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Primary Pulmonary Ewing Sarcoma or Askin Tumor (PNET of the Thoracopulmonary Region) - a Rare Clinical Case in our Practice

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Abstract

Primary pulmonary Ewing sarcoma is a rare disease belonging to the Ewing sarcoma tumor family. The origin of these rarely diagnosed primary undifferentiated neoplasms with possible localization in different organs and tissue structures is still unknown. We present a rare clinical case of primary pulmonary extraskeletal Ewing sarcoma in a woman 35 years old. The purpose of this article is to emphasize the difficult histological and differential diagnosis, requiring a wide panel of immunohistochemical markers. Despite the maximum possible radical surgery, given the local biological malignancy of this exceptionally rare tumor with a poor prognosis, we performed postoperative intensity modulated radiotherapy (IMRT).

Keywords: Primary pulmonary ewing sarcoma, Extraosseous primitive neuroectodermal tumor (PNET), Immunohistochemistry, PET/CT, Surgery, Radiotherapy

1. Introduction

Ewing's sarcoma family tumors (ESFT) includes Ewing sarcoma (osseous and extraosseous), primitive neuroectodermal tumor (PNET) of the bone and soft tissues, Askin tumor (PNET of the thoracopulmonary region) [1]. Extraskeletal Ewing's sarcoma (EES) has also been reported in the pelvis, buttocks, upper limbs, mediastinum, and abdominal organs [2]. Pulmonary EES is rare, and fewer than 30 pulmonary PNET cases have been reported thus far [1,3]. Immunohistochemistry is compulsory to confirm the diagnosis [4]. We present a rare clinical case of primary pulmonary EES in a woman 35 years old. The purpose of this article is to emphasize the difficult diagnosis of this rare disease at a young age and the individual assessment of the necessary therapeutic approach.

2. Clinical Case

We present a 35 -year -old woman. On the occasion of a complaint of subjective shortness of breath in April 2024, a lung CT was carried out on which a rounded lesion was found with a sharp outline in the fifth segment of a left lung measuring 52 x42 mm suspected for an echinococcal cyst. In September 2024 she entered the thoracic surgery clinic, where a video-assisted partial resection of the left lung was performed. Intraoperatively- Through two thoracoports to the left reached the left pleural cavity. The lung is free from adhesions. In the lower part, a cystic pulmonary formation is located, which is partially resisted. A biopsy of the thoracic pleura was performed.

Histological Result: Pulmonary parenchyma fragments with infiltration of malignant tumor tissue, made up of monotonous moderately large cells with a moderate amount of cytoplasm and large amorphous nucleus with stranded eosinophilic nucleol. The cells are arranged in solid sheets, in places perivascular, similar to neuroectodermal differentiation (Figure 1). The tumor complies with the underlying pulmonary parenchyma.

Immunohistochemistry: Neoplastic cells expose diffusely CD99 (Figure 2 A), Vimentin (Figure 2 B), CD56 (Figure 2 C), ERG and Beta -catenin membrane. Single tumor cells expose Synaptophysin (Figure 2 D). Negative expression for MCK, CK7 (Figure 3 A), CK20 (Figure 3 B), EMA, TTF-1 (Figure 3 C), HMB -45 (Figure 3 D), S100, AR, WT-1, POSE, PAX-5, SMA and P40 CD20, CD25, CD2, CD4, CD5, CD3C (positive in peritumoral plasmocytes), CD31 and CD34 (positive focal in endothelium). The proliferative activity measured by KI 67 is about 25-30% (Figure 4).

Conclusion: Morphology and immunofenotype of neoplasm corresponds to primary pulmonary Ewing sarcoma with a specific genotype. From the preoperative PET/CT-neoplasm in the fifth segment of the left lung, which touches the bone pleura. Other

metabolite active lesions with the type of malignant engagement are not scanned.

