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Challenges and Solutions in Pathological Diagnosis of Malignant Pleural Mesothelioma

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ABSTRACT

The tumor known as mesothelioma affects the serosal membranes, which include the testes' tunica vaginalis, peritoneum, pleura, and pericardium. In nations such as Italy, the global incidence of Malignant Mesothelioma (MM) is approximately 1.15 percent out of a hundred thousand people. Malignant Pleural Mesothelioma (MPM), which makes up around 80% of cases, is the most prevalent type of mesothelioma. Although mesothelioma is not prevalent in the general population as a whole, it is linked to exposure to mineral fibers and industrial contaminants, with asbestos being responsible for approximately 80% of instances. In the upcoming years, it is anticipated that the prevalence of MPM will gradually increase globally due to the continued contamination with asbestos in several nations. The tumor invades neighboring structures, causing pleural effusion, discomfort, and dyspnea, and It proceeds from the prefrontal toward the visceral lining following a pattern such as loco-regional of development. Recent research has examined the role of BAP, which was-1 as well as MTAP in the prognosis for the long-term of MPM as well as the diagnosis of cancer in place. There are several aspects of managing preinvasive lesions in mesothelioma that are unknown and up for debate. Three things are necessary to provide sufferers with the treatment they require: the determination of the illness, the current state of the illness, as well as an accurate and thorough examination of the patient.

Keywords: Mesothelioma; Malignant Mesothelioma; Malignant Pleural Mesothelioma

Introduction

A solid tumor derived from pleural mesothelial cells is known as malignant pleural mesothelioma (MPM). It is linked to prior asbestos contact; testing for the condition is difficult since MPM rarely displays symptoms right away after fiber exposure it can take up to 40 years.[1] The likelihood of recovery from MPM, an uncommon malignancy, is extremely dismal. Klemperer and Rabin provided the initial description of it, distinguishing between the diffuse as well as localized forms of MPM.[2,3] In the US, the yearly incidence of MPM is thought to be 1 in 100,000, with about 3,000 additional instances reported annually. Men are more likely to have it, and most patients are older than 65. The prevalence of MPM in the USA surged at the beginning of the decade but thereafter began to decrease, primarily among patients of males.[4] Nonetheless, MPM rates continue to rise globally. The greatest number in industrialized nations like the United Kingdom along with Australia is anticipated to happen before 2030.[5] On the other hand, it is anticipated that mesothelioma cases will rise sharply in emerging nations because asbestos exposure remains prevalent in work environments.[6,7] Based on the SEER databases, the overall incidence of MPM remained at 0.7 out of 100.000 persons yearly, having a gender disparity of between 0.3 for women and 1.3 among men. Frequency statistics over the past ten years indicate that the number of women has stayed constant, whereas the proportion of men surged in 1992 to about 2.6/100.000 persons/year after which it declined steadily.[8] The single most significant risk factor for MPM is being exposed to asbestos at work. Cement, swimming pools including ceiling tiles, car brake linings, as well as shipbuilders all employ asbestos. It was previously believed that asbestos workers had a 10% lifetime chance of acquiring MPM.[9] The majority of patients are suffering from severe disease when they are diagnosed; the prognosis is terrible, with an average survival time of seven to twelve months whether receiving chemo or palliative treatment, correspondingly.[10] MPM has been scientifically linked to the inhibition of the nuclear deubiquitinase BRCA1-associated protein 1 (BAP1), an essential regulator of gene transcription linked to carcinogenesis.[11,12] A pair of families with a high rate of MPM incidence were found to have germline mutations in BAP1, while 23% of MPM tumor tissues had BAP1 inactivation due to somatic mutations. These new findings indicate that people who have lost BAP1 may be more susceptible to MPM, particularly if they have been exposed to asbestos. Although genetic screening methods are still being developed, close observation and early therapy may be necessary.[13,14] The World Health Organization (WHO) categorization includes three major subtypes: epithelioid, sarcomatous, and biphasic, which vary from one another in terms of average survival. The duration of the epithelioid type is 14 months, whereas both sarcomatous as well as biphasic variants are 3 and 12 months respectively.[15,16] Thus, the likelihood of recovery for MPM is very detrimental and there are limited treatment choices.

