MALIGNANT PLEURAL MESOTHELIOMA – CASE REPORT

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Summary: Introduction. Malignant pleural mesothelioma (MPM) is a rare and highly aggressive tumor. Its occurrence is causally linked to asbestos exposure, which is the leading etiological factor contributing to the development of the disease in more than 80% of cases. It occurs after inhalation of microscopic asbestos mineral fibers, following a long latent period. The time from asbestos exposure to tumor onset is usually several decades. The disease is more common in men. The therapeutic approach is based on a multimodal strategy, combining surgery, chemotherapy, and radiotherapy. Regardless of the treatment applied, the prognosis is always very poor. The aim of this paper is to present the basic characteristics of MPM and to increase fundamental knowledge about the harmful effects of asbestos in the development of the disease. **Case presentation:** A case of malignant pleural mesothelioma in a 64-year-old male patient is described. The main symptoms included dyspnea, cough, and fatigue on minimal exertion. Physical examination of the lungs revealed absent breath sounds on the left side. The initial chest X-ray indicated the presence of a massive left-sided pleural effusion. After drainage of the left pleural space, 3000 ml of fluid was evacuated. A video-assisted thoracoscopic surgery (VATS) was subsequently performed, along with partial pleural decortication and biopsy, which confirmed the diagnosis of MPM, epithelioid subtype. The most likely asbestos exposure occurred 30 to 35 years earlier. **Conclusion**: The presented case of MPM describes a patient who initially exhibited typical nonspecific symptoms, a characteristic unilateral pleural effusion, and later severe chest pain with rapid disease progression. The disease is most often diagnosed at an advanced stage. A history suggesting possible asbestos exposure during the patient's lifetime may raise suspicion and contribute to an earlier diagnosis, at a stage when therapeutic options are somewhat greater..

Ključne reči: male sex, malignant mesothelioma, mineral fibers, pleura, asbestos, prognosis.

INTRODUCTION

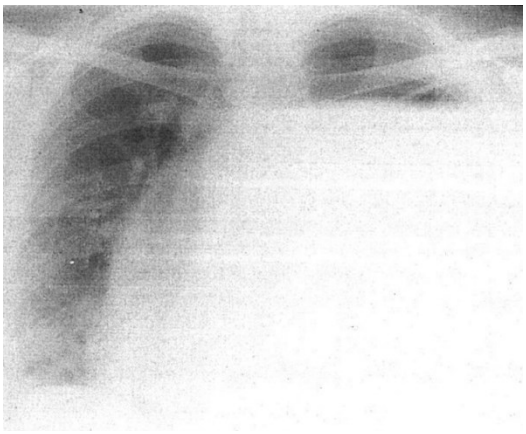
Malignant mesothelioma is a relatively rare but very aggressive tumor. It represents a multifactorial disease in whose development the following factors play a role: asbestos, Simian virus 40, and radiotherapy [1]. It has not been proven that smoking causes the occurrence of MPM, but it contributes to its development. According to data from the literature, its occurrence is causally related to asbestos exposure as the leading etiological factor that contributes to the development of the disease in more than 80% of cases. It appears after inhalation of microscopic asbestos mineral fibers suspended in the air, after a long latent period of several decades. It has a much higher incidence in men, which is explained by the fact that men are more often engaged in occupations that are "risky" in terms of asbestos exposure. Occupational exposure to asbestos has been the subject of numerous studies. Such an association of MPM with occupation is most likely the consequence of not implementing occupational safety measures. A particularly concerning fact is the occurrence of mesothelioma in family members of these workers. The disease also more frequently appears in places where mines of this material are located, because exploitation leads to contamination of the environment (air) and exposure of the population to asbestos (endemic areas) [2]. As a carcinogenic material, asbestos was banned in all European Union member states in 2005, while Serbia introduced a ban on the use of asbestos in all products in 2011, and a Regulation on handling waste containing asbestos was also prescribed. [3].

