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ARTICLE

Nuclear expression of DDIT3 distinguishes high-grade myxoid liposarcoma from other round cell sarcomas

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Abstract

Myxoid liposarcoma (MLPS) is a malignant adipocytic neoplasm with predilection for the extremities. MLPS is genetically defined by a t(12;16) translocation leading to *FUS–DDIT3* (95%) or more rarely t(12;22) leading to *EWSR1–DDIT3*. Low-grade MLPS is characterized by bland spindle cells within a myxoid matrix containing delicate "chicken-wire" vasculature, whereas high-grade ("round cell") MLPS may be indistinguishable from other round cell sarcomas. In many cases, cytogenetic or molecular genetic techniques are applied to confirm the diagnosis. A recent study documented the utility of DDIT3 immunohistochemistry (IHC) in the differential diagnosis of adipocytic and myxoid soft tissue tumors. The purpose of this study was to evaluate DDIT3 IHC as a surrogate for molecular testing in high-grade MLPS. IHC was performed using a mouse monoclonal antibody directed against the N-terminus of DDIT3 on whole tissue sections from 50 high-grade MLPS cases and 319 histologic mimics used as controls (170 on whole tissue sections and 149 on a tissue microarray). Histologic mimics included Ewing sarcoma, *CIC*-rearranged sarcoma, sarcomas with *BCOR* genetic alterations, poorly differentiated synovial sarcoma, alveolar and embryonal rhabdomyosarcomas, mesenchymal chondrosarcoma, desmoplastic small round cell tumor, and neuroblastoma. Nuclear staining in >5% of cells was considered positive. By IHC, 48 (96%) high-grade MLPS showed strong diffuse nuclear staining for DDIT3. Of the controls, 2% of cases were positive, with no more than 25% nuclear staining. An additional 19% of control cases displayed less than 5% nuclear staining. Overall, DDIT3 IHC showed 96% sensitivity and 98% specificity for high-grade MLPS; strong, diffuse staining is also 96% sensitive but is 100% specific. IHC using an antibody directed against the N-terminus of DDIT3 is highly sensitive and specific for high-grade MLPS among histologic mimics and could replace molecular genetic testing in many cases, although limited labeling may be seen in a range of other tumor types.

Introduction

Myxoid liposarcoma (MLPS) is a malignant soft tissue neoplasm with adipocytic differentiation and a predilection for the extremities, particularly the thigh [1, 2]. MLPS comprises up to 30% of liposarcomas overall [3] and is the most common liposarcoma in children and adolescents [4, 5]. MLPS typically presents as a painless, slow-growing, deep-seated mass [6]. MLPS often metastasizes to soft tissue sites, including the retroperitoneum or the contralateral extremity [7, 8], and may present with multifocal synchronous disease [9]. MLPS also metastasizes to bone, most often the spine, and less often metastasizes to lung, a preferred site for other sarcomas [7, 8]. Overall, 5-year survival rates are 70–80% and 10-year survival rates are 50–60% [1, 7], with more favorable survival in children and adolescents [5]. Necrosis, increased patient age, larger tumor size, and the presence of a morphologically round cell component portend a worse prognosis [2, 7, 8].

Histologically, MLPS is typically composed of uniform bland ovoid to short spindle cells in an abundant myxoid matrix with characteristic delicate arborizing "chicken-wire" vasculature and variable amounts of interspersed

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Table 1 Summary of immunohistochemical staining for DDIT3.

Tumor type	Total cases	Positive (%)[a]	0	1+	2+	3+	4+	5+
Myxoid liposarcoma, high grade	50	48 (96)	1	1	0	0	1	47
Pure "round cell" morphology	11	11 (100)	0	0	0	0	0	11
Histologic mimics	319	6 (2)	252	61	6	0	0	0
Alveolar rhabdomyosarcoma	36	0 (0)	32	4	0	0	0	0
Sarcomas with *BCOR* genetic alterations	20	1 (5)	12	7	1	0	0	0
CIC-rearranged sarcoma	20	0 (0)	10	10	0	0	0	0
Desmoplastic small round cell tumor	37	1 (3)	29	7	1	0	0	0
Embryonal rhabdomyosarcoma	75	1 (1)	65	9	1	0	0	0
Ewing sarcoma	38	3 (8)	24	11	3	0	0	0
Mesenchymal chondrosarcoma	20	0 (0)	14	6	0	0	0	0
Neuroblastoma	48	0 (0)	48	0	0	0	0	0
Synovial sarcoma, poorly differentiated	25	0 (0)	18	7	0	0	0	0

0 (0%); 1+ (<5%); 2+ (5–25%); 3+ (26–50%); 4+ (51–75%); 5+ (76–100%).

