Acta Orthop Scand 56, 92–95, 1985

Osteosarcoma with multiple intramuscular metastases

A case report

A 21-year-old man with an osteosarcoma in the proximal tibia was treated by amputation, radio- and chemotherapy. Besides pulmonary metastases, intramuscular metastases repeatedly developed. Cell culture studies of pulmonary and muscular tumors showed different sensitivity patterns for cytostatic drugs; the therapy may have selected different subpopulations of the primary tumor.

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Metastasis in skeletal muscle is unusual and has seldom been reported for osteosarcoma. We report a case of osteosarcoma which repeatedly metastasized to skeletal muscles; perhaps an effect of chemo- and radiotherapy.

Case report

A 21-year-old Japanese man noticed a painless 3 cm lump in his left knee in January 1981. He later had pain at rest and was admitted to our hospital on May 27th with a hard 5 cm tumor in the medial aspect of the left proximal tibia. Radiographs showed a mixed lytic and sclerotic lesion in the proximal tibia with soft tissue extension (Figure 1). Angiography showed marked neovascularity. Plain radiographs of the lungs were normal. Total body scintigraphy with ^{99m}Tc-MDP and with ^{67}Ga-citrate showed increased uptake only corresponding to the tumor. On June 19th (wk 0), an open biopsy was performed; a frozen section revealed an osteosarcoma, which was confirmed by permanent sections showing pleomorphic tumor cells and malignant tumor osteoid (Figure 2). At this time 3 × 40 mg of Adriamycin was injected into the femoral artery and intra-operative radiation with an estimated dose between 50 and 60 Gy was given to the proximal tibia. Chemotherapy was started postoperatively with 3 × 30 mg of Adriamycin every 5–8 weeks and 3 × 150–250 mg/kg of Methotrexate every 3–4 months. Later, vincristine sulphate was used. An above-knee amputation was performed in wk 10; because of delayed wound healing, a reamputation was necessary in wk 31.

A small metastasis was suspected in the left lung on plain radiographs in wk 18. CT of the lungs done in wk 34 showed several metastases. In wk 37, seven metastatic tumors in the right lung and six tumors in the left lung were removed. Nine pulmonary metastases were removed in wk 73 and two in wk 96. The fourth thoracotomy was done in wk 96 and seven metastatic tumors were removed.

In wk 97 a 6-cm tender tumor was noticed in the right vastus lateralis muscle and in wk 99 a painful 3

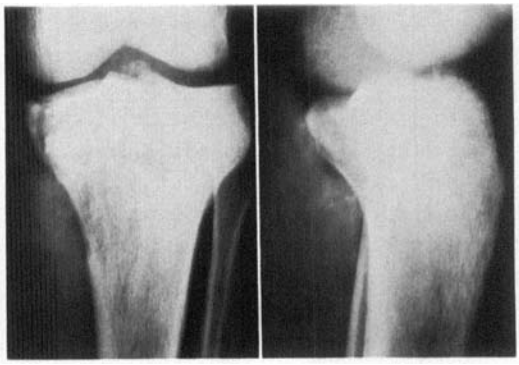

Figure 1. A permeative destruction of the proximal tibia. Tumor extension into the popliteal space.

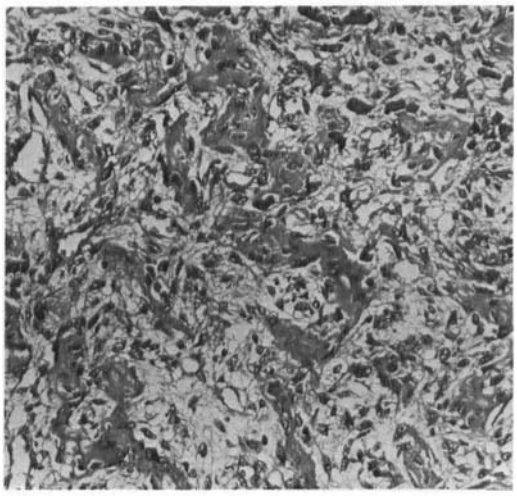

Figure 2. A typical osteosarcoma with pleomorphic cells and tumor osteoid (H-E, ×200).

