

Upper extremity pleomorphic dermal sarcoma in a patient with chronic myelomonocytic leukemia

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Abstract

Background: Pleomorphic dermal sarcoma is a potentially high-grade cutaneous spindle cell tumor that closely resembles atypical fibroxanthoma in the superficial, dermal aspects but with adverse pathological features. Chronic inflammation, as several autoimmune disorders are co-associated with chronic myelomonocytic leukemia.

Case description: We report here an 84-year-old male patient with swelling lump on the upper third of the left arm. Previously he suffered from a type I chronic myelomonocytic leukemia. Based on the initial ultrasound-guided biopsy of the lesion, the histopathological examination revealed an atypical fibroxanthoma. A wide local excision was performed and the diagnosis was revised to pleomorphic dermal sarcoma by the pathologist, based on the currently accepted criteria. Adjuvant radiotherapy was performed.

Conclusion: Differentiating between atypical fibroxanthoma and pleomorphic dermal sarcoma is pivotal. A partial sampling of the skin lesion poses a significant pitfall, as important diagnostic features cannot be assessed. Immunosuppression seems to be involved in the pathogenesis of chronic myelomonocytic leukemia and pleomorphic dermal sarcomas, because of the advanced patient age. HIPPOKRATIA 2019, 23(4): 181-185.

Keywords: Pleomorphic dermal sarcomas, atypical fibroxanthoma, chronic myelomonocytic leukemia, adjuvant radiotherapy

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Introduction

Pleomorphic dermal sarcoma (PDS) was the term proposed by Fletcher for lesions with similar histopathological and immunohistochemical features to those of atypical fibroxanthoma (AFX) but exhibiting deep subcutaneous infiltration, necrosis and/or vascular/perineural invasion¹. These tumors are rare with confusing terminology in the literature, mostly in individual case reports with limited follow-up data or in small series. Differentiating between AFX and PDS is pivotal, as tumors with histological features consistent with PDS appear to confer an increased risk for both local recurrence and metastatic disease²⁻⁴. Most commonly, PDS and AFX occur in older adults (usually the seventh or eighth decade of life) and have a predilection for men. On physical examination, they show a nonspecific clinical appearance, characterized by pink or red papules, nodules with a firm texture, or, less frequently, plaque-like growth pattern³. Ulceration and bleeding are common features, and there was a short history of rapid growth. They are located most commonly on sun-damaged skin of the head or neck, and less commonly of the trunk or extremities³. While dis-

ease pathogenesis remains unclear, immunosuppression has been proposed as an independent risk factor for aggressive PDS⁵.

Chronic myelomonocytic leukemia (CMML), a myeloid neoplasm with features of myelodysplastic/myeloproliferative, has an inherent risk for transformation to acute myeloid leukemia (AML) and may also involve the skin at the time of their blastic transformation⁶. Autoimmune or inflammatory disorders can also be present at the diagnosis and during the follow up of CMML⁷. Herein we present a rare case of a cutaneous PDS in the upper extremity in a patient with previously CMML and a review on the diagnosis and treatment of this tumor, with surgery and radiotherapy treatment.

Case presentation

An 84-year-old man presented with a two-month history of a painless and enlarging subcutaneous mass in the upper third of the left arm. Two years before, he had developed abnormalities (notably anemia) in the peripheral blood counts and underwent bone marrow biopsy for further evaluation: the myeloid series appeared left-shifted

dysplasia markedly with 3 % blasts and promyelocytic 5 %, and hyperplasia erythroid elements. Karyotype was normal. Peripheral blood showed a left shift of white series with monocytosis and dysplasia of monocytes and granulocytes. These features were compatible with a diagnosis of CMML, type 1.

