IMPACT OF ASBESTOS EXPOSURE ON THE PROGRESSION OF PLEURAL MESOTHELIOMA

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ABSTRACT

This paper addresses the relationship between asbestos exposure and the development of malignant pleural mesothelioma, a neoplasm that is difficult to diagnose and has a poor

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prognosis. The aim of the study is to analyze the effects of asbestos on the progression of pleural mesothelioma, describing its pathogenic mechanisms, clinical and diagnostic manifestations and therapeutic options. The methodology used consisted of a review of the scientific literature and the analysis of 10 studies that investigate the etiology, pathophysiology, histopathological findings and treatments of pleural mesothelioma. The results show that exposure to asbestos is the main risk factor for this disease, and that its inhalation causes chronic inflammation, oxidative damage and genetic mutations that culminate in the malignant transformation of mesothelial cells. Clinically, mesothelioma presents insidiously with nonspecific symptoms such as progressive dyspnea, chest pain, and pleural effusion, making it difficult to diagnose early. Histopathological analysis is essential to identify epithelioid, sarcomatoid and biphasic subtypes, which determine prognosis and therapeutic options. Although imaging techniques and immunohistochemical studies are useful for diagnosis, patients are usually diagnosed in advanced stages, limiting treatment options to combinations of chemotherapy with pemetrexed and cisplatin, or to radical surgical procedures that pose high risks. Despite advances in immunotherapy and targeted therapies, the survival rate remains low. In the final considerations, the importance of developing better prevention, early detection and more effective treatment strategies is highlighted, as well as the need to continue with rigorous policies for the control and elimination of asbestos in the workplace and environment. This study reaffirms the urgent need to face this disease in a multidisciplinary manner and improve the quality of life of affected patients.

Keywords: Occupational exposure. Carcinogenesis. Asbestos. Pleural mesothelioma. Asbestos.

INTRODUCTION

Exposure to asbestos has been widely recognized as a major risk factor in the development of various respiratory pathologies, with pleural mesothelioma being one of the most serious and with the worst prognosis. Asbestos is a group of fibrous minerals that, due to its heat resistance and durability properties, was widely used in the construction industry and in manufactured products. However, asbestos fibers are extremely dangerous when inhaled, as they are deposited in lung and pleural tissues, generating a chronic inflammatory process that can lead to the development of malignant diseases, such as pleural mesothelioma. [Acts 1, 2]

This type of cancer, which mainly affects the pleura, is characterized by its direct relationship with the inhalation of asbestos fibers, which can remain in the body for decades before manifesting clinical signs. Despite restrictions on the use of asbestos in many countries, its industrial use and occupational exposure continue to pose a public health challenge, particularly in regions where regulations are less stringent or non-existent. The persistence of this exposure remains a determining factor in the incidence of mesothelioma, and its ability to induce malignant transformation in mesothelial cells has been extensively studied. [3]

From a pathophysiological point of view, asbestos inhalation leads to the activation of chronic inflammatory processes, cell damage and the eventual malignant transformation of mesothelial cells. Asbestos fibers, when inhaled, are deposited in the pleura and, over time, induce inflammatory responses that can evolve into an oncogenic environment. Pleural mesothelioma is distinguished by its aggressive progression and resistance to conventional therapies, underscoring the importance of understanding the mechanisms underlying its development in order to improve diagnostic and treatment strategies. [Acts 4, 5]

In the field of pathological anatomy, pleural mesothelioma is characterized by the proliferation of malignant mesothelial cells that infiltrate the pleura, generating pleural thickening, pleural effusion and, in advanced stages, involvement of lung tissue and adjacent structures. Histopathological and immunohistochemical techniques are essential to differentiate mesothelioma from other pleural neoplasms, given its morphological variability and the coexistence of epithelial, sarcomatoid and biphasic patterns. [6]

Therefore, the present work aims to analyze the impact of asbestos exposure on the progression of pleural mesothelioma, focusing on the semiology, pathophysiology and pathological anatomy aspects of the disease. Likewise, it will seek to identify the factors that influence the aggressiveness of mesothelioma and its resistance to current treatments, in order to provide new perspectives for its clinical approach.

MATERIALS AND METHODS

The present study was developed under a literature review approach, with the aim of analyzing and synthesizing the available scientific evidence on the impact of asbestos exposure on the progression of pleural mesothelioma. To this end, a search of scientific articles was carried out in internationally recognized databases, such as the Virtual Health Library (VHL) and SciELO. The descriptors used for the search included 'asbestos', 'pleural mesothelioma', 'pathophysiology', 'pathological anatomy', and 'occupational exposure', which were used in combination using Boolean operators to refine the results and ensure the relevance of the selected studies.

