CD163 Expression Is Present in Cutaneous Histiocytomas but Not in Atypical Fibroxanthomas

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Abstract

CD163, a hemoglobin scavenger receptor, is expressed in monocytes and macrophages. Recent work has shown that this marker is specific for neoplasms of histiocytic differentiation. Our aim was to test the ability of CD163 to separate cutaneous histiocytomas from their morphologic mimics. We tested the expression of CD163 in 78 cases, including 19 xanthogranulomas, 16 atypical fibroxanthomas, 6 reticulohistiocytomas, 8 epithelioid cell histiocytomas, 9 cases of Langerhans cell histiocytosis, 10 xanthomas, and 10 intradermal Spitz nevi. CD163 expression was seen in all xanthogranulomas, 16 atypical fibroxanthomas, 6 reticulohistiocytomas, 8 epithelioid cell histiocytomas, 9 cases of Langerhans cell histiocytosis, 10 xanthomas, and 10 intradermal Spitz nevi. CD163 expression was seen in all xanthogranulomas and reticulohistiocytomas, 4 epithelioid cell histiocytomas, 2 cases of Langerhans cell histiocytosis, and 8 xanthomas but was absent in atypical fibroxanthomas and Spitz nevi. CD163 is an excellent marker for confirming histiocytic differentiation and is useful in eliminating morphologic mimics such as Spitz nevi from the differential diagnosis. The lack of CD163 in atypical fibroxanthomas argues against a histiocytic origin for this tumor.

CD163 is an acute phase–regulated transmembrane protein that binds haptoglobin-hemoglobin complexes and is implicated as a hemoglobin scavenger receptor.1-3 It is thought to be relatively specific for monocytes and tissue macrophages and has been proposed to function in the innate immune response and resolution of inflammation. Preliminary studies have shown that CD163 has more specificity for histiocytes than CD68, which is an organelle-specific marker that stains lysosomes.

A recent study from Stanford University School of Medicine, Stanford, CA, examined the reactivity of CD163 among normal and neoplastic tissues and found that CD163 expression was restricted to a few distinct neoplasms of histiocytic differentiation.2 In addition, our group has examined the ability of CD163 to distinguish between cellular fibrous histiocytomas and dermatofibrosarcoma protuberans and found that this marker is very helpful in this context, with a sensitivity of 100% and a specificity of 83% for the diagnosis of cellular fibrous histiocytomas.4 These results prompted us to examine the staining pattern of CD163 in cutaneous neoplasms with histiocytic differentiation, with a view to differentiating these neoplasms from their morphologic mimics.5,6

We also wanted to study the ability of CD163 to mark a lesion of purported histiocytic differentiation, atypical fibroxanthoma (AFX). AFX is a neoplasm of mesenchymal derivation that can show myofibroblastic differentiation and histiocytoid features.7 It arises predominantly on the head and neck of elderly patients and usually manifests as a solitary nodule measuring 1 to 2 cm in diameter. Clinical ulceration is common. Histologically, the lesions are composed of spindled cells with fascicle formation, admixed in most cases with large, pleomorphic cells. Because these lesions are often
negative for markers of specific differentiation, there has been an ongoing search for a specific marker that would define this entity and distinguish it from its chief differential diagnostic partners, spindle cell squamous cell carcinoma and malignant melanoma.\(^8\) A recent study purported to show staining of lesional cells in AFX by CD163.\(^9\) Because our experience is somewhat different, we wanted to test these lesions with CD163 as well and to compare the results with other markers known to stain lesional cells of AFX.\(^10,11\)

### Materials and Methods

#### Case Selection

A total of 78 formalin-fixed, paraffin-embedded tissue samples were retrieved from the archives of the Department of Pathology, Stanford University. Cases were selected based on the original diagnosis, and H&E-stained sections and relevant immunohistochemical stains performed at the time of diagnosis were reviewed to confirm these findings. The 78 chosen cases consisted of 11 juvenile xanthogranulomas (JXGs), 8 adult xanthogranulomas, 6 reticulohistiocytomas, 8 epithelioid cell histiocytomas, 9 cases of Langerhans cell histiocytosis, 10 xanthomas, 10 intradermal Spitz nevi, and 16 AFXs. We included intradermal Spitz nevi in our study because they are often part of the differential diagnosis for cutaneous histiocytic neoplasms. All cases of Langerhans cell histiocytosis were S-100+ and CD1a+, and none of the cases of AFX were positive for S-100 or cytokeratin markers (CKAE1 and CK5/6). This study was approved by the Stanford Institutional Review Board.

