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Review paper

Primary pulmonary sarcomas – diagnosis, treatment, prognostic factors

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Abstract

Introduction: Primary pulmonary sarcomas (PPS) are rare types of non-epithelial malignant tumours of the lungs. PPS can originate from mesenchymal elements of bronchial wall, vessels or pulmonary stroma. Since the introduction of immunohistochemical and molecular diagnosis, a significant improvement in description and classification of sarcomas has been achieved.

Aim: The present report was aimed at describing the current state of knowledge concerning diagnosis and treatment of PPS.

Material and methods: A literature review was conducted in context of PPS.

Results and discussion: The majority of available literature concerning PPS is limited to reports based on single cases or small series. PPS not only are devoid of typical clinical symptoms, but also their pathomorphological diagnosis is difficult. Identification and differentiation of sarcomas is increasingly based on molecular diagnosis. The most efficient method of treatment is a radical surgical resection. Neoadjuvant and adjuvant therapy is applied according to the soft-tissue sarcoma guidelines, however, due to the rarity of PPS cases, it is impossible to assess its impact on overall survival.

Conclusions: Early diagnosis of PPS is difficult. Prognosis of PPS is poor, because surgery – the most efficient method of PPS treatment is not possible in many cases. Prognostic factors in PPS include the size of the tumour, histological grading of malignancy and clinical staging according to the lung cancer TNM.

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1. INTRODUCTION

Primary pulmonary sarcomas (PPS) are a diverse group of rare non-epithelial malignant tumours that develop from mesenchymal tissue of the lung.[1,2] PPS can originate from mesenchymal elements of bronchial wall, vessels or pulmonary stroma. They usually infiltrate lung parenchyma and create clearly demarcated, but not encapsulated tumours that can also spread inside bronchi, however, rarely infiltrate bronchial epithelium.[1] Secondary tumours significantly outnumber primary pulmonary sarcomas, with proportion 3000 : 1.[2] Lung sarcomas must also be distinguished from numerous sarcoma-like primary tumours of the lung, including spindle cell- or pleomorphic lung carcinoma, as well as mixed epithelio-mesenchymal tumours.[3] Since the introduction of immunohistochemical and molecular diagnosis, a significant improvement in description and classification of sarcomas has been achieved. Nonetheless, sarcomas still remain a diagnostic dilemma. Lung tumour can be considered as PPS only when both the existence of a primary tumour in another side has been excluded and the differential diagnosis of the examined tumour exclude that it represents another, sarcoma-like neoplasm.[2,3–5]

2. AIM

This paper addresses the current state of diagnostics methods and treatment of primary pulmonary sarcoma.

3. MATERIAL AND METHODS

Over 150 original, reviews, case reports and the chapters of the textbooks concerning PPS were analysed. PPS are rare diseases and the majority of available original articles is limited to descriptions of very small series.

4. RESULTS AND DISCUSSION

4.1. Epidemiology

Lung sarcomas constitute only 0.013%–1.1% of all malignant lung tumours.[5] Median age of patients was 48–51 years.[6–9] No significant correlation between gender and occurrence of PPS has been found.[6–9] There are no characteristic symptoms of PPS. Thoracic pain, haemoptysis and cough are the most common. Porte et al. observed that in 50% of cases PPS did not present with any symptoms.[8] Size of tumour is one of accepted prognostic factors in sarcomas of soft tissues, which also apply to PPS.

The most common PPS are fibroblastic sarcoma and malignant fibrous histiocytoma (MFH). MFH used to be classified as a type of fibrosarcoma, leiomyosarcoma or pleomorphic liposarcoma.[10] It might explain relatively high number of leiomyosarcomas and fibrosarcomas described in the majority of earlier studies.[9] Currently, according to 4th edition of World Health Organization (WHO) *Classification of Tumours of Soft Tissue and Bone*, this type of tumour is considered as undifferentiated pleomorphic sarcoma (UPS).[4]

4.2. Diagnostic imaging

Chest radiography

It is the most common imaging technique that is usually used at the beginning of diagnosis. This examination can provide useful information about location of tumour, deformations of bones and the pattern of calcification of soft tissue or ossification.[11–12]

Ultrasonography (USG)