The selection of articles was limited to publications in English, Spanish and Portuguese, covering a period of five years, from 2019 to 2024. Studies that specifically addressed the relationship between asbestos exposure and the development or progression of pleural mesothelioma were established as inclusion criteria. Articles that did not have full access or that did not meet the previously established criteria were excluded.

Once the results were obtained, the articles were critically evaluated through a detailed reading of the abstracts and, if relevant, of the full text. A data collection table designed specifically for the study was used, in which relevant aspects such as the type of study, the sample, the main findings and the conclusions about the relationship between asbestos exposure and the progression of pleural mesothelioma were recorded. This table allowed an adequate systematization of the information for subsequent analysis and discussion.

Finally, the extracted data were organized and presented according to the key variables of the study: semiology, pathophysiology and pathological anatomy of pleural mesothelioma, with emphasis on how these dimensions are affected by asbestos exposure. The information collected was discussed and compared with previous literature, in order to establish robust conclusions on the topic in question.

THEORETICAL FRAMEWORK

Malignant pleural mesothelioma is a rare and highly aggressive neoplasm that originates in the mesothelial cells that line the pleura, the membrane that surrounds the lungs. His medical history is closely related to exposure to asbestos, a material that has been widely used in industry for its insulating and heat-resistant properties. Over the decades, a strong association between asbestos exposure and the development of pleural mesothelioma has been documented, especially in individuals exposed occupationally in factories, mines, or in the construction industry. [Acts 1, 2]

This type of cancer has a long latency period, usually between 20 and 50 years, which complicates early diagnosis and, in many cases, reduces effective therapeutic options. Clinical presentation usually includes dyspnea, chest pain, and, in more advanced stages, pleural effusion, leading to progressive deterioration of respiratory function. The causes of mesothelioma are almost exclusively linked to exposure to asbestos fibers. [7]

This mineral, when inhaled, is deposited in the pleura, which generates a chronic inflammatory process that, over time, can induce the malignant transformation of mesothelial cells. Other risk factors, although less common, include exposure to ionizing radiation or certain chemicals, as well as inherited genetic mutations, such as those related to the BAP1 gene, which may predispose to the development of the disease. The incidence of mesothelioma has decreased in some regions following the ban on asbestos use, but it remains a clinical concern due to cases that continue to emerge from past exposures. [Acts 8, 9]

Asbestos, or asbestos, is a group of fibrous minerals composed primarily of silicates. There are different types of asbestos, the most common being chrysotile, crocidolite and amosite. The toxicity of asbestos lies in its ability to fragment into small fibers that, when inhaled, penetrate deep into the lungs. These fibers are biologically active and resistant to degradation, causing them to remain in lung tissue for years or even decades. In addition to its association with mesothelioma, asbestos is linked to other respiratory pathologies such as asbestosis, diffuse pulmonary fibrosis, and lung cancer.[8]

The use of asbestos was widespread globally during the 20th century in various industries, including construction, the manufacture of insulation materials, and the automotive industry. However, over time, its danger was recognized, and many countries have banned or severely limited its use. Despite this, asbestos is still present in many old structures and materials, which implies a continuous risk of exposure, particularly in demolition work, renovation or in contaminated areas. Medical surveillance of exposed workers and proper management of asbestos waste are essential to minimise new cases of related diseases. [8]

This mineral continues to be a challenge for both public health and clinical medicine. Research into the mechanisms of action of asbestos, methods of early detection of its effects and therapeutic strategies for the diseases it causes are crucial to improve the prognosis of those affected and prevent new exposures. [8]

In this sense, understanding the pathophysiology of cancer induced by asbestos exposure is essential, as it involves several complex mechanisms that develop over time. Firstly, when asbestos fibres are inhaled, due to their small size and ability to resist

biological degradation, they pass through the defences of the respiratory system and are deposited in the pleura or in the pulmonary alveoli. At these sites, the fibers generate a chronic inflammatory response, which is the basis for many of asbestos' pathogenic effects. [4, 5, 10]

Alveolar macrophages attempt to phagocytose these fibers, but given their size and shape, they fail to eliminate them completely, resulting in sustained activation of these macrophages and the release of pro-inflammatory mediators, such as cytokines and reactive oxygen species (ROS). This prolonged inflammatory process creates a favorable local environment for tissue damage, contributing to the development of fibrosis and, in the long term, to the malignant transformation of mesothelial cells. [4, 5, 10]

