Alveolar soft part sarcoma of the extremities:
an evaluation of four cases

Ekstremite yerleşimli alveoler yumuşak doku sarkomu: Dört olgunun değerlendirilmesi

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We presented four patients (3 women, 1 man; mean age 40 years; range 20 to 56 years) who had alveolar soft part sarcoma in the left arm, right elbow, right tibia, and left thigh, respectively. All the patients presented with a mass. Two patients had lung metastasis at the time of diagnosis. T1- and T2-weighted magnetic resonance images of all the patients showed a soft tissue lesion with hyperintense signal changes and heterogeneous contrast enhancement. Diagnoses were made by histopathologic examination of biopsy samples. All the patients received chemotherapy. Surgical resection was performed in three patients. Two patients with involvement of the left arm and right elbow died within three years after diagnosis. One patient with involvement of the left thigh developed lung and brain metastases at the end of postoperative eight years. One patient with tibial involvement remained disease-free during 10 months of follow-up.

Key words: Neoplasm metastasis; sarcoma, alveolar soft part/therapy/surgery; soft tissue neoplasms/pathology.

Alveolar soft part sarcoma (ASPS) is among the rarely seen tumors; it accounts for 0.5% to 1% of all soft tissue sarcomas.¹ Generally it presents as a slowly growing painful mass in patients 15-35 years old.¹ Only 0.8-1.8% are seen in children.² It can occur in any part of the body, including tongue, uterus, stomach, vagina, bone, vessels and sacrum, and is mostly seen in the trunk and extremities.¹,³-⁷ Metastases are frequent, with metastases generally occurring in lung, brain, bone and lymph nodes.³,⁸

The tumor is rich in terms of vessels; sometimes murmur can be heard as a clinical sign.¹ In such situations it can be confused with arteriovenous malformations. Microscopically, around the tumor cells numerous vascular canals are found.⁴ The tumor's macroscopic appearance is a round or lobulated soft mass; it is seen to be yellowish-white in color.⁹ On light microscopy its polygonal cellular, capillary-surrounded, alveoli-like appearance is characteristic.¹² On electron microscopy, ASPS cells contain typical electrondense polygonal crystals in their cytoplasm.¹³
The potential of primary tumors to develop from bone has been suggested,[10] but a muscular origin has also been suggested by immunohistochemical studies.[11] In molecular studies, specific chromosomal translocation has been shown.[12,13] For tumors that have not metastasized, surgery forms the basis of therapy. Adjuvant radiotherapy and chemotherapy are alternatives used in providing local control and when metastases are present. Lieberman et al.[8] reported in 91 patients a two-year survival rate of 77%, and a five-year survival rate of 60%. In the present report, four patients with ASPS are presented who were among approximately 300 patients treated for a diagnosis of soft tissue sarcoma in our clinic from March 1986 to December 2006.

Case report

Patient 1 – A 39-year-old male patient presented with a complaint of a mass with pain on the posterior aspect of his left arm, present for approximately one month. On plain radiographs a soft-tissue shadow was seen on the proximal lateral humerus. On magnetic resonance imaging (MRI), in the middle to upper region of the humerus posterolaterally, a mass was seen, with no invasion of the bone, with a hyperintense signal on T₁ and T₂-weighted images and heterogeneous uptake of contrast, and measuring 8x11x15.5 cm. On computed tomography (CT) of the lungs there were widespread lung metastases. On fine needle aspiration biopsy, large polygonal tumor cells with eosinophilic cytoplasm, forming an alveolar arrangement in the capillary structure, were seen. With a histopathologic diagnosis of high grade ASPS, the patient underwent four courses of chemotherapy (first course ifosfamide 1.8 g/m², 5 days; Adriamycin 25 mg/m², 3 days; in the other courses Endoxan 750 mg/m², 1 day; vincristine 1.5 mg/m², 1 day; dacarbazine 250 mg/m², 5 days). From a surgical therapy perspective it was accepted that the patient’s situation was late, and the patient died eight months after the initial diagnosis.

Patient 2 – A 46-year-old female patient presented at another center with the complaint of a painless mass at her right elbow that had been present for approximately one year. On plain radiographs the pathology could not be identified, and on the patient’s MRI examination, a lesion was detected at the posterior elbow, extending to the olecranon fossa, 2x3x5 cm in size, with hyperintense signal on T₁ and T₂-weighted images and heterogeneous uptake of contrast. The patient underwent open biopsy, a diagnosis of ASPS was made and later the lesion was excised. In the postoperative period chemotherapy and local radiotherapy were applied in the patient and one year later a recurrence developed. In the investigation of the specimen from the second operation, tumor cells were encountered in the surgical margin and the patient was referred to our clinic. On diagnostic tests distant metastases were detected, and on this basis surgical tumor excision and latissimus dorsi rotation flap were made. In the pathology investigation, tumoral cells were not encountered at the surgical margin. Seven months after this surgery was performed at our center, local recurrence was detected and the patient again underwent surgery, with marginal excision of the tumor. At a follow-up examination three months later, recurrence and lymph node metastasis in the region of the latissimus dorsi flap were detected, and on this basis shoulder disarticulation was recommended to the patient. The patient did not accept this recommendation, and repeat marginal surgery and six courses of adjuvant chemotherapy were applied (ifosfamide 2 g/m², 3 days; Adriamycin 25 mg/m², 3 days). Due to widespread lung metastases the patient died 27 months after applying to our center.

