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A Rare Tumor of the Posterior Mediastinum: Well-Differentiated Liposarcoma

Posterior Mediastenin Nadir Bir Tümörü: İyi Diferansiye Liposarkom

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Abstract

Liposarcoma is one of the most common forms of soft tissue sarcoma in adults, and usually occurs in the lower extremities and retroperitoneum. It has several histological subtypes, including myxoid, well-differentiated, dedifferentiated and pleomorphic. Liposarcomas originating from the mediastinum are extremely rare, and usually grow slowly and remain asymptomatic, but may become symptomatic when they become large enough to press on the adjacent structures. Computed tomography and magnetic resonance imaging provide useful data for diagnosis, while tissue biopsy based on typical pathological features is required for a definitive diagnosis. Complete surgical resection is the first-line treatment option as it is resistant to chemoradiotherapy. Due to the high risk of recurrence, long-term follow-up should be continued. We present here the rare case of a 56-year-old female patient with primary mediastinal liposarcoma who presented with a complaint of cough.

Key words: *Atypical Lipomatous Tumor, CDK4, Well-Differentiated Liposarcoma, MDM2.*

Öz

Liposarkom erişkinlerde en sık görülen yumuşak doku sarkomlarından biridir; genellikle alt ekstremitelerde ve retroperitonda ortaya çıkar. Miksoid, iyi diferansiye, farklılaşmamış (dediferansiye) ve pleomorfik olmak üzere çeşitli histolojik alt tipleri vardır. Mediastenden kaynaklanan liposarkomlar son derece nadirdir. Bu tümörler genellikle yavaş büyürler ve asemptomatik kalırlar ancak büyük boyuta ulaşıp komşu yapılara bası yaptığında semptomatik olabilirler. Bilgisayarlı tomografi ve manyetik rezonans görüntüleme tanı için faydalı veriler sağlar. Kesin tanı için doku biyopsisi gereklidir ve tanısı tipik patolojik özelliklere dayanır. Kemoradyoterapiye duyarlı olmadığından tam cerrahi rezeksiyon birinci basamak tedavi seçeneğidir. Nüks oranı yüksek olduğundan uzun süreli takip yapılmalıdır. Bu yazıda öksürük şikayeti ile başvuran primer mediastinal liposarkomlu 56 yaşında kadın olgu nadir görülmesi sebebiyle sunuldu.

Anahtar Sözcükler: *Atipik Lipomatöz Tümör, CDK4, İyi Diferansiye Liposarkom, MDM2.*

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Liposarcoma, a common soft tissue tumor, accounts for approximately 20% of all mesenchymal malignancies (1), while mediastinal liposarcoma is a very rare primary malignant tumor that accounts for only 0.1–0.75% of all mediastinal tumors (2).

Well-differentiated liposarcoma (WDL), also known as atypical lipomatous tumor (ALT) – a locally aggressive form of adipocytic tumor – is the most common histological liposarcoma subtype, accounting for 40–45% of the total (3, 4). ALT/WDL occurs especially in the deep soft tissues of the proximal extremities (thigh and hip, shoulder and back), and in the retroperitoneum and paratesticular area (5). Although ALT and WDL are morphologically and genetically identical, the term WDL is used for tumors of the retroperitoneum, mediastinum and deep pelvis (in which the chance of reaching negative margins is reduced and local recurrence is increased), while the term ALT includes tumors of the extremities and superficial regions (in which complete excision is possible and curative) (1).

ALT/WDL occurs most frequently in the 5th and 7th decades, and predominantly in adult males (6, 7). Although surgical excision is the optimal treatment option for mediastinal liposarcomas, postoperative recurrence rates range from 50–90% (8).

In this case report, we present to literature a patient with ALT/WDL located in the posterior mediastinum who underwent excision by thoracotomy.

