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The Spindle-Shaped Cells in Cutaneous Kaposi's Sarcoma

Histologic Simulators Include Factor XIIIa Dermal Dendrocytes

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Kaposi's sarcoma is a neoplasm that develops as multifocal lesions, often involving the skin, characterized by a complex histologic picture including numerous vascular spaces, perivascular and interstitial spindle-shaped cells, and extravasated erythrocytes, lymphocytes, and plasma cells. Using an antibody against factor XIIIa, which identifies dermal dendrocytes, numerous factor XIIIa-positive dermal dendrocytes were detected among the spindle-shaped cells in 12 acquired immune deficiency syndrome (AIDS)-associated, and five non-AIDS-associated Kaposi's sarcoma lesions. The factor XIIIa-positive dermal dendrocytes were also increased in histologic simulators of Kaposi's sarcoma such as dermatofibroma, angiomatoid malignant fibrous histiocytoma, granuloma annulare, and early wound healing, but were absent in keloids. The increased number of dermal dendrocytes, which are often in an angiocentric configuration and which also express CD4, lymphocyte function associated antigen-1 (LFA-1), and Leu M3 in Kaposi's sarcoma, may be important to the angioproliferative response. The results suggested that the spindle-shaped cells that are present in a variety of cutaneous lesions are dermal dendrocytes and belong to the reticuloendothelial system, unlike other mesenchymal cell types such as the endothelial cell. Apparently a diverse array of stimuli, including human immunodeficiency virus type-1 (HIV-1) infection and trauma, can stimulate the accumulation of factor XIIIa expressing dermal dendrocytes in the skin. These cells can then participate in different stages of a variety of cutaneous alterations including Kaposi's sarcoma, dermatofibroma, granuloma annulare, and early wound healing. Thus, the factor XIIIa-positive dermal dendrocyte is a common cellular denominator among diverse clinical entities that share some histologic features. (Am J Pathol 1989, 135:793–800)

In our preliminary report of AIDS-associated cutaneous Kaposi's sarcoma (KS), we made the novel observation that many of the spindle-shaped cells associated with the proliferating vessels were factor XIIIa-expressing dermal dendrocytes.[1] In this report, we extend these findings by providing a more complete description of the factor XIIIa-positive dermal dendrocytes in AIDS-associated KS lesions, and non-AIDS-associated or "classical" KS lesions, as well as a description of the pattern of factor XIIIa-expressing dermal dendrocytes in various histologic simulators of KS.[2]

Although KS was first described in 1872, the precise cell of origin has not been identified to date.[3] The histologic features of KS, whether present in its classical form as a relatively indolent disease of elderly individuals, as originally recognized by Kaposi, or as rapidly progressive tumors in young adults infected by the human immunodeficiency virus type-1 (HIV-1),[4] are similiar.[5] The light microscopic features of KS include a highly vascularized lesion with a proliferation of spindle-shaped cells infiltrating between collagen bundles, often accompanied by extravasated erythrocytes, and a variable number of inflammatory cells, including lymphocytes and plasma cells. The histogenetic identity of the spindle-shaped cells in KS has been widely debated during the past century,[6,7] and has recently focused primarily on the endothelial cell (reviewed in reference 8), with some investigators favoring a lymphatic[9,10] rather than a vascular origin.[11] Other suggestions for the cell of origin of the spindle-shaped cells

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include fibroblasts, pericytes, Schwann cells, smooth muscle cells, and reticuloendothelial cells.[12-15] However, with the recent ability to maintain the spindle-shaped cells of KS *in vitro* in long-term culture by using conditioned medium from HTLV-II-transformed T cells, two new observations have been made that cast doubt on the possible endothelial cell origin of these spindle cells.[16,17] First, cultured spindle-shaped cells were found to lack the Weibel-Palade bodies characteristic of endothelial cells, and also factor VIII-related antigen and several enzymes that are also present in cultured endothelial cells.[16,17] Second, it was reported that the cultured Kaposi's sarcoma cells had features that included a dendritic, as well as a spindle-shaped, cellular morphology.