Primary pulmonary Ewing sarcoma without locoregional and distant dissemination (Figure 5). In November 2024, a lateral thoracotomy was performed on the left with a massive radical resection of ewing sarcoma in a block with the adjacent part of the fifth rib and atypical resection of the lingula of the upper lung lobe. Intraoperatively, a 7x 8 cm neoplasm is found /with preliminary histological data for Ewing sarcoma /, intimately adjacent to the fifth rib, infiltrating the upper lung lobe in the lingula area. The neoplasm described was removed as radically as possible with the adjacent part of the fifth rib, as well as atypically with the adjacent part of the lingula. The Hilus lymph node is extirpated.

***Histological Diagnosis-Macroscopically*-Two Containers with Inscription:** 1. "Lung"- a 9 cm long rib and associated with it a pulmonary parenchyma of almost spherical shape and a diameter of 7 cm. In the cut almost completely engaged by a pink red tumor with a homogeneous measurement surface. 2. “Hilar lymph node” with a diameter of 12x7 mm.

Morphological result: A tumor composed of cells with unclear cytoplasmic borders, the nuclei are of a fine priest chromatin, the cytoplasm is pale eosinophilic. The cells form layers and wide cords. The stroma is scarce and richly vascularized by thin -walled blood vessels (Figure 6). The tumor is well distorted by the adjacent pulmonary parenchyma of a fibrous capsule. Part of the rib with a small fragment of the tumor in the bone marrow, but without a direct tumor infiltration. The hilus lymph node is without metastasis with sinus histiocytosis and anthracosis (Figure 7).

Conclusion: Lung engaged by probable Ewing sarcoma. Immunohistochemical (IHC) verification is required. CK AE1/3 with a negative reaction in tumor cells with positive internal control in the pulmonary parenchyma; Synaptophysin- a positive reaction in scattered single tumor cells (Figure 8 A); FLI-1- weakly to moderately pronounced reaction in about 70% of tumor cells; CD99- diffuse positive reaction in almost 100% of tumor cells (Figure 8 B); CD 56- Positive reaction in about 85-90% of tumor cells (Figure 8C); CD 45 with a negative reaction to tumor cells (Figure 8 D) with positive internal control in lymphocytes; SOX 10 (Figure 8 E), Chromogranin A (Figure 8 F), TLE and TDT- with a negative reaction. *Postoperative PET/CT*- Without data on residual tumor tissue, as well as data on lymphogenic and hematogenous dissemination (Figure 9). To reject the extraskeletal Ewing sarcoma of the uterus, the patient did ultrasound and MRI of the uterine body with the following finding: a few small uterine myomas (Figure 10). Due to the nearby resection lines, the local aggressive expansion of the extraskeletal Ewing sarcoma and the young age of the woman, we estimated that it was necessary to conduct a postoperative additive radiotherapy (RT). Figure 11 shows the targeted volumes in the overlapping (fusion) of the images from the postoperative PET/CT of the lungs with that of the planning CT. We conducted an intensity modulated radiotherapy of the VMAT method with daily dose (DD) 1.8 Gy up to total dose (TD) 45 Gy (Figure 12), which the patient suffered without acute side effects from the lungs and heart.

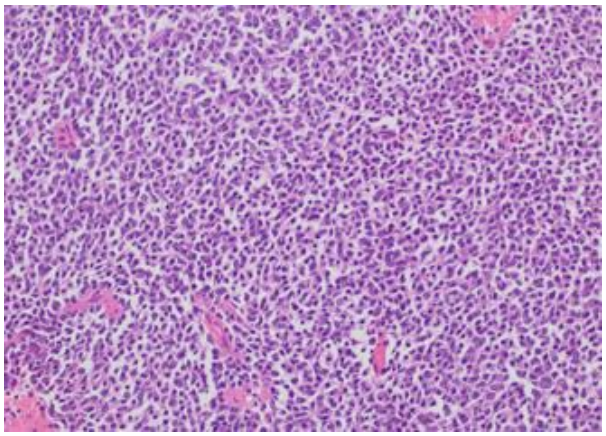

Figure 1: Pulmonary parenchyma fragments with infiltration of malignant tumor tissue, made up of monotonous moderately large cells with a moderate amount of cytoplasm and large amorphous nucleus with stranded eosinophilic nucleol. The cells are arranged in solid sheets, in places perivascular, similar to neuroectodermal differentiation (Hematoxylin-Eosin, original magnification x200