CASE

A 56-year-old female patient with known type-2 diabetes mellitus, coroner artery disease (2 years ago, coronary stent) and hyperlipidemia was admitted with complaints of cough and difficulty in sputum production for a week. She was an active smoker with a 20 pack/year smoking history. A physical examination of all systems was normal, and hemogram and biochemical values were within normal limits. A pulmonary function test revealed FEV1/FVC: 88.7% and FEV1: 87% (2.11 L).

A posteroanterior chest radiograph showed increased opacity in the paratracheal area and mediastinal enlargement in the right upper zone (Figure 1A).

Thorax computed tomography (CT) revealed a sharply defined, lobulated, hypodense mass lesion with a mean density of -99 Hounsfield units (HU), reaching 13x8x7cm in diameter, reaching the largest transaxial diameter, extending from the carina level to below to the neck level, and deviating the trachea and esophagus anteriorly in the retroesophageal area of the posterior mediastinum (Figure 2). A neck ultrasonography revealed a well-circumscribed solid lesion at the mid-lower zone level of the right and left lobes of the thyroid gland starting in the posterior neighborhood of the thyroid gland and continuing to the mediastinum, containing linear echoes and slightly hypoechoic when compared to the thyroid and with very sharp borders. No pathological F-18 fluoro-2-deoxy-glucose (FDG) uptake was observed in the lesion on positron emission tomography (PET-CT), and no significant hypermetabolic findings were identified that could be evaluated in favor of malignancy with FDG affinity in other parts of the body included in the PET-CT examination.

The patient was consulted to thoracic surgery, and a mass excision was performed by thoracotomy (Figure 1B and Figure 3).

Macroscopically, a 12x9x3.5 cm fatty tissue mass was observed, surrounded by a capsule with a smooth surface in most areas and irregularities in focal areas, as well as a collective 6x5x3 cm fat tissue mass, which was sent in parts. The section was in the appearance of homogeneous dirty yellow mature oil. Microscopically, few atypical stromal cells with hyperchromatic large nuclei were observed in the tumor that included fibrous septations in places (Figure 4 and 5). In an immunohistochemical examination, cyclin-dependent kinase 4 (CDK4) was identified in histiocytic and atypical stromal cells (Figure 6). ALT/WDL was first considered due to the presence of atypical stromal cells, the size difference between the lipocytes, the >10 cm lesion diameter and the deep localization of the mass. A molecular analysis was performed for murine double-minute type 2 (MDM2) and CDK4 amplification for definitive diagnosis and typing. Amplification was detected in the CDK4 and MDM2 gene regions by fluorescence using the in situ hybridization (FISH) technique (Figure 7).

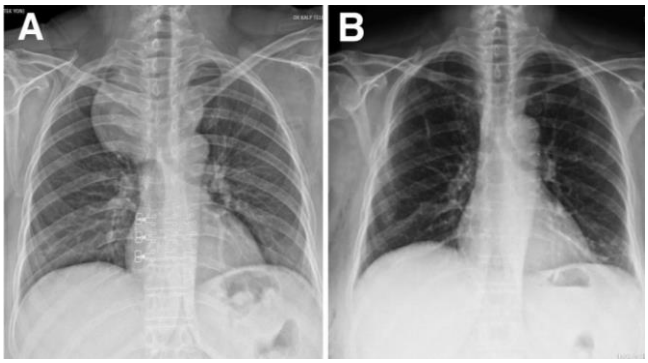

Figure 1: Posteroanterior chest radiograph showing increased opacity in the paratracheal area and mediastinal enlargement in the right upper zone (A); Post-thoracotomy chest X-ray of the patient (B)