Because the cell of origin of these spindle-shaped cells was still unresolved, we asked whether or not they could be related to the dermal dendrocyte,[1] a recently recognized normal constituent of the skin first described by Headington.[18] The dermal dendrocyte is a member of the mononuclear phagocytic system and shares with other monocytes/macrophages the expression of the factor XIIIa antigen.[19,20] Also, both the dermal dendrocyte and cultured KS spindle-shaped cells have the same enzymatic and ultrastructural features.[17,18] The factor XIIIa molecule catalyzes the formation of a peptide bond between gamma carboxamide groups of glutamine and the amino group of lysine on fibrin.[21] It was recently observed that a benign cutaneous lesion known as the dermatofibroma or fibrous histiocytoma, which includes amongst its histologic features proliferating small vessels, spindle-shaped cells, mononuclear cells, and fibrosis, and which may be difficult to distinguish from early lesions of KS,[2,22] is composed of dermal dendrocytes.[23] We also examined the malignant counterpart of the dermatofibroma, ie, an angiomatoid malignant fibrous histiocytoma (MFH) lesion. Granuloma annulare (GA) may be difficult to distinguish from KS lesions,[2] and can occur in HIV-1 infected patients.[24] Furthermore, because Headington initially predicted an increased number of dermal dendrocytes in GA, we examined the number of factor XIIIa cells in both AIDS-associated as well as non-AIDS-associated GA.

We concluded that the spindle-shaped cells in KS lesions and various histologic simulators such as dermatofibroma, GA, and early wound healing, in either the presence or absence of HIV-1 infection, are factor XIIIa dermal dendrocytes.

Materials and Methods

Patients

The AIDS-associated cutaneous KS lesions were obtained from 11 consecutive young homosexual males who tested HIV-1 positive and presented with typical patch/plaque stage skin lesions. In two patients, two different lesions were biopsied as previously described.[1] The non-AIDS-associated classical cutaneous KS patients included five elderly (four men and one woman) individuals (aged 56, 79, 79, 80 and 87) with lower extremity plaque stage lesions that had been present for, respectively, 2, 4, 15, 19 and 20 years. We previously described one of these patients.[25] The dermatofibromas (N = 5) were all present as solitary lesions in otherwise healthy individuals, although HIV-1 serologic studies were not performed. The GA lesions were obtained from five patients who were otherwise healthy, and one patient who was HIV-1 positive. Patients with keloids of the ears (N = 5) and local wide excisions of recently diagnosed (ie, within 1 to 3 weeks) melanomas with previous biopsy sites, but no evidence of residual melanoma were also studied (N = 5). The angiomatoid MFH patient was a 21-year-old woman who presented with a hemorrhagic subcutaneous "cystic" mass in the right shoulder area.

Immunoperoxidase Staining

Paraffin Sections

Skin biopsies were fixed in formalin and routinely processed and 5 μm-thick sections were cut, dewaxed in xylene, and rehydrated. The sections to be stained for factor XIIIa were then incubated with trypsin in phosphate-buffered saline at 37 C for 30 minutes, and endogenous peroxidase blocked with 1% H_2O_2 in methanol for 20 minutes. An avidin-biotin-peroxidase technique (Vectastain ABC Kit, Vector Laboratories, Inc., Burlingame, CA) using the polyclonal antibody to factor XIIIa (Calbiochem Corp., La Jolla, CA, diluted 1:400) or S-100 (Dakopatts, Santa Barbara, CA; diluted 1:250) was used, with 3-amino-9-ethylcarbazole as the chromogen, and counterstained with 1% hematoxylin. Antibody to the extracellular form of Factor XIII, termed XIIIs (Calbiochem), served as a negative control.