On clinical examination, the overlying skin was normal, and no axillary lymphadenopathy was identified. Diagnostic workup, including ultrasound (US) and contrast-enhanced computed tomography (CT) scan (Figure 1), revealed a tumor localized subcutaneously in the upper third of the left arm with lobulated, indistinctive margins, but without infiltration of the adjacent muscles. Positron Emission Tomography/CT (PET/CT) revealed no evidence of lymph node or distant metastasis. A US-guided biopsy of the mass was performed, and the histopathological examination was compatible with a mesenchymal neoplasm of the type of AFX. Immunohistochemically, the neoplastic cells were positive for CD68 (Figure 2) and vimentin (Figure 3), whereas they were negative for CD10, CD31, CD34, smooth muscle actin, desmin, myogenin, CD117, CD5, HMB45, cytokeratins, S100 protein, common lymphocytic antigen, and epithelial membrane antigen. The differential diagnosis of PDS was considered pending confirmation/exclusion after resection of the tumor *in toto*. A wide local excision was performed. Macroscopically, the tumor was whitish, oval, measuring 1.9 cm in greatest diameter, with mildly irregular margins. Microscopic examination revealed a tumor consisting of spindle cells with nuclear atypia, set in a dense, sclerotic, richly vascularised stroma (Figure 4) and storiform pattern with irregular fascicle (Figure 5). The mitotic count was high (15/10 HPF) with frequent atypical forms, but necrosis was not evident. There was an extensive invasion of the reticular dermis, the subcutaneous fat, and focally of the papillary dermis (Figure 6), while one site at the deep surgical margin showed

proximity to malignant cells. Vascular/perineural invasion was not observed. Consequently, the definite diagnosis was compatible with PDS. A hematologic profile at this time revealed a leukocyte (WBC) count of 2.92 K/ μ l (3.5-11), left-shifted with 16.4 % monocytes (2-10), hemoglobin (HGB) 12.6 g/dL (13.5-17.5), hematocrit (HCT) of 38.3 % (40-55), mean corpuscular volume (MVC) 109 fL (76-96), and platelet (PLT) count of 85 K/ μ l (150-350). Two months after surgery, adjuvant radiotherapy (RT) was performed with a shrinking field technique; the radiation dose was 60 Gy. At follow-up, his hematologic profile included WBC: 3.27 K/ μ l with normal differential and monocytes 9.50 %, HGB: 11.5 g/dL, HCT: 34.6 %, MVC: 109.8 fL, and PLT: 130 K/ μ l. He died after a heart attack two years after surgery without any signs of tumor recurrence or metastasis.

Discussion

The relationship between AFX and PDS is unclear. Essentially, AFX and PDS remain a diagnosis of exclusion requiring extensive use of immunohistochemistry with careful interpretation of the findings⁴. AFX and PDS are considered in the differential diagnosis with spindle-cell squamous cell carcinoma (SCC), spindle-cell, malignant melanoma, leiomyosarcoma, and dermatofibrosarcoma protuberans (DFSP) because of their overlapping histopathological features⁴⁻¹⁰. The immunohistochemical expression pattern of PDS is similar to AFX, and no specific immunohistochemical or molecular markers can be utilized for the differential diagnosis⁴⁻⁹. PDS consistently expresses vimentin, CD10, and CD99 and variably stains for actins and CD68. Vimentin positivity means the tumor cells originated from mesenchymal cells. However, these markers are not helpful in the differential diagnosis, as they also stain other types of sarcomas, melanomas, and carcinomas. The most important immunomarkers for differential diagnoses are cytokeratins (to exclude sarco-

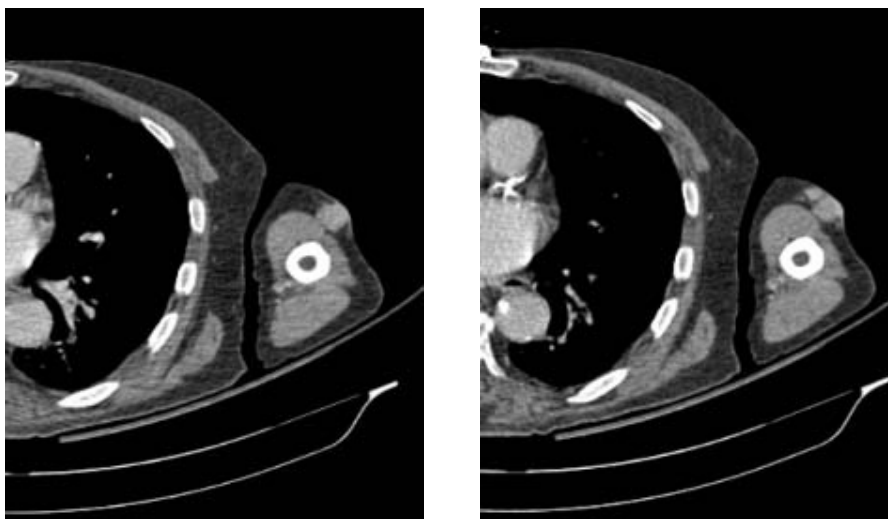


Figure 1: Axial computed tomography images of the thorax (post enhancement) at the time of diagnosis showing subcutaneous nodule in the upper third of the left arm, with lobulated indistinctive margins but without infiltration of the adjacent muscles.

