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## Mesothelioma - a growing medical problem with heterogeneous course

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### Abstract

Mesothelioma is one of the most malignant neoplasms affecting the thin lining of the body's internal organs, known as the mesothelium. The incidence of mesothelioma in recent years has increased. It is assumed that the reason for this situation is the exposure in the past to natural mineral fibers (nickel, beryllium, silica dust), ionizing radiation, some organic compounds and SV40 virus but mostly to asbestos. The time from contact to the first symptoms is about 20-40 years. Probably the peak of morbidity is yet to come. Due to non-specific symptoms such as chest pain, shortness of breath, fluid in the pleural cavity, early detection is very difficult. Additionally, we can deal with mesothelioma which starting point is outside the pleural cavity. In such cases, diagnostics is even more difficult, because the only remaining symptom is pain. Therefore, it is important to pay attention to this growing problem.

## Introduction

Mesothelioma is one of the most malignant neoplasms affecting the thin lining of the body's internal organs, known as the mesothelium. Asbestos is considered as the main etiological factor, but other substances such as natural mineral fibers (nickel, beryllium, silica dust), ionizing radiation, some organic compounds and SV40 virus are also recognized as carcinogens in this disease. The peak incidence of mesothelioma falls after the age of 60 and the incidence among the male population is higher than in female (approximately 9:1). Long incubation time is characteristic for this disease. Average time from exposure to the first signs of the disease is usually longer than 20-40 years. The most common symptoms are: dyspnea, pleural effusion, chest pain. In addition, the general nonspecific symptoms of cancer: weight loss, malaise, weakness, fatigue, sweating, chills, malnutrition. Rare ailments are: spontaneous pneumothorax, laryngeal nerve palsy or superior vena cava syndrome. The diagnosis is usually obtained by biopsy of pleura or fluid, performed transthoracally or by video thoracoscopy (VATS). In the early stages mesothelioma macroscopically presents itself as numerous small nodules located in the parietal or visceral pleura. Along with the progression of the disease, the nodules merge to form tumors, up to several centimeters which form infiltrations and stratifications of pathological tissues within the pleura. Other symptoms such as pleural fluid effusion, infiltrations of diaphragm, mediastinal structures, lymph nodes, pulmonary parenchyma, and peritoneum can be also observed.[1,2] Further development of the disease may lead to metastases. Common locations are: lymph nodes, pericardium, peritoneum, chest wall, mediastinum, diaphragm, stomach, intestines, liver, spleen. Very rarely metastases were also found in skeletal muscles, brain and bones. Unusual locations and unexpected course of the disease are becoming more and more common. Probably due to overall increasing morbidity - 19% increase in 2010-2016 (National Cancer Registry), long incubation period (more or less 15-30 years from exposure to asbestos), as well as mass removal of asbestos as part of the program "The asbestos and products containing removal program" adopted by many European governments. Probably the peak of pleural mesothelioma is yet to come. In the authors' opinion, particular attention should be paid to atypical symptoms that may suggest a diagnosis of pleural cancer. In the available literature, we can increasingly see cases of mesothelioma, where the samples for diagnosis are collected

outside the pleura. We present a case of a patient who was primarily diagnosed from iliolumbar muscle as mesothelioma of the pleura.

Year	2010	2011	2012	2013	2014	2015	2016
Men	175	169	200	210	198	215	209
Women	91	91	99	116	99	105	108
Sum	266	260	299	326	297	320	317

Tab. 1 Number of cases of mesothelioma ICD10 - C45 in 2010-2016. [3] National Cancer Registry [www.onkologia.org.pl](http://www.onkologia.org.pl) access from 10/02/2019.

We can differentiate several histological types pleural tumors: mesothelial tumors lymphoproliferative disorders and mesenchymal tumors. It should be emphasized that the diagnosis should always be based on the results obtained from an adequate biopsy (less commonly cytology, exfoliative and fine-needle aspiration). In this study we will focus mainly on malignant mesothelioma which is a subtype of mesothelial tumors. Thanks to immunohistochemical examinations, we can distinguish individual types that have their own affinity for particular organs. In the diagnosis of pleural mesothelioma, we cannot forget that pleura may also be a place where other malignant and benign changes could occur. [4,5,6]

For pleural mesothelioma, we can use three main methods of treatment: chemotherapy, radiotherapy and surgery. In some protocols we use all three, but it's in phase of clinical trials. Unfortunately, invasive treatment is usually not radical, although this procedure is considered to be the widest possible treatment in thoracic surgery. Mutilation of the organism is usually so large that it is burdened with a huge amount of complications. Because of the intricate location and relation to other tissues, it is virtually impossible to obtain radical resection. It remains a good tool for diagnosing and determining the TNM staging, as well as improving patient quality of life (fluid evacuation). First line chemotherapy is usually: combination doublet chemotherapy of cisplatin, with either pemetrexed or raltitrexed. Unfortunately currently there is no second-line standard of care. Because of the absence standard second-line or further-line therapy, some patients can be enrolled into clinical trials.

The use of radiotherapy in pleural mesothelioma is also limited - it does not allow for radical treatment. We can point out three main indications: palliation, preventive treatment and part of a multimodality treatment. In case of palliative treatment, the main application is, like in surgery, to improve the patient's quality of life majorly by reducing pain. [6]

Due to the above limitations in treatment, the mesothelioma has a low survival rate.