This study aims to investigate some of the common issues faced in mesothelioma diagnosis rather than provide a comprehensive guide to the disease, especially in light of its highly variable appearance as well as characteristics. Even though we acknowledge the value of Cytopathology and agree that, in the hands of a skilled practitioner, it can consistently point to the confirmation of mesothelioma, it is sometimes ambiguous and necessitates biopsy confirmations. Cytology, for instance, lacks confirmation of invasive malignancy, which is typically essential for diagnostic purposes. Numerous categories apply to diagnostic difficulties. Identifying whether or not a biopsy specimen is cancerous or not can be difficult because of the differences between responsive mesothelial hyperplasia versus epithelioid mesothelioma, as well as reactive sarcomatoid or desmoplastic mesothelioma and pleural fibrosis. When determining whether malignancy has developed, it is important to distinguish between sarcomatoid mesothelioma and other forms of malignant connective tumor that may sporadically involve the pleura, as well as between epithelioid mesothelioma as well as metastatic carcinoma, especially in patients with previous history of cancer or peculiar radiology. On the other hand, mesothelioma in situ (MIS) localized lesions remain difficult to diagnose and many elements of its care are up for controversy. This is primarily because MIS was just recently identified as an independent disease and no established recommendations for the management of it are currently being published.

Malignant Pleural Mesothelioma: Genetics and Risk Factors

Although mesothelioma is rare and the production of products including fibers was outlawed in several counties for more than 20 years, the number of cases of MPM is still rising., but it remains legal in others. This is mostly due to an elderly population that is genetically vulnerable, the consequences of asbestos take 20 to 40 years to manifest. The WHO has been monitoring information on epidemiology related to MPM until 1994.[17] MPM is often classified as an invasive cancer once it has progressed throughout all pleural levels. Mesothelial cells undergo neoplastic changes due to an overabundance of genetic defects that drive mutant cells to proliferate.

Mesothelioma Associated with Asbestos

Asbestos is the most significant carcinogenic agent related to MPM. Cancer begins on the outer surfaces, and multiple pathogenetic processes have been identified and proposed.[18] (I) Asbestos fibers are capable of irritating

the pleura, leading to fibrosis or cancer.[19] (II) They can also infiltrate mesothelial cells, disrupt mitosis, and cause DNA alterations that change the makeup of chromosomes.[20] (III) Asbestos produces oxygen-free radicals, which cause DNA damage as well as inhibit repairing systems within cells.[21] (IV) By interfering with early-response protooncogenes, asbestos can cause irregular proliferation of cells via an extracellular signalregulated kinase (ERK) 1 and 2 pathway along with mitogen-activated protein (MAP) kinases.[22] Crocidolite, amosite, and Chrysolite have all been utilized recently, particularly in the decades between the 1960s and the 1970s, for mechanical, industrial, as well as civil/citizen applications.[23,24] There were a few reported occurrences of MPM among the miners along with their loved ones during the 1960s crocidolite asbestos mining in the northwest region of the Cape Province, in South Africa. even though it has been demonstrated that different types of asbestos may have an impact on MPM formation. Certain assertions state that chrysotile is among the least carcinogenic varieties while crocidolite is the worst.[25-27] Although a very frequent as well as widely recognized factor contributing to mesothelioma is without a doubt exposure to asbestos, nearly 20% of patients do not have an antecedent of asbestos exposure. Further investigation along with genetic testing has highlighted the likelihood that chemicals like potassium bromate, nitrosamines, nitrosureas, and ferric saccharate, alongside inheritable characteristics are products of permanent exposure to bio-persistent mineral compounds and radiation therapies, though it's still conceivable that these individuals were accidentally exposed to.[28,29]

Mesothelioma Unrelated to Asbestos

Fibers made from minerals like erionite as well as fluoroedenite that have an arrangement like asbestos-containing materials, are another contributory factor for the emergence of MPM. Furthermore, numerous cancers are connected to radiation; in particular, research has shown a link between being exposed to radiation along with individual cancerous mesothelioma. Carbon nanotube with many walls-7 has been categorized by the International Agency for Research on Cancer (IARC) as a potential carcinogen for humans. Recent research has shown that rats' lungs developed malignant pleural mesothelioma as a result of intratracheal MWCNT-7 instillation.[30,31]

Therefore, it follows that inflammatory signaling proteins are often upregulated in malignancies, whereas MM is not an anomaly. Mice given autologous mesothelioma xenografts cause inflammation before the tumor's formation.[32] The pathophysiology of MPM has been linked to increased levels of interleukins 1, 6, and 10, growth factors like G-CSF, (HGF-Hepatocytes Growth Factor)/ scatter factor, and vascular endothelial growth factor (VEGF), and chemokines like CCL2 (C-C motif ligand 2), CCL5, CXCL1 (C-X-C Motif Chemokine Ligand 1), and IFN-γ. One important damage-associated molecular pattern (DAMP) protein involved in controlling inflammation the protein is known as Fast Movement Unit 1. An autocrine circuit that affects cell survival and proliferation when this mesothelial cell is first developing transition is brought on by exposure to asbestos and erionite.[33] Furthermore, HMGB1 may promote cadherin expression, which in turn promotes cellular mesenchymal growth linked to cancerous phenotypes.[34] The blood level of HMGB1 is viewed in this perspective as an indicator of prediction to evaluate those at elevated danger of suffering MPM, particularly occupational workers, even if the initial studies have only been conducted in a limited group.[35,36] However, even while smoking is linked to several cancers, it doesn't count as a factor that carries risk. Even if individuals have differing views in scientific research about simian virus 40's (SM40) capacity for triggering cancer in humans, the IARC decided not to classify SM40 as carcinogenic in humans.[37]