cm tumor was found in the right deltoid muscle. The intramuscular location of these tumors was confirmed by CT. By this time, a total dose of 0.5 g of Adriamycin, 114 g of Methotrexate and 20 mg of vincristine sulphate had been given. Furthermore, two pulmonary lesions which were found in wk 95 had nearly doubled radiographically by wk 98. Scintigraphy with ^{67}Ga-citrate in wk 100 (Figure 3) and CT (Figure 4) showed multiple intramuscular metastatic lesions: one in the left vastus intermedius, two in the right biceps brachii, one in the left deltoid, one in the right vastus intermedius and two in the left vastus lateralis. These tumors were surgically removed in wk 100. All tumors were found within the muscular tissue. The biggest tumor was that in the left vastus intermedius and measured 12 × 8 × 6 cm; all the others were about 3 cm. Multiple intramuscular metastatic lesions again became apparent and were removed in wk 104; one from the right vastus lateralis, one from the Th 11 level in the erector trunci, and one from the right gluteus medius. Twenty-six lesions were also removed from the left lung. All the soft-tissue lesions were located within the muscles and were removed together with some normal muscular tissue. Histologically, the tumors were not exactly the same, but all had pleomorphic tumor cells and malignant osteoid. Tumor invasion into muscle fibers was also discovered (Figure 5). In wk 105 new tumors were found: one in the right triceps, one in the right infraspinatus muscle, and one in the left deltoid muscle. In wk 107 multiple metastases were apparent in both lungs. By this time, the general condition of the patient had deteriorated and he died in wk 121, October 1983. No autopsy was performed.

Cultured tumor cells were assayed three times for their sensitivity to a variety of anti-cancer drugs according to Ishii et al. (1982): twice for the pulmonary tumors removed in wk 73 and 96 and once for intramuscular tumors removed in wk 100. There was a difference in the sensitivity between the pulmonary and the muscular tumors: the pulmonary tumors were not sensitive to Methotrexate, Vibramycin and Actinomycin-D.

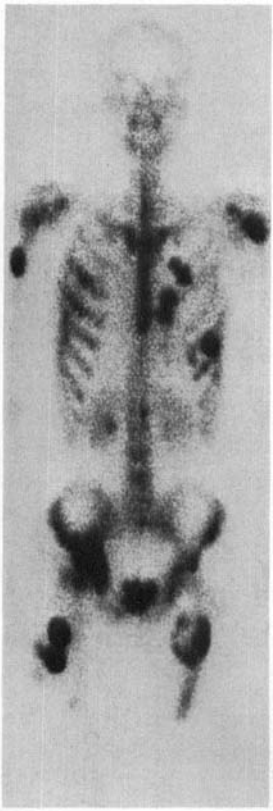

Figure 3. ^{67}Ga-scintimetry wk 100. Multiple metastatic lesions in lungs and skeletal muscles.

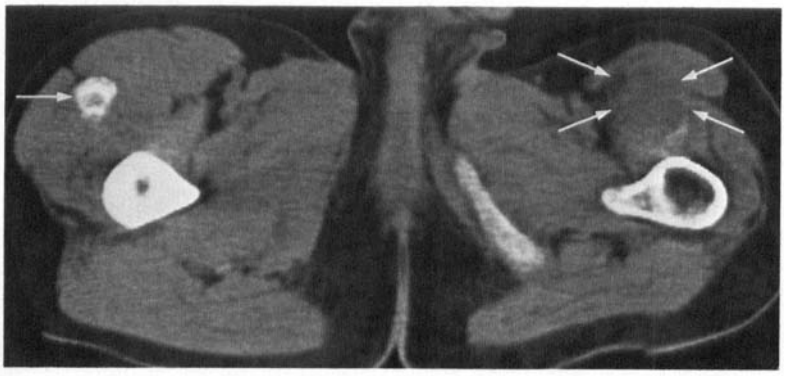

Figure 4. Intramuscular metastases in both quadriceps femoris muscles, wk 104.