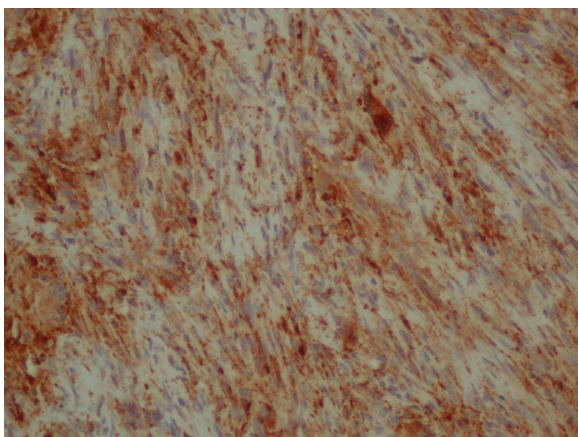


Figure 2: Immunohistochemical examination of the tumor cells, stained positive for CD68 [3,3'-Diaminobenzidine (DAB), x400].

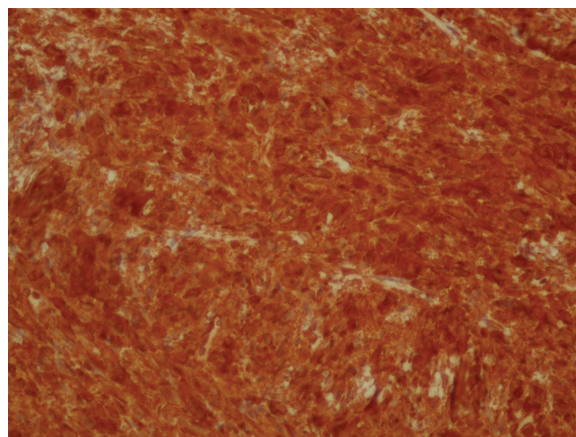


Figure 3: Immunohistochemical examination of the tumor cells, stained positive for Vimentin [3,3'-Diaminobenzidine (DAB), x400].

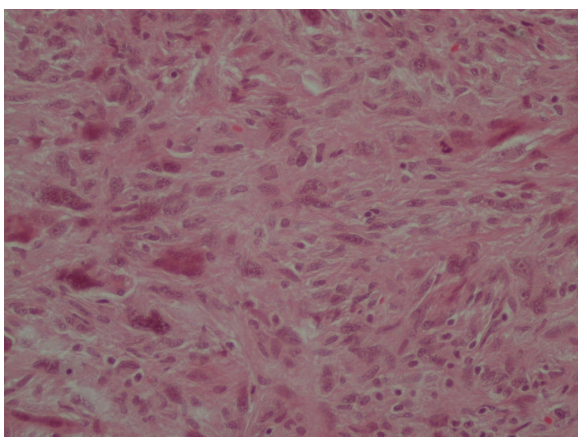


Figure 4: Higher magnification showing spindle cell to round tumor cells, highly pleomorphic and bizarre giant cells with eosinophilic cytoplasm (Hematoxylin and eosin, $\times 400$).

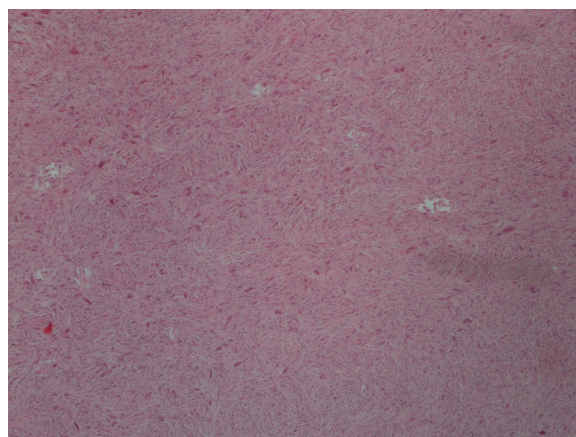


Figure 5: Diffuse infiltration by a pleomorphic dermal sarcoma in a storiform pattern with irregular fascicles (Hematoxylin and eosin, $\times 200$).

