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Original contribution

Claudin-1 is expressed in perineurioma-like low-grade fibromyxoid sarcoma

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Summary Low-grade fibromyxoid sarcoma is a soft tissue sarcoma with recurrent and low metastatic potential, which has characteristic *FUS-CREB3L2* or *FUS-CREB3L1* fusions. Perineurioma is a peripheral nerve sheath neoplasm, which is usually benign. Low-grade fibromyxoid sarcoma and perineurioma can appear morphologically similar, particularly in small biopsy specimens, and distinction between the 2 entities is important for appropriate treatment. Low-grade fibromyxoid sarcoma is negative for most immunohistochemical markers, whereas perineuriomas stain variably for epithelial membrane antigen, CD34 and claudin-1, a tight-junction associated protein. We studied 15 cases of genetically proven low-grade fibromyxoid sarcoma that at least focally resembled perineurioma, with antibodies to claudin-1 and epithelial membrane antigen. Of these, 11 showed positivity for epithelial membrane antigen and all 15 were positive for claudin-1; in all cases, expression of claudin-1 was equal to or greater than the corresponding epithelial membrane antigen expression. This study emphasizes that claudin-1 is significantly expressed in low-grade fibromyxoid sarcomas. This has implications toward the accurate diagnosis of both tumors, and, as positivity for claudin-1 in low-grade fibromyxoid sarcoma is not previously documented, suggests that there might be underdiagnosis of low-grade fibromyxoid sarcoma. Although positivity for claudin-1 remains useful as an adjunct marker for perineurioma, it should be taken in context with clinical findings, morphology, and the additional immunoprofile.

1. Introduction

Low-grade fibromyxoid sarcoma, a malignant tumor most frequently arising in the deep soft tissue of younger adults, has a deceptively bland microscopic appearance [1,2]. Two balanced translocations have been demonstrated for LGFMS: t(7;16)(q32-34;p11) and the rarer variant t(11;16)(p11;p11) [3], resulting in *FUS-CREB3L2* and *FUS-CREB3L1* fusion genes, respectively. These can be detected using paraffin-fixed, formalin-embedded tissue by reverse transcriptase–polymerase chain reaction [4] or fluorescence in situ hybridization (FISH) [5]. Although most LGFMS show at least focal epithelial membrane antigen (EMA) expression [4], they are negative for all other markers, including CD34. LGFMS has considerable morphologic and immunohistochemical overlap with perineurioma. Soft tissue perineuriomas are peripheral nerve sheath neoplasms, most

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of which are benign and which most frequently occur on the trunk or extremities of adults. Although most occur in superficial soft tissues, a smaller number arise deeply [6]. Perineuriomas are, by definition, EMA-positive, although this is often weak or focal, and up to 64% express CD34 [6]. A subset of perineuriomas also show membranous expression of claudin-1 [7]. Claudin-1 is considered a useful adjunct marker to differentiate perineurioma from other neoplasms, such as LGFMS [7], in the absence of other data such as molecular genetic analysis. We have noted both EMA and claudin-1 expression in cases of translocation-proven LGFMS and therefore evaluated a series of genetically confirmed cases of LGFMS to assess the expression of these markers in this tumor.

2. Materials and methods

Cases of low-grade fibromyxoid sarcoma accessioned between 1994 and 2008 were retrieved from the consultation files of 2 of the authors (E.C. and C.F.), and the surgical pathology archives of our respective institutions. All lesions had been submitted for diagnostic histopathology reporting, with diagnosis of low-grade fibromyxoid sarcoma based on standard and accepted criteria [1,2], and included one case that had been previously reported as perineurioma. All specimens were formalin-fixed and paraffin-embedded. Cases with atypical features such as nuclear pleomorphism were excluded. All cases had at least focal whorled, fascicular, or storiform morphology (Fig. 1A), similar to the architecture of perineurioma. These also included one case with foci of typical hyalinizing spindle cell tumor morphology, studied for comparison (Fig. 1B). Cases in which a large proportion of tumor showed collagenous rosette formation were discarded. All cases had previously been found to be negative for CD34. Suitable cases that had no molecular genetic confirmation for the FUS-CREB3L2 translocation were submitted for cytogenetic analysis.