It enables assessment of size, location and consistence of sarcomas. Using endobronchial ultrasound (EBUS) or esophageal ultrasound (EUS) it is possible to analyze tumours bordering mediastinum, pulmonary hilus and big blood vessels.[13] Ultrasonography (USG) complemented with colour laser Doppler flowmeter helps to assess the intensity and pattern of tumour vascularisation. Sarcomas can show increased peripheral blood flow as a result of necrosis in the centre of tumour. USG is useful in percutaneous biopsy. The use of 3D imaging in USG gives a clear picture of tissue structures and is useful in carrying out interventions based on multi-dimensional images.[14]

Computer tomography

It is preferred examination in lung tumours.[15,16] It is also the best technique in assessment of lesions in bone architecture.[15] Computer tomography (CT) is useful in collection of samples for histopathological analysis in fine-needle aspiration (FNA) or core biopsy (CB).

Magnetic resonance imaging

This examination is superior to CT in terms of image quality, ease of detection and clarity of lesion's boarders. Magnetic resonance (MR) with fast image acquisition and intravenous delivery of gadolinium-diethylenetriaminepentacetate (Gd-DTPA) has significantly increased diagnostic potential and made it a useful tool in differentiation between benign and malignant sarcomas, monitoring response to chemotherapy and early detection of cancer renewal.[17] MR angiography (MRA) using gadolinium is particularly useful in imaging of anatomical abnormalities of vessel supplying timorous masses. MR spectroscopy (MRS) provides information about increased cell division and therefore is useful in detection of malignant tumours.[18]

Positron emission tomography

Positron emission tomography (PET-CT) with fluoro-D-glucose (FDG-PET) is useful in assessment of intermediate and highly differentiated sarcomas as they show high uptake of FDG. However, it is less useful in poorly differentiated sarcomas as they show low uptake of FDG.[19] FDG can increase accuracy of initial stage assessment.[20] In a prospective study with approved soft-tissue sarcomas it was found to have similar accuracy to conventional imaging

methods, such as CT and MR in detection of primary tumours, higher accuracy in detection of metastases to lymph nodes (95%) and metastases to bones (90%); CT was more accurate in detection of metastases to lungs.[16] Franzius et al. showed that PET-CT was more accurate than scintigraphy (SCT) in detection of metastases to bones.[21] Schuetze et al.[22] in a study based on 46 patients with soft-tissue sarcomas of medium and/or high degree of differentiation, reported significant differences in SUV_{max} after two to four cycles of chemotherapy. By identifying metabolic changes in sarcoma after first chemotherapeutic cycle and after completion of neoadjuvant therapy, FDG-PET test can help predict histological response. Metabolic response seems to be a better predictive factor for histological rather than morphological response according to Response Evaluation Criteria In Solid Tumors (RECIST) and therefore is useful in order to avoid continuing chemotherapy when it is no longer necessary.[22] FDG-PET is a valuable tool in detection of tumour recurrence because of its sensitivity and specificity of FDG-PET in detection of local recurrence and distant metastases. Interpretative difficulties may arise from false positive results due to inflammation or false negative results due to low degree of cell heterogeneity in recurrent neoplasms.[23] The decrease rate of SUV_{max} after treatment is considered a predictive factor. In a study including 238 patients Eary et al. showed that not only the SUV_{max} value but also heterogeneity of FDG uptake in sarcoma is an independent prognostic factor. Heterogeneous uptake was observed in more malignant tumours where cell differentiation (varying growth rate) and necrosis occurred more frequently.[24] New markers based on radioisotopes, such as 3'-deoxy 3'[18F] fluorothymidine (FLT) are developed. Varying uptake rate of FDG enables selection of tumour fragment optimal for FNA and CB biopsy performed under CT control.

4.3. Invasive diagnosis

It should always be strived to achieve the histopathological diagnosis before startingtreatment of patients suspected with soft-tissue sarcomas.[4,11,25]

Transthoracic FNA is an important part of PPS diagnosis, as it is possible to differentiate between non-epithelial and epithelial tumours in obtained cytological smears. However, this method has many limitations arising mainly from small biopsy size. Therefore, core needle biopsy under control of CT or USG, open lung biopsy or thoracoscopic biopsy is recommended.[25]

Core biopsy, performed under control of CT and/or USG, allows collection of representative samples from the tumour. EBUS allows visualisation of lesion, vascular flow assessment using Doppler USG and collection of samples for the diagnostic purpose. Park et al.[13] described two cases where EBUS-TBNA was carried out in order to collect diagnostic samples for differentiation between tumour and pulmonary embolism. Using this method Caraway identified pulmonary artery sarcoma in patients with B-cell lymphoma.[26] Accuracy of aspiration biopsy by means of EBUS and EUS might be improved by preparing cell blocks which are paraffin fixed formalin embedded blocks (PFFE) made from cytology smears. However, due to heterogeneity of sarcomas and small sample size, tumors might be misdiagnosed.