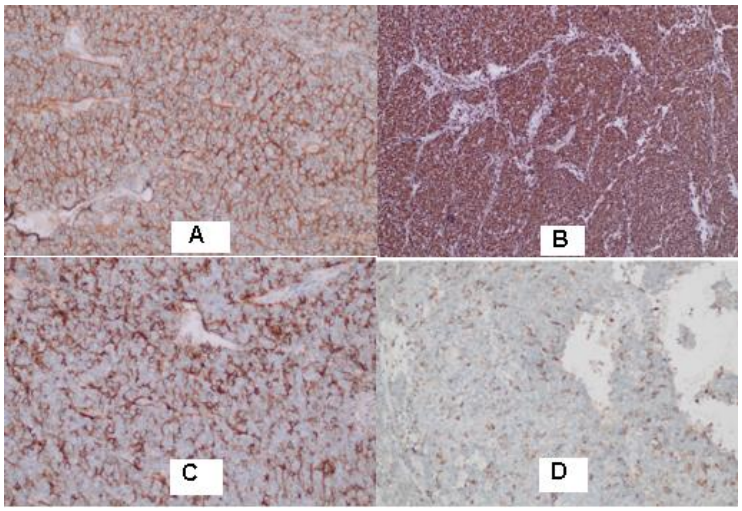

Figure 2: Immunohistochemistry- A) Neoplastic cells with diffuse positive membrane reaction for CD99; B) Positive reaction for Vimentin; C) Positive membrane reaction for CD56; D) Single tumor cells with a positive reaction for Synaptophysin x 100.

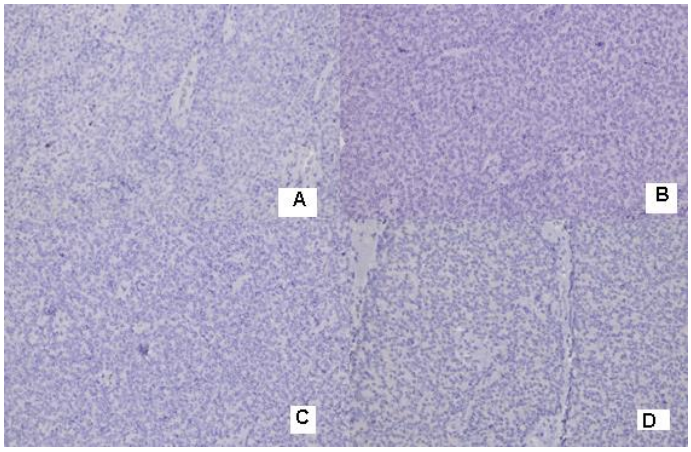

Figure 3: Immunohistochemistry- Negative expression reaction for A) CK7; B) CK20; C) TTF-1; D) HMB -45 x100

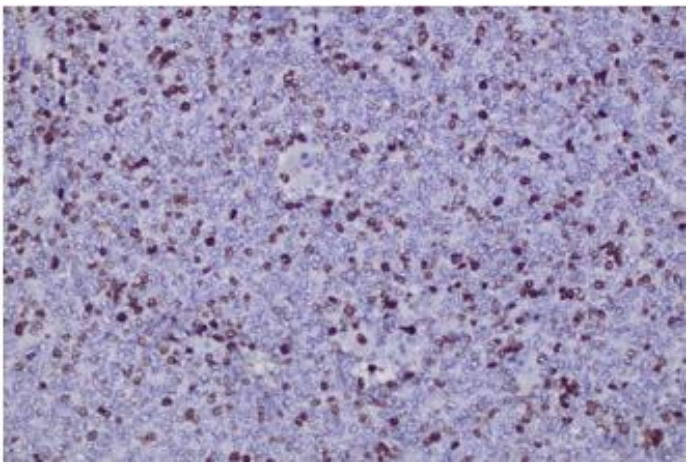

Figure 4: Immunohistochemistry - High level of the proliferation marker Ki 67 25-30% x100

