Abstract. Resection for a mass in the proximal thigh was performed on a 57-year-old woman, the diagnosis of which was extraskeletal osteosarcoma. In pathological findings, tumor cells gradually decreased from the central area of the mass composed of spindle cell sarcoma and were replaced by fibrocollagenous tissue with no sarcoma cells. CD8+, T-cell-restricted intracellular antigen-1 (TIA-1)+, granzyme B+ T lymphocytes appeared to infiltrate the mass lesion, so that we hypothesize that the immunological system was likely to be involved via T lymphocytes in triggering spontaneous regression in this case. One of the most unusual phenomena in cancer biology is the spontaneous regression of a tumor. Here, we report on the first case of extraskeletal osteosarcoma characterized by partial spontaneous regression of the primary lesion.

Extraskeletal osteosarcoma (EOS) is characterized as a matrix-producing high-grade neoplasm, and a rare soft tissue sarcoma (1, 2). Patients with EOS generally have poor prognosis and the majority develop metastatic disease within several years of diagnosis, even if radical excision is achieved (1-4). Spontaneous regression of malignancy in cancer is a rare event and is reported sparsely in virtually all types of cancer (5, 6). To date, five cases of spontaneous regression of a metastatic lesion in osteosarcoma of bone (7-9) and one EOS (10) have been described. Although two cases of regression of the primary lesion in osteosarcoma of bone have been described (11, 12), no case of this phenomenon in the primary site of EOS has been reported. We present the first report of an EOS case characterized by unique histological features of partial spontaneous regression of malignancy of the primary lesion in pathological findings.

Case Report

A 57-year-old Japanese woman first noticed a mass on the medial side of her right proximal thigh one year before surgery. The mass enlarged without any pain during the first six months of that year, after which it remained stable in size but increased in hardness. The patient’s past medical and family history were unremarkable, and no apparent history of trauma or radiotherapy around the thigh was noted. On physical examination, a hard mass measuring 7 by 7 cm in diameter was palpated in the thigh. The mass did not adhere to skin and was mobile on palpation. Laboratory data were within normal limits except for a high level of alkaline phosphatase (463 U/l, normal: 110-360 U/l).

Radiographs showed a mass with mineralization in the medial part of the right thigh (Figure 1). Magnetic resonance images (MRI) revealed a well-defined mass in the sartorius muscle of the right thigh (Figure 2). In general, this lesion showed isodence signal intensities on T1-weighted images, and high signal characteristics and partial inhomogenity with small areas of loss of signal intensity on T2-weighted images. After contrast medium administration, heterogeneous enhancement was observed.

Since a biopsy specimen contained fibrocollagenous tissue with no tumor cells, resection biopsy was performed. The mass was easily resected marginally because it was not adhesive to surrounding tissues. Macroscopically, the resected specimen had a bony shell and clear margin with a gritty, fibrous appearance (Figure 3). Microscopically, the tumor, especially the central portion, was composed of spindle cell sarcoma with lace-like osteoid and bone formation (Figure 4). The cellularity, nuclear atypia and tumor cells gradually decreased from the central area composed of sarcoma cells.
and the necrotic area was increased with replacement by fibrocollagenous tissue (Figure 5). Necrosis was observed in the periphery. The shell consisted of fibrocollagenous tissue, and finally tumor cells were completely absent (Figure 6). The reverse zone phenomenon was not observed. In immunohistochemical findings, the neoplastic cells were negative for CD99, c-kit, CD34, alpha-smooth muscle actin (α-SMA) and cytokeratin axon exchanger 1/3 (CK-AE1/AE3). The presence of T-cell-restricted intracellular antigen-1 (TIA-1), granzyme B and CD8 lymphocytes was confirmed in tumor (Figure 7). The histological diagnosis was an extraskeletal osteoblastic osteosarcoma with tumor differentiation score 3; mitosis count score 1; tumor necrosis score 2 and histological score 3.

Five weeks after the initial surgery, we performed additional wide resection, including the remnant sartorius muscle, rectus femoris fascia and adductor longus fascia. At present, two years and two months postoperatively, there is no local recurrence or metastasis.

Discussion

Extraskeletal osteosarcoma is a relatively rare soft tissue tumor, which is reported to account for approximately 1% of all soft tissue sarcomas and fewer than 5% of all osteosarcomas (1, 3). It is defined as a malignant mesenchymal neoplasm that produces an osteoid and/or cartilaginous matrix and arises in soft tissues (1, 2). In a previously reported large series of EOS, almost all of the tumors were histologically classified as high-grade sarcomas (1-4). Patients with EOS generally have a poor prognosis and the majority develop metastatic disease within 3 years of diagnosis (1). The reported overall mortality rate due to the tumor in a larger series exceeds 60% and the 5-year survival rate is reported to be 37% (1, 13).