Mediastinoscopy did not confirm metastases to lymph nodes of mediastinum. Intraoperative diagnosis based on examination of cryostat sections is also difficult. In a study of Janssen et al., analysis of 11 frozen sections were carried out and 8 patients (73%, $n = 11$) were suspected for mesenchymal tumour. In 1 case, however, obtained results were false-negative.[9] Martini et al.[5] also noticed difficulties in determining the proper diagnosis based on *ad hoc* examination of biopsies or their small volume.

4.4. Pathomorphological diagnosis

Soft tissue tumours are a heterogeneous and complex group of neoplasms which are difficult to diagnose based on their morphological appearance not only due to their rarity, but also diverse histologic presentation.[4,27] On the light microscopic examination with routine haemotoxylin and eosin (H&E) staining numerous difficulties may occur in clear identification of histological type of a particular tumour. Soft tissue tumours can be mimicking by benign tumours (such as spindle cell or pleomorphic lipoma), other malignant tumours (such as melanoma, lymphoma, giant cell carcinoma) or even inflammations.[28,29] Very useful diagnostic tool to distinguish between tumor types is immunohistochemistry (IHC) (Table). Last two decades have brought rapid growth in cytogenetic and molecular testing, which are now widely implemented into soft tissue sarcomas diagnosis. Molecular data can be used to establish the degree of histological grade, predict chemotherapy outcome, personalize therapy[28,30] as well as to investigate prognostic and predictive factors.[31,32] Among 117 tumors types listed in 4th edition of WHO classification of soft tissues and bone tumours, 53 (45%) shows repetitive molecular abnormalities.[4,33–35] One of the most frequent type of PPS is synovial sarcoma characterized by proliferation of epithelioid and spindle cells. The diagnosis is usually confirmed by evaluation of typical chromosomal translocations (X;18) (p11.2; q11.2) which results from fusion of SYT to SSX 1 and SSX 2 genes.[36] Molecular methods commonly used in clinical practice include conventional cytogenetic analysis, fluorescent *in situ* hybridization (FISH), polymerase chain reaction (PCR) and its variations, classical (Sanger) or new generation sequencing (NGS) and comparative genomic hybridization (CGH). Each of the above techniques has advantages and limitations which can make it more or less suited for analysis of particular clinical cases.[37–39] FISH is the most robust tool for analysis of formalin-fixed paraffin-embedded tissue samples, where specific DNA probe is conjugated to respective fluorochrome to detect various chromosomal abnormalities. Because the same mutations may lead to development of different tumours, interpretation of FISH and other molecular data should be always compared with morphological and immunohistochemical data.[40] Because none of available diagnostic methods is completely specific and sensitive, it is necessary to employ appropriate diagnostic

Table. Molecular and immunohistochemical testing in selected soft tissue tumors.