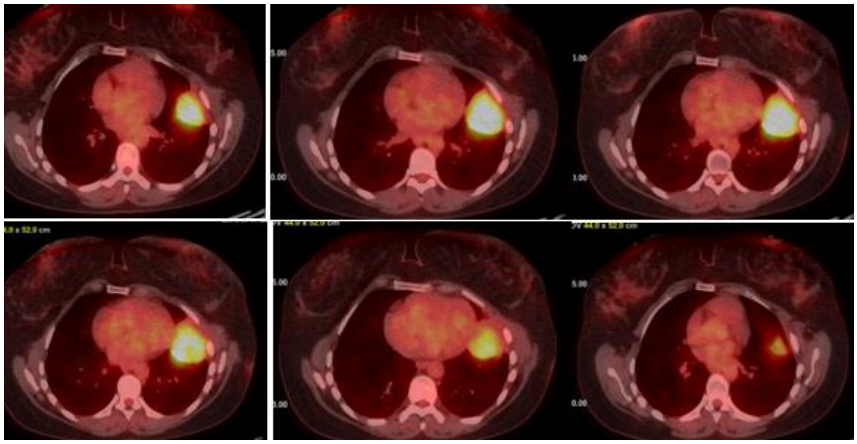

Figure 5: Preoperative PET/CT- Neoplasm in the fifth segment of the left lung, which touches the bone pleura. Other metabolite active lesions with the type of malignant engagement are not scanned

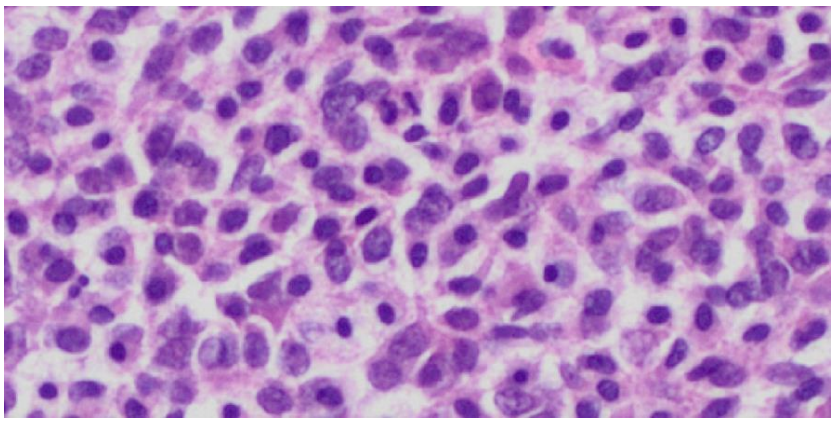

Figure 6: A neoplasm composed of cells with unclear cytoplasmic borders, the nuclei are of a fine priest chromatin, the cytoplasm is pale eosinophilic. The cells form layers and wide cords. The stroma is scarce and richly vascularized by thin -walled blood vessels. (Hematoxylin-Eosin, original magnification x400

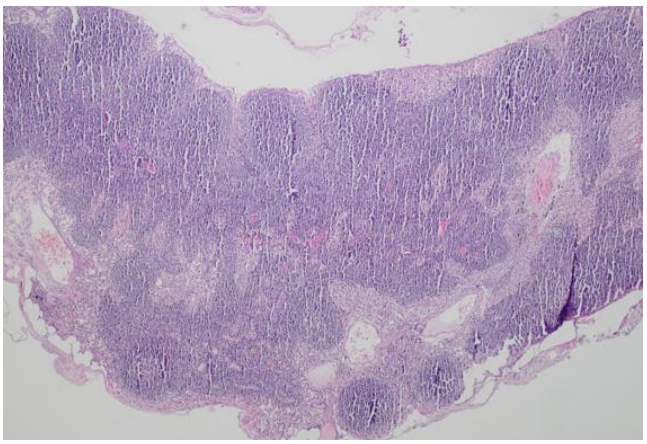

Figure 7: The hilus lymph node is without metastasis with sinus histiocytosis and anthracosis (Hematoxylin-Eosin, original magnification x200