#### Immunohistochemical Studies

Immunohistochemical studies were performed on conventional sections of formalin-fixed, paraffin-embedded tissue stained with an antibody directed against CD163 using a Ventana BenchMark XT system (Ventana Medical Systems, Tucson, AZ).\(^12,13\) In addition, 7 cases of AFX were stained with CD10 and CD99 using the Ventana BenchMark system. Mild retrieval, used for CD163, consisted of a pretreatment period of 30 minutes, and standard retrieval, used for CD99 and CD10, consisted of a pretreatment period of 1 hour. The View 3,3’diaminobenzidine chromogen system (Ventana) was used for detection.

Staining for CD163 and CD99 localized predominantly to the membrane, although weak to moderate cytoplasmic staining was observed in most cases with membrane reactivity. CD10 showed membrane staining only. Normal tissue monocytes and macrophages served as positive internal controls for CD163, and these were present in all negative cases. A case of primitive peripheral nerve sheath tumor served as positive external controls for CD199, and the germinal center of tonsils served as positive external controls for CD10. Skin epidermal cells served as negative internal controls for all 3 antibodies. Immunoreactivity was reported as follows: strongly positive, intense staining of at least 20% of lesional cells; weakly positive, intense staining of at least 5% but fewer than 20% of lesional cells or faint or moderate staining of at least 20% of lesional cells; and negative, staining of fewer than 5% to no staining of lesional cells. Positive scoring consisted of the sum of cases reported as strongly or weakly positive.

#### Results

Clinical information for patients is given in Table 2, the results of immunohistochemical studies with CD163 are given in Table 3, and the results for CD99 and CD10 in cases of AFX are given in Table 4. The 11 cases of JXG and 8 cases of adult xanthogranuloma were characterized by dermal proliferations of histiocytes, foam cells, and varying numbers of Touton-type giant cells. The 16 cases of AFX were composed of a dermal mixture of pleomorphic spindle and epithelioid cells, histiocytes, and occasional multinucleated giant cells. The 6 cases of reticulohistiocytoma were composed of histiocytes with large vesicular nuclei and giant cells with “ground-glass” cytoplasm.\(^5\) The 8 cases of epithelioid cell histiocytoma showed numerous large epithelioid cells with eosinophilic cytoplasm and prominent vesicular nuclei. The 9 cases of

#### Table 1

<table>
<thead>
<tr>
<th>Antigen</th>
<th>Clone</th>
<th>Pretreatment</th>
<th>Antibody Dilution</th>
<th>Source</th>
<th>Automated Stainer</th>
<th>Staining Pattern</th>
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<tbody>
<tr>
<td>CD163</td>
<td>10D6</td>
<td>Mild retrieval</td>
<td>1:100</td>
<td>Novocastra, Newcastle upon Tyne, England</td>
<td>Ventana BenchMark, Ventana Medical Systems, Tucson, AZ</td>
<td>Membrane/cytoplasm</td>
</tr>
<tr>
<td>CD99</td>
<td>12E7</td>
<td>Standard retrieval</td>
<td>1:40</td>
<td>DAKO, Carpinteria, CA</td>
<td>Ventana BenchMark</td>
<td>Membrane/cytoplasm</td>
</tr>
<tr>
<td>CD10</td>
<td>56C6</td>
<td>Standard retrieval</td>
<td>1:20</td>
<td>Novocastra</td>
<td>Ventana BenchMark</td>
<td>Membrane</td>
</tr>
</tbody>
</table>

* Mild retrieval, incubation for 30 min in EDTA, pH 8.0-8.5; standard retrieval, incubation for 1 h in EDTA, pH 8.0-8.5.
Langerhans cell histiocytosis were characterized by a dermal infiltrate of atypical histiocytic cells with large reniform nuclei; in most cases, the atypical cells were epidermotropic. The 10 cases of xanthoma showed dermal proliferations of foam cells with pale cytoplasm and small, vesicular nuclei. The 10 cases of Spitz nevi were primarily intradermal collections of spindled and epithelioid melanocytes that formed nests and showed adequate maturation with dermal descent; some of them contained an inflammatory infiltrate of lymphocytes with dermal melanophages.

We found that CD163 was expressed in all cases of JXG, adult xanthogranuloma, and reticulohistiocytoma in Image 1A, Image 1B, and Image 1D. In these entities, all of the lesional cells stained, including the Touton-type giant cells and foam cells in xanthogranuloma and the large epithelioid cells with ground-glass cytoplasm in reticulohistiocytoma. Expression was seen in 8 of 10 cases of xanthoma but in only 2 of 9 cases of Langerhans cell histiocytosis Image 2A. In contrast with reticulohistiocytoma, only 4 of 8 cases of epithelioid cell histiocytoma stained with CD163. In the negative cases, none of the epithelioid cells stained, whereas there were many positive small spindled histiocytes in the background Image 1E and Image 1F. No staining was seen with cases of Spitz nevi.

