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Review

Malignant Pleura Mesothelioma: Clinical Perspectives

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Abstract

Malignant pleural mesothelioma (MPM) is a primary health issue which preoccupies the health professional community worldwide. The main cause of the disease is the environmental exposure to asbestos. Because of the lack of relevant symptomatology, the disease is usually diagnosed at an advanced stage. Despite the progress in the therapeutic means, the mortality of the disease remains high. The optimal approach to the disease consists of the preventive efforts to remove asbestos materials, the early diagnosis and proper early therapeutic treatment. Despite the fact that new cases of MPM are diagnosed, it is believed that the incidence of the disease is declining. In this study an overview of the epidemiology, etiology, mechanisms of pathophysiology and symptomatology of MPM is carried out.

Key words: Malignant pleural mesothelioma, Asbestos, Epidemiology, Pathogenesis, Symptomatology.

Introduction

Malignant pleura mesothelioma (MPM) is an occupational-related form of cancer of the thoracic cavity and remains a diagnostic and therapeutic challenge [1, 2]. Mesothelioma arises from the pleura in 70-90% [1-4] and from the peritoneum in 10-30% of the cases [5]. Rarely it can arise from testicles (<1%) [6] or the pericardium (<1%) [7]. This oncological entity arises from the mesothelial cells of the pleura [1, 8, 9]. The disease has no symptoms in the early stages. Despite the advances in the therapeutic approach of the disease, the prognosis is ill-favoured. Selected patients can be treated surgically in the context of

multidisciplinary therapy [1, 10-12].

The most clearly related cause of the MPM is the airborne asbestos exposure [1, 3]. Despite the fact that the disease is relatively rare, great interest has been developed around MPM. This interest is attributed mainly to the judicial disputes that had led to the prohibition of the use of asbestos material in industry and construction [1, 3, 7]. In this review, the epidemiology, pathogenesis and clinical appearance of the more common, aggressive and diffuse MPM are described.

Epidemiology

MPM had rarely been reported in the first half of the 20th century. Gradually with the use of asbestos, the frequency of MPM increased in the middle of the 20th century [1, 3]. According to the World Health Organization (WHO) data between 1994 and 2008, 92,253 deaths related to MPM have been recorded. 78% of the patients were male and 22% female [4]. The death rate of MPM may vary in each country [3, 8]. The percentage of documented deaths attributed to MPM continentally correspond to 2,5% in Africa, 25,9% in America, 13% in Asia, 54% in Europe and 4,6% in Oceania. 88,1% of MPM deaths were recorded in the developed, high income countries and only 11,82% in the middle and low income country group. The country with the majority of MPM deaths between 1994 and 2008 was the United States (US) [4]. Between 2003 and 2008 19,011 cases of MPM were documented. According to Henle *et al.* 93,2% of MPM patients belonged to the Caucasian race. In a percentage >75,1% MPM was diagnosed in ages of >65 years.[9] However, because of the prohibition of asbestos use, it is believed that the frequency of MPM in the US will decrease.[3] According to WHO, the United Kingdom (UK) follows, having 14,6% of MPM deaths worldwide.[4] Despite having banned the import of asbestos for two decades into the UK, Health and Safety Executive data for 2012 show that MPM caused 2535 deaths in England, Wales and Scotland [13]. According to the WHO list with the top ten countries with MPM deaths between 1994 and 2008, Japan follows further with a percentage of 12,1%, Germany with 10,4% and France with 7,2%.[4] Kishimoto *et al.* reported that about 79% of MPM cases in Japan was due to asbestos exposure.[14] This asbestos exposure in Japan was partly due to working in the US naval base and shipyards.[15] As far as Germany is concerned,1397 people died of mesothelioma in 2010 [16]. The rates of mesothelioma in developing countries fall short of the real numbers due to the absence of sufficient registry data. In many countries, asbestos was used in 1970's and is still used, but no mesothelioma cases were recorded [3, 17]. Park *et al.* reported that one mesothelioma case has been overlooked for every four to five reported cases [17].

Nowadays in the US about 2,500 new MPM cases are being diagnosed every year [8]. In western Europe, 5,000 MPM patients die every year due to MPM [4, 8]. The highest frequency of MPM diagnosis has been recorded in the UK and in Australia [4]. Between 1982 and 2011, 13,036 individuals were newly diagnosed with malignant mesothelioma, 690 of which were diagnosed in 2011 [18]. The epidemiology and death rate of MPM presents differences not only between countries, as mentioned above, but also between regions within a country [4]. For example, in Italy and in the UK, MPM is more often in areas where cement industries, shipyards, oil refineries and petrochemical industries are established [4, 8, 19-22].