At a second level, oxidative damage caused by chronic inflammation and the presence of asbestos fibers contributes to the genetic instability of cells. Reactive oxygen species generated by inflammation induce mutations in cellular DNA, which interferes with normal DNA repair mechanisms and causes cumulative genetic alterations. [4, 5, 10]

Among the most relevant mutations are those that affect tumor suppressor genes such as BAP1, which plays a crucial role in the regulation of the cell cycle and the response to DNA damage. The loss of BAP1 function has been directly related to the predisposition to mesothelioma. Other affected genes include CDKN2A and NF2, which are also involved in the regulation of cell growth and differentiation, and whose alteration facilitates the uncontrolled proliferation of affected cells.[Acts 9, 11, 12]

Finally, asbestos' ability to trigger carcinogenesis is not limited to direct DNA damage. The fibers can also stimulate processes such as angiogenesis and the activation of pro-oncogenic signaling pathways, which favor the survival and expansion of malignant cells. In addition, recent studies suggest that asbestos fibers induce epigenetic changes, altering gene expression without modifying the DNA sequence, further contributing to the malignancy of cells. This pro-tumor environment, sustained by chronic inflammation, oxidative damage, and genetic and epigenetic alterations, creates an ideal substrate for the development of pleural mesothelioma and other neoplasms related to asbestos exposure. [Acts 9, 11, 12]

Understanding the pathophysiological mechanisms underlying pleural mesothelioma is key to adequately addressing its clinical manifestations and diagnosis. The clinical symptoms of mesothelioma often present in an insidious manner, with symptoms that can be mistaken for other common respiratory conditions, delaying diagnosis in many cases. Common signs and symptoms include progressive dyspnea, persistent chest pain, and in many cases, recurrent pleural effusion. [Acts 13, 14]

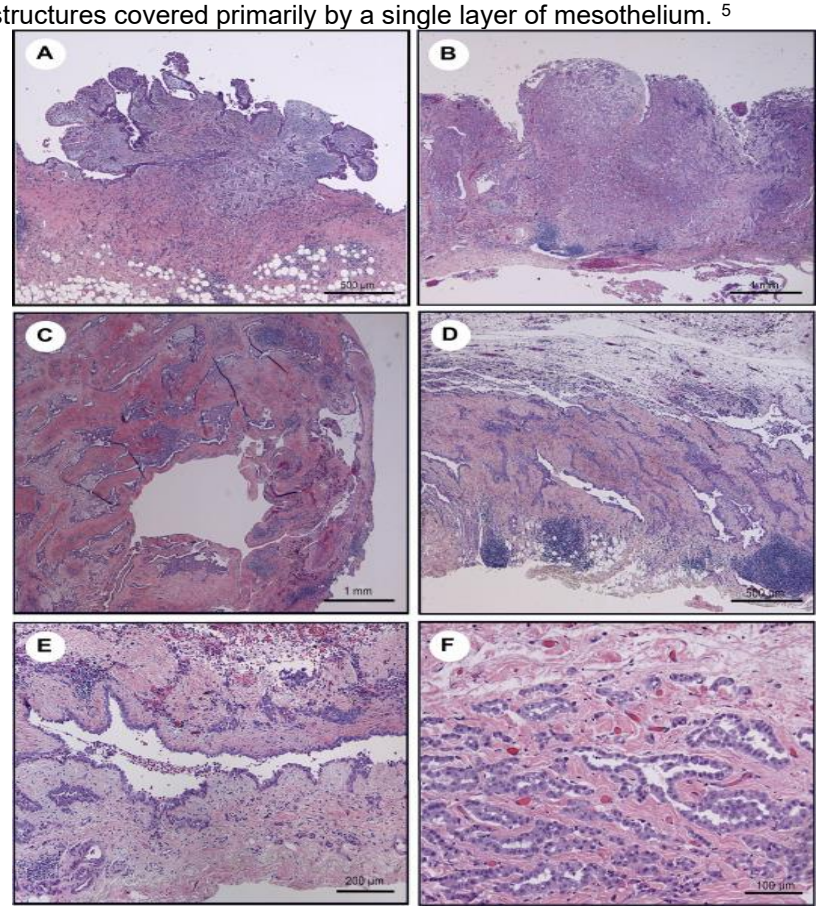
These symptoms are usually associated with local invasion of the tumour into the pleura and, in advanced stages, there may be weight loss, fatigue and non-productive coughing. The semiology of pleural mesothelioma is crucial, since physical examination can detect decreased breath sounds, dullness to percussion due to pleural effusion, and signs of pulmonary restriction. Once suspicious clinical symptoms are established, diagnosing pleural mesothelioma requires a combination of imaging methods and invasive testing. [Acts 13, 14]