Frozen Sections

In two cases of Kaposi's sarcoma, six-mm punch biopsies of skin were taken, embedded in gum tragacanth (Sigma Chemical Co., St. Louis, MO) mounted on cork, and frozen in isopentane chilled in liquid nitrogen and stored at −70 C until use. Cryostat sections of 5-μm thickness were cut, fixed in chilled acetone, and stained as described above employing monoclonal antibodies to CD1, CD3, CD8, and Leu M3 (anti-Leu 6, Leu 4, and Leu 2a, respectively; Becton Dickinson, Burlingame, CA), monoclonal antibody to CD4 (T4, Coulter Corp., Hialeah,

FL), monoclonal antibody to lymphocyte function associated antigen-1, LFA-1 (TS1.18, Carol Clayberger, Stanford University, CA), and intercellular adhesion molecule-1, ICAM-1 (RR1/1, Tim Springer; Dana Farber Cancer Institute, Boston, MA) as previously described.[26]

Results

In both the AIDS-associated, as well as in the classical, KS lesions, there were increased collections of factor XIIIa-positive cells among the stromal spindle-shaped population. The factor XIIIa-positive cells included collections of spindle-shaped cells, as well as individual dendritic-shaped cells interspersed among the collagen bundles. In general, there was a greater proportion of the spindle-shaped cells that were factor XIIIa positive in the five cases of classical KS lesions than in the 12 cases of AIDS-associated KS lesions. In all five of the classical KS lesions, the factor XIIIa-positive cells represented approximately 30% of the spindle-shaped cells within the lesions (Figures 1 and 2). The factor XIIIa staining pattern in all of the KS lesions was also noted to be heterogeneous, with some spindle-shaped cells strongly positive and other adjacent spindle-shaped cells with identical cytologic features being negative as previously reported.[1] There were no factor XIIIa-positive endothelial cells, but many factor XIIIa-positive spindle-shaped cells maintained an angiocentric configuration. Furthermore, occasional interstitial factor XIIIa-positive spindle-shaped cells were also in close proximity to the ill-defined vascular slit-like spaces that were characteristic of KS lesions (Figure 2). The factor XIIIa-positive cells possessed oval-to-elongate nuclei containing a fine chromatin pattern with a small solitary nucleolus and a somewhat irregular, undulating, nuclear membrane (Figure 2, inset).

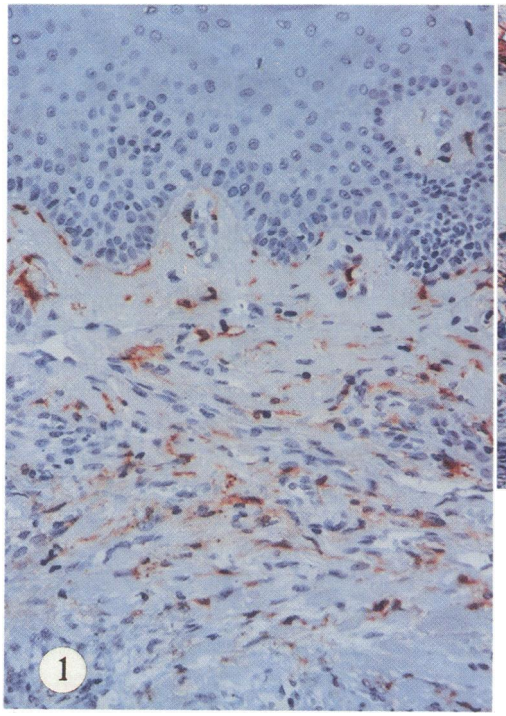
To exclude a Schwann cell, Langerhans cell, or fibroblast origin for the spindle-shaped cells, S-100, CD1, and LFA-1 stainings were performed, respectively. The anti-S-100 staining pattern included identification of Langerhans cells in the epidermis, dermal nerve twigs, and rare dermal mononuclear cells as previously reported,[25] but not the spindle-shaped cells in the dermis (Figure 3a, b). The anti-CD1 stain for Langerhans cells[27] also revealed scattered intra-epidermal-positive cells, but only occasional dermal mononuclear cells and no spindle-shaped cells (data not shown). It should be noted that there were fewer intraepidermal Langerhans cells as detected by both anti-S-100 and anti-CD-1 antibodies in the AIDS-associated KS lesions compared with the classical KS lesions (Figure 3a, b).[28] The anti LFA-1 antibody was selected because it reacts with all leukocytes, but not with fibroblasts,[29] and was observed to react with all of the mononuclear cells as well as with more than 80% of the dermal dendrocytes[30] and spindle-shaped cells (data shown previously[1]). The normal fibroblasts in the sections were easy to distinguish from the dermal dendrocytes because they did not react with the LFA-1 antibody and had much longer, narrower nuclei with smooth rather than irregular nuclear membranes compared with the dermal dendrocytes. Although there was a relative paucity of CD4-positive mononuclear cells compared with CD8-positive mononuclear cells in the inflammatory infiltrates, there were CD4-positive spindle-shaped and dendritic cells within the factor XIIIa-expressing population in the dermis (Figure 4). The factor XIIIa-positive spindle shape cells also expressed Leu M3 (Figure 4, inset) confirming a monocyte/macrophage lineage.[30] The endothelial cells strongly expressed ICAM-I, but there was no significant expression by mononuclear cells, and focally the dermal dendrocytes also expressed ICAM-1 (data not shown).