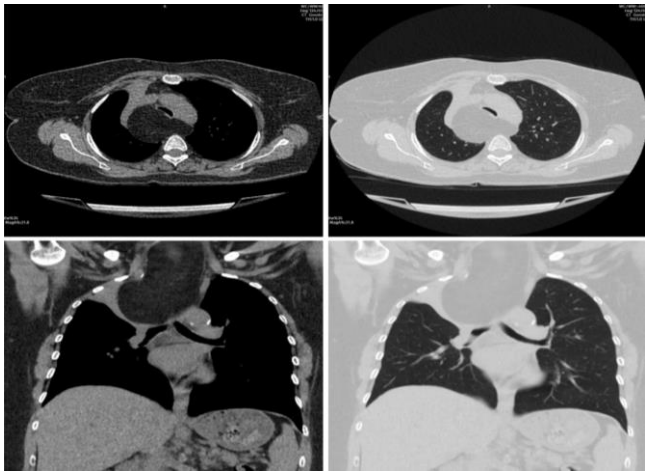

Figure 2: Thorax CT image of the patient at the time of diagnosis in which a sharply demarcated, lobulated contour, hypodense mass lesion compatible with lipoma can be seen in the retroesophageal area in the posterior mediastinum, starting from the carina level below and extending to the neck level above, deviating the trachea and esophagus anteriorly

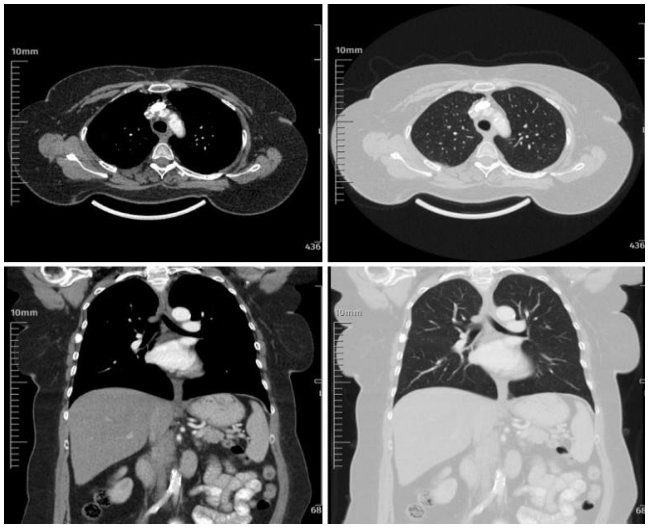

Figure 3: Post-thoracotomy chest thorax CT of the patient

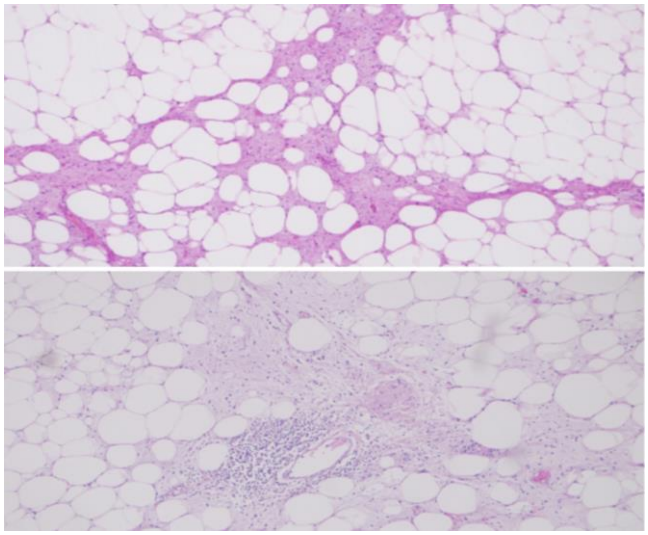

Figure 4: Adipose tumor containing fibrous septations and chronic inflammatory cells between fat lobules (H&E X10)

Since the tumor size was very large (>10 cm), 25 postoperative adjuvant radiotherapy (RT) sessions were given to the chest and neck region in order to prevent local recurrence. The patient was asymptomatic at 5 months postoperatively, and no recurrence or metastasis was detected. She continues to be followed closely by oncology, both clinically and radiologically.

