CD138 (Syndecan-1) Expression in Bone-Forming Tumors

Amberly L. Nunez, MD, Gene P. Siegal, MD, PhD, Vishnu V.B. Reddy, MD, and Shi Wei, MD, PhD

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Abstract

CD138 (syndecan-1), a cell surface proteoglycan, is sensitive and specific for plasmacytic differentiation in hematologic disorders. Expression of CD138 has been observed in a majority of epithelial neoplasms and, rarely, soft tissue tumors. However, its expression in bone tumors has not been evaluated. We studied CD138 expression in 27 osteosarcomas, 12 benign bone-forming tumors (osteoid osteoma and osteoblastoma), and 17 reactive bone cases. CD138 expression was also evaluated in a tissue microarray (TMA) constructed from 24 osteosarcomas, 24 chondrosarcomas, 12 giant cell tumors of bone, and 9 normal bone samples. Membranous expression of CD138 was found in an average of 31% of osteosarcoma cases (16/51; 14/27 [52%] in in-house cases; 2/24 [8%] in TMA cases) and in 83% of osteoid osteoma/osteoblastoma cases. CD138 expression was also evaluated in a tissue microarray (TMA) constructed from 24 osteosarcomas, 24 chondrosarcomas, 12 giant cell tumors of bone, and 9 normal bone samples. Membranous expression of CD138 was found in an average of 31% of osteosarcoma cases (16/51; 14/27 [32%] in in-house cases; 2/24 [8%] in TMA cases) and in 83% of osteoid osteoma/osteoblastoma cases (10/12). Subsequent immunoglobulin κ and λ stains were negative in the CD138+ cases. All cases of chondrosarcoma, giant cell tumor of bone, and normal/reactive bone tested were nonreactive with anti-CD138. Our results show that CD138 reactivity for neoplastic cells in bone is not a definitive marker for plasmacytic origin, and caution is required to interpret CD138+ cells from a bony lesion for which a hematologic etiology has not been established.

CD138 (syndecan-1) is a transmembrane heparan sulfate cell surface proteoglycan that mediates a number of cellular functions, including cell-to-cell adhesion, cell-matrix interaction, and cell proliferation and differentiation. The molecule has an important role in the maintenance of cell morphologic features. Within the clinical spectrum of hematologic disorders, expression of syndecan-1, recognized by CD138-clustered antibodies, is highly sensitive and specific for plasmacytic differentiation. In addition, other B cell–lineage hematopoietic neoplasms may also express the molecule, including immunoblastic diffuse large B-cell lymphoma and marginal zone lymphoma. However, its expression is typically limited to the cell population with plasmacytoid morphologic features.

In normal nonhematopoietic tissue, CD138 is expressed exclusively by epithelial cells, with the most intense signals found in squamous and transitional epithelia. CD138 immunoreactivity has been observed in epithelial neoplasms of various origins, including those of prostate, colorectum, kidney, and squamous cell origins, although its expression may be lost when normal epithelial cells undergo malignant transformation. CD138 reactivity has also been found in malignant melanomas with epithelioid morphologic features.

Syndecan-1 antigen cannot be readily detected in differentiated mesenchymal cells by immunohistochemical analysis, although low levels of the molecule are produced by endothelial cells in cell culture. CD138 reactivity has further been reported in a variety of soft tissue tumors. However, the majority of these tumors exhibited cytoplasmic reactivity, and cell membrane positivity was not established.

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epithelial elements of synovial sarcomas. Expression of CD138 in bone tumors has not been reported in the English language literature. In this study, we aimed to investigate immunoreactivity to anti-CD138 in common bone tumors, namely osteosarcoma, osteoid osteoma, osteoblastoma, chondrosarcoma, and giant cell tumor of bone.

Materials and Methods

After approval by the institutional review board, the surgical pathology database of our institution was searched to identify cases of osteosarcoma, osteoid osteoma, and osteoblastoma. A total of 32 consecutive cases of osteosarcoma were retrieved for a 6-year period (January 2005 to January 2011), of which 5 cases were excluded from further analysis owing to a lack of tumor cells in the subsequent levels. The remaining 27 cases consisted of 13 needle core biopsy specimens and 14 noncore specimens, including incisional biopsy, curettage, and surgical excision specimens. We retrieved 12 cases of benign bone-forming tumors (7 osteoid osteomas and 5 osteoblastomas), including 7 needle core biopsy specimens and 5 noncore specimens. In addition, 17 cases of reactive bone (including fracture callus, reactive new bone formation, and osteomyelitis), consisting of 1 needle core biopsy and 16 noncore specimens, were also included. The patients' demographic information was recorded. In addition, a tissue microarray (TMA) from US Biomax (Rockville, MD), consisting of 60 bone tumors and 9 cases of normal bone (triplicate cores per case, core diameter of 1.0 mm), was also included.

