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Expression of dog1 in low-grade fibromyxoid sarcoma: A study of 19 cases and review of the literature

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ABSTRACT

DOG1 is a highly-sensitive marker often included in the immunohistochemical panel for the diagnosis of gastrointestinal stromal tumors (GISTs). Recent research has shown that DOG1 may also be expressed by low-grade fibromyxoid sarcomas (LGFMSs); this may give rise to diagnostic error when the sarcoma is located in the abdominal cavity. This paper reports on immnohistochemical expression of DOG1 in 19 LGFMSs using two different monoclonal antibodies: K9 (Leica, Novocastra Laboratories, Newcastle upon Tyne, UK) and SP31 (Thermo Scientific, Freemont, USA). All LGFMSs displayed the standard histological pattern of alternating myxoid and fibrous areas, low cellularity and bland spindle-cell morphology. Positive staining for MUC4 was observed in 18/19 cases (94.7%), while there was rearrangement of the FUS gene in 14/19 (73.7%) cases and of the EWR1 gene in 2/19 (10.5%). The sarcoma staining negative for MUC4 displayed FUS gene rearrangement. Whole-section immunohistochemistry revealed positive staining for DOG1 in 8/19 cases (42.1%), though only with clone K9. Cytoplasmic as well as membrane staining was observed in all cases; staining was focal (10–30%) and of varying intensity (1 + to 2 +).

In conclusion, DOG1 clone K9 exhibited low sensitivity (42.1%) for the diagnosis of LGFMS, although higher than clone SP31. Since the two clones display similar sensitivity and specificity for GIST diagnosis, SP31 would appear to be more specific for this purpose, since no reaction was observed here with LGFMS, a GIST-mimicking lesion.

1. Introduction

Low-grade fibromyxoid sarcoma (LGFMS) is a rare sarcoma characterized by bland cytological features and an indolent clinical course, with local recurrence and delayed distant metastasis [1-3]. In the first published report, Evans [1] described two patients with soft-tissue fibromyxoid lesions of fibroblastic appearance, initially diagnosed as “benign fibroma” and “fibromatosis”, respectively; one patient died of pulmonary metastatic disease 94 months after diagnosis of the primary tumor. Although the claim that low-grade fibromyxoid sarcoma was a distinct entity was initially greeted with some scepticism, new cases were soon identified; the immunohistochemical profile was documented and morphohistological variations from initial histological findings were reported [3-7]. Definitive confirmation that this was a distinct clinical entity came from molecular biology, with the demonstration of a recurring balanced translocation (7;16) (q34;p11) or t(11;16) (p11;p11), leading to fusion of the *FUS* gene with the *CREB3L2* or *CREB3L1* genes, respectively [6,8]. Later research discovered evidence of *EWSR1-CREB3L1* gene fusion [9], particularly in lesions progressing to sclerosing epithelial fibrosarcoma (SEF) or with hybrid findings (LGFMS-SEF) [10].

Although LGFMSs typically occur in the trunk and extremities, they have also been reported in other locations, including the abdominal cavity [11]. Thway et al. [12] recently noted DOG1 expression in some LGFMSs, and recommended differential diagnosis with gastrointestinal stromal tumors (GIST).

This paper determined the extent and intensity of DOG1 expression in 19 LGFMSs with molecular characterization, employing two widely-

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used commercial anti-DOG1 antibodies (K9 and SP1), and assessed the value of this immunohistochemical technique for the differential diagnosis of LGFMS and GIST.

2. Materials and methods

Cases were from patients diagnosed between 2000 and 2015 at the Joint Pathology Management Unit run by two teaching hopsitals in Seville, Spain: the Virgen Macarena Hospital and the Virgen del Rocío Hospital. Almost all 19 cases selected stained positive to MUC4 (18/19) (1:500; clone 8G7; Santa Cruz Biotechnology, Santa Cruz, CA), and rearrangement of the FUS gene (14/19) or the EWSR1 gene (2/19) was observed by FISH using Vysis LSI FUS and LSI EWSR1 Dual Color Break Apart Probes (Abbott Molecular, Des Plaines, IL).

Immunohistochemical examination of DOG1 expression was carried out on whole sections 4 μm thick, processed with xylol and hydrated through decreasing alcohol concentrations. Immunostaining was performed using the VENTANA® system (Benchmark Ultra, Tucson, Arizona) and the OptiView DAB IHC Detection Kit. The primary antibodies used were antiDOG1 (1:50; clone K9) from Leica, Novocastra Laboratories (Newcastle upon Tyne, UK) and antiDOG1 (1:100; clone SP31) from Thermo Scientific (Freemont, USA). Each sample was evaluated by two pathologists as follows: staining intensity was classed as weak, moderate or strong; the extent of cytoplasmic staining was graded according to percentage (0, no staining; 1 +, < 5%; 2 +, 5–25%; 3 +, 26–50%; 4 +, 51–75%; and 5 +, 76–100%).

3. Results

Clinical data and immunohistochemical and molecular findings are shown in Table 1. Patients (13 female; 6 male) were aged between 7 and 74 (median: 43). There was only one child. Lesions were located in the leg/thigh (8 cases), buttocks [4], foot [2], lung [2], chest wall [1], cervical region [1] and abdominal cavity [1]. Tumor size ranged from 5 cm to 21 cm (median: 12 cm). In all cases, follow-up was > 12 months. Both lung lesions were metastases from primary tumors diagnosed elsewhere. The abdominal lesion was extraperitoneal and associated with the iliac muscle.

