Myofibroblast Transformation in Metastatic Extramedullary Chronic Myeloid Leukemia: A Case Report

ABSTRACT

Primary and metastatic carcinomas have a reactive stroma characterized by many myofibroblasts. These cells have also been documented in nonepithelial malignancies, such as sarcomas, malignant melanoma, and lymphoid tumors but in generally far fewer numbers. In non-Hodgkin’s lymphoma, Hodgkin’s disease, and leukemia, myofibroblasts are rather rarely documented. In particular, there appear to be no reports of myofibroblasts in either primary bone marrow/peripheral blood leukemia or secondary deposits of leukemia. In this paper, a case of a relapsed chronic myeloid leukemia appearing in an inguinal lymph node is described, containing many myofibroblasts. The case is detailed and presented with a discussion on the role of myofibroblasts in the progression of nonepithelial cancers.

Keywords: chronic myeloid leukemia, electron microscopy, extramedullary, myofibroblast

Both primary and metastatic carcinomas have a reactive stroma containing large numbers of myofibroblasts [1–3] (see these publications for the early literature), and this stroma may constitute as much as a half of the bulk of the tumor mass [4]. Myofibroblasts have also been documented in nonepithelial malignancies, such as sarcomas [5], malignant melanoma [6], and lymphoid tumors [7] but, perhaps significantly, in far fewer numbers than in carcinomas. This finding suggests some fundamental differences in the mode of development or progression for sarcomas, malignant melanoma, and lymphoma, on the one hand, compared with carcinoma, on the other [8]. Specifically with regard to hemolymphoid neoplasms (non-Hodgkin’s lymphoma, Hodgkin’s disease, and leukemia), myofibroblasts are rather rarely documented. They have been observed in
nodular sclerosing Hodgkin’s disease [7] and are present in certain and rare non-Hodgkin’s lymphomas showing sclerosis (Eyden, unpublished observations). There are no reports, as far as we can ascertain, on the presence of myofibroblasts in either primary bone-marrow/ peripheral blood leukemia or secondary deposits of leukemia. In this paper, we describe a case of a relapsed chronic myeloid leukemia (CML) appearing in a lymph node of a middle-aged woman, which contained many myofibroblasts. The case is described and presented with a discussion on the role of myofibroblasts in the progression of nonepithelial cancers.

**MATERIALS AND METHODS**

Tissue from the left inguinal lymph node (see Clinical and Laboratory Findings, below) was fixed in histological formalin for normal histology and immunohistochemistry, while a piece of the fresh tumor tissue was fixed in phosphate-buffered 2.5% glutaraldehyde, then osmium tetroxide, before it was dehydrated in ethanol and embedded in epoxy resin. Ultrathin sections were stained in uranyl acetate and lead citrate and examined in a JEOL JEM-1220 electron microscope.

**CLINICAL AND LABORATORY FINDINGS**

A 48-year-old woman was diagnosed with chronic-phase chronic myeloid leukemia (CML), she was treated with IFN-α and imatinib, which resulted in complete hematological remission. Three and a half years later, she presented with systemic lymphadenopathy. Biopsy of a left inguinal lymph node revealed an infiltration of myeloblasts (Figure 1a) positive for myeloperoxidase (Figure 1b), CD34, CD33, and lysozyme, and negative for CD3 and TdT. CD20 was positive between the residual lymphocyte aggregates (Figure 1c). Spindle cells positive for α-smooth-muscle actin (SMA) were distributed between myeloblasts, and increased numbers of SMA-positive cells were located in the vicinity of capillaries (Figure 1d). Transmission electron microscopy demonstrated that the spindle cells contained abundant rough endoplasmic reticulum (rER), peripheral smooth-muscle myofilaments with focal densities (Figure 2), and modestly developed fibronectin fibrils/fibronexus junctions at cell surfaces (Figure 3) — the full complement of typical ultrastructural features of the myofibroblast [2].

