10.1053.paor.2000.0271 available online at http://www.idealibrary.com on IDEAL

CASE REPORT

# Pleomorphic Liposarcoma of a Young Woman Following Radiotherapy for Epithelioid Sarcoma

Zsolt OROSZ, Béla ROHONYI[1], Antal LUKSANDER[2] and János SZÁNTÓ[3]

Department of Human and Experimental Tumor Pathology, National Institute of Oncology, Budapest,
[1]Department of Pathology and [2]Department of Surgery, Erzsébet Hospital, Sopron,
[3]Department of Oncology, Medical and Health Science Center, University of Debrecen, Hungary

**A case of a metachronous epithelioid sarcoma and pleomorphic liposarcoma in a young woman is described. The first tumor was an epithelioid sarcoma (ES) with focal rhabdoid features localised in the left calf while the second lesion developed seven years later in the same region was diagnosed as pleomorphic liposarcoma resembling myxofibrosarcoma („myxoid variant of malignant fibrous histiocytoma") predominantly composed of moderately differentiated spindle cells. Multiple foci of uni- and plurivacuolated lipoblasts were seen. Following the resection of ES the patient received 57 Gy radiation to the region, therefore we regarded the second tumor as a radiation induced liposarcoma. A further interesting feature of this case is that the development of pleomorphic liposarcoma preceded by 6 months the solitary right parabronchial metastasis of ES and after 4 months of metastasectomy a third tumor developed at the site of the first lesion. This tumor showed dedifferentiation toward pleomorphic malignant fibrous histiocytoma. Our case represents a unique case of postirradiation liposarcoma developed on the base of ES.** (Pathology Oncology Research Vol 6, No 4, 287–291, 2000)

*Keywords:* epithelioid sarcoma, pleomorphic liposarcoma, postirradiation sarcoma

## *Introduction*

Postradiation sarcoma (PRS) is defined as a sarcoma developed within a previous radiation field after a latency period of at least 2 years.[12] This rare complication of radiation therapy occurs in approximately 0,1% of patients, who undergo irradiation.[14] Histologically PRS are most frequently malignant fibrous histiocytomas, less frequently osteosarcomas, fibrosarcomas, malignant peripheral nerve sheath tumors or angiosarcoma.[12] PRS-s with other morphology than the above mentioned, such as liposarcoma, are extremely rare.[5]

In the classic form, epithelioid sarcoma (ES) occurs in the distal parts of extremities of young adults as a slowly growing, often multiple soft tissue neoplasm. Metastases develop in about 40% of the patients, usually following repeated recurrences.[4,6,9] In general, recurrences and metastases have the same histological pictures as the primary tumor does. Liposarcoma is primarily a tumor of adult life with a peak incidence between 40 and 60 years. Occasionally examples do occur in younger patients and there are only sporadic reports its association with radiation therapy.[5]

We report a case of a pleomorphic liposarcoma which developed 7 years after of tumor-free period in the region of previously excised ES in a young woman. The patient received adjuvant radiotherapy to the region of resected ES with adjuvant chemotherapy. After the resection of liposarcoma, further recurrences developed and the disease-free intervals became shorter. Histologically, these recurrences showed dedifferentiation toward pleomorphic malignant fibrous histiocytoma. This case represents an example of the extremely rare postirradiation liposarcoma, with the unique metachronous mode of development on the base of an ES. We do not know of a similarcase in the literature.