CASE REPORT

The patient is a 64-year-old male. A retired machine locksmith. Smoker for over 40 years, about 20 cigarettes per day, rarely consumes alcohol. In his personal medical history previously healthy, without other comorbidities. The patient states that he felt the

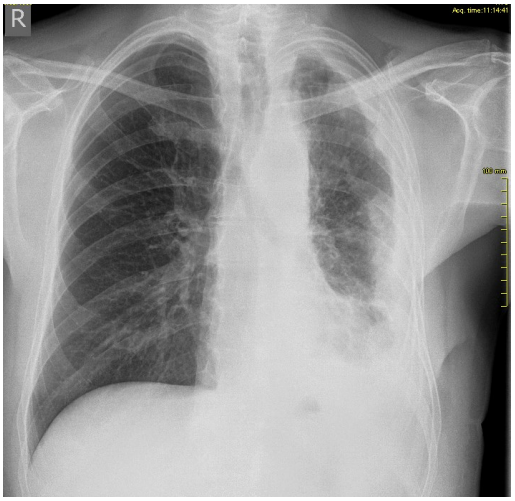
first symptoms at the beginning of June 2018. The main complaints are shortness of breath, a feeling of choking, and fatigue on minimal exertion. Cough has been present for several months before that, since March 2018. Elevated blood pressure for the past two weeks, BP 160/100 mmHg, previously normal blood pressure. Evaluated by an internist, received antihypertensive therapy and was further referred to a pneumophysiologist. Auscultation of the lungs on the left reveals completely absent breath sounds, without accompanying sounds, while in the other parts of the lungs the breath sounds are normal. Blood oxygen saturation is 97%.

Figure 1. Initial chest radiograph



Chest radiography (Figure 1) indicates a left hydropneumothorax, with an infraclavicularly present hydro-air level. The cardiac silhouette is displaced to the right. All laboratory and biochemical analyses are within reference values. After the basic laboratory and diagnostic examinations performed at the Health Center Knjaževac, the patient was further referred to the Special Hospital for Pulmonary Diseases Ozren on 26.06.2018. Two days later he was transferred to the Clinic for Thoracic Surgery, University Clinical Center Niš, for further treatment, where he was hospitalized several times in the following period. During the first hospitalization at this clinic, an initial drainage of the left pleural space was performed, with approximately 3000 ml of fluid evacuated. Cytological and bacteriological analyses did not indicate the presence of tumor cells or infection.
During the next hospitalization, surgery was performed on 24.07.2018., video-assisted thoracoscopy (VATS), partial pleural decortication and biopsy were done, and the material was sent for histopathological examination. In the histopathological report dated 11.09.2018., malignant pleural mesothelioma, epithelioid variant, was diagnosed. On the follow-up PA chest radiograph from 16.09.2018. (Figure 2), the left hemidiaphragm and left costophrenic angle are obscured by a laterally ascending shadow—pleural effusion is present. The remaining part of the lung parenchyma on the left shows reduced transparency.

Figure 2. Control radiography of the chest



In the conclusion of the chest MSCT dated 24.09.2018: in the pleural cavity on the left, a heterogeneous-density lesion is present diffusely, with denser fluid content, accompanied by compressive atelectasis and a soft-tissue component; the described lesion primarily corresponds to a neoplastic process with empyema. In the remaining lung parenchyma, micronodular changes and mediastinal lymphadenopathy are present. In the bony structures, apart from degenerative changes, there are no other MSCT findings.