As is the case with normal skin, when the factor XIIIa-positive dermal dendrocytes are closely oriented around blood vessels, many of the factor XIIIa-positive spindle-shaped cells in all of the KS lesions maintained an angiocentric configuration. However, the factor XIIIa-positive cells only included the perivascular spindle-shaped cells and not the endothelial cells that line the vascular spaces (Figures 1 and 2). Occasional factor XIIIa-positive spindle cells also contained phagocytic hemosiderin deposits. The phagocytic ability of the factor XIIIa-positive spindle-shaped cells was similar to that previously recognized as characteristic of dermal dendrocytes to the extent that it engulfed hemosiderin and melanin.[18]

Figure 5 reveals a representative view of a dermatofibroma demonstrating innumerable factor XIIIa-positive dermal dendrocytes arranged in a storiform pattern. As previously noted,[23] the spindle-shaped stromal cells at the periphery of the lesion stained more strongly than the central, more fibrotic areas.

Figure 6a reveals numerous, strongly factor XIIIa-positive spindle cells in the angiomatoid MFH. The factor XIIIa-positive cells had relatively narrow nuclei with indulating nuclear membranes, evenly dispersed heterochromatin compared to the factor XIIIa-negative cells, which had larger, plump nuclei with the vesicular chromatin and nucleoli (Figure 6b). It should be noted, however, that throughout this large tumor, both factor XIIIa-positive and -negative populations were intimately associated, suggesting important, biologically relevant interactions between these spindle cells. This heterogeneous staining pattern of the spindle cells from the angiomatoid MFH is similar to that seen with dermatofibroma and other variants of MFH.[31,32]

Figure 7 reveals the presence of factor XIIIa-positive dermal dendrocytes within the interstitial portion of a GA lesion from a non-AIDS patient. In general, the more advanced GA lesions with large central necrobiotic zones



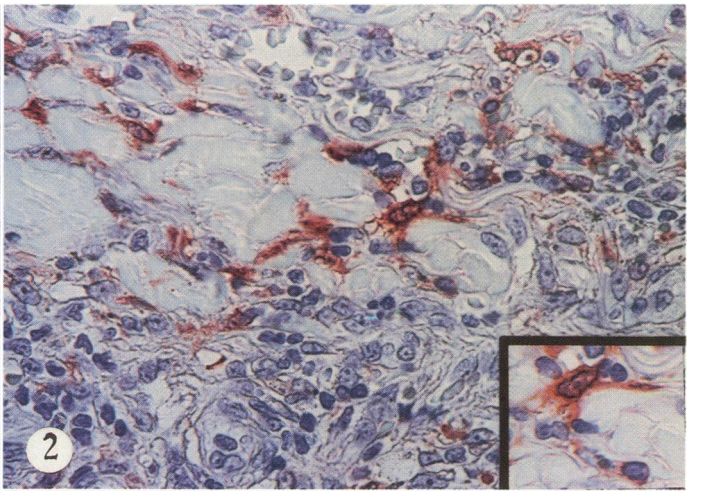
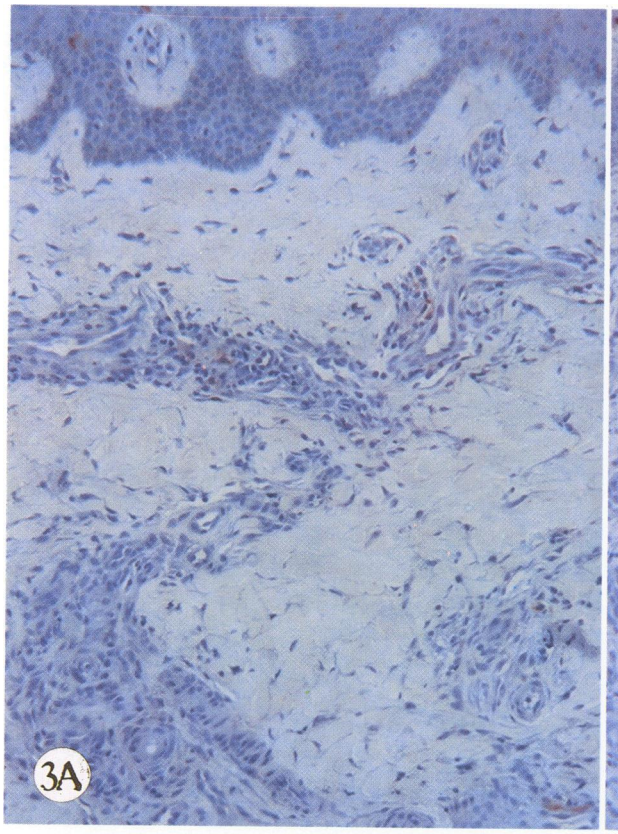