Generally, the prevalence of MPM is estimated to 10-30/1.000.000 in men and 2/2.000.000 in women. MPM is on average responsible for the deaths of 15.000-20.000 people every year worldwide. The disease appears in the age group of 50-70. The presentation of the disease in younger patients is considered to be very rare. The disease has also an extreme latent period. This period varies from 20 to 40 years [1, 4, 8]. However, a brief asbestos exposure can theoretically also result in MPM. The disease's manifestation is calculated to occur after an asbestos exposure longer than 5 years. However, a quantitative analysis estimating the lowest levels of asbestos exposure needed to cause the disease has never been reported [1, 4, 8, 14, 16].

What is more, asbestos fibers have been detected in many healthy people not suffering from the disease [23]. Nevertheless, it is certain that through the prohibition of the asbestos use, the asbestos exposure will decline. It is believed therefore that the asbestos epidemic in the US has already had its peak in 2004. On the other hand, it is believed that Europe's peak will be in 2020. In the future 250,000 deaths are yet to be expected because of MPM [4].

Pathophysiology

The association between MPM and asbestos exposure has been thoroughly studied over the last decades. This connection was first described by Wagner *et al.* [24] in 1960. The correlation between the development of MPM and asbestos exposure is calculated to be about 80%. A significant rise of the MPM prevalence was noticed after the widespread use of asbestos. Before the wide commercial asbestos use, MPM was rare [8]. The development of MPM in animals after exposure to asbestos fibers has also been

demonstrated in animal models [25]. The risk of developing MPM is about 10% for workers that were possibly exposed to asbestos over their lifetime. However, this risk rises up to 70% among workers with proven exposure to asbestos [26]. Smoking of tobacco products seems not to affect the development of MPM. However, the possibility of death because of a thoracic malignancy (lung cancer or MPM) rises in these patients [26, 27] (23-25).

There are six types of asbestos. However, the majority of asbestos fibers can be divided in two large categories. They are either amphibole or serpentine [8]. The serpentine fibers are present in the 90% of the asbestos type that is used in the US. This form of asbestos can be found in brake linings, ship building, cement, ceiling and pool tiles. Chrysotile, which is also known as white asbestos, compromise 95% of this asbestos group [8]. However, the oncogenic capability of chrysotile is questionable [8, 28]. Of the amphiboles, amosite (brown asbestos) and crocidolite (blue asbestos) had the most industrial applications [8].

The biggest asbestos deposits are found in Canada, Russia and South Africa. In Europe there are asbestos deposits in Italy, Greece and Cyprus [4] [29-33]. Asbestos is a non-flammable material and has a great mechanical endurance. This characteristic, combined with the fact that asbestos is a good thermal and electrical insulator material, has led to its wide use in the construction industry. As a result, asbestos has been used in the past as insulation material in household products, in floor tiles, wire and in paints. For this reason, as well as due to its low cost, asbestos has been widely used in construction and in ship building. As a result, almost the entire population of Western countries has theoretically been exposed to asbestos. Nowadays, the majority of world countries have banned the use of asbestos products. However, in the developing world in many countries, because of the insufficient control, asbestos may still be used [4, 8] [34, 35].

Nowadays the groups that are at risk of developing MPM are the group of workers who have occasional exposure to asbestos. These groups of employees involve plumbers, builders, sailors, workers in shipyards and workers who install insulation or renovate buildings. These populations are the new high risk groups that have historically replaced the workers in asbestos mines [4, 21, 36-38].

The domestic asbestos exposure is also considered to be an important risk factor [4]. For example, women who lay or wash their husband's work clothes at home are also exposed. Their children might also be indirectly exposed. In these groups, the risk of a MPM development is estimated to be 10% and the difference in the frequency observed among men and women is due to the different nature and amount of asbestos exposure. Obviously the greatest risk concerns the asbestos-exposed workers [4, 39, 40].

The exact mechanism of development of MPM has not been verified yet. It is believed that asbestos fibers are trapped in the lower lung segments where they trigger an inflammatory reaction [41]. This inflammatory reaction can become chronic. As a result, this prolonged inflammatory reaction of the pleura can lead to the production and release of reactive oxygen species (ROS), reactive nitrogen species (RNS), cytokines, and growth factors which may consequently trigger the molecular cellular pathways that lead to MPM oncogenesis. In addition, the changes that are triggered by the asbestos fibers in the cellular level can cause DNA damage and can interfere with the mitosis process. Moreover, MPM cells appear resistant to apoptosis mechanisms, thus providing a mechanism for the continuous growth of malignant transformed cells. According to another hypothesis, the suppression of the tumor suppressor genes may enhance the development of the malignancy [3, 4, 8, 40, 42-44]. As far as the asbestos type is concerned, it is thought that the chrysolite fibers are quickly removed from the lung without being translocated in the pleural cavity and initiating an inflammatory reaction that may possibly lead to MPM. On the other hand, amphibole asbestos fibers are quickly translocated in the pleura and can result in a chronic inflammation of the pleura [3, 41]. However, the WHO has concluded that all asbestos fiber types can potentially cause human cancer [3].

