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Primary Pulmonary Fibrosarcoma with Bone Metastasis: A Rare Case Report

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Abstract: ***Introduction: Fibrosarcomaia a rare and high level tumor that were derived from mesenchymal cell, arises from pulmonary parenchyma, the pulmonary artery, its branches, and the bronchi. The prevalence of primary pulmonary sarcomas are extremely rare, only 0.1 to 0.5% from all of pulmonary neoplasm cases. The undifferentiated pleomorphic sarcoma (UPS) is a rare tumor, which found for less than 0.2% of all lung tumor cases. Case: This is a case report of rare Primary pulmonary Fibrosarcoma with bone metastases by discovering apositive vimentinstaining indicates the mesenchymal origin of fibrosarcoma. However, the family of patient refused treatment. Conclusion: Radical resection is considered to be the only treatment that can achieve cure or prolong survival if the tumor appears to be resectable. Chemotherapy in patients with advanced – phase fibrosarcomas is based on anthracyclines as the first - line treatment, and doxorubicin is the most commonly used drug.***

Keywords: Primary Pulmonary Fibrosarcoma, Bone Metastasis, vimentin, chemotherapy

1. Introduction

A rare, extremely dangerous tumor with mesenchymal cell origins is called fibrosarcoma. It comes from spindle - shaped fibroblasts, with an abnormally high division rate that have undergone pathological transformation. Fibrosarcoma falls under the category of fibroblastic/myofibroblastic sarcomas in the WHO classification of soft tissue sarcomas. The adult type of fibrosarcoma and congenital or infantile type of fibrosarcoma and could be separated from one another. Unlike infantile type, which WHO classifies as a highly malignant tumor that seldom metastasizes, adult - onset fibrosarcoma is categorized as an intermediate malignant tumor. [1]

In 0.1 to 0.5 percent of all lung neoplasms cases, primary pulmonary sarcomas were commonly found. Less than 0.2 percent of lung tumors are undifferentiated pleomorphic sarcomas (UPS), an uncommon malignancy. Compared to initial pulmonary sarcomas, lung metastases from extrapulmonary primary sarcomas more frequently found. Primary undifferentiated pleomorphic lung sarcoma is still an extremely uncommon cancer with a dismal prognosis. [2]Most cases of fibrosarcoma occur in patients between ages of 25 and 79 while adult - type fibrosarcoma is most prevalent in ages of 30 and 60. [1]

Primary pulmonary sarcomas (PPS) is a rare variant of non - epithelial malignanciesthat arises from themesenchymal tissue of the lung. PPS can originate from vascular, mesenchymal bronchial wall, or lung interstitial components. They mostly infiltrate lung parenchyma, producing tumors that are clearly defined but not encapsulated. Rarely, also spread into bronchi. Primary pulmonary sarcomas are substantially outnumbered by secondary tumors, with ratio 3000: 1. In a prospective study using authorized soft - tissue sarcomas, it was discovered similar accuracy to traditional imaging techniques of CT and MRI in detecting primary tumors, higher accuracy in detecting metastases to lymph nodes (95%) and metastases to bones (90%). [3]

2. Case Report

Mrs. C, 18 years old Java student, major complained of shortness of breath, cough, and chest pain. The patient has experienced shortness of breath for three months. Cough was found in the last months, coughing up white phlegm, volume ½ tsp per cough, blood was not found, history of coughing up blood was found six months ago. Chest pain was found on the left, fell like been stabbing with Vas score: 4 and did not radiate to back. Fever and night sweats were not found. Weight loss was found, which is a loss of 15 kg in 6 months. History of exposure to mosquito coils was found for the last ten years.

The patient was previously treated at RantauPrapat Hospital and only did a chest X - ray and a non - contrast chest CT scan, then the patient was referred to Adam Malik Hospital. The patient was a passive smoker for 15 years—the patient's

house was with an abscessed roof and tiled floor in a densely populated area. The patient works in a residential area.

On physical examination, the patient's consciousness was compos mentis who looked moderately ill with blood pressure 130/90 mmHg, heart rate 108 bpm, respiratory rate 26 rpm, SpO_2 96% room air, temperature 36.7^{0}C, and VAS: 4. Head, Neck, Cor, abdomen, and extremities examination within normal limits. On thoracic examination, proportion anterior and posterior were regular, asymmetrical with breathlessness on left hemithorax, tactile fremitus left <right, weakened fremitus in upper to lower left lung. The examination found dim in the upper to lower left lung on percussion. Auscultation was weak in the upper to lower left lung. There was no additional sound of rhonchi (- / -) or wheezing (- / -).