Figure 1. *Classical KS with collections of factor XIIIa-positive red stained spindle-shaped cells in the dermis (but not endothelial cells) embedded in a collagenous stroma interspersed with vascular spaces and interstitial lymphocytes. The lesion was removed from the lower extremity and has solar elastosis (original magnification ×100).* **Figure 2.** *Classical KS demonstrating that only perivascular spindle-shaped cells dissecting between collagen bundles are factor XIIIa positive. Note that this site of prominent factor XIIIa-expression is accompanied by a relatively dense lymphocytic infiltrate (original magnification ×250).* **Inset:** *A factor XIIIa-positive dermal dendrocyte with multiple cytoplasmic processes and an oval nucleus with undulating nuclear membrane and small, solitary central nucleolus (original magnification ×300).*



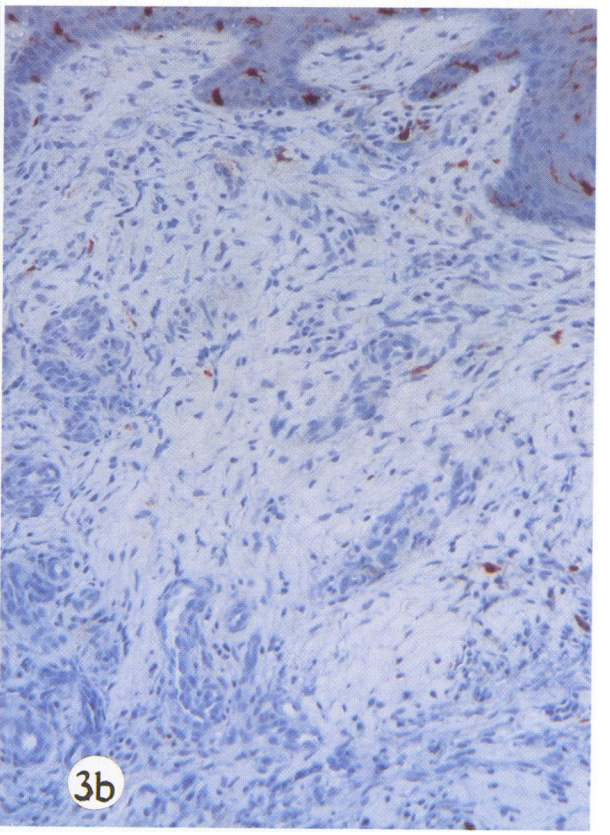
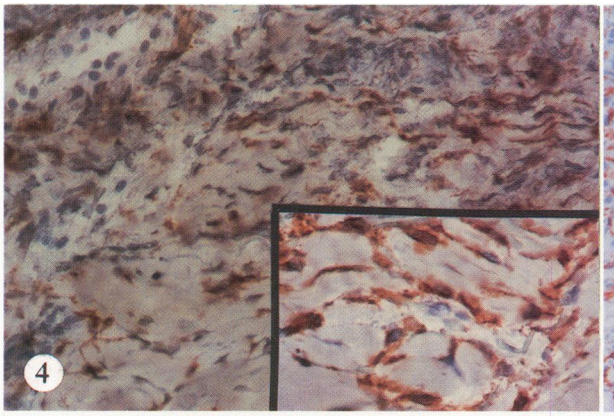
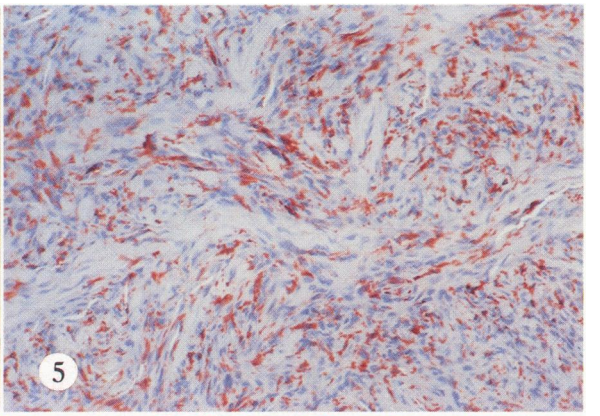
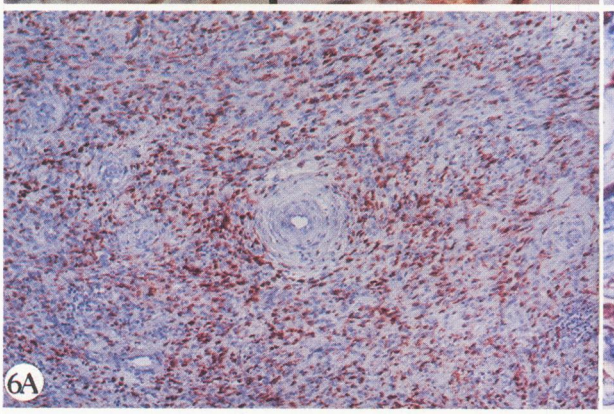
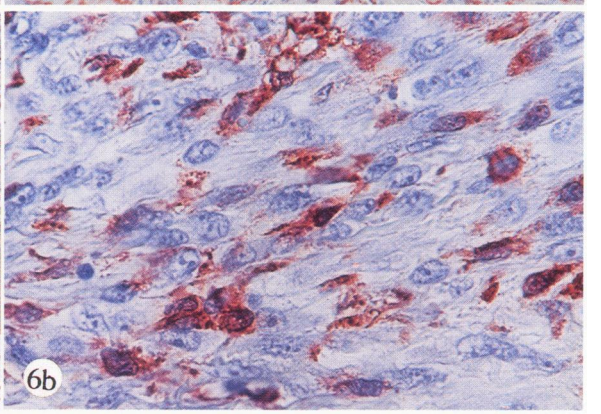


Figure 3. *The S-100 reactive intraepidermal LC are markedly diminished in the AIDS-associated KS* **(a)** *compared with the non-AIDS-associated KS* **(b)**. *However, neither lesion has any S-100-positive spindle-shaped cells in the dermis (original magnification ×75).*