Table 1. In vitro drug sensitivity of pulmonary and muscular metastases of an osteosarcoma

	Adriamycin	Vincristine	Methotrexate	Vinblastine	Actinomycin D
Lungs					
wk 73	+	±	−	−	−
wk 96	+	−	−	−	−
Muscle					
wk 100	+	±	±	+	+

In both locations the tumors were insensitive to Cisplatin, Endoxan, Bleomycin and Mitomycin C.

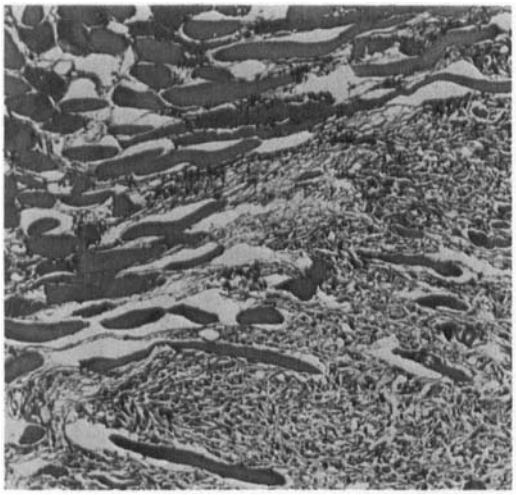

Figure 5. Metastasis in skeletal muscle invading muscle fibers (H-E, ×200).

Discussion

Osteosarcomas most often metastasize to the lung and less often to the skeleton, pleura, kidney and liver (Uribe-Botero et al. 1982). Metastases of osteosarcoma to the heart have been reported (Jeffree et al. 1975, Seibert et al. 1982) but metastasis into skeletal muscle is very rare. Ishida et al. (1983), Chin et al. (1977) and Watanabe et al. (1978) reported one case each. Jeffree et al. (1975) found two cases with an intramuscular metastatic lesion among 135 cases. We have found no report on osteosarcoma which repeatedly metastasized intramuscularly and into so many different muscles as in our case.

Neoplasms consist of heterogeneous cell populations with different growth capabilities, metastatic tendencies, degrees of tumorogenicity, antigenicity, and karyotypes, etc. (Fidler et al. 1978, Springfield 1982, Sugarbaker & Ketcham 1977). Fidler (1973) established highly metastatic strains of murine malignant melanoma; after intravenous injection of melanoma cells, lung metastases developed, which were excised, passed in tissue culture and reinjected intravenously. The strain, which was produced after ten repetitive selection processes, produced more lung metastases than the original tumor. Thus, a subpopulation with different biological characteristics was selected (Bosman et al. 1973).

One interpretation of our case is that subpopulations of tumor cells with an affinity to muscular tissue selectively survived the radiotherapy and chemotherapy. Another interpretation is that the biological characteristics of the tumor, particularly those of the cell surfaces, which are decisive factors in cell-to-cell recognition, changed by sublethal irradiation so that tumor cells developed an affinity to muscular tissue (Fidler et al. 1978, Gernstein & Bosmann 1975, Sato et al. 1972, Sato & Kojima 1971, Shur & Roth 1975, Stein et al. 1962). The different sensitivity to anti-cancer drugs of the pulmonary and muscular tumors may indicate a biological difference.

A third interpretation is that the chemotherapy given changed the immunological conditions and the pattern of metastases (Eccles & Alexander 1975, Fuji & Mihick 1975, Glaves & Waiss 1975, Shur & Roth 1975, Sugarbaker et al. 1970, Sugarbaker et al. 1971).

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