The results of staining with CD163 in cases of AFX were compared with staining with CD10 and CD99 Image 3. With CD10 in particular, strong staining was seen in the large, pleomorphic cells of AFX (all or a subset). These cells were not highlighted by CD163, although positive internal controls were present. CD99 was likewise negative.

**Discussion**

CD163 is a monocyte-macrophage–derived differentiation antigen, which was found to be a member of the scavenger receptor superfamily. A recent large study from Stanford examined the expression pattern of CD163 in a wide range of

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**Table 1**

Select Clinical Information for Cases Studied

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Total No. of Cases</th>
<th>Age Range</th>
<th>M/F Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Juvenile xanthogranuloma</td>
<td>11</td>
<td>4 mo-12</td>
<td>9:2</td>
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<tr>
<td>Adult xanthogranuloma</td>
<td>8</td>
<td>25-56</td>
<td>6:2</td>
</tr>
<tr>
<td>Atypical fibroxanthoma</td>
<td>16</td>
<td>45-86</td>
<td>16:0</td>
</tr>
<tr>
<td>Reticulohistiocytoma</td>
<td>6</td>
<td>29-53</td>
<td>4:2</td>
</tr>
<tr>
<td>Epithelioid cell histiocytoma</td>
<td>8</td>
<td>20-75</td>
<td>5:3</td>
</tr>
<tr>
<td>Langerhans cell histiocytosis</td>
<td>9</td>
<td>1-51</td>
<td>5:4</td>
</tr>
<tr>
<td>Xanthoma</td>
<td>10</td>
<td>1-71</td>
<td>4:6</td>
</tr>
<tr>
<td>Intradermal Spitz nevi</td>
<td>10</td>
<td>5-45</td>
<td>3:7</td>
</tr>
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</table>

* Given as years unless otherwise indicated.

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**Table 2**

CD163 Staining in Cutaneous Histiocytoses and Their Morphologic Mimics

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Immunoreactivity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Cases</td>
</tr>
<tr>
<td>Juvenile xanthogranuloma</td>
<td>11</td>
</tr>
<tr>
<td>Adult xanthogranuloma</td>
<td>8</td>
</tr>
<tr>
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</tr>
<tr>
<td>Langerhans cell histiocytosis</td>
<td>9</td>
</tr>
<tr>
<td>Xanthoma</td>
<td>10</td>
</tr>
<tr>
<td>Intradermal Spitz nevi</td>
<td>10</td>
</tr>
</tbody>
</table>

* Strong positive, intense staining of at least 20% of lesional cells; weak positive, staining of at least 5% but fewer than 20% of lesional cells or faint to moderate staining of at least 20% of lesional cells; negative, staining of fewer than 5% to no staining of lesional cells.

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**Table 3**

CD10 and CD99 Staining in Atypical Fibroxanthoma

<table>
<thead>
<tr>
<th>Antigen</th>
<th>No. of Cases</th>
<th>Immunoreactivity</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Strong Positive</td>
<td>Weak Positive</td>
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<tr>
<td>CD99</td>
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<td>0</td>
</tr>
<tr>
<td>CD10</td>
<td>7</td>
<td>7</td>
</tr>
</tbody>
</table>

* Strong positive, intense staining of at least 20% of lesional cells; weak positive, staining of at least 5% but fewer than 20% of lesional cells or faint to moderate staining of at least 20% of lesional cells; negative, staining of fewer than 5% to no staining of lesional cells.
A, Cases of juvenile and adult xanthogranuloma are characterized by histiocytes admixed with lymphocytes and Touton-type giant cells (H&E, ×20). B, The lesional cells are strongly highlighted by CD163 (×20). C, Cases of reticulohistiocytoma are characterized by a relatively uniform population of large histiocytes with "ground-glass" cytoplasm (H&E, ×20). D, The lesional cells are again strongly highlighted by CD163 (×20). E, Epithelioid cell histiocytoma contains enlarged epithelioid histiocytes with eosinophilic cytoplasm (H&E, ×20). F, In some of the cases, only spindled small histiocytes are highlighted by CD163 (×20).
tissues using tissue microarrays and found that CD163 was largely limited to lesions of monocyte-macrophage differentiation. Based on our initial studies with CD163 and fibrous histiocytomas, we wanted to study the expression pattern of CD163 in skin histiocytic neoplasms. Similar to the results of Nguyen et al., we found that all of our cases of xanthogranuloma (adult and juvenile) and reticulohistiocytoma stained positively with CD163. These findings are similar to those of the recent study by Miettinen and Fetsch, who studied 44 lesions composed of epithelioid histiocytes, previously termed reticulohistiocytoma, for which they proposed the name “solitary epithelioid histiocytoma.” In this study, Miettinen and Fetsch found that CD163 strongly highlighted all cases of this entity.