matoid or spindle cell SCC), S-100 and melanogenesis markers (to exclude melanoma), and desmin, actin, and H-caldesmon (to exclude leiomyosarcoma). Leiomyosarcoma can be excluded by SMA negativity. Angiosarcomas are excluded due to no reactivity for the usual vascular antigens, such as CD31, CD34. Liposarcoma or malignant peripheral nerve sheath tumor (S-100), rhabdomyosarcoma (desmin), malignant melanoma (S-100 and HMB-45), malignant lymphoma (LCA) are also excluded. S100, desmin, S-100, HMB-45, and LCA are the antibodies of liposarcoma, rhabdomyosarcoma, malignant melanoma, and malignant lymphoma, respectively. Negative histiocytic markers such as CD68 and lysozyme allow histiocytic sarcoma to be excluded⁸⁻¹⁰.

Some authors consider AFX a less aggressive, superficial variant of PDS, while others view AFX as a distinct malignancy⁹. Whereas AFX is limited to the dermis, PDS is characterized by infiltration into subcutaneous fat, necrosis, lymphovascular, or perineural invasion, all predic-

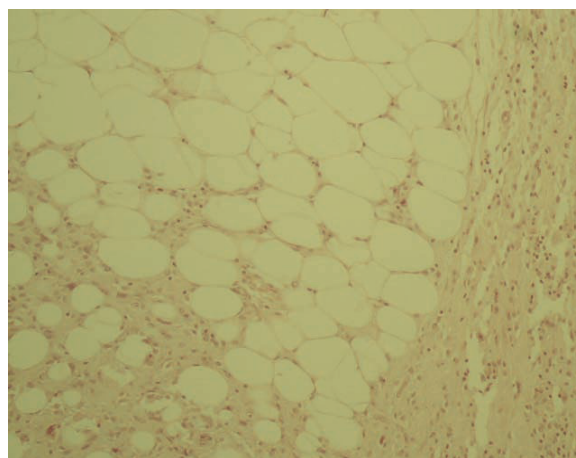


Figure 6: Pleomorphic dermal sarcoma. Neoplastic involvement of the reticular dermis and subcutaneous fat tissue. (Hematoxylin and eosin, x200).

tive of aggressive behavior including distant metastases. The tumor cells of PDS are large, ill-defined, and asymmetrical with diffusely infiltrative or pushing growth and extension into deep subcutaneous adipose tissue, skeletal muscle, fascia, or galea. They are composed of sheets of pleomorphic epithelioid and spindle cells showing abundant and occasionally vacuolated cytoplasm and containing hyperchromatic or vesicular nuclei with prominent and often multiple nucleoli. Mitoses are numerous, including atypical forms. Ulceration is common, and tumor necrosis is absent in 50 % of cases, like in our patient. Lymphovascular invasion and perineural infiltration may be additional observations. Clinically, PDS is regarded as a tumor of low-grade malignant behavior with a local recurrence risk of 28 % and a metastatic risk of 10 %^{4,9}. There is considerable debate regarding the genetic basis of AFX and PDS. To date, a wide range of copy number alterations and genetic alterations were detected in AFX and PDS, including *TP53*, *CDKN2A*, *TERT* promoter, *NOTCH1* and *NOTCH2*, and *FAT1*¹¹. *TERT* promoter mutations are frequent and represent the most common mutation described in these tumors. *CDKN2A* deletion may represent a potential biomarker if validated in future studies¹¹⁻¹². The copy number profiles identified and similar gene mutations prove strongly that AFX and PDS are related and potentially represent entities along a common tumor spectrum¹². Therefore, these findings do not fully resolve the long-standing debate as to the relationship between AFX and PDS¹². Accordingly, lesions otherwise typical of AFX characterized by larger tumor size with extensive involvement of the subcutis, musculature or fascia, tissue necrosis, or perineural or perivascular invasion, best classified as PDS, will be considered of paramount importance in determining the prognosis and the correct clinical management¹¹⁻¹². Cutaneous and subcutaneous lesions are commonly detected on imaging. CT, PET/CT scan, and magnetic resonance imaging (MRI) are valuable in accurate tumor staging and post-treatment evaluation, with MRI being quite helpful in assessing the local extent of disease¹³. Also, CT describes skin thickening, subcutaneous fat infiltration, and multifocal local spread from the primary tumor accurately. PET/CT scan is useful if seeking metastases, additional lesions, or particularly lymph node extensions¹³. Tumors with histopathological features consistent with PDS are inherently higher risk, and thus imaging may be helpful in certain cases, particularly in evaluating the extent of local infiltration before surgery. Although typically MRI is suited best for defining the anatomy of the tumor and its surrounding structures, the signal intensity characteristics of PDS are not specific, and the true histologic nature of the tumor or other soft-tissue masses often cannot be diagnosed by imaging alone, with few exceptions (e.g., lipoma)¹⁴. However, no single imaging technique can provide a specific histologic diagnosis of PDS, and consequently, biopsy is necessary¹⁵. Fine-needle aspiration biopsy (FNAB) can be utilized, but sensitivity is poor, ranging from 60 % to 80 %¹⁰. This is due to the