**DISCUSSION**

The essential feature of the case report detailed here is the prominent myofibroblastic reaction found within a metastatic inguinal node deposit of CML, from a primary bone-marrow-based leukemia presenting some 3.5 years earlier. This is a rare documentation of reactive and ultrastructurally confirmed myofibroblasts in a metastatic leukemic deposit. These observations prompted an analysis of our archival cases, and here a case of granulocytic sarcoma of the uterine cervix was identified associated with acute myeloid leukemia in which ultrastructurally identifiable myofibroblasts were identified (see Banik et al. [9] for further details of this case). The interest of these observations lies in the fact that epithelial cancers progress with an involvement of and indeed a requirement for the myofibroblast, whereas it appears that nonepithelial malignancies rely far less on this cell for neoplastic progression. In primary carcinomas, the growth of the tumor involves reactive myofibroblasts: these cells interact with carcinoma cells to produce molecules that degrade matrix (including basal lamina), induce migration, and stimulate angiogenesis [4], the ultimate target in the primary site allowing for the initial step in metastasis.

Clinically, CML consists of a chronic phase and an acute phase. Although the acute phase usually occurs within 2–4 years of the chronic phase and presents with a high ratio of blast cells in peripheral blood and bone marrow, about 7–17% of patients show extramedullary involvement in the acute crisis, with lymph node, bone, skin, and soft tissue mostly affected [10]. There have been no reported cases of myofibroblast involvement in extramedullary relapse of CML. Nor in primary, marrow-based leukemias are there any demonstrated myofibroblasts. Perhaps, therefore, other mesenchymal elements—interstitial cells and vessels—might be the co-operating cells that promote and permit the spread of leukemic cells. At the same time, leukemic cells can be expected to have fewer barriers to accessing the vasculature, a further reason to explain the lesser need for reactive myofibroblasts or their equivalents in primary bone-marrow disease.

In the development of metastatic disease, leukemias and, for example, carcinomas, may use some common mechanisms, and one of these would appear to involve the myofibroblast: these appear in large numbers both in carcinomatous stroma and in the nodal deposit described in this report of CML. The detailed interactions between leukemic cells and stromal constituents and cells are far less well studied than the corresponding situation for carcinoma. In general terms, the homing to specific tissue sites of malignant cells (including leukemic ones) is in part dependent on the presence on their surfaces of molecules with specificities for specific matrix molecules. In the case of hairy cell leukemia, these include integrins α4β1 and α5β1, which interact with fibronectin, vascular cell adhesion molecule, and CD44, the latter interacting with the matrix glycosaminoglycan, hyaluronan [11].
and promoting tumor cell migration. Clearly, such detailed studies need to be applied to other leukemias to develop a more comprehensive understanding of the mechanism of spread to metastatic sites.

Figure 1. Light microscopy: (a) H&E stain of inguinal node deposit, (b) myeloperoxidase, (c) CD20 staining of residual lymphocyte aggregate, and (d) SMA staining of stromal cells and vessels.
Figure 2. Spindled stromal cell showing rough endoplasmic reticulum (*) and peripheral myofilaments (arrows).

Figure 3. Fibronexus in a spindled stromal cell showing rough endoplasmic reticulum (*), intracellular myofilaments (arrows), and delicate extracellular fibronectin (arrows).
An interesting if subtle point of difference between carcinoma and leukemia, in terms of the mechanism of spread, is that in carcinoma, both carcinoma cells and precursors of myofibroblasts are circulating in the blood vascular system, since at least some of the myofibroblasts appear to be derived from bone marrow and enter the circulation as circulating fibrocytes [12, 13]. In the case of the leukemic deposits, again both malignant leukemic cells and the reactive myofibroblast precursors are circulating prior to the homing-in process, but both leukemic cells and myofibroblast precursors derive from the bone marrow. The enhanced numbers of myofibroblasts around vessels, as seen in this case, may reflect myofibroblastic exit from the vasculature, or possibly an origin of myofibroblasts from pericytes, which themselves may represent a temporary tissue population following derivation from bone-marrow-derived circulating fibrocytes [13].

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

REFERENCES