*Received:* March 30, 2000; *revised:* August 8, 2000; *accepted:* Nov 4, 2000

*Correspondence*: Zsolt OROSZ MD, Department of Human and Experimental Tumor Pathology, National Institute of Oncology; H-1122 Budapest, Ráth György u. 7-9. Hungary. Tel.: 36-(1)-224-86-00/1376; Fax: 36-(1)-224-86-20, E-mail: zso@oncol.hu

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*Table 1.* **Results of immunohistochemical studies in primary, recidive and metastatic tumors**

| *Antigen specificity and source* | *1st tumor, epithelioid sarcoma* | *2nd tumor, pleomorphic liposarcoma* | *3rd tumor, metastatic epithelioid sarcoma* | *4th tumor recidive pleomorphic liposarcoma* |
|---|---|---|---|---|
| Cytokeratin (lu-5)*; Biogenex | pos. | neg. | pos. | neg. |
| EMA*; Biogenex | pos. | neg. | pos. | neg. |
| Vimentin*; Biogenex | pos. | pos. | pos. | pos. |
| α-SMA, (1A4)*; DAKO | foc. pos. | neg. | scattered pos. cells | neg. |
| Desmin*; DAKO | neg. | neg. | neg. | neg. |
| S100#; DAKO | foc. pos. | foc. pos. (in lipoblasts) | scattered pos. cells | scattered pos. lipoblasts |
| CD31*; DAKO | neg. | neg. | neg. | neg. |
| CD34*; DAKO | neg. | neg. | neg. | neg. |

*-monoclonal antibody; #-polyclonal antibody, foc.- focally positive; EMA- epithelial membrane antigen; SMA- smooth muscle actin

### *Clinical history*

In December 1989 a previously healthy 16-year-old girl with unremarkable past history was admitted with one-year history of a slowly growing painful mass in the upper lateral third of left calf. On radiological and ultrasonographic examination the mass was located beneath the cutis and infiltrated the muscle but was not attached to the fibula. The tumor was excised with tumor free margins. The initial histological examination raised the diagnosis of malignant extrarenal rhabdoid tumor or epithelioid sarcoma. Following the histological diagnosis the patient was treated by radio- and chemotherapy. She received 57 Gy irradiation to the left calf and three cycles AIVA (adriamycin, vincristin, iphosphamide, adriamycin) combination chemotherapy. The control abdominal ultrasonograms, chest roentgenograms and computer tomograms of the calf were negative. Five years after tumor excision she delivered a healthy child without complication. In July 1997 the patient noticed a second mass the size of tennis ball in the region of primary tumor. A second operation was performed. This tumor was located deeper and infiltrated the capitis of gastrocnemic muscle. The patient received further 40 Gy irradiation to the left calf. In October 1997 a staging MRI examination revealed a tumor mass adjacent the right main bronchus extending to the mediastinum; consequently a right pneumonectomy was performed. In January 1998 she presented with a new swelling in her calf. This tumor was also excised. One year later multiple lung metastases developed and the patient died. No autopsy was performed.

### *Materials and Methods*

The specimens were fixed in 10% buffered formalin and processed by standard technique to paraffin wax. Sections were stained with hematoxylin and eosin, periodic acid-Schiff without diastase, and Gömöri's reticulin stains. The same paraffin blocks were utilised to prepare sections for immunohistochemical study. A panel of mono- and polyclonal antibodies and the results of their reactions are shown in *Table 1*. For development standard avidin-biotin and peroxidase-antiperoxidase techniques were employed.

### *Pathologic findings*

#### *Gross description*

*1st tumor*. The specimen consisted a 7x4x3 cm firm, nodular greyish-white tumor with a small amount of resected skeletal muscle at periphery.

*2nd tumor*. A greyish mass measuring 5 cm in its greatest diameter with foci of glistening, yellowish areas, haemorrhage and necrosis was removed.

*3rd tumor (in the lung)*. Following thoracotomy, a lobulated yellowish-white mass measuring 3 cm in its maximum diameter was found adjacent the right main bronchus. The parenchyma and the bronchial tree seemed normal. The surgical specimen also consisted of lymph nodes of the peribronchial, vena cava superior, mediastinal and carina region and part of the mediastinal adipose tissue.

*4th tumor (in the calf)*. The specimen consisted of a 9x8x6 cm firm, fasciculated white tumor with a small amount of resected muscle.

