. Such analyses have allowed us to distinguish between fumarate hydratase-deficient leiomyoma (FH-LM) and LM-BN [7] In this short-communication, we review and summarize recent progress in the characterization of molecular and genetic alterations in LM-BN. We compare the molecular differences in LM-BN and benign and malignant uterine smooth muscle tumors and discuss the relationship between LM-BN and LMS.

Clinical and Pathologic Findings

LM-BN is usually an incidental finding from myomectomy or hysterectomy for leiomyoma [5] The mean age of patients with LM-BN is 42.5 to 49.8 years, about 10-15 years younger than those with LMS.8 Based on several large case series studies [1-5] LM-BN has a low rate of recurrence (2-7%) with no disease-related death. LM-BN may present differently in color (tan, pink, white, yellow, and brown) and consistency (slightly soft and less bulging due to its cellular nature). Grossly, these tumors are well circumscribed and occasionally show ischemic necrosis. Tumor size ranges wildly, from 0.7 to 20 cm, with mean tumor size of 7 cm [5]. A tumor-infiltrating growth pattern was seen in 0-8% of LM-BN in four of the five reviewed studies [1-5] LM-BN concerning for risk of LMS have diffuse distribution and/or a high density of nuclear atypia. For recurrent LM-BN, hysterectomy is the treatment of choice for women who have completed their family. For those who wish to preserve fertility, successful pregnancy after myomectomy has been described, but women should be informed of the likelihood of recurrence, and followed-up vigilantly with imaging studies.

Microscopically LM-BN shows broad, heterogeneous histologic and growth patterns. Nuclear atypia usually presents as large, pleomorphic, and bizarre and hyperchromatic nuclei or multi-nucleated giant cells. Such nuclear atypia is also described as degenerative (Figure 1). The density and distribution of nuclear atypia vary from case to case. Most cases show focal or multifocal nuclear atypia surrounded by typical leiomyoma (Figure 1A), but some LM-BN have diffusely nuclear atypia. The mitotic index in LM-BN has been restrictively defined as <5/10 in a high-power field (WHO 2020) [6] Studies suggested that the clinical course of LM-BN with [6-9] mitoses is no worse than that of low mitotic index tumors [3,5] Mitotic count and tumor necrosis are the most important features that distinguish LM-BN from smooth muscle tumor of uncertain malignant potential (STUMP) or LMS. Accurate diagnosis of LM-BN is challenging due to the similarity of tumor cellular characteristics with STUMP and LMS. Many of the latter tumors contain areas of bizarre and pleomorphic nuclear features. Two previous large studies found that up to 29% of LM-BN and other benign variants of uterine smooth muscle tumors were misdiagnosed as LMS [9]. In one study of 59 LM-BN cases by Croce et al. 310 cases were originally misdiagnosed as leiomyosarcoma. Though most LM-BN can be readily recognized or correctly diagnosed, the histological overlap between LM-BN and LMS indicates similar histogenesis at the cellular level that continues to pose challenges to diagnosis.

Not all leiomyomas with nuclear atypia are LM-BN. Recent work identified a subset of leiomyoma with nuclear atypia that harbor somatic or germline fumarate hydratase mutations/deficiency, defined as fumarate hydratase-deficient leiomyoma (FH-LM). Further analysis revealed subtle differences in nuclear atypia that readily differentiate FH-LM from LM-BN (Figure 1B) [5] Detection of fumarate hydratase deficiency by immunohistochemistry or molecular analysis can be used to differentiate FH-LM from LM-BN [10] For example, we found that 51% of LM-BN are immune-negative for FH and 21% harbored the FH gene mutation [7,11]. Found that 67 of 108 cases of LM-BN had altered FH. Intravenous leiomyomatosis with nuclear atypia is another rare tumor variant that is usually associated with HMGA2 overexpression [12]. After careful diagnostic exclusion, LM-BN is a relatively rare and unique leiomyoma variant and its molecular relationship to other uterine smooth muscle tumors, in particular LMS (Figure 1B), is discussed below.