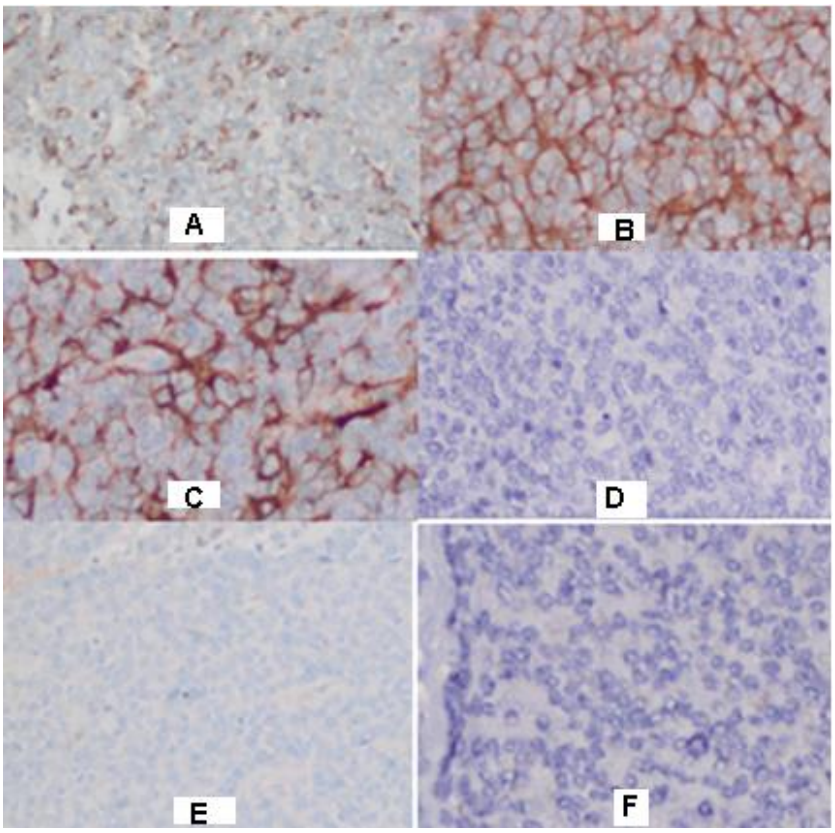

Figure 8: A) Synaptophysin with a positive reaction in scattered single tumor cells x 400; B) CD99 with diffuse positive reaction in almost 100% of tumor cells x 400; C) CD 56- Positive reaction in about 85-90% of tumor cells x 400; D) CD 45 with a negative reaction to tumor cells with positive internal control in lymphocytes x 400; E) SOX 10 with a negative reaction to tumor cells x 400; F) Chromogranin A with a negative reaction to tumor cells x 400

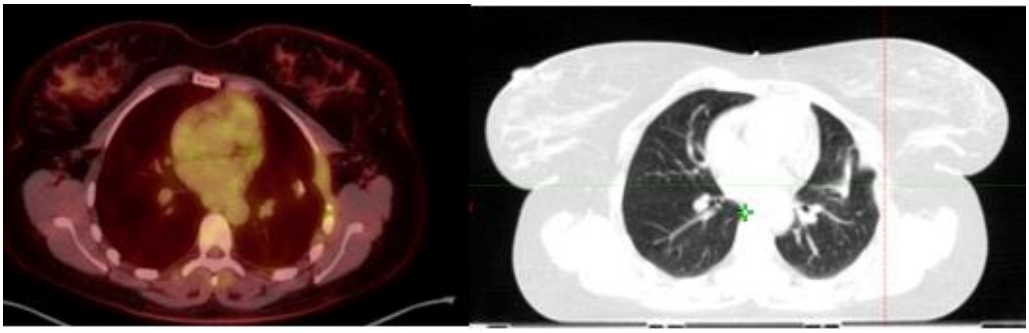

Figure 9: Postoperative PET/CT and CT- Without data on residual tumor tissue, as well as data on lymphogenic and hematogenous dissemination