Patient 3 – YA 20-year-old female patient presented at our clinic with a complaint of a mass with pain on the anterior surface of her right tibia that had been present for three months. On plain radiographs, a lesion measuring approximately 4x2 cm causing destruction and expansion of the cortex was detected on the tibial diaphysis (Figure 1). On computed tomography, a mass associated with cortical breakdown and destruction and measuring approximately 60 mm in length was detected. On MRI examination, in the middle region of the right tibia a 4-cm-long intramedullary mass, with slight contrast enhancement, hypointensity on T₁ images and hyperintensity on T₂ images, was detected; and in the proximal 1/3 of the calf posteriorly, another mass was detected, measuring approximately 8x5x3.5 cm, with hyperintensity on T₁ and T₂-weighted images, and initially appeared to be a hemangioma (Figure 2). On lung CT multiple metastases were detected, and with the goal of making a histopathologic diagnosis, open biopsy of the tibia was performed. After histopathologic investigation a diagnosis of ASPS was made, and for the lesion in the gastrocnemius on the same side that was seen on MRI and thought to be a hemangioma, tru-cut bi-
opsy was performed. This lesion’s histopathologic diagnosis was also ASPS, and on this basis the lesion in the soft tissue was accepted as the primary focus, and the lesion in the tibia as a metastasis (Figure 3). Two courses of neoadjuvant chemotherapy were applied (ifosfamide 3150 mg/day, 1 day; mesna 3150 mg/day, 5 days; Adriamycin 44 mg/day, 3 days). Two months later, for the soft tissue mass, marginal excision was performed and the diagnosis of ASPS was histopathologically confirmed. Three weeks later in a second operation, wide-margin tumor resection with intramedullary nailing and cementing were performed on the tibia. On the microscopic examination, tumoral cells were not encountered in the surgical margin.

Eight months of therapy with imatinib 3x100 mg were provided to the patient by the medical oncology department. In the postoperative 10th month of follow-up the patient had no complaints.

**Patient 4** – A 56-year-old female patient presented at our clinic with a complaint of a mass on her

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**Figure 1.** This anterior-posterior radiograph of the tibia shows a lytic mass causing cortical breakdown and expansion.

**Figure 2.** (a) This fat-saturation $T_2$ coronal image shows an intramedullary lesion in the right tibia, approximately 4 cm in craniocaudal size, with hyperintensity. (b) At the proximal tibia posteriorly, within the gastrocnemius muscle, a hyperintense lesion with no-signal tortuous vessel structures on it are seen.
anterior left thigh that had been present for approximately one month. On plain radiography no pathologic findings were encountered. On MRI, a soft-tissue mass on the anteromedial aspect of the thigh was detected, 10x8x6 cm in size, without bone invasion, and with hyperintensity on T1- and T2-weighted images. As a result of open biopsy the patient was diagnosed as having ASPS, and distant metastases were not detected. After the patient underwent surgery with wide resection, four courses of chemotherapy were applied (ifosfamide 2 g/m2, 5 days; Adriamycin 25 mg/m2, 3 days). Despite an eight-year period of follow-up in which local recurrence and metastases did not develop, in the latest examination, metastases in the lung and brain were detected. The patient went to another center and does not continue in our follow-up.

Discussion

Alveolar soft part sarcoma is a very rarely seen soft tissue sarcoma. It occurs more in young patients and is seen more in women.\(^1\) In adults it is more frequent in the extremities (particularly the lower extremity), and in children it is more frequent in the head and neck region.\(^1\) Ogose et al.\(^10\) reported that approximately 10% of these tumors can occur as primary bone tumors. Three of our patients were over 30 years of age; three were women. The tumor occurred in the lower extremity in two of them and in the upper extremity in two.

Patients generally present with pain and mass, and due to the tumor being slow-growing, metastases are detected at diagnosis in an important number of patients.\(^1\) All four of our patients had a complaint of mass, and two had an additional complaint of pain. In two patients lung metastases were detected at diagnosis.