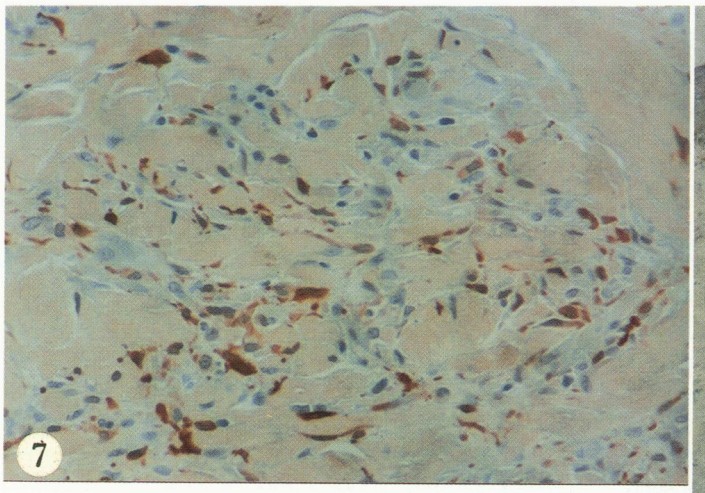


Figure 4. *HIV-1-associated KS demonstrating numerous CD4-positive spindle-shaped cells in which the cells appear to be aligned horizontally in the perivascular stroma (original magnification ×200).* Inset: *A collection of spindle-shaped cells that are Leu M3 positive (original magnification ×250).* Figure 5. *A non-AIDS-associated dermatofibroma with innumerable factor XIIIa-positive dermal dendrocytes arranged in a storiform pattern (original magnification ×150).* Figure 6. a: *Angiomatoid MFH with numerous factor XIIIa-positive, red stained spindle-shaped cells with a dense mononuclear cell inflammatory infiltrate. Note that the spindle-shaped cells are arranged in a storiform pattern around the proliferating blood vessels (original magnification ×100).* b: *Angiomatoid MFH demonstrating heterogeneity in factor XIIIa expression among the spindle-shaped cells (original magnification ×250).* Figure 7. *A non-AIDS-associated GA lesion demonstrating focal necrobiotic collagen, surrounded and infiltrated by factor XIIIa-positive dermal dendrocytes (original magnification ×150).* Figure 8. *A keloid with broad bands of collagen, dilated vessels, and no factor XIIIa-positive cells (original magnification ×30).*

were nearly devoid of factor XIIIa-positive cells, but the factor XIIIa-positive cells tended to surround and infiltrate the adjacent dermis. In fact, the more closely the light microscopic appearance of the GA lesion resembled KS, the greater the relative frequency of factor XIIIA-positive dermal dendrocytes within the stroma. Similar findings, including increased numbers of factor XIIIa-positive spindle-shaped cells, were observed in the AIDS-associated GA lesion.

Figure 8 reveals the absence of factor XIIIa-positive cells in a keloid. None of the keloids examined had significantly increased numbers of stromal cells positive for factor XIIIa. In contrast, during early wound healing when there was a granulation-like reaction occurring, including a significant lymphocytic infiltrate, there were numerous factor XIIIa-positive spindle-shaped cells in the stroma (data not shown). However, as the lesion became more fibrotic with less lymphocytic inflammation, the number of factor XIIIa-positive dermal dendrocytes diminished, which is similar to the variable numbers of dermal dendrocytes seen in different zones of dermatofibromas.[23] There was no significant expression of factor XIIIs amongst the spindle-shaped cell populations in any of the aforementioned lesions.

Discussion

Based on these results, we propose that the factor XIIIa-expressing dermal dendrocyte may be the cell of origin of the spindle-shaped cell that has been cultured from lesions of AIDS-associated KS, and represents a significant proportion of the stromal spindle-cell population in KS lesions.[1,4,5] However, in addition to our novel observation that factor XIIIa dermal dendrocytes are important constituents of the spindle-shaped cell population in AIDS-associated KS,[1] we also found that this increased number of dermal dendrocytes is not strictly limited to HIV-1 infection, because the five elderly patients with "classical" KS also had significant numbers of factor XIIIa dermal dendrocytes among the spindle-shaped cell populations. Furthermore, in various histologic simulators of KS, including AIDS-associated and non-AIDS-associated lesions such as dermatofibromas, GA, and early wound healing, there were increased factor XIIIa-positive spindle-shaped cells in the stroma. Thus, we propose that the common cellular denominator for apparently diverse clinical conditions, which share various histologic features, is the dermal dendrocyte. Depending on the type of antigenic stimulus, and perhaps on the genetically determined immunologic responsiveness of the individual, activation and local accumulation of dermal dendrocytes can give rise to locally expansile lesions such as KS or dermatofibroma and can also participate in early wound healing, GA, and psoriasis.[1] The increased number of factor XIIIa-positive dermal dendrocytes in the skin is relatively specific, as certain cutaneous disease states such as keloids and other fibrocellular processes including dermatofibrosarcoma protuberans lack these cells.[23]