Chest x-rays are usually the first test requested, revealing the presence of pleural effusion or pleural thickening. However, computed tomography (CT) and magnetic resonance imaging (MRI) are more accurate tools for assessing tumor extent and characteristics. Pleural biopsy is the definitive diagnostic method, as it allows tissue samples to be obtained for histopathological analysis. [Acts 13, 14]

Histopathological findings in malignant pleural mesothelioma are essential for its definitive diagnosis and for differentiating this neoplasm from other pleural pathologies, such as metastatic adenocarcinoma or lung carcinoma. There are three main histologic subtypes of mesothelioma: epithelioid, sarcomatoid, and biphasic, each with different morphological features and prognosis.[6]

Epithelioid mesothelioma, which is the most common subtype and has the best relative prognosis, is characterized by the presence of uniform cells with rounded or oval nuclei that form tubular or papillary structures. These cells are usually well differentiated, which can make it difficult to distinguish them from other epithelial tumors. Sarcomatoid mesothelioma, on the other hand, has a poorer prognosis and features spindle cells with a sarcomato-like growth pattern, which can sometimes lead to diagnostic errors. Biphasic mesothelioma combines features of both epithelioid and sarcomatoid types, and its prognosis usually depends on the predominance of one or the other [component.6]

Figure 1. Histology of diffuse epithelioid malignant mesothelioma of the pleura (hematoxylin and eosin staining). (A) Invasive myxoid papillary lesion. (B) Coarse confluent area of partially myxoid exophytic mesothelial growth. (C) Tip of a large exophytic polypoid lesion with inward mesothelial growth. (D) Large tubular structures in the pleura. (E) Greater magnification of the large tubular structure seen in the image above. (F) Tubular structures covered primarily by a single layer of mesothelium. [5]



Immunohistochemistry plays a key role in the diagnostic confirmation of mesothelioma, especially when morphological findings are inconclusive. The markers most commonly used to diagnose mesothelioma include calretinin, mesothelin, WT-1, and D2-40, which are positive in most cases of epithelioid mesothelioma. On the other hand, the identification of cytokeratins and vimentin can help confirm sarcomatoid cases. These markers, together with traditional morphological studies, make it possible to differentiate mesothelioma from other neoplasms that can affect the pleura, such as lung or metastatic adenocarcinoma. [6]

Overall, the combination of clinical evaluation, advanced imaging studies, and histologic analysis is essential for the accurate diagnosis of pleural mesothelioma. Early diagnosis remains a challenge, but it is essential to optimize therapeutic management and improve the prognosis in these patients.[14]

Treatment of malignant pleural mesothelioma remains challenging due to the aggressive nature of the disease and its usually delayed diagnosis. Treatment options include a combination of surgery, chemotherapy, and radiation therapy, although the choice

of treatment depends on the stage of the disease, histologic subtype, and the patient's overall condition. [15]

Surgery is considered in patients with localized disease and good functional status. There are different surgical approaches, the most common being pleurectomy/decortication, which involves resection of the affected pleura, and extrapleuropneumonectomy, a more extensive surgery that includes resection of the lung, pleura, diaphragm, and ipsilateral pericardium. Although extrapleuropneumonectomy offers a more radical approach, it is also associated with higher morbidity and mortality, so its indication should be carefully evaluated. Surgery, in any modality, is often combined with other adjuvant therapies to improve long-term outcomes.[15]

Chemotherapy remains the mainstay of treatment for most patients, especially those with advanced disease who are not candidates for surgery. The standard regimen includes a combination of pemetrexed and cisplatin, which has been shown to improve survival in these patients. In addition, other agents have been explored, such as bevacizumab, a monoclonal antibody that inhibits angiogenesis, which has shown some benefit in combination with traditional chemotherapy. However, response rates remain limited, which has driven the search for more effective therapies. [15]