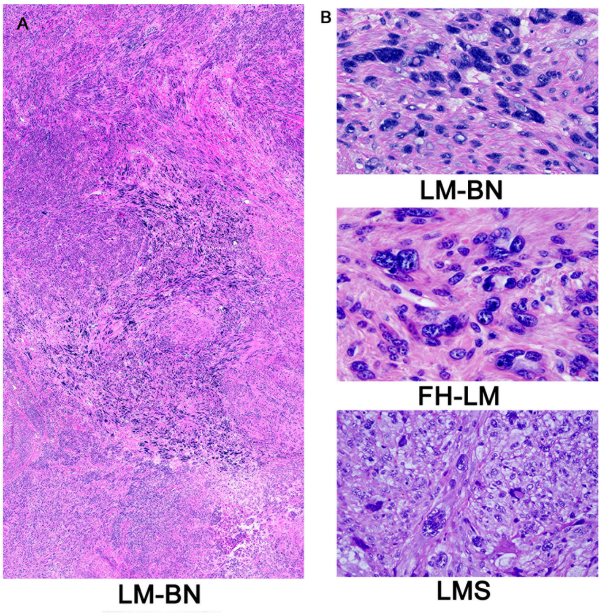

Figure 1: Cyto-histologic features in LM-BN, FH-LM and LMS. A. Photomicrograph of LM-BN surrounded by typical leiomyoma. B. Photomicrographs illustrated a side-by-side comparison of the nuclear features in LM-BN, FH-LM and LMS.

Molecular Fingerprints

Histologic evaluation remains the sole diagnosis of LM-BN1 and no reliable biomarkers clearly distinguish it from LMS. Published data on selected genetic alterations show that LM-BN shares more molecular alterations with LMS than leiomyoma [13-17] Additional studies confirm that LM-BN harbor molecular changes commonly seen in LMS (Figure 2A) [13,18] For example, p16 is a surrogate marker originally identified in the majority of LMS and its expression was found to significantly overlap in LM-BN; up to 60% of LM-BN were found to have diffuse immunoreactivity for p16 in tumor cells (Figure 2A and 2C) [19, 20] A similar trend of p53 mutations and other gene mutations was identified in both LM-BN and LMS (Figure 2A) [13] The frequent alteration of these oncogenic markers in both LM-BN and LMS make them of limited value in differential diagnosis [14] but does raise questions about the underlying tumorigenic mechanisms that lead to two completely distinct cell fates.

The application of NGS to the genome-wide molecular analysis of uterine smooth muscle tumors has provided unprecedented opportunities to uncover the global genomic alterations in different tumor types and facilitate our understanding of the molecular basis of these diseases. With whole-genome sequencing analysis, LMS is characterized by genomic instability, with pervasive, seemingly random karyotypic abnormalities, especially in copy number changes [21,22] the most frequently reported regions of chromosomal loss are 1p36.32, 4q35.1, 13q14, and 17p13, and the most frequent gains are in chromosome arms 1q21, 17p12, 19q13.21 [23-26]. Interestingly, many recent studies have demonstrated that LM-BN is also a genomically unstable tumor with molecular changes shared with LMS [19,20]. In our recent study, we examined CNV patterns by whole-genome sequencing of LM-BN

and LMS, and found widespread genomic CNVs involving nearly all chromosomes in both diseases, either at the chromosome arm or focal level (Figure 2B) [27] Both LM-BN and LMS show more genomic loss/deletions than gains in similar genomic regions. Of note, the mean cumulative size of the unbalanced genomic regions was slightly lower in LM-BN than LMS (Figure 2C) [18,27] these regions contain many important candidate oncogenes and tumor suppressor genes, which are potentially related to LM-BN and LMS tumorigenesis. Upon comparing CNVs between LM-BN and LMS, we found 37 common CNV peaks including 8 gains and 29 losses. These 37 significant CNV foci demonstrated overlapping genomic copy number changes among LM-BN and LMS. When combining gene mutations and genomic alterations in different uterine smooth muscle tumors by PCA analysis, LM-BN was found to be genetically more proximal to LMS than leiomyoma (Figure 2D). Of note, genomic alterations seen more often in LMS than in LM-BN are regions in the RB, PTEN, TP53, ATRX, FGF1, JAK2, KRAS, CDK4, FGF10, MYC, CCNE1, TDO2, PRDM16 and VIPR2 genes [25,28,29] LMS was also characterized by recurrent homozygous deletions of PDCD1, which encodes PD-1 [28] These findings suggest that as a DNA unstable tumor, LM-BN is stagnant at its early stage through a gain of some genomic alterations but may require additional critical molecular changes for malignant transformation [30].