Because reticulohistiocytomas and xanthogranulomas without significant numbers of Touton-type giant cells can mimic melanocytic lesions such as Spitz nevi, we included Spitz nevi in our study. These were all negative for CD163. This can be an important differential diagnostic consideration because JXGs and Spitz nevi usually occur in young children, and JXGs, in particular, can have dermal mitotic figures, which can be a disconcerting finding. Moreover, S-100 and CD68 can both highlight melanocytic lesions and can lead to the underdiagnosis of subtle lesions of JXG that do not have characteristic morphologic findings. S-100, in particular, can highlight interdigitating cells admixed with the inflammatory infiltrate accompanying lesions of JXG. This finding can be mistakenly interpreted as positive staining of a melanocytic lesion. In this particular context, CD163 can be very helpful because melanocytic lesions are uniformly negative with this marker.

It is important to note that CD163 cannot distinguish between xanthogranulomas and reticulohistiocytomas, and the distinction may eventually lie in a careful examination of the morphologic features of the lesion and correlation with clinical findings. Cells with ground-glass cytoplasm are

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A, Cases of Langerhans cell histiocytosis contain numerous atypical Langerhans cells with reniform nuclei and eosinophilic cytoplasm (H&E, ×40). B and C, In most cases, the lesional cells are strongly highlighted by CD1a (B, ×40) but not by CD163 (C, ×40).
unusual in xanthogranulomas, and foam cells and Touton-type giant cells are unusual in reticulohistiocytomas. It is interesting that only a small group of Langerhans cell histiocytosis stained with CD163. This further defines the scope of staining of histiocytic lesions by CD163 and is perhaps not surprising, given that the groups of Langerhans cell histiocytoses and non–Langerhans cell histiocytoses are thought to be distinct by immunohistochemical studies. The staining pattern with CD163 in epithelioid cell histiocytomas is similar to that seen in cellular fibrous histiocytomas as described previously, supporting further the idea that epithelioid cell histiocytomas are a variant of fibrous histiocytomas.

A recent study by Pouryazdanparast et al also examined the breadth of staining with CD163 in histiocytic neoplasms and had similar results to those reported in this article. An important distinction, however, is that the authors of the previous report had reported staining of CD163 in AFX. Although a group from Stanford initially reported expression of CD163 in 1 (33%) of 3 cases of AFX, in our anecdotal experience, AFX was largely negative for this marker. To test this in a larger cohort, we stained 16 cases of AFX with CD163 and with CD10 and CD99, which are established but relatively nonspecific markers for AFX (Image 3). Although CD10 highlighted the large pleomorphic cells of AFX, CD163 failed to highlight this population in all cases of AFX that we tested.

There may be several reasons for the discrepancies between the initial Stanford findings, the findings of Pouryazdanparast et al, and the findings in the present study. First, there are histiocyte-rich AFXs in which CD163 expression can be overinterpreted. Second, it is possible that in the prior Stanford study, a histiocyte-rich variant of atypical fibrous histiocytoma was mistaken for an AFX because these 2 lesions can have significant histologic overlap. Although it is possible that rarely, the lesional cells of AFX may express CD163, in our hands, this appears to be an extremely uncommon event. In our opinion, therefore, this makes histiocytic...
derivation for these tumors less likely, and caution should be used in the interpretation of this marker in lesions of AFX. Future studies addressing the origins of AFX may shed more light on this conundrum.

It is interesting that we also found that CD99 did not highlight the lesional cells of AFX, although we were able to document a positive external control in all cases. This result is different from the findings of Hartel et al.\(^{10}\) who found that CD99 was expressed in all 17 cases of AFX, in contrast with cases of malignant fibrous histiocytoma, in which they found that only 9 (35%) of 26 cases were positive for this marker. The discrepancy could be because we used the 12E7 clone (DAKO, Carpinteria, CA) and Hartel et al.\(^{10}\) used the O13 clone (Cell Marque, Hot Springs, AR). The remainder of our methods seem comparable. Monteagudo et al.\(^{10}\) reported similar findings; they found that 19 (73%) of 26 cases of AFX expressed CD99 when the O13 clone (Signet, Dedham, MA) was used.

CD163 is a useful stain for distinguishing cutaneous neoplasms derived from histiocytes from their morphologic mimics. This finding can be useful in cases of foam cell–poor and Touton-type giant cell–poor xanthogranulomas, which can morphologically mimic intradermal Spitz nevi and/or Spitzoid melanomas. In addition, lack of staining with CD163 in a majority of cases of Langerhans cell histiocytosis suggests that Langerhans cells are phenotypically distinct from lesions derived from tissue macrophages, such as xanthogranulomas. Finally, we found that lesions of AFX did not stain with CD163, which argues against derivation from tissue macrophages for this tumor.

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