Radiation therapy, although not curative in most cases, is used as a palliative treatment to control symptoms, such as chest pain or recurrent pleural effusion. In some cases, it is also used as postoperative adjuvant therapy to reduce the risk of local recurrence. In recent years, emerging therapies, such as immunotherapy, have gained ground in the treatment of mesothelioma. Drugs that inhibit immune checkpoints, such as PD-1 and CTLA-4 inhibitors, have shown promise in clinical trials, offering new hope for patients with advanced mesothelioma. However, access to these therapies is still limited and requires more research to define their role in standard treatment. Acts 15, 16

RESULTS AND DISCUSSION

The review of the 14 studies analyzed in the table below shows remarkable consistency in the identification of asbestos as the main etiological factor of malignant pleural mesothelioma. In all the studies reviewed, the strong relationship between exposure to this fibrous mineral and the development of mesothelioma is confirmed, with a latency period that can reach 50 years, which greatly complicates the early detection of the disease. Acts 1, 2

Table 1: Asbestos as the main etiological factor of malignant pleural mesothelioma.

I am a student	Title	Type of Study	Sample	Main Findings	Conclusions
1	Asbestos Exposure and Malignant Pleural Mesothelioma	Systematic review	17 studies, 1,104 patients	High correlation between asbestos exposure and mesothelioma, latency of 42 years, and 100% mortality.	Asbestos exposure is a determining factor in mesothelioma. Better preventive strategies are needed.
2	Pleural Mesothelioma: A Rapid Evolution of an Indolent Disease	Case report	A 58-year-old patient	Epithelioid mesothelioma with rapid progression and pleural solid masses.	Mesothelioma can progress rapidly with no known exposure.
3	Advances in blood and pleural biomarkers for mesothelioma	Narrative Review	Review of recent studies	Mesothelin and other biomarkers can help in diagnosis, although validation is lacking.	Identifying biomarkers can improve early diagnosis.
4	Occupational and Environmental Asbestos Exposure and Survival of Patients with Asbestos-Related Cancer	Follow-up study	546 patients with mesothelioma and 902 with lung cancer	Occupational exposure reduces survival.	Occupational exposure and proximity to asbestos sources reduce survival.
5	Molecular mechanisms in the progression of mesothelioma	Review of molecular mechanisms	Several studies focused on genetic and molecular markers	Mutations in key genes such as BAP1 affect prognosis.	Targeted therapies based on molecular markers can improve management.
6	The role of HMGB1 in the development of mesothelioma	Narrative Review	Experimental and clinical studies	HMGB1 promotes chronic inflammation that facilitates the progression of mesothelioma.	HMGB1 could be a therapeutic target.
7	Diffuse pleural mesothelioma: advances in diagnosis and treatment	Narrative Review	Studies on diagnostic techniques and emerging therapies	Importance of immunotherapy and multidisciplinary approaches.	Multidisciplinary and personalized approaches improve the

					prognosis .
8	Asbestos load in the lungs of mesothelioma patients	Estudio postmortem	95 deceased mesothelioma subjects	Identification of critical concentrations of asbestos fibers in lung tissue.	Assessment of asbestos burden in the lungs is key to causal attribution .
9	Malignant Pleural Mesothelioma: An Update	Narrative Review	Recent Articles on Pleural Mesothelioma	Advances in pathophysiology, diagnostic and treatment methods.	More studies are needed to validate new diagnostic techniques.
10	Histopathologic Features in Asbestos-Induced Mesothelioma	Histopathological study	Histological specimens from patients with mesothelioma	Key histopathological patterns in mesothelioma.	Histopathology is key to understanding the progression of mesothelioma

Source: Prepared by the authors.

The findings in relation to the types of asbestos (chrysotile, crocidolite, amosite) reinforce the existing consensus in the literature on its ability to generate chronic inflammatory damage, which leads to irreversible cellular changes. The toxicity of these minerals is manifested through the inhalation of their fibers, which, when deposited in the lungs and pleura, trigger a prolonged inflammatory process and oxidative damage that contributes to carcinogenesis.[Acts 7, 8]

From a clinical point of view, the results of the studies analysed confirm that pleural mesothelioma is an insidious disease, with non-specific symptoms in its initial stages, such as progressive dyspnea and chest pain, which are frequently associated with other respiratory pathologies. [Acts 13, 14]

This finding is consistent with what has been previously described in the literature, where the semiology of mesothelioma is difficult to distinguish clinically until the disease is in advanced stages. Physical examination reveals indirect signs, such as decreased breath sounds and dullness to percussion, due to pleural fluid accumulation, underscoring the need for a high index of suspicion in patients with an occupational history of asbestos exposure. [Acts 13, 14]