DISCUSSION

Primary mediastinal liposarcomas are very rare (9). Liposarcomas have several histological subtypes, such as myxoid, well-differentiated, dedifferentiated and pleomorphic, and all of these liposarcoma subtypes have been reported to occur in the mediastinum. ALT/WDL is the most common type of liposarcoma in the mediastinum (10, 11).

ALT/WDL can be categorized histologically as adipocytic (or lipoma-like), sclerosing, spindle cell and inflammatory types, with the most common forms being adipocytic (or lipoma-like) and sclerosing (12). Adipocytic (or lipoma-like) liposarcomas can reach large sizes with well-circumscribed, lobulated masses, as in the present case, and may not be differentiated from benign lipomas macroscopically, making microscopic examination necessary. ALT/WDLs are adipocytic neoplasms characterized by a proliferation of pleomorphic mature adipocytes in different patterns containing atypical hyperchromatic stromal cells. They intersect with fibrous septa, and may have myxoid or fibrous components and areas of fat necrosis (5). Our case was diagnosed based on a histological examination and molecular pathological test. The molecular pathological examination of CDK4 and MDM2 genes is considered the optimum approach to the distinguishing of well-differentiated liposarcoma from lipoma. The immunostaining technique for MDM2 and CDK4 is low cost and is regularly adopted due to its high compatibility with the FISH method, although the FISH approach to the detection of MDM2 and CDK4 gene amplification, however, is more sensitive and specific than immunohistochemistry. A histological material FISH technique should be used to differentiate between the tumor and other adipocytic neoplasms when the tumor is larger than 10 cm, and in suspicious atypical lesions, recurrent lesions, in those with retroperitoneal and abdominal localizations, and in cases with alarming clinical and radiological features (13, 14). In our case, the FISH method was used due to the presence of atypical stromal cells, the size difference between the lipocytes, the lesion diameter greater than 10 cm and the deep localization of the mass,

and the amplification was positive in the MDM2 and CDK4 genes, leading to the diagnosis being clarified as ALT/WDL.

Based on the limited number of cases reported in literature, ALT/WDL mostly occurs in the anterior mediastinum (12, 15-17), and is more common in adult males between the ages of 40 and 60 (7). Our 56-year-old female case had a tumor originating from the posterior mediastinum.

The behaviors of tumors in the mediastinum are similar to those in the lower extremities and retroperitoneum, which are the most common sites, respectively. Mediastinal ALT/WDL usually grows slowly and up to 15% of patients may be asymptomatic. The laxity and mobility of tissues and the mediastinal state of these structures allow them to gradually adapt and accommodate slow-growing tumors. Tumors can thus reach large sizes, and subsequently, to press on neighboring structures causing such symptoms as superior vena cava syndrome, Horner's syndrome, dysphagia, dyspnea, cough, spinal nerve palsy and tachycardia (3, 7). In our case, the patient presented to us with acute cough.

The predominant finding of mediastinal liposarcoma on conventional chest radiography is an enlarged mediastinum, although trachea and vessel deviation may also be prominent. The mediastinal enlargement was detected in the posteroanterior chest X-ray of our case.

Mediastinal liposarcomas can appear as a fat-containing masses to solid masses with low attenuation values ranging from -50 to -150 HU on thorax CT (18), while larger values may be related to necrosis, heterogeneity or the soft tissue component of liposarcomas. When well-differentiated, they are more radiolucent, homogeneous and well-circumscribed like lipomas, while other liposarcomas may be irregularly-circumscribed, of greater density and radiopaque. The CT findings of ALT/WLD are similar to those of lipomas, and usually involve a large amount of fat covering more than 75% of the tumor volume (9). In our case, a hypodense mass lesion compatible with a lipoma of -99 HU density (low density) was observed. Thorax CT is also useful for determining the size of the lesion before surgery, as well as the size and location of the residual tumor after surgical resection (17). Magnetic resonance imaging provides more valuable information in terms of revealing any mediastinal vessel invasions (2).