2-year survival rate	
localized stage	41% - 46%
nearby areas and/or lymph nodes (stages II and III)	26% - 38%
distant metastases	17%

Tab. 2 2-year survival rate [7]

5-year survival rate	
localized stage	13% - 16%
nearby areas and/or lymph nodes (stages II and III)	5% - 10%
distant metastases	less than 1%

Tab. 3 5-year survival rate [7]

49 years old woman was admitted to the emergency unit (EU) because of a very strong pain in the right iliac fossa in December 2011. Patient claimed that since a month, pain had been gradually arising and radiating to the leg abdomen and chest. Family doctor diagnosed neuralgia lumbaris and treated her with non-steroidal anti-inflammatory drugs. Despite medications the pain persisting and in the day of admittance to EU was unbearable. Computed Tomography (CT) revealed a pathological swelling along right iliolumbar muscle (116/41/40mm), fluid in the right pleural cavity and pathological mass below the bifurcation of the trachea, reaching the right hilum of the lung (70/53/30mm). Patient was admitted to Pulmonary Department, where right side thoracocentesis (900ml), EBUS-TBNA + FNA + cellblock (mediastinal lymph nodes group 7) and ultrasound-guided iliolumbar muscle biopsy were performed. Pathomorphological and Immunohistochemical evaluation revealed: neoplasma malignum epithelioides: mucykarmin (-), CK (+), CK7 (-), TTF1 (-), CK19 (+), S-100 (-), CEA doubtful, calretinin (+).

After oncological consultation patient was qualified for chemotherapy: Cisplatin + Pemetrexed, (7 cycles). Patient underwent treatment without complications and reported improvement in general condition and complete pain relief.

Control PET-CT 18FDG (January 2014) showed right pleural thickening with coexisting fibrous changes without significantly elevated accumulation of 18FD glucose. Abdomen, pelvis, bones without metabolically active proliferation. Based on these findings patient was treated with Pemetrexed monotherapy (32cycles).

Control CT (June 2014) presented fluid in the right pleural cavity and pleural thickening. Changes below the bifurcation of the trachea and in iliolumbar muscle remained the same.

Further CT evaluation (October 2014) remained the same, with no signs of progression.

In June 2015 another EBUS/TBNA was performed in order to diagnose enlarged lymph nodes groups 7 and 4L, immunohistochemical assessment: TTF-1 (-), WT-1 (-), Calretynina (+), CK5/6 (+), Mesothelina (+). Which indicated recurrence of the disease.

From May 2015, due to radiological progression (irregular and inhomogeneous mass in the retroperitoneal space 125/55/33mm), chemotherapy cisplatin + pemetrexed - 6 cycles was administered.

Control CT examination (September and November 2015) showed regression of previously described peritoneal mass (93/28/20mm). Since November 2015 patient was treated with pemetrexed - 6 cycles.

Because of drug-induced neutropenia, the second cycle of chemotherapy was twice postponed. In addition, patient complained of irritable bowel syndrome.

Control CT scan from January 2016 – status idem.

In December 2016 the tumor from abdomen was excised with a piece of Iliopsoas muscle.

In the postoperative histopathology examination: Mesothelioma epithelioides (tubulo-papillary variant) radicality - 1.

Control PET/CT (January 2017) showed multiple active metabolically changes, which seemed to be metastases in the chest and abdomen.

In February 2017 patient was operated in thoracic surgery department. During operation a lot of pleural adhesions were noticed. Macroscopically pulmonary pleura was completely clean, pericardial sac covered with small tumors resembling lymph nodes. Additionally tumor located in the mediastinum was infiltrating surrounding tissue and large vascular trunks, which due to the risk of bleeding, made it impossible to be removed. With the help of metal clips the biggest changes were marked for future radiotherapy. Due to the lack of histopathology diagnosis from the chest area, the largest o tumor of the pericardial sac was dissected. Pathomorphological evaluation revealed: mesothelioma.

## **Discussion**

Mesothelioma remains a difficult diagnostic and therapeutic problem. Diagnosis is often delayed due to non-characteristic clinical and radiological symptoms. The basis of the diagnosis

is histological and immunohistochemical evaluation of tissue material. According to pathomorphological assessment, there are three main mesothelioma types: sarcomatoid, epithelioid and biphasic. Development, course and prognosis of the disease, depending on the specific cell types, vary considerably. Additionally, despite the development of immunohistochemical procedures, mesothelioma and adenocarcinoma of the lung differentiation is still creating many difficulties.

The incidence of mesothelioma increases and the expected peak incidence will probably be approx. in 2020 [8]. Higher number of cases will probably be associated with uncharacteristic symptoms and different extrapulmonary manifestations. New atypical symptoms and localizations of mesothelioma can be observed around the world, like pseudoachalazja [9], lower limb pain [10], hydrocele [11] anterior mediastinum [12] or like in our case abdominal pain. This may lead to delay of the proper diagnosis and consequently adequate treatment which may worsen the prognosis and survival of the patients.

The more frequent occurrence of atypical forms and unusual locations makes it difficult to effectively treat this disease. Presentation of new, occasional locations and symptoms should contribute to greater awareness of patients and physicians, which may improve the effectiveness of diagnosis and treatment.

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