Deparaffinized sections of formalin-fixed tissue from each case were stained with antibodies to EMA (monoclonal

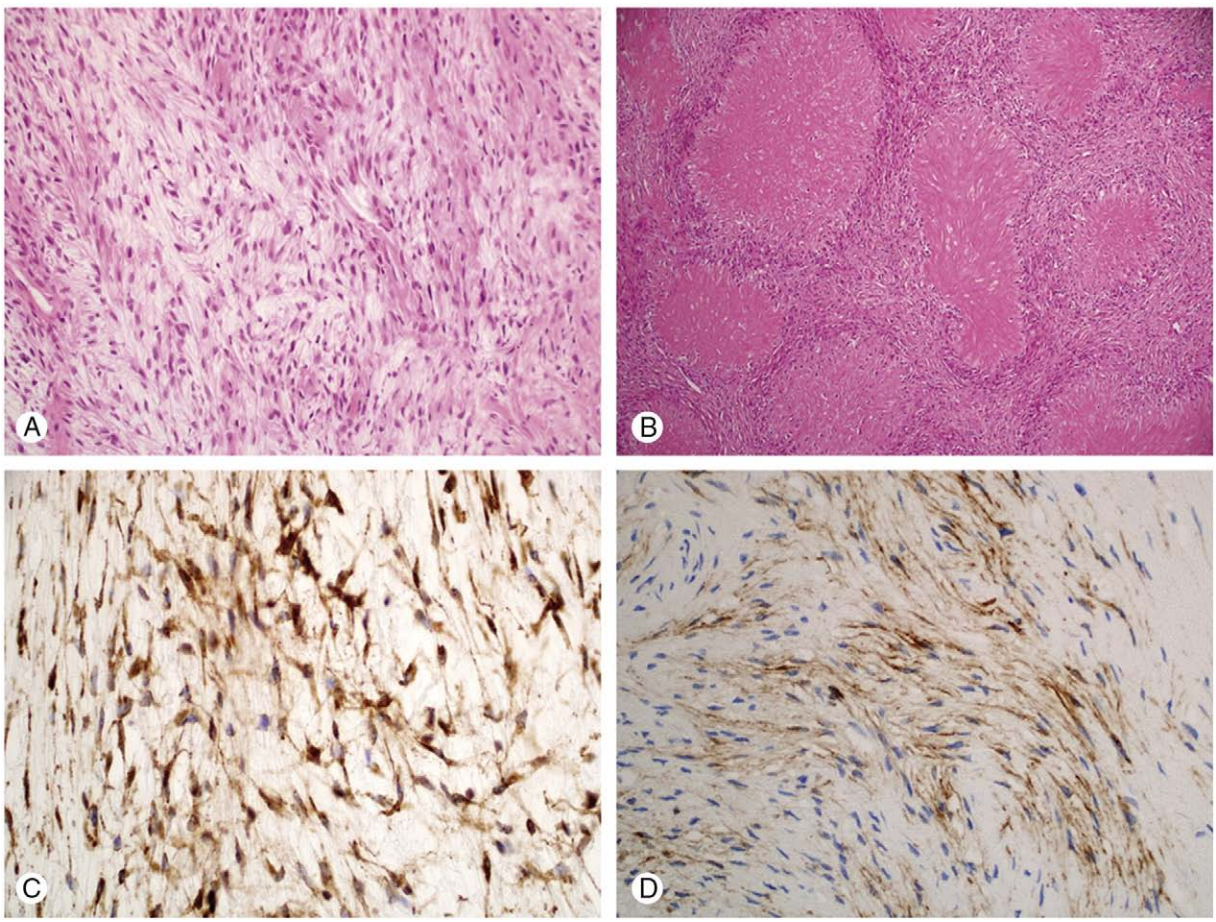

Fig. 1 A, LGFMS with bland, fascicular architecture, similar in morphology to perineurioma (original magnification ×200). B, LGFMS: hyalinizing spindle cell tumor with giant rosettes (original magnification ×100). Although one case with this morphology was included in the study, all other tumors with this appearance were omitted. C, LGFMS showing strong membranous positivity for claudin-1 (original magnification ×400). D, LGFMS showing EMA expression, which is more focal than that seen with claudin-1 and sometimes restricted to only a few small areas within the tumor (original magnification ×400).