Tumor type according to WHO	Chromosomal abnormality	Detection metod / Genes	Immunohistochemistry
Adipocytic tumours			
Atypical lipomatous tumor / well differentiated liposarcoma (ALT/WDLPS)*	ring/giant marker chromosome 12	FISH *MDM2*, *CDK4* amplification	MDM2 (N), CDK4 (N)
Dedifferentiated liposarcoma (DDLPS)***	ring/giant marker chromosome 12	FISH *MDM2* amplification	MDM2 (N), CDK4 (N)
Myxoid liposarcoma (MLPS)***	t(12;16)(q13;p11) t(12;22)(q13;q12)	FISH *FUS- DDIT3* FISH *EWSR1 -DDI T3*	-
Fibroblastic/myofibroblastic tumours			
Solitary fibrous tumor (SFT)**	inv(12)(q13q13)	RT-PCR *NAB2-STAT6*	CD34 (C), STAT6 (N)
Low-grade fibromyxoid sarcoma (LGFMS)***	t(7;16)(q34;p11) t(11,16)(p11;p11)	FISH *FUS-CREB3L2* FISH *FUS-CREB3L1*	MUC4 (C)
Sclerosing epithelioid fibrosarcoma (SEF)***	t(7;16)(q33;p11)	FISH *FUS-CREB3L2*	MUC4 (C), EMA (C,M)
Skeletal-muscle tumours			
Embryonal rhabdomyosarcoma (ERMS)***	loss of 11p15	–	Desmin (C), myogenin (N), MyoD1 (N)
Alveolar rhabdomyosarcoma (ARMS)***	t(2;13)(q35;q14) t(1;13)(p36;q14)	FISH *PAX3-FKHR* FISH *PAX7-FKHR*	Desmin (C), myogenin (N), MyoD1 (N)
Tumours of uncertain differentiation			
Synovial sarcoma (SaSy)***	t(X;18)(p11;q11)	FISH *SYT-SSX1*	EMA (C) , TLE1 (N)
Alveolar soft part sarkoma (ASPS)***	t(X;17)(p11;q25)	FISH *ASPL-TFE3*	TFE3 (N)
Clear cell sarcoma of soft tissue (CCS)***	t(12;22)(q13;q12) t(2;22)(q34;q12)	FISH *EWS-ATF1* FISH *EWS-CREB1*	HMB-45 (C), Melan-A (C), SOX10 (N)
Extraskeletal myxoid chodrosarcoma (EMC)***	t(9;22)(q22;q12)	FISH *EWSR1-NR4A3*	Rarely S-100 (C) and CD117 (C)
Extraskeletal Ewing sarkoma/PNET (EEWS/PNET)***	t(11;22)(q24;q12) t(21;22)(q22;q12)	FISH *EWSR1-FLI1* FISH *EWSR1-ERG*	CD99 (M), FLI-1 (N)
Neoplasm with perivascular epithelioid cell differentiation (PEComa)***	TFE3 rearrangements or amplification	FISH *TFE3*gene fusions	desmin (C), melan-A (C), HMB45 (C), TFE3 (N), CD117 (C)
Desmoplastic small round cell tumor (DSRCT)***	t(11;22)(p13;q12)	FISH *EWSR1-WT1*	Desmin (dot-like), CK (C,M), EMA (C,M), WT1 (N)

Comments: * Intermediate (locally aggressive) tumours; ** Intermediate (rarely metastasizing) tumours; *** Malignant tumours; N – nuclear staining; C – cytoplasmatic staining; M – membranous staining, FISH – fluorescence in situ hybridization; RT-PCR - Reverse transcription polymerase chain reaction.

algorithms based on interpretation of morphology, immunohistochemistry and molecular biology in correlation with clinical data.

4.5. Treatment

Treatment plan should be developed by a multidisciplinary team consisting of pathologist, radiologist, surgeon, oncologist and radioterapist. Effectiveness of treatment is higher in specialised centres.[41,42] Surgery is a primary method of treatment. Resection is determined by size of tumour, connections with another anatomical structures and degree of functions that could be lost. The surgery also includes resection of lymph nodes of the chest. The purpose of surgical treatment is to achieve a tumour-free margin. Because it is hard to identify lung sarcoma the standard strategy of treatment in this type of tumour is similar to lung cancer. Lobectomy and pneumonectomy are still a 'gold standard' in surgical treatment of PPS.[6–9,43–45]

Regnard et al. reported that they were able to perform a radical resection in 20 out of 23 patients (83%); 13 lobectomies were carried out (in 6 patients it was expanded by resection of thoracic wall and in 1 patient by resection of pericardium) and 7 pneumonectomies (in 5 patients it was expanded by partial resection of pericardium and in 1 pa-