According to the decision of the Pulmonology Oncology Council from 25.09.2018, treatment with first-line chemotherapy using the pemetrexed–cisplatin regimen was planned. In the meantime, further disease progression occurred. Poor appetite and progressive weight loss were present. The appearance of central neurological symptoms was suspected, including impaired

communication, occasional disorientation to time, instability, and intermittent loss of sphincter control (occasional urinary incontinence). Pain was constantly present. From analgesic therapy, Ibuprofen 600 mg tablets 2×1 and Tramadol 50 mg tablets 2–3×1 were administered, but due to insufficient analgesic effect, the use of a Fentanyl transdermal patch 25 micrograms/h was soon initiated. The patient was hospitalized at the Oncology Clinic, University Clinical Center Niš, on 15.10.2018. Laboratory and biochemical analyses showed azotemia and hypercalcemia (urea 16.4 mmol/L, creatinine 179.4 μmol/L, Ca 4.26 mmol/L). Due to clinical deterioration and poorer performance status, chemotherapy was not indicated. Because of the elevated serum calcium levels, a decision was made to administer bisphosphonates, and urgent treatment was initiated. Therapy with Zoledronic acid 4 mg ampoule was administered without complications. However, progressive central neurological deterioration ensued, and the patient died before the first cycle of the planned systemic therapy.

Due to the specific nature and diversity of his occupations, asbestos exposure was likely present on multiple occasions throughout his life. However, the most probable critical exposure to asbestos may have occurred 30 to 35 years earlier..

DISCUSSION

Malignant mesothelioma can have different localizations and arises from mesothelial cells of serous membranes that line body cavities and organs (visceral or parietal pleura, peritoneum, pericardium, or, rarely, the coverings of other organs, e.g., the tunica vaginalis of the testis). Most commonly diagnosed is malignant pleural mesothelioma (MPM), accounting for over 70% of cases. The tumor appears after a very long latent period of several decades. The time from asbestos exposure to tumor development is at least 25 years, and according to some authors, more than 50 years. Due to this long latent period, MPM is most often diagnosed in patients over 60 years of age. Among patients with confirmed high-risk occupations, the most common were machine-fitters, as in our patient [1,4].

Asbestos includes six naturally occurring silicate minerals. It consists of soft, thin, silky fibrous crystals. There are two types of asbestos fibers: amphibole (most commonly used: crocidolite or blue; amosite or brown asbestos; fibers are long, thin, and straight – needle-like) and serpentine (chrysotile or white asbestos; fibers have a serpentine shape) [5]. Asbestos was widely used worldwide, especially in the second half of the last century. Due to its favorable physical properties, it had broad applications: it is a good conductor of heat, does not burn or carbonize, and is durable. All forms of asbestos fibers can be responsible for disease development. Some forms are more pathogenic than others. Thinner and longer fibers have the greatest carcinogenic potential. All types of asbestos are very stable and do not degrade spontaneously over time; however, processing or damage produces asbestos dust. This dust is easily inhaled and reaches the alveolar sacs. The exact mechanism by which asbestos fibers reach the pleura and mesothelial cells is not fully clarified. Over a long period, these fibers cause chronic inflammation, fibrosis, and malignant alterations. Oncogenesis is not fully understood. MPM most likely arises as a result of inactivation of tumor suppressor genes. The most frequent changes are loss of function of the CDKN2A tumor suppressor gene, NF2 inactivation, and mutation or deletion of the BAP-1 tumor suppressor gene (BRCA1-associated protein 1) [6]. All these factors together contribute to the development of MPM.

Symptoms of mesothelioma vary depending on the localization and stage of the disease. After a long latent period, initial symptoms are usually nonspecific and mild. In pleural mesothelioma, complaints include breathing difficulties, progressive dyspnea, and rapid fatigue with minimal exertion. In our patient, all these symptoms were present. The cough was dry and exhausting, and hemoptysis (coughing up blood) may occur. Our patient did not have hemoptysis, but the cough was present. Some symptoms may result from pleural effusion. Elevated blood pressure is not described as a symptom of MPM, but in our patient, it was likely a consequence of massive left-sided pleural effusion. Pleural effusions can be massive and often recurrent. During effusion drainage, transient relief occurs, followed by pain. Chest pain is the leading symptom of MPM and is thought to result from tumor infiltration into surrounding structures. Severe chest pain was also present in our patient. Neurological symptoms in the patient may be a possible consequence of disease dissemination to the CNS.