Chest X - ray showed a solitary pulmonary mass and minimal pleural effusion. On MSCT Scan Thorax with IV Contrast examination, a heterogeneous density mass appeared, post - contrast in upper and middle right lung adhering to the chest wall and vascular pushing the trachea to right side, left bronchus narrowing, fluid collection visible in left subdiaphragm, concluded as a left lung mass with left pleural effusion (T4NXM1A).

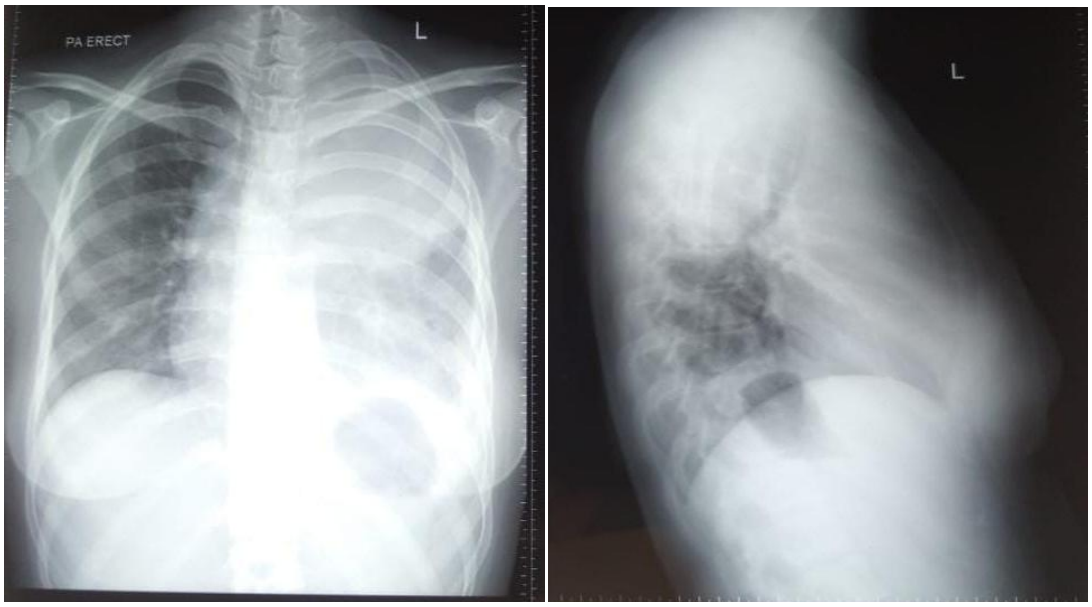


Figure 1: Chest X - ray examination showed a solitary pulmonary mass and minimal pleural effusion