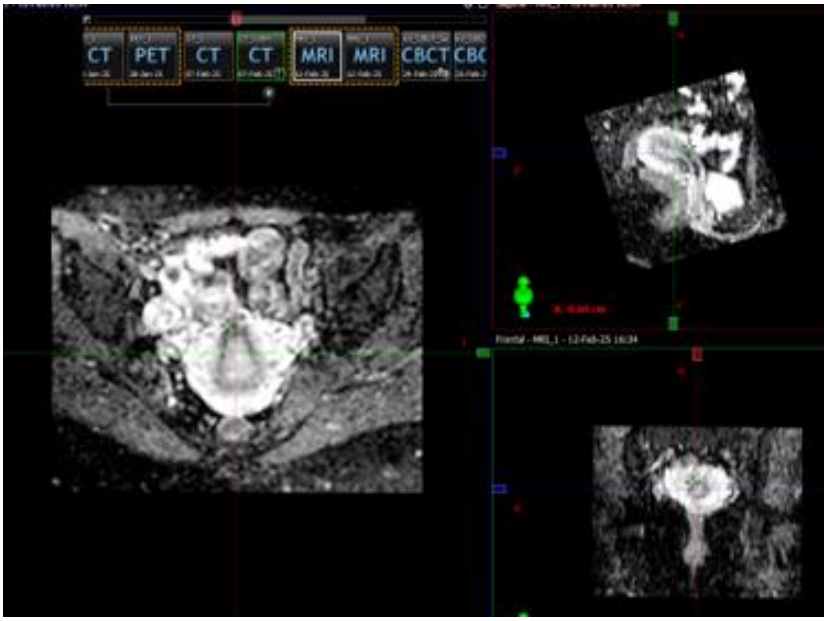

Figure 10: MRI of the uterine body with: a few small uterine myomas.

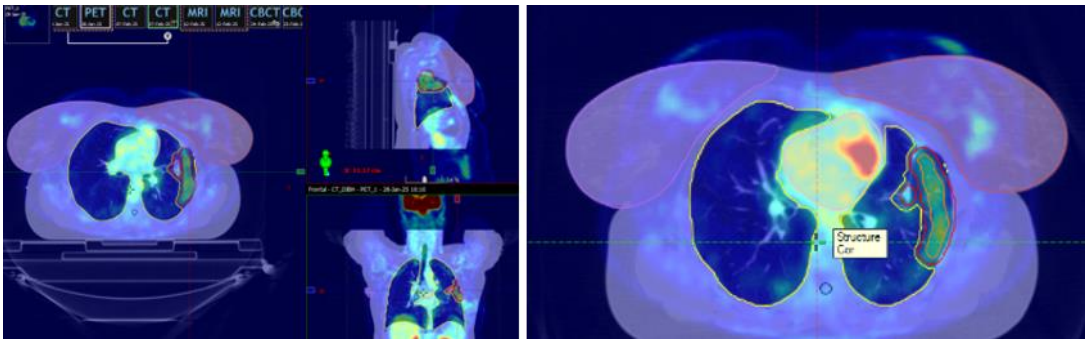

Figure 11: The targeted volumes in the overlapping (fusion) of the images from the postoperative PET/CT of the lungs with that of the planning CT

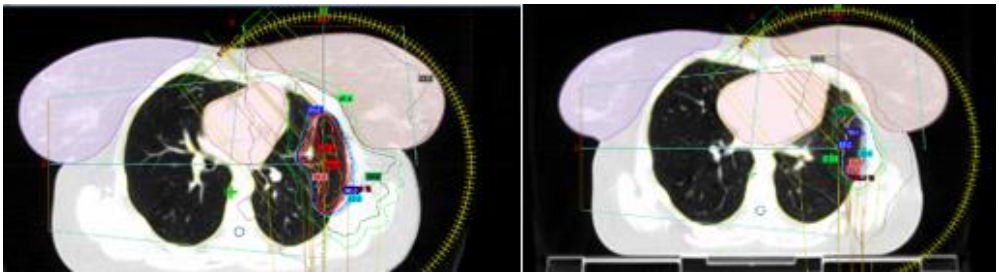

Figure 12: Intensity modulated radiotherapy (IMRT) of the VMAT method In the area of suboptimal resection lines with daily dose (DD) 1.8 Gy up to total dose (TD) 45 Gy. To reduce the dose in the heart, radiation is performed with deep respiratory inspirium.