Regarding the pathophysiology, the studies reviewed emphasize the role of the chronic inflammatory process and oxidative damage as drivers of mesothelioma development. The failure of alveolar macrophages to remove asbestos fibers perpetuates continuous inflammation, releasing pro-inflammatory mediators and reactive oxygen species that damage cellular DNA. Studies on genetic markers highlight the importance of mutations such as those affecting the BAP1 gene, which have been observed in many cases of mesothelioma, reinforcing the idea that exposure to asbestos not only induces an inflammatory response, but also profound molecular alterations that predispose to cellular malignancy. [10, 11, 12]

Histopathological findings confirm the typical morphological characteristics of malignant pleural mesothelioma, differentiating into three subtypes: epithelioid, sarcomatoid and biphasic. The epithelioid subtype, which is the most common, is associated with a better prognosis compared to sarcomatoid, which shows greater aggressiveness and poorer response to treatment. In all studies, the importance of immunohistochemistry is highlighted as a fundamental resource for the differential diagnosis between mesothelioma and other pleural neoplasms, using specific markers such as calretinin, mesothelin and WT-1. [6]

In relation to diagnosis, the studies analysed reinforce the use of advanced imaging techniques, such as computed tomography (CT) and magnetic resonance imaging (MRI), which allow an accurate assessment of tumour extension. Pleural biopsy remains the gold standard for definitive diagnosis, and thoracentesis, combined with thoracic ultrasound, facilitates diagnosis in patients with pleural effusion. Immunohistochemical analysis is essential to confirm the diagnosis, since mesothelioma can mimic other pleural and pulmonary neoplasms.[Acts 13, 14]

The results of this review demonstrate the consistency of the data in relation to the etiology, clinical presentation, pathophysiology and diagnostic methods of malignant pleural mesothelioma. However, one of the main challenges remains the early detection of the disease. Despite the advances, the diagnosis of pleural mesothelioma is made in advanced stages in most cases, which considerably limits the therapeutic options and the patient's prognosis. [14]

In terms of treatment, studies show that current therapies, such as chemotherapy with pemetrexed and cisplatin, offer an improvement in survival, but the results remain modest. The introduction of immunotherapy, while promising, has not yet proven to be a definitive solution for most patients, and access is limited. This raises an urgent need to

develop new targeted therapies that build on mesothelioma-specific genetic and molecular alterations, such as mutations in BAP1 and other genes.[Acts 15, 16]

Advances in the field of biomarkers, both blood and pleural fluid, are promising, but have not yet translated into widespread clinical use. The studies reviewed suggest that mesothelin and other markers have potential to improve early diagnosis, but their sensitivity and specificity in some subtypes of mesothelioma remain limited. This is an area of research that should be prioritized to improve clinical outcomes and reduce mortality associated with this disease. [Acts 15, 16]

FINAL CONSIDERATIONS

The present work has confirmed that exposure to asbestos is the main determinant in the development of malignant pleural mesothelioma. The results obtained agree that asbestos fibers, once inhaled, trigger a cascade of inflammatory events and genetic mutations that culminate in the malignant transformation of mesothelial cells. This finding reinforces the need to continue applying asbestos control and removal policies to reduce the incidence of the disease in the coming decades.

On a clinical level, early diagnosis remains one of the main challenges, as the initial symptoms of mesothelioma are nonspecific and easily confused with other pleural diseases. Despite advances in imaging techniques and biomarker identification, patients continue to be diagnosed in advanced stages, severely limiting therapeutic options. It is essential to improve early detection methods to intervene in more favorable stages of the disease.

From a therapeutic perspective, current treatments, including chemotherapy with pemetrexed and cisplatin, have shown modest improvements in survival, but are not curative. Immunotherapy and new targeted therapies hold promise for the future, although they are still in the early stages of evaluation. This indicates that more effective therapeutic approaches, based on the molecular biology of mesothelioma, are needed to improve patient outcomes.

The importance of immunohistochemistry in the diagnosis of mesothelioma was highlighted, especially in the differentiation of other pleural tumors. The identification of histological subtypes (epithelioid, sarcomatoid and biphasic) is crucial not only for diagnosis, but also to guide treatment and establish prognosis, which highlights the relevance of these analyses in clinical practice.

Therefore, this study has reaffirmed the severity of malignant pleural mesothelioma as a direct consequence of asbestos exposure, and highlights the urgent need to advance

early detection, prevention, and the development of more effective therapies. Preventive strategies and surveillance of at-risk groups remain critical to reducing the global burden of this devastating disease.

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