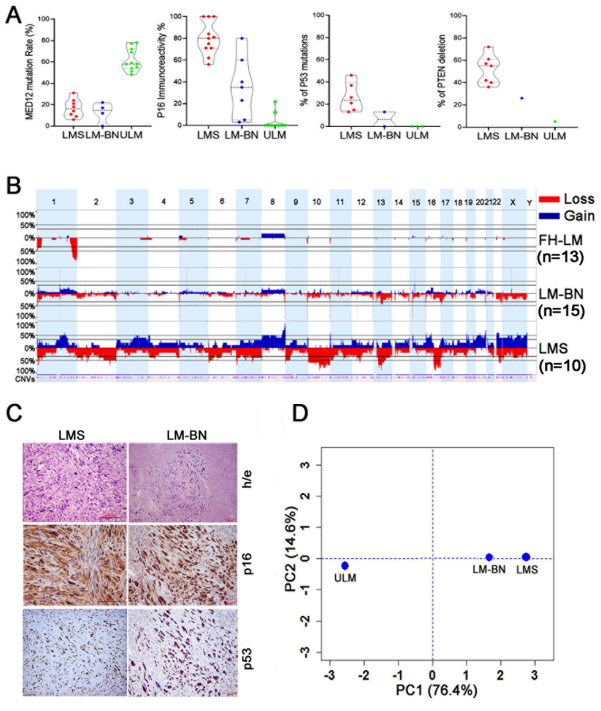

Figure 2: Molecular and genomic features of LM-BN and LMS. A. Dot plots illustrated the gene mutation fingerprints in LM-BN, LMS and usual type leiomyoma (ULM). Each dot represented an average mutation rate from one of 38 publications (detail see our previous publication in Cancer13). B. Copy number alterations (CNAs) identified in FH-LM, LM-BN and LMS (detail please refer to our recent publication in Cancer Science27). C. Immunohistochemistry examples for p16 and p53 in LM-BN and LMS. D. PCA analysis of tumor proximity in ULM, LM-BN and LMS.

Conclusion

In summary, despite their different clinical presentation, LM-BN and LMS share many histologic, immunohistochemical, and molecular changes. These similarities raise questions about whether these two tumor types arise from a similar mechanism of tumorigenesis in early disease development. It will be important to determine the specific genetic changes that drive these two tumors in different directions and how and when such changes happen through the stages of tumorigenesis. The presence of large and pleomorphic nuclei or giant multinucleated tumor cells in both LM-BN and LMS may be a good example of a shared cell replication error in tumor development. Dr. Liu recently proposed a very attractive concept that all human neoplasms might be initiated by a mistake in endo-replication that produces polyploid giant tumor cells, which may recapitulate the pattern of cleavage-like division in blastomeres and lead to dedifferentiation of somatic cells by a programmed process known as “the giant cell cycle.” Under this theory, LM-BN and LMS may represent different stages of somatic polyploid giant cell dedifferentiation.

Identification of the molecular differences between LM-BN and LMS will not only provide valuable knowledge to advance our understanding of these tumors’ behavior, but will also inform the development of tools for accurate diagnosis and clinical management of LMS, a deadly disease. As additional molecular and cellular analyses of LM-BN provide us with new insights into the cause of the disease and tumorigenesis, the name “LM-BN” as recommended by WHO may need to be revisited as “degenerative atypia” may not truly reflect this tumor’s nature.

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Conflict of Interest

Authors have nothing to disclose.

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