3. Discussion

Extraskeletal Ewing sarcoma (EES) is a rare entity that belongs to the ES family of tumors (ESFT), which is a group of small round tumor cells that share a common neural histology and genetic mechanism [5-8]. The ESFT encompass all the previous terminologies such as Ewing sarcoma of bone, extra-skeletal Ewing sarcoma, peripheral primitive neuroectodermal tumour, Askin tumour of thoraco-pulmonary region, and atypical Ewing sarcoma based on the presence of a unifying pathognomonic chromosomal translocation [9-18].

The ESFT are an entity composite of malignant small round blue cell tumors with different degrees of neuroectodermal differentiation [19,20]. They are characterized by strong continuous cell membrane

expression of CD99 protein, and genetic translocation involving Ewing's sarcoma (EWS) in □90% of cases [21]. Pathological findings typically reveal the presence of small round cells characterized by poor differentiation, hyperchromatic nuclei, high nuclear-cytoplasmic ratios, and the formation of Homer–Wright rosettes [22]. By 2020, 34 patients with ESFT were published in English literature in various organs (ovary, cervix, vagina, kidneys, bladder, breast, brain) of which 4 patients with primary pulmonary ES. The median age of patients with lung involvement was 33.5 (range: 32-41)years. Immunohistochemistry for CD99 and FLI1 was positive in all 4 [23]. The disease arises from some mesenchymal or neural crest–derived stem or progenitor cell and hence may show variable neuronal, mesenchymal, and epithelial differentiation [10,14,24]. The diagnosis of EES is mainly based on histopathology and immunohistochemistry of tumor specimens. Under a light microscope, the tumor cells are small and round, uniform in size with a round to oval in the nucleus, and sparse in the cytoplasm. Tumor cells are arranged in flakes or lobules, which are separated by vascular fibrous tissues [25]. Figure 1 and Figure 6 shows monotonous moderately large cells with unclear cytoplasmic borders, the nuclei are of a fine priest chromatin, the cytoplasm is pale eosinophilic. The cells form layers and wide cords. The stroma is scarce and richly vascularized by thin-walled blood vessels. Neoplastic cells do not form the rosettes of Homer–Wright. EES shows cytologic features similar to those of its skeletal counterpart, with a continuum from the typical/small cell form in the majority of cases to the intermediate and atypical/large cell variants in a minority of cases [26]. The large cell pattern, also known as "atypical Ewing sarcoma," features large cells with prominent nucleoli, a mild degree of nuclear pleomorphism, and eosinophilic cytoplasm, which may lead to rhabdoid cells [27]. Immunohistochemical (IHC) staining demonstrated positive membranous expression of CD99 , CD56, Vimentin, Synaptophysin and high levels of the Ki67 proliferation marker [22]. Membranous CD99 and nuclear Fli-1 staining was seen in 10 and 16 tumors, respectively, and concurrent expression of both markers was seen in both central and Ewing sarcoma/peripheral PNETs [28]. Such a typical immunohistochemistry is also reported in our clinical case in Figure 2, Figure 4 and Figure 8/ ABC, but only single cells take into account a positive immunohistochemical reaction to Synaptophysine (Figure 2/D and Figure 8/A), which is indicative of neuroectodermal differentiation. By immunohistochemistry, 17 PNETs expressed at least 1 marker of neuronal differentiation, including synaptophysin, NSE, CD56, S100, and chromogranin in 10, 8, 14, 8, and 1 tumor, respectively [28]. Ewing sarcomas are often positive for one or more neuroendocrine immunohistochemical stains, such as synaptophysin and neuron-specific enolase, which highlights areas of neuroectodermal differentiation present in these tumors [29,30]. Antibodies against CD56 may be useful in the identification of neuroendocrine malignancies, especially if the cells do not express CD45, indicating a non-leucocyte origin [31]. A similar immunohistochemical reaction to the CD56 and CD 45 is found in the clinical case presented (Figure 8/C and Figure 8/D). Histological morphology of tumor cells together with the immunohistochemical analysis support the final diagnosis of cytologically atypical primary pulmonary Ewing sarcoma with moderate neuroectodermal differentiation.