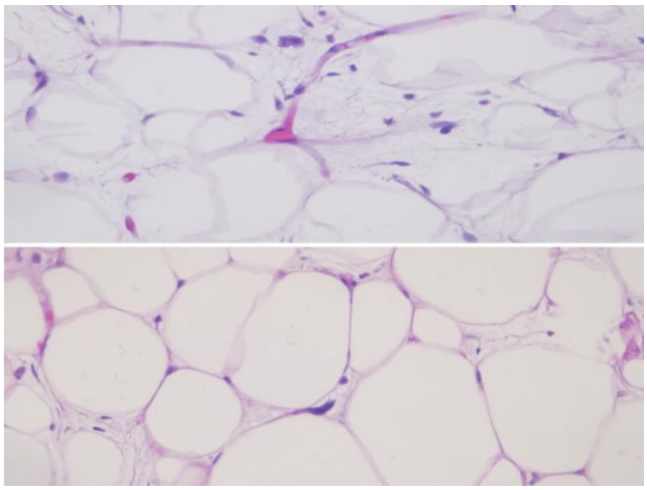

Figure 5: Atypical stromal cells, with significant shape and size differences discernible between adipocytes (H&E X40)

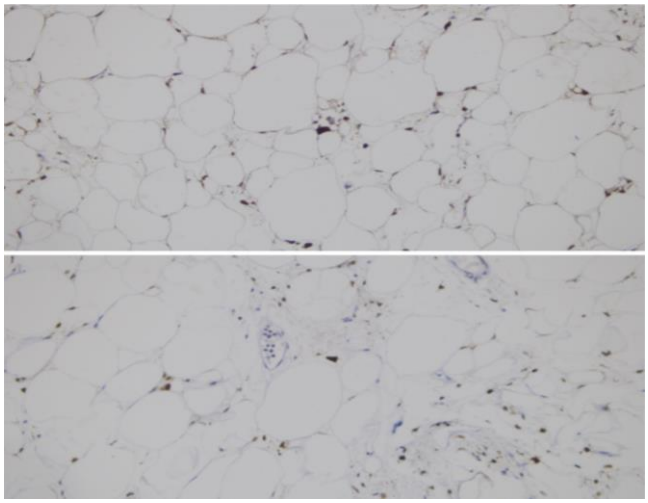

Figure 6: CDK4 positivity in histiocytic and atypical stromal cells in immunohistochemical examination

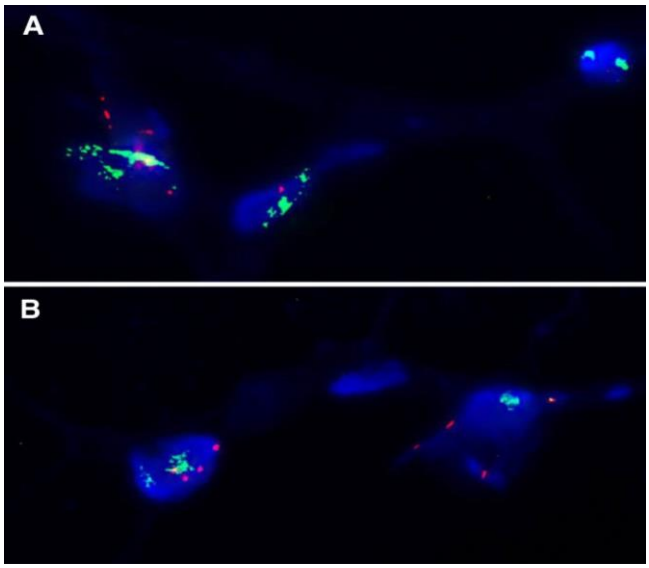

Figure 7: Amplification positivity in the MDM2 gene regions using the FISH technique (A); Amplification positivity in CDK4 gene regions using the FISH technique (B)

There have been several earlier studies identifying the FDG PET properties of lipomatous tumors, including PET

studies showing a correlation between SUVmax (degree of metabolic activity) and liposarcoma tumor grade, and higher grade tumors tending to have greater FDG uptake (19). If a fat-containing lesion has significant (>25%) internal soft tissue content on CT, it should be considered suspicious for liposarcoma, regardless of FDG activity, as both ALT/WDL and myxoid liposarcoma can occur with low metabolic activity. In other words, low FDG activity should not be assumed to be a sign of benignity (19). In our case, no pathological FDG uptake was observed on PET-CT. Since ALT/WDL is a low-grade malignant atypical lipomatous, well differentiated tumor, FDG uptake may not be observed.