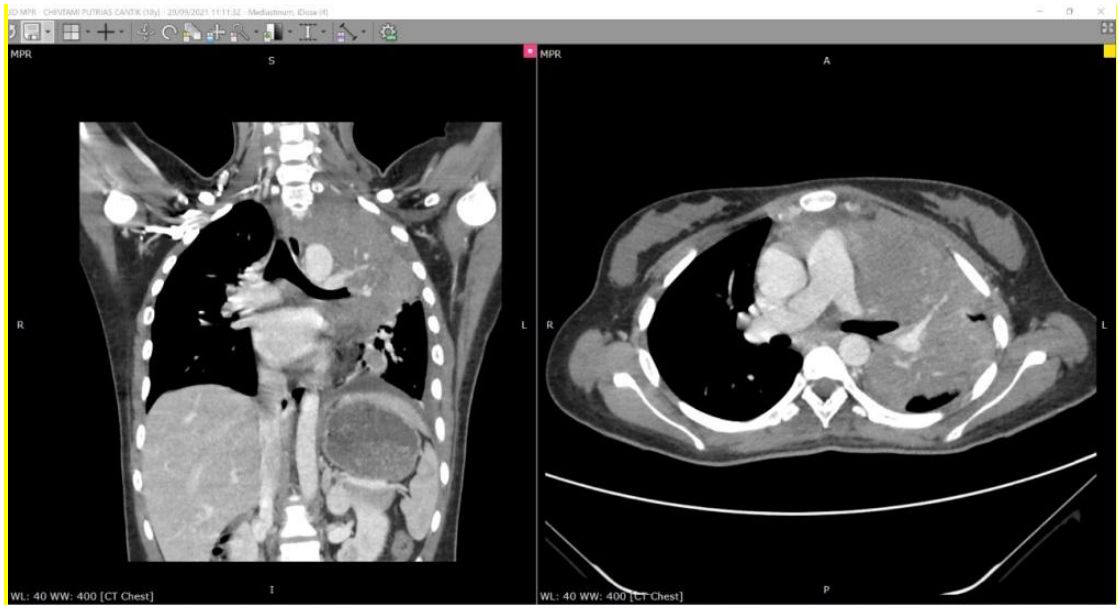


Figure 2: MSCT Scan Thorax with IV Contrast examination showed left lung mass with left pleural effusion (T4NXM1A).

On thorax Single Photon Emission Computed Tomography (SPECT) examination, there were pathologically increased radioactivity arrests (multiple hot spots) on the VII cervical vertebrae, I - V thoracic vertebrae, and left posterior II - III rib. Then it was concluded that there was a process of bone metastases.

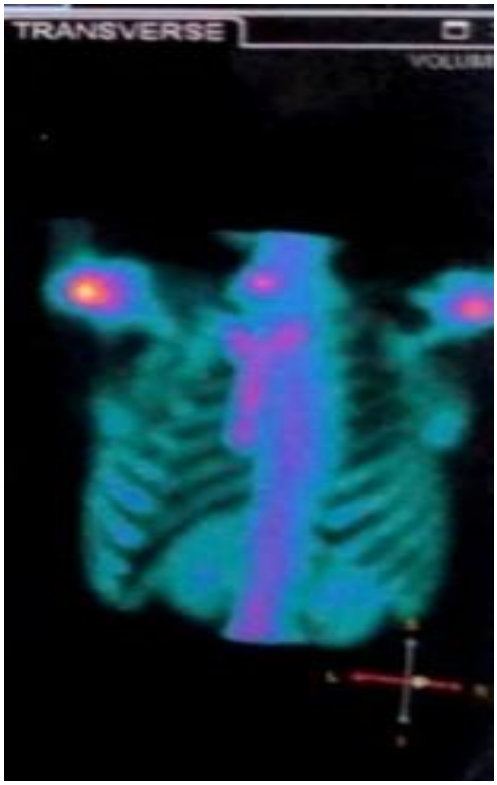


Figure 3: Thorax SPECT examination showed that there was a process of bone metastases.

Examination of tumor markers showed LDH 173 U/l, AFP 0.43 ng/ml, CEA 1.91 ng/ml, β - HcG<1.2 mIU/ml, Cyfra 21 - 1 0.98 ng/ml, SCC 0.4 ng/ml. On bronchoscopy, the examination found a tumor in the upper left lung. On TTLB/TTNA examination with CT SCAN Guidance, histopathological results were found fragmented mass consisting of pleomorphic tumor cells proliferation with enlarged nuclei, round oval and spindle shapes, irregular nuclear membrane, hyperchromatic, eosinophilic cytoplasm. Atypical mitoses were found. The stroma consists of fibro collagenous connective tissue accompanied by an infiltration of inflammatory lymphocyte cells. Necrosis and interstitial bleeding were also seen in several foci. It concluded as spindle cell sarcoma, while on cytology examination, it was found that smear preparation consisted of pulmonary TTLB consisting of spindle - shaped cells oval and spindle - shaped nuclei, coarse chromatin, hyperchromatic, and eosinophilic cytoplasm. The background of the smear consisted of red blood cells and minimal lymphocytes, then concluded as C5 (malignant smear), which is a sarcoma (spindle cell).