On plain radiographs, soft-tissue shadow and calcification can rarely be seen.\(^{14}\) In situations where bone is affected, destruction can be seen. In our third patient, cortical expansion and destruction due to the metastasis in the tibia were seen on plain radiography (Figure 1). In the first patient, soft-tissue shadow was observed. On computed tomography, bone destruction and central necrosis can be seen, as well as contrast enhancement due to the rich vascular structure.\(^{15}\) In the third patient, for a more detailed investigation of the lesion causing bone destruction seen on plain radiographs, CT was used. Here the malignant character of the lesion causing thinning and destruction in the cortex was seen. Due to its aggressive nature, sclerosis and periosteal reaction around the lesion are not expected on radiologic examinations.\(^{16}\) In the radiologic differential diagnosis, lymphoma, plasmacytoma, Ewing sarcoma, malignant fibrous histiocytoma and other aggressive bone lesions like these should be kept in mind. For the evaluation of soft-tissue lesions in our patients, MRI was preferred. ASPS shows increased signal intensity on both T1- and T2-weighted images, and because of this it can be confused with hemangiomas.\(^{17}\) Other MRI characteristics of ASPS are flow voids and heterogeneous contrast uptake in images obtained when gadolinium is given. Due to the more prominent arterial structure in ASPS, flow voids are more apparent than in hemangioma. In our patients, notable characteristics were hyperintensity on both T1- and T2-weighted images, the presence of flow voids, and heterogeneous contrast enhancement. In the differential diagnosis, tumors showing hyperintensity on T1-weighted images, such as clear cell sarcoma, metastatic melanoma, liposarcoma, and soft-tissue tumors associated with hemorrhage should be kept in mind. However, in these tumors, flow voids are not seen.\(^{17}\) Also, on CT, unlike hemangioma, in ASPS peripheral contrast enhancement and central necrosis can be seen. For the evaluation of the tumor’s distant metastases and bone invasion, scintigraphic methods can also be used.\(^{18}\)

Histopathologically, ASPS can be confused with alveolar rhabdomyosarcoma, paraganglioma, metastatic renal cell carcinoma, metastatic hepatocellular carcinomas and endocrine neoplasias.\(^1,4,19,20\) On the

![Figure 3. Large polygonal tumor cells with eosinophilic cytoplasm are seen to form an alveolar arrangement among the capillary structures (hematoxylin-eosin, x 400).](image)
histopathologic exam, the characteristic appearance is one resembling alveoli composed of polygonal cells and surrounded by capillaries.\cite{2} Malignant melanoma, granular cell tumor, paraganglioma and alveolar rhabdomyosarcoma can also give an alveolar appearance on histology. When diagnosis is difficult, the observation of typical crystals on electron microscopy and the use of immunohistochemical studies designed for tumor typing can be useful. For the diagnosis of ASPS, although various epithelial, neural and muscle-related immunohistochemical parameters are being investigated, no specific indicator has been reported.\cite{21}

Metastases from ASPS generally go to lung, brain and surrounding bones. In addition to brain and lung, metastases to locations such as chest wall, retroperitoneum, liver and spleen have been shown.\cite{3} It has been reported that 40% of patients have lung metastases at initial diagnosis.\cite{8} In the literature, late metastases have attracted attention, and a lung metastasis occurring 35 years after surgery for a tumor in the parotid gland has been reported.\cite{1}

In the treatment of localized ASPS the most important step is the excision of the tumoral tissue with microscopically clean surgical margins.\cite{3} Although adjuvant chemotherapy and radiotherapy are used, their effectiveness is debatable.\cite{3,10}

In terms of prognostic factors, at the time of diagnosis, the presence of metastasis, the tumor’s being larger than 5 cm and the presence of bone involvement on the side of the tumor are the most important factors in a poor prognosis.\cite{3,10} For tumors smaller than 5 cm in diameter, while 5, 10 and 15 year survival rates are 72%, 65% and 65% respectively, for tumors larger than 5 cm in diameter these figures have been reported to be 46%, 9% and 0%.\cite{10} For patients in whom no metastases are detected at the time of diagnosis, while the 5, 10 and 15 year survival rates are 81%, for patients with metastasis at diagnosis a five year survival rate of 46% and a 10 year survival rate of 0% have been reported.\cite{10} Age, gender and location of the primary tumor have been reported to have no effect on prognosis.\cite{10}

For soft tissue sarcomas in the extremities, in providing local control, the surgical margin’s being microscopically clean is very important.\cite{22} Local recurrence of ASPS can reach rates of 20%.\cite{8} Sherman et al.\cite{23} provided very good local control with radiotherapy in six patients who had ASPS, and reported that routine radiotherapy was necessary. Ogose et al.\cite{10} reported that in patients having insufficient surgical margins, radiotherapy should be considered. According to the accepted view, radiotherapy and chemotherapy have no significant effects on prognosis.\cite{3,4,8,24,25} Among our patients, radiotherapy was applied only in the second one, but despite this, new recurrences emerged.

In conclusion, as with many types of tumors, for ASPS preoperative biopsy and diagnosis, followed by well-planned surgery, are very important in terms of preventing serious complications that can occur later. For this type of tumor, the making of a diagnosis before metastasis develops, and the tumor’s resection with microscopically clean surgical margins, increase the chance of success in therapy.

References
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