#### *Light microscopy and immunohistochemistry*

*1st tumor*. The tumor is composed of a multinodular proliferation of polygonal epithelioid cells. The tumor nodules frequently show central necrosis *(Figure 1)* and are surrounded by hyalinized connective tissue with a rich inflammatory infiltrate. The cytoplasm of the tumor cells is pale, eosinophilic and contains an occasional vacuole. Focally multinucleated giant cells and cells with rhabdoid features i.e. paranuclear hyaline-like inclusion, eccentric nuclei are seen. The epithelioid and rhabdoid-like tumor

cells show strong immunoreactivity with vimentin, EMA, and cytokeratin (lu-5). Focal reactivity for S-100 and -smooth muscle actin is observed. CD31 and CD34 reactions are negative.

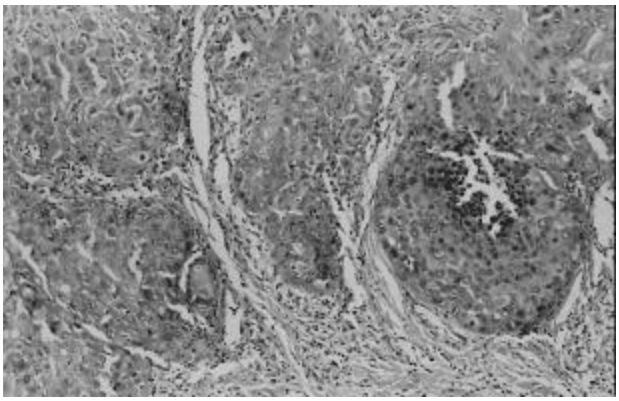

*Figure 1. Characteristic nodular pattern of epithelioid sarcoma with central necrosis. HE x 40*

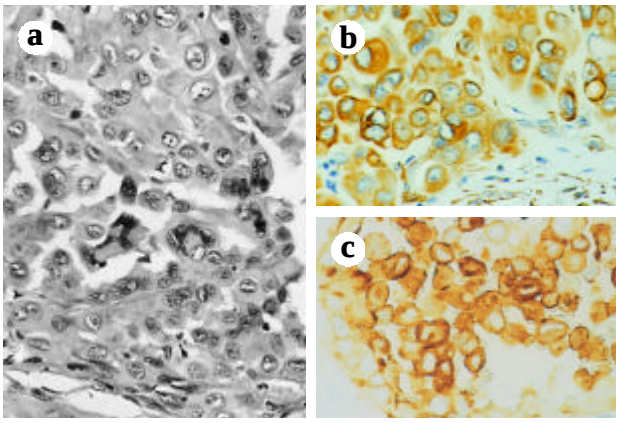


*Figure 2. Tumor cells of ES with copious cytoplasm, vesicular nuclei. Note the multinucleated tumor cells. (a) HE x 100. The tumor cells showed strong positivity for vimentin (b) and for EMA (c)*

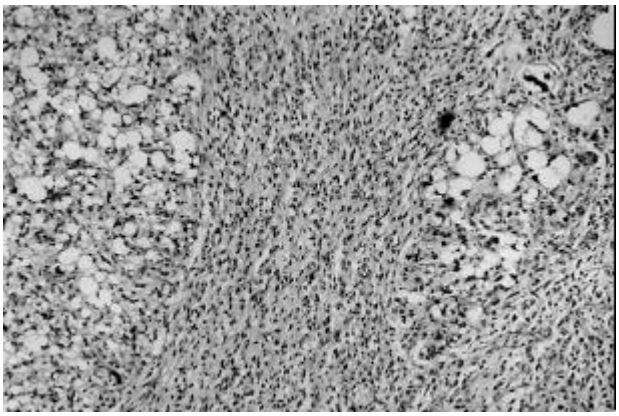

*Figure 3. Second tumor in the calf. Foci of differentiation toward liposarcoma shows neoplastic uni- and plurivacuolated lipoblasts. Some cells have typical scalloped nuclei. HE x 40*