[a]Positivity was defined as the presence of nuclear staining in greater than 5% of cells.

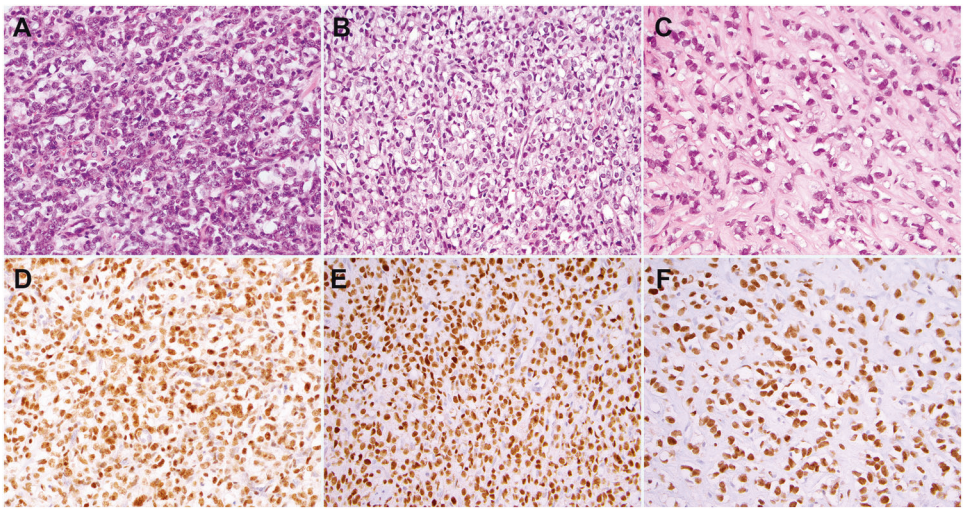

Fig. 1 Immunohistochemistry for DDIT3 in myxoid liposarcoma (MLPS). High-grade MLPS showing pure round cell morphology obscuring the characteristic vascular network (**A**). High-grade MLPS with round cell morphology and clear cytoplasm, mimicking Ewing sarcoma (**B**). High-grade MLPS composed of cords of round cells within a sclerotic matrix in a sclerosing epithelioid fibrosarcoma-like pattern (**C**). All three cases display strong and diffuse nuclear positivity with the DDIT3 N-terminus antibody (**D**–**F**).

small uni- or bivacuolated lipoblasts [1, 4]. Prominent mucin pools often impart a microcystic pulmonary edema-like pattern, typical of low-grade MLPS. High-grade MLPS (previously termed "round cell liposarcoma") is characterized by increased cellularity and mitotic activity, higher nuclear grade, and diminished to absent myxoid stroma, often with areas of round cell morphology. High-grade MLPS with pure round cell morphology may be indistinguishable from other round cell sarcomas, including Ewing sarcoma, poorly differentiated synovial sarcoma, and *CIC*-rearranged sarcoma. Diagnosis is particularly challenging on small biopsy specimens, as the characteristic delicate vascular network may not be appreciated, and lipoblasts may be absent.

MLPS is genetically defined by the recurrent t(12;16)(q13;p11) translocation seen in >95% of cases, which generates a chimeric oncogene fusing the N-terminal transcriptional activation domain of *FUS* (formerly *TLS*) with full-length *DDIT3* (formerly *CHOP*) [10–12], leading to arrest of terminal adipocytic differentiation and tumorigenesis [13]. In <5% of cases, a recurrent t(12;22)(q13;q12) translocation leads to the *EWSR1–DDIT3* fusion oncogene, with no known differences in presentation, histology, or prognosis [14, 15]. FUS and EWSR1 are both ubiquitously expressed in normal tissues and contain N-terminal transcriptional activation domains [11, 14]. DDIT3 is a nuclear-localized DNA-binding transcription factor upregulated during DNA damage and involved in regulating adipogenesis [10, 11]. Although a number of *FUS–DDIT3* and *EWSR1–DDIT3* transcript variants have been reported, none appear to have prognostic significance [2, 15]. These fusions have not yet been identified in other neoplasms and are therefore pathognomonic for MLPS.