tient by resection of atrium). In Thoracic Surgical Unit, Massachusetts General Hospital in Boston, lobectomy and bilobectomy were carried out in 52% of cases (12 patients), including 2 sleeve resections and 1 lobectomy expanded to carina of trachea.[7] In 1 case resection was expanded to thoracic wall. Seven patients (30%) underwent pneumonectomy. In 3 of these patients, surgery was carried out using extracorporeal circulation: in 2 cases the lung was resected along with tumour infiltrating pulmonary artery and entrance to right chamber was reconstructed using homograph; in 1 patient pneumonectomy was expanded to atrium. Another patient that underwent pneumonectomy had infiltrations in left atrium and diaphragm. Above-mentioned resections turned out to be radical (R_0) in 14 patients (60%). Operational mortality was 5%.[7] Among 18 patients analyzed by Porte et al., 12 patients (66%) underwent lobectomy and 6 patients (33%) underwent pneumonectomy. Because of problematic locations, these surgeries were expanded to adjacent anatomical structures in 6 patients (33%): resection of ribs was carried out in 3 patients, resection of diaphragm in 2 and one of pneumonectomies required resection of superior vena cava and left atrium which was carried out without extracorporeal circulation. R_0 surgeries comprised 89% of all treatments. Porte argues that lobectomy, or if necessary, pneumonectomy, are the standard in surgical treatment of PPS, whereas not-anatomical resections (wedge or segmental resection) seems to increase risk of tumour recurrence.[8] In analysis presented by Janssen et al., in 11 cases (50%) radical surgeries (R_0) were carried out. 13 patients underwent lobectomy and bilobectomy, including 1 sleeve lobectomy and 1 resection expanded to a segment of another lobe. One patient underwent pneumonectomy. Four patients underwent non-anatomical resection.[9]

PPS rarely spread through lymphatic vessels,[46] it seems reasonable to carry out lymphadenectomy of mediastinum, similarly to treatment of lung cancer.

Infiltration of right pulmonary artery and left atrium, as well as large mass of tumour taking up the entire thoracic cavity in one of the patients convinced Porte to implement neoadjuvant chemotherapy.[8] Two patients received six cycles of chemotherapy based on ifosfamide, doxorubicin and dacarbazine, which reduced the tumour size over 50%. Third patient from this group received two cycles of chemotherapy without any response, however, pneumonectomy was R_0. Wu et al. described a patient with solitary fibrous tumor who received neoadjuvant chemotherapy.[8,47]

Adjuvant radiotherapy is usually used when there is a microscopically positive margin after surgical treatment (R_1), but eventual advantages of this form of treatment were not confirmed yet. Chemotherapy was carried out on 4 patients with poor prognosis i.e. large, poorly differentiated tumours (grade 3).[8] In a study by Mac Cormack and Martini[46] no impact of radiotherapy on survival was found. Chemotherapy after non-radical resection also did not have any impact on survival.[9]

Therapeutic benefit of immunotherapy was already established for the treatment of numerous solid neoplasm. In recently published phase II clinical trial SARC28 objective responses to checkpoint inhibitor, pembrolizumab were observed in 18% of patients with soft tissue sarcomas.[48]

4.6. Treatment outcomes

The highest overall survival (OS) was achieved after primary radical resection. Janssen at al. reported 24 months median OS with 44% 5-year OS. Similar 5-year OS was described in other series,[6,8,9] while Bach et al. reported 69% 5-year OS.[10] Survival of patients that were considered inoperable or did not undergo R_0 surgery was poor.[4,6–9]

4.7. Prognostic factors

Confirmed prognostic factors in sarcomas are: histological grade (G), histological type, size of primary tumour (less than 5 cm vs. more than 5 cm), surgical margin (R), anatomical localization, age of patient (less than 50 years vs. more than 50 years), depth of infiltration, duration of symptoms and presence of distant metastases.[4]

Prognostic factors in PPS are still under investigation as the low number of patients and published data make it difficult to establish repetitive factors. It was shown that complete resection of primary sarcomas significantly improves prognosis.[6–9] Patients with tumours larger than 5 cm had worse prognosis, size under 3–4 cm appeared as good prognostic factor.[9,48,49] Bach et al. revealed that patients with MFH had better prognosis.[7] Janssen et al.[9] considered histological grade as one of prognostic factors. However, other authors[6–8] observed that degree of histological grade did not have impact on survival. Regnard and Porte et al. suggested that stage of development based on TNM when adopted to PPS is one of prognostic factors.[6,8]

5. CONCLUSIONS

Thanks to developments in diagnostic techniques, it becomes increasingly easier to identify PPS. Complete resection is the best method of PPS treatment. Neoadjuvant chemotherapy can increase a chance of complete resection. Adjuvant treatment has not been confirmed to improve outcome and requires further investigation. Extensive tumour size is a poor prognostic factor. Studies including larger set of PPS patients are necessary.

Conflict of interest

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