Several predisposing factors in the development of EOS have been reported with radiation (2, 14) and trauma (1) described as being major incriminating factors. Furthermore, EOS arising from myositis ossificans or heterotopic ossification has been described (15). In the present case, there was no clear history of radiation or trauma. Differential diagnosis based on plain x-ray and MRI findings suggested myositis ossificans, chondroma, synovial sarcoma, chondrosarcoma and EOS. The criteria for the diagnosis of primary EOS are the presence of a uniform morphological pattern of sarcomatous tissue that excludes the possibility of malignant mesenchymoma, the production of malignant osteoid or bone by the sarcomatous tissue, and the ready exclusion of an osseous origin (14). In the present case, the tumor was composed of spindle cell sarcoma with irregular bone formation and the lace-like osteoid or bone formations observed microscopically led to diagnosis of this tumor as EOS.

Interestingly, histological findings revealed tumor cells gradually decreasing, and being completely replaced by fibrous tissue. Similarly, in previous reports, in breast cancer the intraductal component spontaneously disappeared and was replaced by fibrous tissue (16, 17). The cause of replacement of the fibrous tissue in regression of breast cancer is not clear, but a correlation between the cause of regression and periductal fibrosis formation (17) is suspected. A previous paper reported constitutive expression of cell-associated interleukin-1α by oncogene-transformed fibrosarcoma cells.
causing regression of tumors in mice, with the tumor mass being replaced gradually by fibrotic scar tissue with the accumulation of CD8+ T-cells (18). Cytotoxic T lymphocytes promote apoptosis by secretion of granzymes, and granzyme B, a natural serine protease, leads to apoptosis through both caspase cascade-dependent and -independent pathways (19). TIA-1 stimulates alternative splicing of premessenger RNA for the Fas receptor, resulting in promotion of apoptosis (20). In the present case, CD8+, TIA-1+, granzyme B+ T lymphocytes appeared to infiltrate the lesion; thus, we hypothesize that the immunological system was likely to be involved via T lymphocytes in triggering spontaneous regression in this case.

Figure 3. Resected specimen showing bony shell.

Figure 4. High-power view of the histopathological specimen showing spindle cell sarcoma with osteoid formation (hematoxylin-eosin; ×400).

Figure 5. Low-power view of the specimen showing gradual decrease of tumor cells from the central area of the mass composed of spindle cell sarcoma, with their replacement by fibrocollagenous tissue with no sarcoma cells (hematoxylin-eosin; ×3).

Figure 6. Hematoxylin-eosin staining of the specimen showing partial regression.

Figure 7. Immunoreactivity of the specimen for TIA-1 (×400).
Spontaneous regression is very rare and is defined as being when a cancer partially or completely disappears without treatment (21). Renal cell carcinoma, malignant melanoma, neuroblastoma and choriocarcinoma accounted for more than 50% of all spontaneous regressions, although this phenomenon is reported in virtually all types of cancer (22); however, the apparent incidence and mechanisms involved are unknown. Mechanisms affecting spontaneous regression include (23) immunological factors, growth factors and cytokines, elimination of a carcinogen or an antigen, hormonal factors, tumor necrosis or inhibition of angiogenesis, apoptosis, differentiation, postoperative affection, and telomerase inhibition. Of the many possible mechanisms that have been proposed to explain cancer regression, Everson and Cole reported immunological mechanisms as comprising the most important factor in spontaneous regression (24). The correlation between immunosuppression and the risk of neoplasia, and spontaneous regression after reduction of immunosuppressive treatment suggests that the immune system plays an important role in progression and regression of the cancer (25-27). Immune mechanisms for regression were demonstrated in renal cell carcinoma and malignant melanoma (28, 29). In the present case, the lymphocyte infiltration strongly suggests that the patient’s anticancer immune response affected tumor elimination.

Several papers have reported spontaneous regression in osteosarcoma of bone: five cases of spontaneous regression of a metastatic lesion (7-9) and two cases of a primary site (11, 12). In these reports, it was hypothesized that influencing factors were the resection of the primary site in four cases and radiation therapy for the primary lesion in one case with regression of metastasis. The main factor was open biopsy in two cases of regression of the primary lesion. In terms of EOS, only one case with regression of a metastasis has been described (10) and the influencing factor was considered to be resection of the primary tumor. This present case is the first report of an EOS case characterized by histological features of partial spontaneous regression of the primary lesion. Because histological findings revealed the regression of malignancy at the time of biopsy, there is no apparent influencing factor in this case.

Treatment for EOS involves wide resection, radiotherapy and chemotherapy (2-4, 30). In previous reports, wide resection followed by irradiation appeared to be the most effective types of therapy (2). The influence of adjuvant chemotherapy is unclear for EOS (2, 30), while chemotherapy is essential therapy for osteosarcoma of bone. In the present case, additional wide resection was performed, but neither radiation nor chemotherapy were carried out, at the patient’s request. These additional and adjuvant therapies may not have been necessary for this case, because this malignant tumor was surrounded by a fibrous shell without tumor cells, and appeared to be undergoing the process of spontaneous regression.

Spontaneous regression of osteosarcoma is an extremely rare biological event. Further understanding of this phenomenon will result in the development of significant adjuvant therapeutic strategies.

References