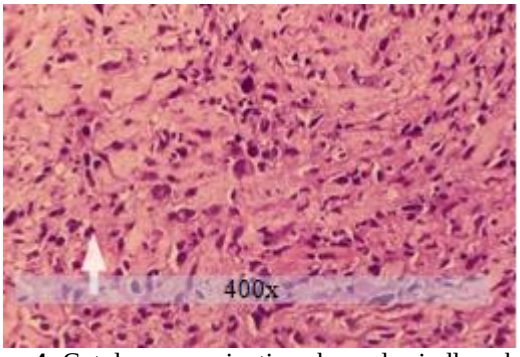
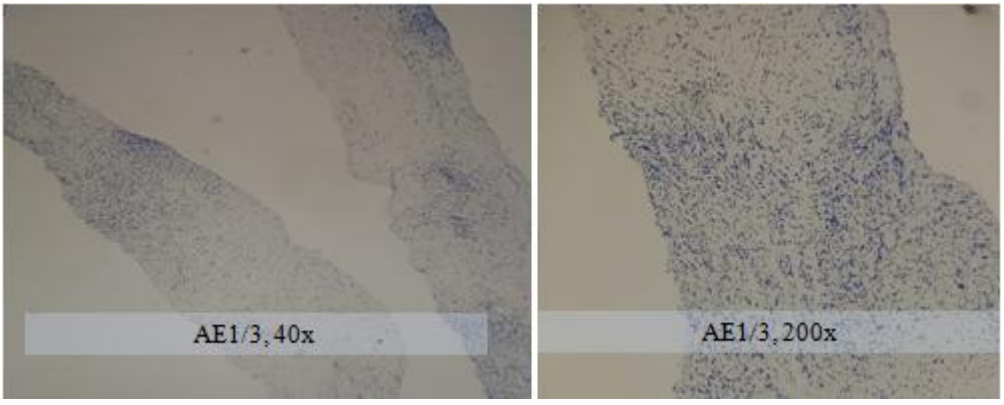


Figure 4: Cytology examination showed spindle - shaped cells, oval and spindle - shaped nuclei, coarse chromatin, hyperchromatic, and eosinophilic cytoplasm. A, B: Magnification 100x; C, D: Magnification 400x

On immunohistochemical examination, it was found that vimentin was positively stained with diffuse staining of tumor cells, AE1/3, CD 30, CD 45 was negative, and it was concluded that this case was more in line with Sarcoma (Fibrosarcoma). The patient was then diagnosed with primary pulmonary fibrosarcoma and treated with chemotherapy.



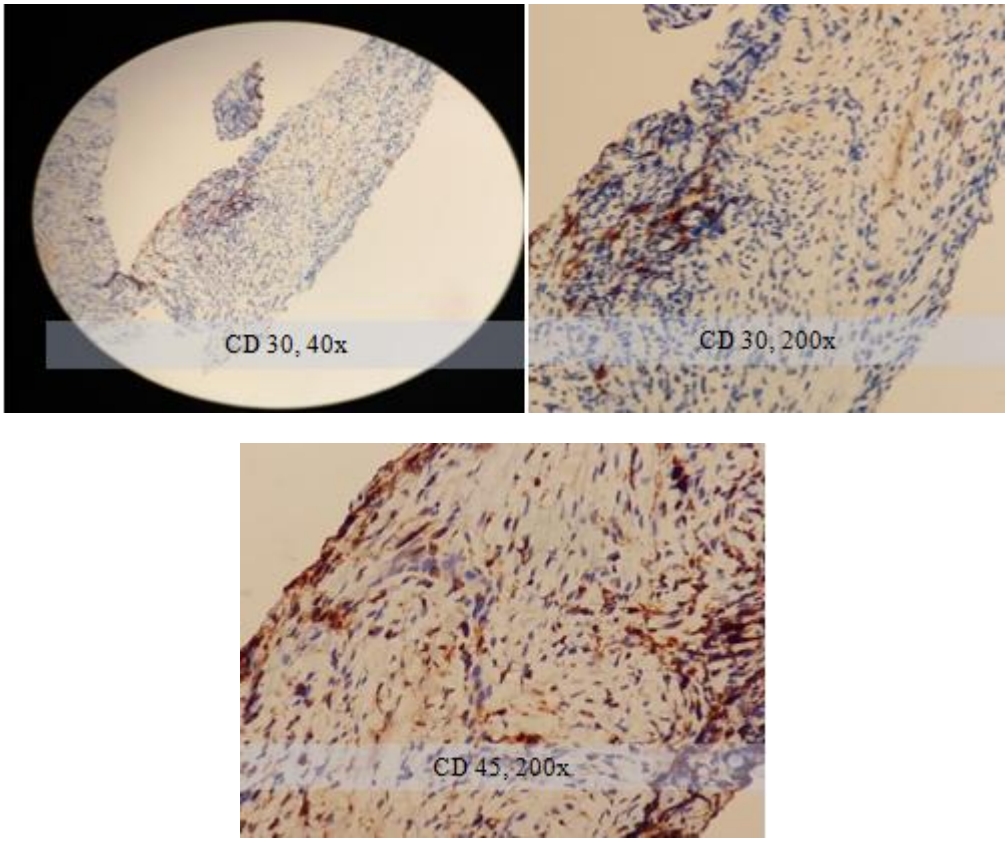


Figure 5: AE1/3, CD 30, CD 45 immunohistochemical examination was negative - unstained tumor cell. Magnification 40x and 200x