Mesothelioma and the BAP-1 Hereditary Cancer Predisposition Syndrome

Gluconeogenesis, apoptosis, cell differentiation, gluconeogenesis, transcription, and nuclear material are all regulated by the nuclear protein BAP1. A condition involving uveal as well as cutaneous melanoma, mesothelioma, and additional neoplasms is believed to be caused by a germ-line alteration in BAP1.[38] Although BAP1 mutations may result in increased vulnerability, genetic study suggests that the high prevalence of mesothelioma in families where just one member works near asbestos can be due to the fibers moving through the individual's clothes and skin to other members of the family. Notably, relative to another type, BAP1 alterations appear to prompt more often for epithelial MPM; this finding has significant consequences for diagnosis and prognosis.[39]

BAP-1's participation in chromatin remodeling is one of its main functions. In actuality, it modifies the intricate equilibrium of histone H2A ubiquitination, which is thought to be connected to cancerous pathways, to modify chromatin architecture.[40] Furthermore, BAP-1 controls the reaction to injury to DNA in a variety of ways. The BRCA1/BARD1 complex interacts with BAP1 to carry out the DNA damage-repairing pathway. In the RAD51-mediated procedure BAP-1, also referred to as homology of DNA repair, is responsible for regulating the replication of the RAD51, BARD 1, and BRCA1 genes.[41,42] Host Cell Factor 1 (HCF1) is responsible for controlling the cell cycle and promoting cell proliferation by facilitating the transition of the cell cycle from the G1 to the S phase. Research has indicated the significance of BAP-1 in this procedure; if BAP-1 is knocked down at this level, the cell

cycle may be disrupted during the G1 phase.[43,44]
BAP-1 additionally plays a role in regulating the regulation of the genes linked to cell proliferation, in addition to HCF1 and YY1.[45] Furthermore, a connection between BAP-1 along apoptosis regulation has been demonstrated by recent investigations. Regarding BAP-1, which is found in the endoplasmic reticulum (ER), it participates in the process linked to apoptosis that releases calcium from the ER into the cytoplasm.[46]
There are two kinds of BAP-1 alteration: somatic as well as germline, and both are linked to a higher chance of developing cancer.[47] The BAP-1 germline variation is an autonomously dominant variation that is typified by frameshift as well as missense mutations. Three investigations have highlighted an increased risk of inherited malignancies among those suffering from uveal melanoma, cutaneous melanoma, cancer of the pleura, and carcinoma of the kidney who had a germline change of BAP-1. The autonomously dominant mode of inheritance for the germline BAP-1 alteration was validated by studies conducted on mice. People and afflicted households are at a greater risk of getting the presence of MPM along with additional cancers due to the BAP, which was a variant in this demographic.[48] This type of mutation is typical of BAP-1 TPDS, which is commonly referred to as "tumor predisposition syndrome." 85% of people with BAP-1 TPDS would get at least one malignancy, with a mean age beginning at 50 years old.[49] Those with a germline mutation typically develop similar neoplasms to the somatic BAP-1 alteration. Eighty-four percent of individuals with disseminated uveal melanomas have intrinsic BAP-1 mutation. Spontaneous melanomas and somatic BAP-1 alterations might be more likely to result in dissemination. In summary, irrespective of the degree of asbestos exposure, a mutation in the tumor-suppressor gene BAP-1 is linked to a greater likelihood of developing MPM. A germline BAP-1 variant is responsible for the development of the BAP-1-associated genetic cancer risk syndrome. Compared to wild-type MPM, germline as well as somatic BAP-1 MPM exhibit a longer survival rate.[50] To accurately identify mesotheliomas in situ MIS, pleural tissues must undergo routine analysis to determine the BAP-1 status.[51]