*2nd tumor*. The tumor infiltrating the surrounding skeletal muscle comprises moderately cellular areas with myxoid matrix in which elongated, curvilinear capillaries are seen. The spindle shaped or stellate tumor cells demonstrate moderate pleomorphism and mitotic activity *(Figure 2a)*. These areas show gradual transition to hypercellular, non-myxoid, more pleomorphic areas in which numerous, often atypical mitotic figures and multinucleated, bizarre giant cells are observed. Within these fields scattered foci of differentiation toward adipose tissue with uni- and plurivacuolated lipoblasts are identified *(Figure 2b)*. In the examined several sections no epithelioid cells are disclosed. Both spindle cells and lipoblasts are positive for vimentin. Lipoblasts are positive with anti-S100 antibody. Antibodies directed against desmin, α-smooth muscle actin, EMA, cytokeratin (lu-5), CD31, CD34 yield negative results.

*3rd tumor*. The tumor localised to the right main bronchus shows a multilobular pattern similar to the first tumor. The nodules are composed of large epithelioid cells arranged in solid and discohesive aggregates. The nuclei are vesicular round or oval with moderate variation in size. Some giant nuclei are also present. Nucleoli are small, often inconspicuous. The immunohistology of the lung metastasis is identical with the primary tumor. The lymph nodes show anthracosis without evidence of tumor cells and the mediastinal adipose tissue contains residual thymus.

*4th tumor*. The third tumor developed in the calf is similar to the hypercellular areas of the *2nd* tumor. Conspicuous cellular pleomorphism and mitotic activity are seen. Myxoid matrix can be observed only in minute foci present and only scattered lipoblasts are present. The tumor cells show positivity only for vimentin. All other reactions are negative but S100 reveals positivity in scattered lipoblasts.

## *Discussion*

After long-term follow-up the risk of development of PRS is 0.03-0.8%.[14] The amount of irradiation therapy received by patients with PRS has been reported to range between 1600 and 12440 cGy.[12,14,16] The most frequent histologic types of PRS are osteosarcoma, malignant fibrous histiocytoma and fibrosarcoma.[1,12] The most common primary tumors in the reviewed series of PRS-s are breast and female genital tract cancer, testicular cancer and Hodgkin's disease.[10,11,13,16] No data are known about the risk of second malignancy after irradiation for soft tissue sarcoma.

The primary tumor which developed in the calf of our patient shows characteristic clinical and histological features of ES. The occasional immunoreactivity for α-smooth muscle actin is non-specific features and do not contradict the diagnosis of epithelioid sarcoma.[8] The CD34 reactivity, especially in vimentin negative cases[2] can be a valuable marker in the identification of ES, however, similarly to the

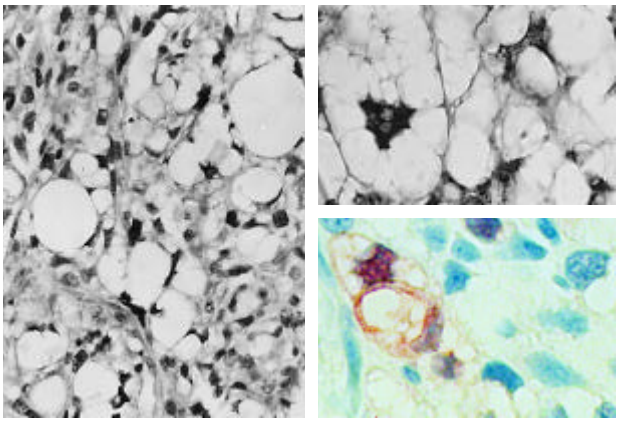

*Figure 4. Pleomorphic liposarcoma HE x100. Upper right: typical florette-like lipoblast. Lower right: S-100 positivity in a lipoblast.*