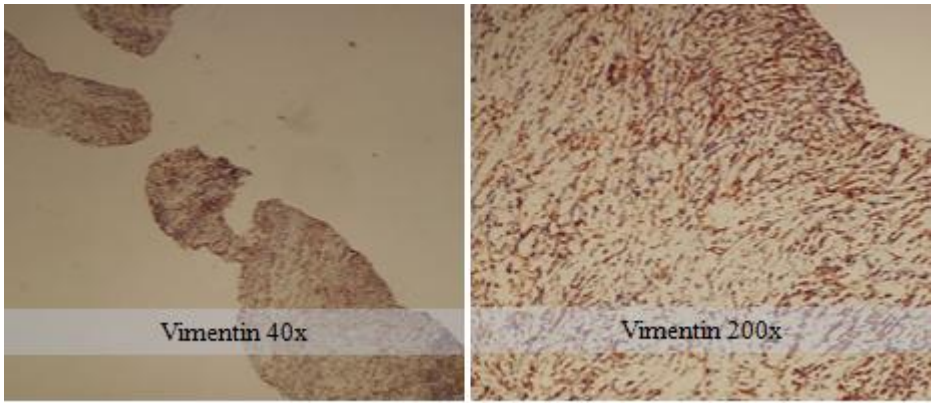


Figure 6: Vimentinimmunohistochemical examination was positively stained with diffuse staining of tumor cells. Magnification 40x and 200x

This patient was admitted to Haji Adam Malik hospital and was given analgesics (MST 10 mg twice a day). in this patient has been recommended to get chemotherapy, but unfortunately the patient and family refused chemotherapy. The patient had died 14 months after diagnosis.

3. Discussion

Primary pulmonary sarcomas (PPS) is a rare variant of non - epithelial malignant tumors that arise from mesenchymal of lung tissue, including bronchial wall, blood vessels, and pulmonary stroma. Its prevalence is only from 0.013percent to 1.1 percent of malignant lung tumors are lung sarcomas. The most effective methods for treating these tumors include radical surgical procedures. Histological type, size of the initial tumor, grade TNM of lung cancer, histological grade (G), and surgical margin are recognized prognostic variables in sarcomas (R). The disease only recurred locally following non - anatomical resection. The median *Progression - free survival* (PFS) was 36 months as opposed to 12 months for anatomical surgeries. Surgery was used to treat every instance of local recurrence following non - anatomical resection. [4]A fibrosarcoma in children is very less aggressive and most curable than children older than 15 years, and also mentioned "infantile fibrosarcoma" (IFS) [5–10.]

Undifferentiated pulmonary sarcoma (UPS), pT4N0M1a stage IV A, and genetic analyses of resected tissue revealed v - Ki - ras2 Kirsten rat sarcoma viral oncogene homolog (KRAS) mutation. A case of a KRAS mutation and a PIK3CA (phosphatidylinositol 3 - kinase p110 subunit alpha) mutation occurring simultaneously was described by Li et al. The RAS/mitogen - activated protein kinase (Ras/MAPK) and phosphatidylinositol 3 - kinase (PI3K)

/mTOR pathways were both shown to be activated in majority of UPS patients, according to Serrano et al., KRAS is a proto - oncogene that is found at 12p12.1 and is regularly mutated; mutations in this gene are found in 17–25% of all malignancies. The maintenance of tumor phenotype and aggressionisis triggered by constitutive the activation of signaling pathways growth factor, of which RAS/MAPK and PI3K/mTOR often stimulate the oncogenic of soft tissue sarcomas[11]