Immunohistochemistry (IHC) has historically not been utilized for the diagnosis of MLPS, except to exclude other round cell malignant neoplasms in the differential

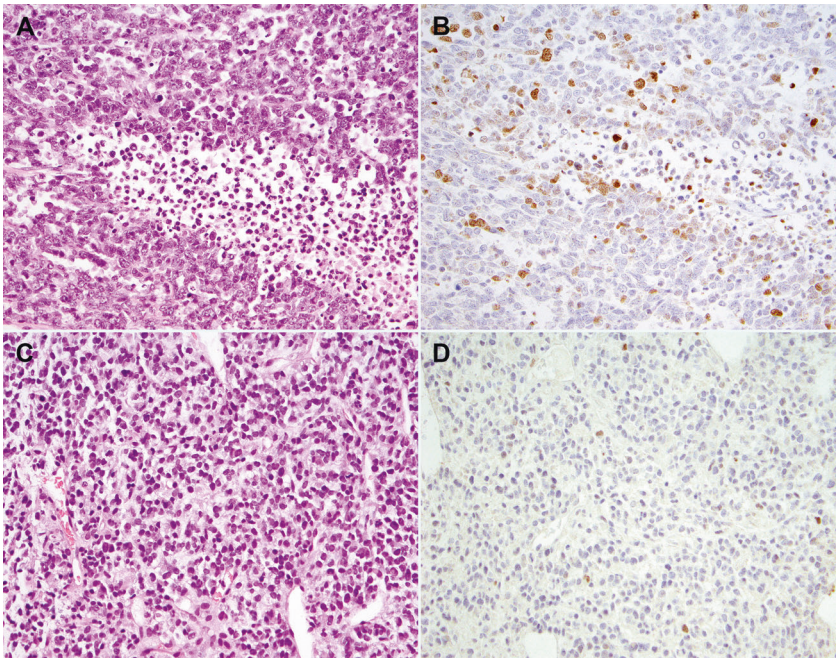

Fig. 2 Immunohistochemistry for DDIT3 in other round cell sarcomas. Ewing sarcoma with focal necrosis (**A**). The tumor cells surrounding the area of necrosis show variable staining for DDIT3 (**B**). *CIC*-rearranged sarcoma (**C**) with rare cells positive for DDIT3 (**D**).

diagnosis. Thus, confirmation of a t(12;16) or t(12;22) translocation by cytogenetics, identification of *DDIT3* rearrangement by fluorescence in situ hybridization (FISH) [16], or detection of a fusion transcript by RT-PCR [15] is often utilized to confirm the diagnosis of MLPS, particularly in high-grade MLPS and those with pure round cell morphology. Availability of an ancillary IHC assay to distinguish high-grade MLPS from histologic mimics would be of great diagnostic value. A recent study has documented the utility of DDIT3 IHC with a novel monoclonal antibody against the N-terminus of DDIT3 in distinguishing MLPS from other myxoid and adipocytic soft tissue tumors [17]. The purpose of this current study was to evaluate DDIT3 IHC as a surrogate for molecular testing specifically in high-grade MLPS among other round cell malignant neoplasms.

Results

A total of 50 high-grade MPLS cases (27 genetically confirmed, 27 with at least 5% round cell morphology, 11 with pure round cell morphology) and 319 histologic mimics as controls were evaluated by IHC for DDIT3 (results summarized in Table 1). DDIT3 IHC was positive in 96% of MLPS cases and 2% of controls. Although positivity was defined as nuclear staining in greater than 5% of tumor nuclei, 47 (94%) MLPS cases showed strong diffuse 5+ nuclear staining for DDIT3, approaching 100% of neoplastic cells in most cases (Fig. 1). One case showed strong diffuse 4+ staining (50–75% nuclear positivity). Of the two negative cases, one showed weak 1+ staining (<5%) and one was entirely negative. These two cases with less than 5+ DDIT3 staining, both with confirmed *DDIT3* rearrangement by FISH at the time of original diagnosis, were among the oldest in the study (from 2015). Of note, for these cases, archival unstained slides had been in storage for 5 years; we believe the "negative" results may be secondary to loss of antigenicity. With the exception of these 2015 cases, no high-grade MLPS cases showed weak or moderate staining intensity. All other cases with confirmed *DDIT3* rearrangement ($N = 24$) were diffusely positive for DDIT3 by IHC.

Of the controls, 252 (79%) cases revealed no staining (score 0), including all alveolar rhabdomyosarcomas, *CIC*-rearranged sarcomas, mesenchymal chondrosarcomas, neuroblastomas, and poorly differentiated synovial sarcomas. Of the six positive non-MPLS cases, three were Ewing sarcomas, with one each desmoplastic small round cell tumor, embryonal rhabdomyosarcoma, and a sarcoma with *BCOR* genetic alteration. All displayed less than 25% nuclear staining (2+, heterogeneous weak to strong staining intensity) (Fig. 2). An additional 19% of cases, interpreted as negative, revealed 1+ staining (<5% nuclear staining, heterogenous intensity), manifested as either scattered cells throughout the tumor or focal clusters of cells around areas of necrosis (Fig. 2). Overall, these results indicate that DDIT3 IHC shows 96% sensitivity and 98% specificity for high-grade MLPS. Strong, diffuse staining is also 96% sensitive but is 100% specific.