inability to obtain immunohistochemical stains on most samples from FNAB. Complete surgical excision at the time of presentation, even with narrow margins, appears to prevent recurrent and metastatic disease and is considered the treatment of choice. Neoplasm extending to resection margins, perineural, intravascular, or deep fascia invasion, necrosis, large size, or an immune-compromised status are considered risk factors for recurrence or metastasis. Davidson et al¹⁶ found that tumors extending beyond the dermis had 29.4 % chance of local recurrence and 11.8 % chance of metastasis. Tardio et al¹⁰ reported a rate of 20 % local recurrence, all in patients with incomplete resections. Postoperative RT is debatable and may be necessary if intralesional, or even marginal tumors are discovered on pathologic study at the time of surgical resection, as in our patient. RT may help decrease the likelihood of local recurrence and possibly metastasis¹⁷. RT is usually administered as adjuvant therapy, in a combined dosage of 60-66 Gy with conventional fractionation. The fields of radiation cover the entire surgical bed with a margin including the biopsy and surgical scars and drain site, which should receive mostly 50 Gy. A boost dose of at least 10-16 Gy is considered for the highest risk areas¹⁸. Neoadjuvant RT has comparable effects on local disease control as adjuvant therapy in tumors that are larger and deeply invasive. Traditional chemotherapy is typically employed only for widespread disease. Although chemotherapy has been largely ineffective, a recent analysis of genome-wide sequencing and the discovery of key oncogenic mutations has permitted the identification of several potential therapeutic molecular drug targets that may have future clinical utility in the treatment of AFX or PDS¹⁹. Immunosuppression may play an additional pathogenetic role in the development of AFX and PDS as reflected by the advanced age at presentation (as our patient), the high rate of associated visceral, and hematologic malignancies, and other causes of immunosuppression⁵. Some studies have shown an association between lymphoproliferative disorders and the development of PDS. In this context of a prior hematopoietic malignancy such as non-Hodgkin lymphoma or chronic lymphocytic leukemia, PDS may present in atypical ways, such as bone or skin involvement²⁰. A recent study exploiting the Surveillance Epidemiology and End Results program database registered an increased standardized incidence ratio for PDS in patients with CMML²¹. Auto-immune or inflammatory disorders can also be present at the diagnosis of CMML, predating the diagnosis, or less frequently occurring during the follow up of CMML^{5,22}. A history of infection or inflammatory condition is associated with an increased risk of CMML. In most cases, CMML arises because of the natural aging of hematopoietic stem cells. CMML can present with leukemia cutis, as an initial manifestation and has an inherent risk for transformation to AML^{6,23}. Extramedullary manifestations of CMML are uncommon and are seen in organs such as the spleen, liver, skin, and lymph nodes²⁴.

In conclusion, the reported case underlines the simi-

larities of AFX and PDS and the difficulties in their diagnosis. On partial biopsies, the final diagnosis should be deferred to complete excision. Importantly, adjuvant RT may be suggested in this type of tumor. Furthermore, different causes of immunosuppression occurring in the elderly remain of fundamental importance to account for any relation between CMML and PDS.

Conflict of interest

The authors declare no conflict of interest.

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