Specific questions about symptoms such as paraesthesia, pain, previous lesions, changes in the mass's size and consistency, surgical procedures, and radiation treatments was carried out in first contact with patients which is include a complete medical and family history in the anamnesis. [1] Pulmonary sarcoma typically manifests in young to middle - aged people and does not exhibit a preference for either gender. The most frequent clinical symptom is a cough, frequently accompanied by hemoptysis, followed by chest pain. Loss of weight and low - grade fever are uncommon. On a chest X - ray, these tumors can also appear as incidental tumours. Clinical, radiographic, pathological, and immunohistochemical tests are necessary for the diagnosis of primary pulmonary synovial sarcoma in order to rule out alternative main tumors and metastatic sarcoma. [12]

Deep soft tissues are frequently the site of fibrosarcomas. A spherical shape, a hard consistency, an average size of 3 to 8 cm, and a sharp separation from the surrounding tissue define tumor mass. This tumor may go unnoticed for a long time due to its sometimes deep localisation, the fairly vague and frequently painless soft - tissue swelling, and ("tip - of - iceberg" phenomenon). Anorexia, weight loss, and decreased performance may accompany the advanced stages of fibrosarcoma. [1]

Alternately, X - rays and computed tomography (CT) can be used to identify bone involvement. The detection of distant metastases can be aided by CT scan of chest, abdomen, and pelvis, a whole - body MRT, or a PET - CT scan. It is possible to employ a less invasive approach like a fine - needle aspiration (FNA) biopsy or a core needle biopsy. Surgical biopsies are recommended if tumor size > 3 cm and minimally invasive treatments not responded. Excisional biopsy should be used to sample soft tissue tumors that are 3 to 5 cm in size. When tumors are larger than 5 cm, incisional biopsies can be performed in which only a portion of the tumor is removed. [1]

Accurate sarcoma classification and diagnosis depend on immunohistochemistry. Even though it frequently tests positive for actin, keratin, desmin, EMA, CD99, and CD34. UPS is one ofexclusion diagnosis because positive stains typically do not aid in diagnosis. Our patient’s tumor tissue also exhibited microscopic characteristics indicative of UPS, including variable cellularity, storiform pattern, erratic fascicles, pleomorphic, and, peculiar tumor cells with foamy cytoplasm and clear atypia; on the inflamed collagenous stroma background, multinucleated giant cells were also seems, as well as a number of mitotic figures, including atypical forms. [2]

Monomorphic spindle - shaped fibroblasts that are parallelly organized are a hallmark of fibrosarcoma. These fibroblastic strands are frequently perpendicular with appearance of a herringbone pattern. The cytoplasm is minimal, and nuclei are conspicuous, with variation increased uneven and number of nucleoli, granular chromatin, coarse. Rare pleomorphism exists. The degree of tumor malignancy is correlated with the amount of hemorrhagic and necrotic tissue, mitotic cells, and interstitial collage. It is difficult to distinguish clearly between other spindle - cell neoplasms and fibrosarcoma using histopathology examination. [1]

The mesenchymal origin of fibrosarcoma is shown by positive vimentin staining. The most prevalent myogenic markers are desmin, muscle - specific actin (MSA), and alpha - smooth muscle actin (α - SMA). S - 100 protein is one of neuronal marker that differentiated benign peripheral nerve sheath tumors from malignant ones (MPNST). Positive spindle - cell angiosarcomaimmunostains, CD34, CD 31, and factor VIII (von Willebrand factor) immunostains indicate vascular cancers. Vimentin is most the only positively stained marker in fibrosarcoma. As indicators of myofibroblastic differentiation, smooth muscle actin (SMA) and/or muscle - specific antigen (MSA) may occasionally be seen. Sometimes CD34 can be found in fibrosarcomas that develop secondarily from either solitary fibrous tumor (SFT). [1]

One of primary pulmonary sarcoma which most common causes bone metastases was primary pulmonary epithelioid inflammatory myofibroblastic sarcoma (EIMS) while the cases was extremely rare. The EIMS tumor is aggressive, poor prognosis, and is prone to local recurrence. The tumor usually has metastatic disease at presentation, with the brain and skeleton appearing to be the favored locations of metastases. The tumor typically manifests as a single parenchymal mass or as a pleural mass with relatively brief symptoms (6 months). [13]