Some general symptoms, such as malaise, general weakness, fatigue, loss of appetite, and weight loss, were also present in our patient during the later course of the disease. Occasionally, fever, chills, and night sweats may occur, usually in advanced stages of the disease.

Standard chest radiography is a first-line diagnostic method, although it is not sufficiently sensitive or specific. A common finding on radiography is the presence of a unilateral pleural effusion. Cytological analysis of punctured pleural fluid has a sensitivity ranging from 13% to 75%, but it may be negative or false-negative. In the described patient, it was negative. Chest CT is an indispensable diagnostic procedure that provides valuable information about the pleura (thickening, calcifications), characteristics of effusions (if present), and the condition of mediastinal lymph nodes and organs.

Percutaneous biopsy is both a diagnostic and therapeutic procedure for MPM. Video-assisted thoracoscopy (VATS) is the most reliable method, providing an adequate sample for morphological and immunohistochemical analysis. Macroscopically, these tumors appear as diffuse pleural thickening. Pathohistological diagnosis is the gold standard. Histologically, tumors are divided into subtypes: epithelioid, sarcomatoid, and biphasic, which consists of a mixture of the two types [1,4]. In our patient, the diagnosis of epithelioid MPM was established, which is the most frequent type, accounting for about 60% of cases. It has a better prognosis, responds better to therapy, and has longer average survival. Although there are three histological subtypes of MPM, the WHO in 2021 proposed a complex and comprehensive classification of pleural and pericardial tumors [7,8], taking into account histological characteristics, prognosis, disease extent, BAP1 tumor suppressor gene immunohistochemistry, CDKN2A homozygous deletion, and other factors.

The therapeutic approach is based on a multimodal strategy, combining surgery, chemotherapy, radiotherapy, and immunotherapy. Despite significant progress in recent years, treatment options remain limited. Current therapeutic modalities prolong survival but do not provide complete cure.

Operability depends on tumor size and the patient's general condition. Stages I to IIIa are operable if the tumor is still localized and of the epithelioid type. In later stages with metastases, surgery has a palliative benefit.

Chemotherapy is the most commonly used treatment modality for mesothelioma and is applied in all stages. Pemetrexed and cisplatin constitute the first-line chemotherapy regimen. Some patients may respond better to other recommended combinations, such as pemetrexed with carboplatin, or cisplatin with gemcitabine [9]. Radiotherapy has most often been applied palliatively to relieve symptoms in later stages of disease, although technical advances have allowed significant improvements in MPM management [10].

In recent years, immunotherapy with monoclonal antibodies has been implemented. Nivolumab in combination with ipilimumab is indicated as first-line treatment for patients with unresectable MPM. Treatment continues until disease progression, unacceptable toxicity, or for up to 24 months. Patients treated in this way have shown significant improvement [11].

Malignant pleural mesothelioma is a highly aggressive tumor. The disease is incurable in later stages, and the prognosis is always very poor. Expected survival is less than 18 months from the onset of initial symptoms, while survival for advanced disease without therapy is 6–8 months.

According to a study conducted in 2019 in an endemic area of Turkey [2], postoperative survival results showed a median survival period of 19.6 months. Among 13 patients, the longest survival of 32 months was observed in a patient who underwent postoperative hyperthermic chemotherapy after pleural decortication..

CONCLUSION

There are anamnesis data that deserve attention: sex, age (over 60 years, due to the long latent period), occupation, and smoking history. The described case represents a typical patient with MPM, who initially presented with typical nonspecific symptoms such as cough, dyspnea, and fatigue, along with a characteristic unilateral pleural effusion, and later developed severe chest pain and rapid disease progression. The disease is most often diagnosed at an advanced stage. Anamnestic data regarding possible asbestos exposure during life may raise suspicion and contribute to an earlier diagnosis, at a stage when therapeutic options are

somewhat greater and may, for a limited time, prolong survival. The most important measure is primary prevention: to prevent asbestos exposure or to safely remove asbestos-containing material. MPM is a rare disease, but it should be considered in the differential diagnosis, as it is a highly aggressive tumor..

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