Immunohistochemical stains for CD138 were performed in all cases. Tumors were scored as positive and assigned a range of positivity (<5%, 5%-25%, 26%-50%, and >50%) when unequivocal membranous staining was identified regardless of strength. The cases with positive CD138 staining were subsequently stained for immunoglobulin κ and λ (IgK and IgL).

Results

A total of 12 benign bone-forming tumors (7 osteoid osteomas and 5 osteoblastomas), from 5 males and 7 females, 6 to 68 years old (mean, 24.5 years), were evaluated. The anatomic sites of tumor were predominantly femur (n = 6), but also included tibia (n = 2), ulna (n = 2), and humerus and sacrum (1 case each). Ten cases (5 needle core biopsy specimens and 5 noncore specimens) showed at least focal membranous staining of tumoral cells with CD138. Semi-quantitative evaluation of these cases revealed 3 cases with less than 5% staining, 1 case showing 5% to 25% reactivity, 5 cases exhibiting 26% to 50% staining, and 1 case displaying more than 50% reactivity. There was no significant difference in the percentage of positive staining between the core biopsy and the noncore specimens.

We evaluated 27 in-house osteosarcoma cases from 15 males and 12 females, 10 to 77 years old (mean, 26 years). The anatomic sites of tumor were predominantly femur (n = 9), humerus (n = 5), tibia (n = 4), and pelvis (n = 4) but also included fibula, calcaneus, clavicle, vertebra, and lung.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Clinical Characteristics of Bone Tumor Cases</th>
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<tbody>
<tr>
<td></td>
<td>Normal/Reactive (n = 26)</td>
</tr>
<tr>
<td></td>
<td>In-house (n =17) TMA (n = 9)</td>
</tr>
<tr>
<td>Sex, No. (%)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>7 (41)</td>
</tr>
<tr>
<td>Female</td>
<td>10 (59)</td>
</tr>
<tr>
<td>Age (y)</td>
<td>Mean 55</td>
</tr>
<tr>
<td></td>
<td>Range 23-77</td>
</tr>
</tbody>
</table>
| TMA, tissue microarray.
metastasis (1 case each; Table 1). These included 23 cases of conventional type (16 osteoblastic, 2 chondroblastic, 2 mixed osteoblastic and chondroblastic, 1 mixed osteoblastic and fibroblastic, 1 osteoblastic with dedifferentiated leiomyosarcoma, and 1 malignant fibrous histiocytoma-like), 2 cases of small cell type, and 2 cases of parosteal osteosarcoma. Of the cases, 14 (6 needle core biopsy specimens and 8 noncore specimens) showed at least focal membranous staining for CD138, including 12 conventional type (7 osteoblastic, 2 chondroblastic, 1 mixed osteoblastic and chondroblastic, 1 mixed osteoblastic and fibroblastic, and 1 osteoblastic with dedifferentiated leiomyosarcoma), 1 small cell type, and 1 parosteal osteosarcoma. Semiquantitative evaluation revealed that 1, 5, 4, and 4 cases with CD138 immunoreactivity were identified on a scale of less than 5%, 5% to 25%, 26% to 50%, and more than 50% tumor cell positivity, respectively (Tables 2 and 3). As seen in osteoid osteoma/osteoblastoma cases, there was no significant difference in the percentage of positive staining between the core biopsy and noncore specimens.

All 17 in-house cases of reactive bone, from 7 men and 10 women, 23 to 77 years old (mean, 55.2 years), were non-immunoreactive with CD138 (Table 2). A TMA consisting of 60 bone tumors and 9 cases of normal bone was evaluated. The neoplastic cases included 24 osteosarcomas derived from 15 males and 9 females (14-64 years old; mean, 31 years), 24 chondrosarcomas derived from 13 males and 11 females (12-70 years old; mean, 40 years), and 12 giant cell tumors of bone derived from 5 men and 7 women (28-52 years old; mean, 36.8 years). Two cases of osteosarcoma, both osteoblastic, were positive for CD138 in the range of 5% to 25%. All cases of chondrosarcoma, giant cell tumor of bone, and normal bone were negative for CD138 (Table 2). Furthermore, normal bone adjacent to osteosarcoma in in-house cases showed nonimmunoreactivity with CD138 (data not shown).

Thus, CD138 expression was seen in 10 (83%) of 12 osteoid osteoma/osteoblastoma cases and in a total of 16 (31%) of 51 osteosarcoma cases, including 14 (52%) of 27 inhouse cases and 2 (8%) of 24 TMA cases, but not in chondrosarcomas, giant cell tumors of bone, or normal/reactive bone. All CD138+ cases were negative for subsequent IgK and IgL staining (data not shown).