presented case, not always expresses. The second tumor which developed seven years later in the same region is histologically surprisingly different and raises two questions which should be answered. The first is the possible association of the second sarcoma with radiation therapy. The criteria of PRS-s established by Cahan et al[3] and modified by Laskin et al[12] are that the tumor must arise in a region of prior irradiation, has a latency period of at least two years and proof that the sarcoma is histologically different from the radiated primary lesion. We believe that our case fits these criteria as the patient received radiation to the left calf, had a latent period of 7 years and the second sarcoma was entirely different from primary ES. The second problem is to prove that the second tumor is a plemorphic *liposarcoma*. Large areas resembled myxofibrosarcoma ("myxoid variant of malignant fibrous histiocytoma") composed of nonlipogenic spindle cells with less differentiated pleomorphic areas, however in small islands there is a gradual transition to lipoblastic areas. These lipoblasts had pleomorphic, scalloped nuclei. It is known that there is

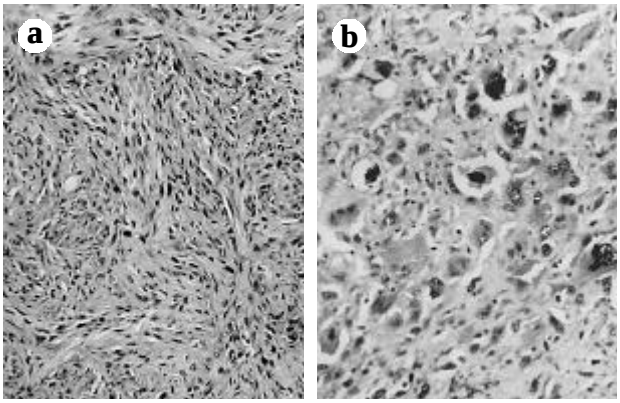


*Figure 5. Malignant fibrous histiocytoma, storiform pattern (a) and pleomorph areas (b) HE x40*

considerable overlap between the morphology of different pleomorphic sarcomas. However, the clear cut differentiation toward adipose tissue, the S100 positivity of lipoblasts and the absence of any other component support the diagnosis of pleomorphic liposarcoma in our case.

So far to our knowledge the histological appearance of the recurrent and metastatic epithelioid sarcomas is similar to that of the primary neoplasm. The three changes observed in the histological appearance i.e. (1) dedifferentiation, (2) abrupt change to a higher grade sarcoma and (3) acquisition of differentiation[7] has not been reported in epithelioid sarcomas. This statement is also true for the fibroma-like variant of ES reported by Mirra et al[15] et al in 1992 in which bland spindle cell proliferation predominates in storiform or desmoid-like pattern. In the recurrent fibroma-like variant of ES Mirra et al[15] observed increasing anaplasia but not change in the histological appearance. In the second tumor of our case the spindle cells were pleomorphic and negative for epithelial markers, consequently the diagnosis of recidive ES with fibroma-like features could be excluded. Postirradiation liposarcoma is extremely rare, Enzinger[5] mentiones only one such case.

We concluded that the pleomorphic liposarcoma in our case is a radiotherapy induced tumor. There are two reasons to explain the development of postirradiation pleomorphic liposarcoma in the region of resected ES. The first reason is the *de novo* tumorgenesis when the malignant transformation is due to direct radiation effect to the normal mesenchymal cells; and the second is that the microscopic residual or recurrent ES dedifferentiates to high grade sarcoma. Because of the short interval (only six months) between the development of this liposarcoma and the parabronchial, histologically typical metastasis of ES, and of the fact that either the metastatic or the recidive ES may be a late event we prefer the second possibility. The fourth tumor which developed in our patient represents the dedifferentiation of pleomorphic liposarcoma toward the storiform-pleomorphic variant of MFH. This observation is in agreement of the hypothesis that storiform-pleomorphic MFH is not a distinct entity but the dedifferentiation stage of different tumors.

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