CT showed the location, size, and internal tissue structure of the tumor, which is of great importance in evaluating the feasibility of tumor resection and formulating the treatment plan [25]. Magnetic resonance (MR) imaging is performed prior to biopsy to help determine the optimal biopsy site and to avoid the distortion caused by post biopsy changes [32]. MRI and fluorodeoxyglucose positron emission tomography (FDG PET) imaging are used for initial diagnosis and detection of metastasis, respectively [33-35]. Gynecologic PNETs have been reported in the ovary [36], broad ligament [37], uterine corpus [38], uterine cervix [39], vagina [40], and vulva [41]. In a differential diagnostic plan on the presence of a PNET with a gynecological localization and the presence of a solitary pulmonary metastasis, we decided that uterine MRI was needed (Figure 10). 18-Fluorodeoxyglucose positron emission tomography showed that Ewing sarcoma of the lung often showed large volume, smooth edge, and high fluorodeoxyglucose uptake [42]. In Figure 3, we present the preoperative PET/CT in our patient, which shows a large rounded formation in the left lung with high metabolic activity, touching to the 5th rib. Intraoperatively turns out that the tumor is surrounded by a fibrous capsule that distinguishes it from the surrounding pulmonary parenchyma, and from the pathochistological result, the resection lines prove to be extirpated in a healthy. The presence of a fibrous capsule around the tumor, as well as the large amount of plasmocytes, B cells, and T cells around the tumor cells, determines the high level of autoimmune reaction in the presented clinical case (Figure 6). Previously, EES was treated using the soft tissue sarcomas protocol [43]; however, the current treatment recommendation by the National Comprehensive Cancer Network (NCCN) is local treatment (surgery and/or radiotherapy) plus chemotherapy [44,45].

Management of primary pulmonary EES/PNET usually needs aggressive multimodality treatment with upfront generous surgery followed by chemotherapy plus or minus radiotherapy [46]. Considering that EES is a highly invasive malignant tumor, the most effective treatment is surgical resection combined with postoperative chemotherapy and high-dose radiotherapy (RT) [47]. The overall 5 year survival rate is better in patients who undergo complete resection, with wide surgical margins compared with suboptimal margins [48]. Surgery is generally the recommended treatment option for patients with resectable pulmonary PNET, where marginal or wide resection is possible [45,49]. In cases where surgery is not a feasible option, a combination of chemotherapy and radiotherapy should be considered as an alternative treatment approach [22]. The efficacy of adjuvant chemotherapy remains controversial, as it does not result in a significant reduction in the risk of death [50,51]. In situations where complete tumor removal is not achievable, a combination of radiotherapy (RT) or chemoradiation (Ch-RT) is recommended [22]. Figure 9 shows the postoperative PET/CT, which does not take into account a residual tumor, but due to the suboptimal resection margins, as well as

the high proliferative index KI 67 30% (Figure 4), taking into account the malignant nature of this undifferentiated neoplasm, we considered that postoperative RT was required. Another reason for the need for postoperative RT is the initial surgery at which a partial tumor resection was performed, as well as the pathohistological result from the second surgery with a small tumor fragment in the bone marrow in part of the researched rib. We conducted an IMRT of the VMAT method in the area of suboptimal resection lines with daily dose (DD) 1.8 Gy up to total dose (TD) 45 Gy (Figure 12), which the patient suffered without acute side effects from the lungs and heart. Total dose 45 Gy is sufficient for the preventive irradiation of nearby resection linings. The patient was evaluated for active monitoring, namely through a pulmonary MRI after 2 months and PET/ CT after 3 months.

4. Conclusion

The primary lung Ewing sarcoma is an extremely rare neoplasm with published about 35 clinical cases in the world. It is mostly diagnosed at a young age. Due to the large histopatological variation of non -differentiated tumors from the Ewing sarcoma family, a very wide range of immunohistochemical and genetic analysis is required. Due to the extremely aggressive nature of these extraosseous tumors, the main treatment for localized disease without distant metastases is surgical, at discretion accompanied by postoperative RT and/ or chemotherapy. Active monitoring through a pulmonary MRI and PET/ CT is required.

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