Table 1
Low-Grade Fibromyxoid Sarcoma: Clinical, Molecular Features and Immunohistochemical MUC4 and DOG1 Expression.

Case N°	Age	Sex	Location of lesion	FISH STUDY rearrangement of FUS or EWSR1	MUC4 expression	DOG1(K9) expression (%)
1	32	♀	Buttock	FUS	+	–
2	60	♂	Thigh	FUS	+	10%
3	29	♀	Buttock	FUS	+	–
4	43	♀	Thigh	FUS	+	20%
5	7	♀	Right foot	FUS	+	30%
6	56	♀	Buttock	EWSR1	+	–
7	34	♂	Thigh	FUS	+	–
8	26	♀	Thigh	FUS	+	30%
9	56	♂	Lung metastasis	EWSR1	+	–
10	32	♀	Buttock	FUS	+	–
11	52	♂	Lung metastasis	FUS	+	–
12	61	♀	Ankle	FUS	+	10%
13	31	♀	Cervical region	FUS	+	–
14	22	♂	Leg	Negative	+	10%
15	51	♀	Thigh	Not evaluable	+	–
16	51	♀	Thigh	FUS	+	–
17	34	♀	Thigh	FUS	–	–
18	74	♀	Chest wall	FUS	+	30%
19	57	♂	Abdominal cavity	Not evaluable	+	10%

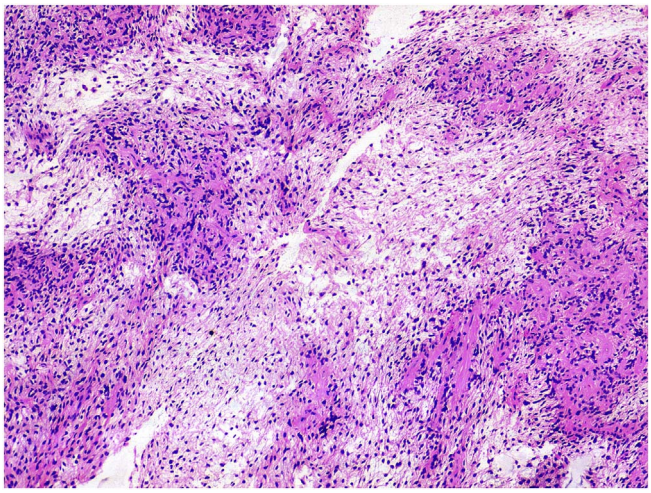

Fig. 1. Low-magnification panoramic view of LGFMS, showing hyalinizing, hypocellular areas of spindle cells alternating with areas of myxoid stroma (hematoxylin-eosin, 200 × magnification).

Typical histological features [1] were observed in all cases. Fibrous areas were more predominant than myxoid areas (Fig. 1). Giant collagen rosettes were identified in 3 cases (15.8%) (Fig. 2). Strong, diffuse overexpression of MUC4 was detected in 18/19 cases (94.7%) (Fig. 3); FISH identified rearrangement of the FUS gene in 14/19 (73.7%) and of the EWSR1 gene in 2/19 cases (10.5%). None of the cases exhibited positive staining for the anti-DOG1 antibody clone SP31, while positive cytoplasmic and membrane staining for anti-DOG1 clone K9 was observed in 8/19 cases (42.1%) (Fig. 4). In all cases, immunostaining was focal (10–30%) and of varying intensity (1 + to 2 +).

4. Discussion

The DOG1 gene (discovered on GIST-1) was identified through gene microarray studies in GISTs [13]. Later, a specific antibody was generated to the coded protein FLJ10261, and increased expression was found not only in typical GISTs but also in KIT-WT tumors. Protein FLJ10261, also known as anoctamin 1 (ANO1), ORAOV2, TAOS2 and TMEM16, is a Ca^{2+}-activated Cl^{-} channel widely expressed on interstitial cells of Cajal [14-17].

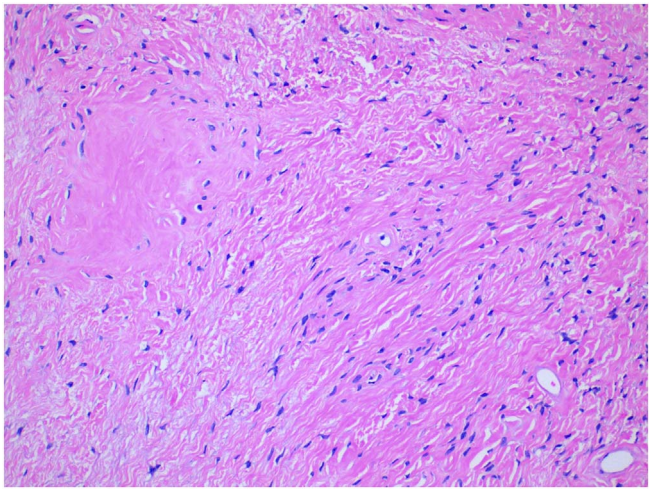

Fig. 2. Tumor with giant rosettes, with hyalinized central collagen surrounded by plump to oval cells (hematoxylin-eosin, 200 × magnification).

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