The cause of the variation in the extent of factor XIIIa expression by the spindle-shaped cells in KS lesions or its simulators is not known. It appears that factor XIIIa expression is only transient rather than constitutive, and that there is greater factor XIIIa expression when there are more lymphocytes in the surrounding infiltrate, a possible result of local modulation through the T cell's IFN-γ production, with induction of factor XIIIa.[33] Thus, the most predominant expression of factor XIIIa occurred in the angiomatoid MFH patient who was not immunocompromised and who had a dense inflammatory cell infiltrate, followed by the elderly patients with KS, and lastly by the HIV-1 patients with only minimal host inflammatory response and the least amount of factor XIIIa reactivity among the spindle-shaped cells. The possible local deficiency of IFN-γ in the HIV-1-associated KS lesions was supported by the relative absence of ICAM-1 expression by factor XIIIa-positive dermal dendrocytes, as well as by the absence of keratinocyte ICAM-1 expression. Recently, we observed that IFN-γ increased ICAM-1 expression on keratinocytes,[26] as well as on factor XIIIa-expressing dermal dendrocytes, in short-term organ culture of normal skin.[30] Because ICAM-1 has about 20% sequence homology with retroviral envelope proteins,[34] it is possible that in the HIV-1-infected patients, the cells that are infected by virus may contain virally coded proteins that can homotypically interact with ICAM-1. That the factor XIIIa dermal dendrocytes may be targets for the HIV-1 infection is supported by their ability to express CD4, as well as by their phagocytic capability.[35,36] The expression of LFA-1 by the dermal dendrocytes in AIDS-associated KS lesions[1] may be of potential pathophysiologic importance, because these skin lesions could be important clinical sites of syncytium formation between the dermal dendrocyte and CD4-positive T lymphocytes that contribute to T cell depletion in HIV-1-infected individuals.[37]

Our working hypothesis to explain these current immunohistologic findings is that, immediately after a variety of stimuli, a distinct subpopulation of bone-marrow-derived circulating monocytes enter the skin, and as they infiltrate and accumulate within the collagenous stroma of the dermis, they elongate forming spindle-shaped cells with dendritic cytoplasmic processes. As the inflamed and edematous stroma is replaced by increasing amounts of either normal-appearing or necrobiotic collagen with disappearance of lymphocytes, the number of factor XIIIa-expressing dermal dendrocytes diminishes. Our recent observation concerning the number of factor XIIIa-positive spindle-shaped cells in early, inflammatory *versus* chronic, fibrotic rheumatoid synovium is consistent with this hypothesis (Nickoloff and Griffiths, manuscript in preparation). Because others have noted the close association of den-

dritic cells, which express factor XIIIa and Leu M3, with collagen-rich anatomic zones of other organs, including the capsular connective tissue of the lymph node[20,38] and the portal area of the liver,[39] we propose, by combining our current results with these other investigators, to rename this cell the "collagen associated dendrophage" or CAD cell. The last portion of this name expresses the distinctive dendritic processes and the observable phagocytic capacity of these cells. Although conventional division of nonlymphoid mononuclear cells into dendritic cells as opposed to macrophages has been conceptually useful up until now,[40] the currently described cell population apparently bridges these distinctive groups and makes this classification schema less clear. Obviously, a greater appreciation of the specific immunologic function of this cell type will be required to provide greater insight into its ontogeny and role in both normal and disease processes in multiple organ systems. If it can be demonstrated that the LFA-1, CD4, ICAM-1, Factor XIIIa-positive dermal dendrocyte is activated by any molecular component of the HIV-1 genome, than this could explain why certain skin diseases that contain increased numbers of dermal dendrocytes such as psoriasis, KS, and GA are found to be specifically associated with, or exacerbated in, AIDS patients.[41] Finally, other non-HIV-1 viruses may be playing a etiologic role in this group of cutaneous lesions because dermatofibromas, which contain the largest relative percentage of dermal dendrocytes, have been previously linked to immunosuppression and DNA-type viral infection.[42] Whether or not there are different types of viruses responsible for producing KS, psoriasis, granuloma annulare, and/or dermatofibromas, all of which could activate dermal dendrocytes in either AIDS patients or otherwise healthy individuals, remains an important issue for future investigation.

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