Discussion

This study aimed to evaluate a recently described DDIT3 N-terminus mouse monoclonal antibody [17] for

distinguishing high-grade ("round cell") MLPS from other round cell sarcomas. Scapa et al. evaluated this monoclonal antibody in 46 MLPS (6 of which were high grade) and in 264 adipocytic and myxoid neoplasms commonly considered in the differential diagnosis with low- or intermediate-grade MLPS. In their study, 100% of MLPS cases showed nuclear positivity for DDIT3 by IHC, with the majority of cases showing >80% moderate-to-strong diffuse staining in tumor nuclei and the remainder showing >50% staining [17]. While no controls were diffusely positive for the antibody, 12 control cases showed minimal staining (1–10%) in tumor nuclei, including dedifferentiated and pleomorphic liposarcomas, solitary fibrous tumor, and myxofibrosarcoma. Overall, the high specificity and sensitivity of DDIT3 IHC for MLPS among adipocytic and myxoid neoplasms supported the utility of this antibody in confirming the diagnosis.

Low- and intermediate-grade MLPS can be identified histologically by classic morphology with distinctive chicken-wire vasculature in a myxoid stroma. High-grade MLPS, in contrast, can be difficult to distinguish from other round cell neoplasms, particularly those cases with diffuse or pure round cell morphology obscuring the classic vascular pattern. As such, cytogenetic or molecular genetic testing for *DDIT3* rearrangement is often used to confirm the diagnosis of high-grade MLPS [15, 16], especially on small biopsy specimens. We thus aimed to validate this DDIT3 antibody in a series of high-grade MLPS with focal to pure round cell morphology compared to a large number of other round cell malignant neoplasms. DDIT3 IHC was performed on 50 MLPS and 319 histologic mimics as controls. Overall, this antibody was found to be 96% sensitive and 98% specific for high-grade MLPS, mirroring the excellent results of this antibody recently reported for MLPS among lipomatous and myxoid neoplasms [17]. DDIT3 IHC could therefore essentially obviate the need for confirmatory genetic testing in most cases.

This highly sensitive and specific DDIT3 antibody represents another addition to the armamentarium of recently developed antibodies for the diagnosis of translocation-associated mesenchymal neoplasms, such as STAT6 for solitary fibrous tumor (with *NAB2–STAT6* fusions) [18], CAMTA1 for epithelioid hemangioendothelioma (*WWTR1–CAMTA1* fusions) [19], FOSB for pseudomyogenic hemangioendothelioma (*SERPINE1–FOSB* or *ACTB-FOSB* fusions) [20], and an SS18-SSX fusion-specific and SSX C-terminus antibody for synovial sarcoma (*SS18–SSX* fusions) [21]. These IHC tests have been implemented in many clinical laboratories; the high sensitivity and specificity of such markers (in contrast to conventional lineage markers) allow them to serve as practical, rapid, and inexpensive replacements for molecular genetic testing. Importantly, since it recognizes the N-terminus of DDIT3, which in MLPS pairs with either FUS or EWSR1 to create a fusion oncoprotein, this antibody is expected to recognize the tumor-specific oncoprotein regardless of the fusion partner.

Qualitatively, DDIT3 IHC in MLPS revealed diffuse, strong, crisp nuclear staining, often approaching 100% of tumor nuclei, allowing for uncomplicated interpretation of the antibody in nearly all positive cases. No recent cases displayed negative or equivocal staining with DDIT3. Three MLPS cases showed less (or negative) staining: 4+, 1+, and no staining, respectively. All were performed on unstained slides generated in early 2015 (among the oldest of the cases evaluated); the results may be secondary to loss of antigenicity over time. Only 2% of controls were interpreted as positive, and of these, none showed greater than 25% positive tumor nuclei. Of these six positive cases, three were Ewing sarcomas with genetically confirmed *EWSR1* rearrangement. The other three cases were a desmoplastic small round cell tumor, embryonal rhabdomyosarcoma, and a sarcoma with *BCOR* rearrangement. Several 2+ cases showed upregulation of DDIT3 expression around areas of necrosis (Fig. 2), a pattern also seen in a subset of cases with 1+ staining. The remaining 1+ and 2+ cases showed an apparently random distribution of scattered positive cells. Unlike the uniformly diffuse and strong staining seen in MLPS cases, the DDIT3 staining in control cases was variable in intensity (sometimes within the same tumor), with no perceptible pattern among different tumor types showing 1+ or 2+ staining.