Radiation therapy has also been accused as a possible cause for MPM. Patients with non-Hodgkin lymphoma and breast cancer have been treated with radiation therapy and additionally developed MPM [26]. In addition, the Simian Virus SV-40, a polyoma virus, has been detected in patients with MPM without an obvious asbestos exposure. Current research should be oriented to the identification of these molecular pathways, a clarification of which could lead to the development of suitable vaccines in the future [3].

Symptomatology

The mean age of presentation of MPM symptomatology is the sixth decade of life. It used to be believed that the manifestation of MPM could be an acute thoracic pain. However, the main symptomatology clinically appears due the developed pleural effusion [1]. In this way, the most common symptoms are dyspnea and thoracic pain. After the

drainage of the pleural effusion, this symptomatology withdraws. The thoracic pain may also be explained by the infiltration of the thoracic wall and the intercostal nerves. A deterioration of the dyspnea symptomatology may imply the progression of the disease and is possibly the manifestation of a trapped lung [1, 3]. The pleural effusion can be gradually absorbed; thus the pleura thickens and forms a thick crust that shields the lung. The disease infiltrates the lung fissures and confines the lung on the diaphragm and the thoracic wall. The MPM can expand locally and infiltrate the adjacent organs. The consequent clinical symptoms depend on the organ which is infiltrated. As a result, dysphagia, pain, compression of the spine and neuropathy may occur during the evolution of the disease. However, the progress of the symptomatology can be due to the infiltration of the thoracic wall or the mediastinum. The displacement and the pressure of the contralateral lung can worsen the symptoms. The infiltration of the pericardium can lead to a malignant pericardial effusion, a cardiac tamponade or myocardial metastases. Superior vena cava syndrome, pericarditis and arrhythmias can be also detected. From the local infiltration of the diaphragm, the tumor can expand to the peritoneal cavity. As a result, ascites can be also detected by the primary care physician. Superior vena cava syndrome, pericarditis and arrhythmias may also occur. The diaphragm can also be infiltrated and in this case the mesothelioma can expand in the peritoneal cavity. This can explain the presence of ascites in some cases. Metastases on the contralateral lung can also be diagnosed. Like the primary malignancy, they may also be manifested as malignant pleural effusions. Rare symptoms include coughing, hemoptysis, fever, weakness, hoarseness, dysphagia and Horner syndrome. The diagnosis of the disease is set on average three months after the manifestation of the first symptoms. However, a number of the patients may refer to a physician even six months after the appearance of the initial symptoms. Pneumothorax could be a rare first manifestation of the disease presented with acute chest pain and dyspnea. One third of the patients also report having fever, weight loss and fatigue. In some cases the patients are totally asymptomatic and the disease is accidentally diagnosed in a routine chest x-ray. In many autopsies, distal metastases of MPM have been detected. For example, metastases have been detected in hilar, tracheobronchial and supraclavicular lymph nodes. However, these metastases rarely present direct clinical manifestations. Metastases in the liver, brain and adrenal glands have also been reported. Death may occur due to infection, respiratory failure and general cancer cachexia [1, 3, 8]. From the clinical examination, a reduction of the respiratory whispering can be detected. In addition, by thorax percussion bluntness can be observed. The patient may also report reduced vocal vibrations. Clubbing is unlikely to be observed if the disease is not combined with an accompanying lung malignancy [44]. Lymph nodes can be palpated [45]. Hepatomegaly and ascites can be noticed [46]. In the chest wall, palpable masses can be observed at thoracocentesis points or at thoracotomy [47].

Conclusion

MPA is a malignant disease with a low life expectancy. The absence of specific clinical features of the disease makes it difficult to detect at an early stage. The ban of the use of asbestos is believed that will be a drastic step towards the reduction of the occurrence of the disease. However, in developing countries, asbestos continues to be in use due to its low cost and insufficient controls. Malignant pleural mesothelioma (MPM) is particularly aggressive and nowadays there is increased interested in immunotherapy for both first-line and salvage settings. Early investigations of interleukin-2 (IL-2) and interferon alfa-2a/b have been limited by modest response rates and toxicity, whereas cytokine gene therapy is currently being investigated and shows early promise. To date the most prominent class of immunotherapies to be trialed with mesothelioma has been immune checkpoint inhibitors (CPI) and early results are encouraging, particularly for agents targeting the PD-1/PD-L1 pathways. The combination of immunotherapy and radiation therapy may allow for complimentary immunologic effects that can enhance antitumor response [1, 11, 12, 48, 49].

Competing Interests

The authors have declared that no competing interest exists.

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