In patients with mediastinal liposarcoma, a complete surgical resection with largely negative margins is usually curative and is considered the optimum treatment approach. ALT/WDL is considered a low-grade malignancy that rarely metastasizes, but should be followed carefully as recurrence or differentiation may occur (6), and it should be kept in mind that ALT/WDLs have no potential for metastasis unless dedifferentiated (20). It has been reported that patients can benefit from repeated surgical resections in cases of recurrence (6).

Since these tumors are resistant to chemotherapy and RT, such treatments have limited effect on survival (8). Radiotherapy may be valuable for the palliation of unresectable cases, but is very likely to result in mediastinal fibrosis in this region, and the effect of chemotherapy has not yet been determined (12). The application of radiotherapy before and after the operation has also been suggested. In our case, a wide surgical resection was performed and a negative surgical margin was achieved, and adjuvant RT was given after the operation to prevent local recurrence given the large size of the tumor.

Histological typing is very important in determining the type and extent of treatment. Due to differences in the treatment approaches, prognosis and long-term follow-up, it is important to preoperatively differentiate between simple lipoma and well-differentiated liposarcoma (4) as the survival of patients with differentiated or pleomorphic liposarcoma is significantly shorter than those with myxoid or well-differentiated liposarcoma (7).

The most important factor in prognosis is anatomical location. If the tumor is deeply located (mediastinum, retroperitoneum, spermatic cord), the chance of achieving negative surgical margins decreases, the risk of local recurrence increases, and the risk of death increases as a result of uncontrolled local effects (5,9). In such cases, local recurrence is more common than metastasis. with a prevalence of around 40%, often occurring within the first 6 months (20). Tumors located in central body cavities, however, tend to envelop vital structures or may simulate normal adipose tissue, making negative margins very difficult to obtain.

CONCLUSION

Although primary mediastinal liposarcomas are very rare, they should be considered in the differential diagnosis of mediastinal tumors (16). Their anatomical location may complicate complete surgical resection, and recurrences may develop in the event of positive margins. Furthermore, despite their slow growth, these tumors are associated with a poor prognosis, and so it is important to ensure the continued postoperative clinical follow-up of patients, given the likelihood of recurrence.

CONFLICTS OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

Concept - G.K.K., O.O., I.Y., S.M.A.; Planning and Design - G.K.K., O.O., I.Y., S.M.A.; Supervision - G.K.K., O.O., I.Y., S.M.A.; Funding - G.K.K., S.M.A.; Materials - G.K.K., I.Y.; Data Collection and/or Processing - G.K.K., O.O.; Analysis and/or Interpretation - G.K.K., O.O.; Literature Review - G.K.K., S.M.A.; Writing - G.K.K.; Critical Review - O.O., I.Y.

YAZAR KATKILARI

Fikir - G.K.K., O.O., I.Y., S.M.A.; Tasarım ve Dizayn - G.K.K., O.O., I.Y., S.M.A.; Denetleme - G.K.K., O.O., I.Y., S.M.A.; Kaynaklar - G.K.K., S.M.A.; Malzemeler - G.K.K., I.Y.; Veri Toplama ve/veya İşleme - G.K.K., O.O.; Analiz ve/veya Yorum - G.K.K., O.O.; Literatür Taraması - G.K.K., S.M.A.; Yazıyı Yazan - G.K.K.; Eleştirel İnceleme - O.O., I.Y.

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