The frequency rate of pulmonary sarcoma was 72.72%. The median time between diseases was 15 months. Patients with metastatic illness had a median OS of 4 months, compared to a population - wide OS of 10 months. Only surgical intervention affected survival. [14]If the tumor appears to be resectable, radical resection has been known as the only therapy that can lead to prolonged survival or cure. The function of perioperative chemotherapy, however, is still debatable. These tumors have a quick clinical progression and a significant risk of metastasis or recurrence. Even the tumor appears indifferent to both of radiotherapy and chemotherapy, a palliative strategy that combines either chemotherapy or radiotherapy may be used in an advanced stage. [2]The combination of ifosfamideand doxorubicin or doxorubicin monotherapy is the suggested course of treatment for advanced sarcoma soft tissue. We choose doxorubicin monotherapy as the neoadjuvant therapy choice, despite the fact that combined therapy typically causes bone marrow damage[15].

Anthracyclines are main agent of chemotherapy for patients with advanced - stage fibrosarcomas. Doxorubicin is most frequently used in this situation. Actinomycin D and ifosfamide can also achieve response rates exceeding 15% in

addition to doxorubicin. [1]Despite the development of immune - checkpoint inhibitors, such as pembrolizumab (anti - PD - 1 antibody), atezolizumab (anti - PD - L1 antibody), nivolumab (anti - programmed cell death 1 [PD - 1] antibody), durvalumab (anti - PD - L1 antibody), and ipilimumab, significant advancements have been made in treatment of lung cancer (anti - cytotoxic T lymphocyte antigen four antibodies). [11]

After the decreased lung volume surgery or the procedure of lung transplant, preoperative pulmonary rehabilitation (Prehab) has been proven to dramatically enhance quality of life, dyspnea symptoms in COPD patients, and exercise tolerance. Such patients may have severely impaired postoperative ventilation or diffusion capacity due to lung tissue loss, which puts them at risk for dyspnea, cardiac problems, and mortality. As a result, some patients with subpar pulmonary function or marginal are deemed inoperable and are instead referred for radiation, palliative care, or systemic anticancer therapy. Preoperative and postoperative pulmonary rehabilitation can be tailored for high - risk patients to minimize their frequency of pulmonary problems after surgery, = postoperative outcomes, including mortality, and duration of hospitality. [16]

Unfavorable prognostic factors for fibrosarcoma include I high histologic grade, (ii) a high mitotic figure count (> 20/10 HPF), (iii) significant tissue necrosis (> 50%), (iv) a reduction in collagen fibers in favor of an increase in cellularity, (v) tumors that are highly localized, (vi), and tumors size larger than 5 cm. The recurrence rate ranges from 12 to 79 percent, with average of 40 to 50 percent, depending on patient's age, tumorlevel, and histology of tumor margin. Five years after an adequate tumor removal, recurrences occurs in 10–20 percent of patients. [1]

The role of adjuvant chemotherapy as succesfull treatment in improving outcomes for fibrosarcoma patient with metastatic disease have been reported in Iran[17]. It was also noted that in the case of fibrosarcoma may exhibit unpredictable clinical behavior[18]. Pulmonary metasectomy was also introduced and have been reported as surgical indications in fibrosarcoma patients, gender and tumour origins should be a concern in this case[19]. Pulmonary metasectomy should be a concern in patient with Ewing's sarcoma bone, that shows relapse on their lung. Metasectomy can lead to better prognosis in patients, even it's pulmonary noduls was more than one[20].

4. Conclusion

Fibrosarcoma is a rare, highly malignant tumor derived from mesenchymal cells. Pulmonary sarcomas can arise from the lung parenchyma, the pulmonary artery, the bronchi, and its branches. The tumor mass is characterized by a spherical shape, firm consistency, an average 3–8 cm size, and a sharp demarcation from the surrounding tissue. The positive vimentin staining indicates the mesenchymal origin of fibrosarcoma. Bone is the third most common site of metastasis of primary lung cancer Radiation therapy was used primarily to improve pain management or reduce the risk of pathological fractures in nearly one - third of patients**.** Radical resection is established as the only treatment that can achieve cure or prolonged survival if the tumorappears to be resectable.

However, the role of perioperative chemotherapy is still debatable, and complementary radiotherapy (RT) can be a second choice in addition to surgery to optimize local control. Chemotherapy in patients with advanced fibrosarcomas is in accordance with anthracyclines as the first - line treatment, which is doxorubicin is the most widely applicables drug. In 10–20% of patients whose tumors had been adequately resected, recurrences occur within five years.

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