In summary, a recently validated mouse monoclonal antibody directed against the N-terminus of DDIT3, initially found to be highly sensitive and specific for MLPS among adipocytic and myxoid neoplasms, is also highly sensitive and specific for high-grade "round cell" MLPS among round cell sarcomas. Strong, diffuse staining is 96% sensitive and 100% specific. Although IHC for DDIT3 may replace molecular or cytogenetic confirmation of *DDIT3* rearrangement in most cases of MLPS, additional confirmatory studies are needed.

Materials and methods

Cases were retrieved from the surgical pathology and consultation files of Brigham and Women's Hospital (Boston, MA) and Stanford Hospital (Stanford, CA) and the consultation files of two of the authors (CDMF and JLH). For most cases of MLPS (diagnoses made between 2015 and 2020 for all cases), existing archival unstained slides were retrieved from storage. Representative hematoxylin and eosin-stained slides of whole tissue sections (WTS) for each case were reviewed to confirm the diagnoses. A TMA for a subset of control cases was generated using a tissue arrayer

(Beecher Instruments, Silver Spring, MD), as previously described [22], with at least 0.6 mm diameter cores taken from representative formalin-fixed paraffin-embedded (FFPE) blocks. In total, 369 tumors were evaluated (50 MLPS, 319 histologic mimics as controls), 220 in WTS and 149 by TMA, with the breakdown by tumor type as follows: 50 high-grade MLPS (50 WTS), 36 alveolar rhabdomyosarcomas (20 WTS, 16 TMA), 20 sarcomas with *BCOR* genetic alterations (20 WTS), 20 *CIC*-rearranged sarcomas (20 WTS), 37 desmoplastic small round cell tumors (20 WTS, 17 TMA), 75 embryonal rhabdomyosarcomas (20 WTS, 55 TMA), 38 Ewing sarcomas (20 WTS, 18 TMA), 20 mesenchymal chondrosarcomas (20 WTS), 48 neuroblastomas (10 WTS, 38 TMA), and 25 poorly differentiated synovial sarcomas (20 WTS, 5 TMA). Of the 50 high-grade MLPS cases, 26 were genetically confirmed at the time of original diagnosis by *DDIT3* FISH and one by *FUS* gene rearrangement. All Ewing sarcoma, *CIC*-rearranged sarcoma, and poorly differentiated synovial sarcoma cases were also genetically confirmed at the time of diagnosis. IHC was performed on 4-µm thick FFPE sections following pressure cooker antigen retrieval (Target Retrieval Solution, pH 6.1, Dako, Carpinteria, CA, for WTS; 0.01 M citrate buffer, pH 6.0 for TMA) using a mouse monoclonal antibody directed against the N-terminus of DDIT3 (clone 9C8; Abcam, Cambridge, UK) at 1:750 dilution (40-min incubation) and the EnVision+ System, HRP (Dako) for WTS cases and 1:400 dilution (30-min incubation) and the VECTASTAIN ABC kit (Vector Laboratories Inc., Burlingame, CA) and DAB chromogen (Abcam) for TMA cases. Appropriately selected positive and negative controls were used with each iteration of IHC. The staining intensity in each case was characterized as weak, moderate, or strong, and the extent of immunoreactivity was scored according to the percentage of tumor cells with nuclear staining: 0 (0%), 1+ (<5%), 2+ (5–25%), 3+ (26–50%), 4+ (51–75%), and 5+ (76–100%). Positivity for the antibody was defined as the presence of nuclear staining of any intensity in greater than 5% of tumor cells (i.e., score of 2+ or greater). Diffuse labeling was defined as nuclear staining in greater than 50% of tumor cells (4+ or 5+).

Data availability

Access to data that are not available within the article can be provided by the authors upon request (direct contact to JLH).

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Author contributions EB and JLH designed the study; MAB, CDMF, GWC, and JLH provided materials and reagents; EB and GWC acquired and analyzed the data; EB wrote the paper; and all authors read and approved the final paper.

Compliance with ethical standards

Conflict of interest The authors declare no competing interests.

Ethics approval This study was approved by the Institutional Review Boards of the Brigham and Women's Hospital and Stanford University School of Medicine.

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