### Discussion

The role of syndecan-1 in malignancies has been studied in various neoplasms, and variable results were observed in different tumor types and differentiation. In general, expression of the molecule was reduced during the transformation from benign to malignant in epithelial cells, with poorly differentiated tumors showing the greatest loss of syndecan-1. Decreased staining of CD138 has been demonstrated in squamous cell carcinoma of the head and neck, colorectal adenocarcinoma, renal cell carcinoma, and hepatocellular carcinoma. In contrast, CD138 has been shown to be overexpressed in prostatic and pancreatic adenocarcinomas. In addition, CD138 immunoreactivity has also been demonstrated

### Table 2
Summary of CD138 Immunoreactivity

<table>
<thead>
<tr>
<th>Diagnosis/Specimen Type</th>
<th>CD138+ Cells</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0%</td>
</tr>
<tr>
<td>Osteoid osteoma/osteoblastoma</td>
<td>2</td>
</tr>
<tr>
<td>Noncore specimen</td>
<td>1</td>
</tr>
<tr>
<td>Total (n = 12)</td>
<td>2 (17)</td>
</tr>
<tr>
<td>Osteosarcoma</td>
<td>7</td>
</tr>
<tr>
<td>Noncore specimen</td>
<td>6</td>
</tr>
<tr>
<td>Total (n = 27)</td>
<td>13 (48)</td>
</tr>
</tbody>
</table>

* Data are given as number of cases or number (percentage) of cases.

### Table 3
Percentage of CD138+ Cells in In-house Bone-Forming Tumor Cases

<table>
<thead>
<tr>
<th>CD138+ Cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osteoid osteoma/osteoblastoma</td>
</tr>
<tr>
<td>Noncore specimen</td>
</tr>
<tr>
<td>Total (n = 12)</td>
</tr>
<tr>
<td>Osteosarcoma</td>
</tr>
<tr>
<td>Noncore specimen</td>
</tr>
<tr>
<td>Total (n = 27)</td>
</tr>
<tr>
<td>0%</td>
</tr>
<tr>
<td>&lt;5%</td>
</tr>
<tr>
<td>5%-25%</td>
</tr>
<tr>
<td>26%-50%</td>
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<tr>
<td>&gt;50%</td>
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</tbody>
</table>
in other epithelial neoplasms, including mammary, gastric, pulmonary, and urothelial carcinomas; in medullary and papillary carcinoma of the thyroid; and in thymomas.²

Rarely, CD138 expression has been reported in some soft tissue tumors, including synovial sarcoma, alveolar soft part sarcoma, malignant epithelioid schwannoma, and fibromatosis.²⁹ However, the vast majority of CD138 immunoreactivity in these tumors was in the cytoplasm, whereas a membranous staining pattern was seen only in the epithelial elements of synovial sarcoma. Positive CD138 immunostaining was also reported in a case of leiomyosarcoma, although the staining pattern was unclear.²

To our knowledge, this is the first study to examine CD138 expression in bone tumors. Our results show that approximately 80% of benign bone-forming tumors and one third of osteosarcomas demonstrated CD138 expression in a membranous staining pattern, while all cases of chondrosarcoma, giant cell tumor of bone, and normal/reactive bone were nonreactive or demonstrated a nonspecific cytoplasmic staining pattern. While CD138 expression in bone-forming tumors was rarely diffuse, the staining was typically focal and patchy in the majority of the in-house cases. The fact that only 2 (8%) of 24 cases of osteosarcoma from the TMA displayed CD138 positivity was most likely due to the limited amount

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**Image 1** Osteosarcoma. Sections show small clusters of atypical cells (A, H&E, ×400) with immunoreactivity for CD138 in a membranous pattern (B, ×200). Note that no osteoid production or new bone formation was evident in this biopsy specimen. A subsequent biopsy showed matrix-producing, highly pleomorphic cells with atypical mitoses. The presence of tumor osteoid resulted in a diagnosis of osteosarcoma (C, H&E, ×200; D, H&E, ×400).
of tumor present in the TMA and the inability to evaluate the entire lesional tissue. Thus, CD138 expression in more than 50% in-house osteosarcoma cases likely represents the true rate of CD138+ osteosarcomas.

Our data indicate that CD138 expression in bone lesions is not a definitive marker for plasmacytic origin, but also can be seen in benign and malignant bone-forming tumors. While osteoid osteomas and osteoblastomas may be distinguished from plasmacytic neoplasms by their clinical manifestations and radiologic characteristics, the expression of CD138 in osteosarcoma may represent a potential diagnostic pitfall, especially in a bone biopsy specimen in which the nature of the lesion needs to be determined from a limited amount of tissue. Thus, caution is required to interpret CD138+ cells from a bony lesion for which a hematologic etiology has not been established, especially when not all neoplastic cells are immunoreactive with CD138. In addition, when plasma cell neoplasm is in the differential diagnosis, IgK and IgL, along with other appropriate markers and radiologic correlations, are needed to reach the correct diagnosis.

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