NF2 and CDKN2A's Impact on the Development of Malignant Mesothelioma

By using fluorescent in situ hybridization (FISH) on the spindle cell component, it may be possible to identify homozygous deletion of the CDKN2A(p16) gene in comparison to BAP1 loss. This could help differentiate between ambiguous instances as well as benign florid stromal reactions, as well as the actual sarcomatoid element that makes up biphasic MPM.[52] A person's risk of developing meningiomas, malignant mesothelioma, bilateral vestibular schwannomas, and spinal schwannomas is increased by the tumor suppressor gene NF2. [53] About 40% of mesotheliomas have an NF2 mutation, which causes the transcriptional coactivator YAP (Yes-Associated Protein) to be hypo-phosphorylated. The transcriptional activation of genes linked to cell proliferation, such as cyclin D1 (CCDN1), and growth factors, such as connective tissue growth factors (CTGF), happens when YAP is hypo-phosphorylated. One of the two primary effectors of the Hippo pathway, YAP, has an ortholog in TAZ, the gene that codes for tafazzin. According to data from twelve of the 14 MPM samples, MPM is one of the few tumors that has mutations in genes linked to the hippocampus pathway.[54] The p16 gene is a member of the INK4 family, which is a modulator of cyclin-dependent kinase 4a that suppresses tumor growth as well as cell division.[55,56] It is found on chromosome 9p21, and certain cancers are linked to the absence of heterozygosis.[55] Numerous proteins that control the RB1, which is p53 process in addition to regulating the cell cycle are encoded through the p16 genomes. The pRb-E2F circuit is inhibited by P16 throughout the cell cycle. pRb synthesizes CDK4 and CDK6 throughout cell division, starting after the G1 stage and continuing into the S phase. One genetic change that is commonly observed in cancer involves the genomic deactivation of p16.. In pancreatic adenocarcinomas (85%) as well as breast cancer (20%), P16 is frequently inactivated. [57] If pleural proliferations or probable malignant mesothelioma are found after a biopsy investigation, P16 FISH analysis is crucial.[58] In addition to BAP-1 loss, the loss of CDKN2A/p16 function is significantly linked to the growth of MPM and would be taken into account when cytologically evaluating pleural effusions. Sarcoidosis mesothelioma is mostly linked to this lack of function .[59]

Management of MPM

Clinical signs of malignant pleural mesothelioma or pleural proliferation are usually nonspecific and mild. The most prevalent medical symptom is pleural effusion. On a chest X-ray, it usually appears as a unilateral pleural effusion. In addition, if pleural hypertrophy is seen, an X-ray may not be the only test done to diagnose MPM.
During CT scanning for diagnosis, pleural thickness, interlobar fissure involvement, chest wall invasion, and pleural effusion are typically identified. A recent examination of CT diagnostic efficacy found that the test had a pleural malignancy sensitivity of 68% as well as a specificity of 78%.[60] MRI provides superior soft tissue contrast in comparison to CT (20). A gadolinium contrast agent may improve the delineation of T3 disease and aid in the identification of potential neoplastic foci in the diaphragm, pericardium, or chest wall.[61] To facilitate the assessment of the locoregional tumor extension, a clear view of the endothoracic architecture, and, when necessary, the application of an efficient chemical

pleurodesis, thoracoscopy is frequently performed during the diagnostic stage. A safe method for verifying a histological diagnosis is to take at least five biopsies of the troublesome pleura during a medical thoracoscopy to acquire a representative sample of the lesions along with probably even the seemingly normal pleura. Appropriately deep parietal pleural samples are necessary to measure the chest wall's intrusion of muscle as well as fatty tissue.[62,63] The preferred method in certain situations, and required in the case of intricate pleural spaces (such as low and loculated effusion), is video-assisted thoracoscopy (VATS). This technique enables the practice of additional pleurotomies using straight optics without the need for a functioning route and additional tools required for a more complicated method. Thoracoscopy has a very high diagnostic sensitivity, with percentages as high as 98%.[64] Remarkably, to control a recurrent or large pleural effusion, obliteration of the pleural space may also be necessary for pleurodesis in its advanced phases.[65,66]

It doesn't appear to be for lack of desire or effort, but regrettably, there aren't many options when it comes to treating MPM. According to National Multifunctional Oncology Program recommendations, a chemotherapy drug called in combination with cisplatin and perhaps bevacizumab is the primary treatment option for MPM [67,68]. A humanized monoclonal antibody called bevacizumab suppresses vascular endothelial growth factor (VEGF), one of the major growth factors involved in the pathophysiology of MPM. It has been shown that adding bevacizumab to pemetrexed with cisplatin greatly improves overall survival (OS) in 448 MPM patients.[69] Vinorelbine, gemcitabine, and other biological treatments are examples of second-line therapy.[70] Individuals who are willing to assume risks associated with surgery only and whose tumor stage is low are candidates for surgical therapy, specifically pleurectomy/decortication. If this cytoreduction may greatly enhance the patient's lifestyle without causing undue morbidity, It might require removing the malignant cell bulk including the pleura that is in part. Lymph nodes involved should receive special attention; they should be sampled throughout the surgery, and a positive result significantly lowers survival.[71,72]

Potential Association between In Situ Mesothelioma and Mesothelial Hyperplasia

As previously mentioned, the VATS technique is a wise managerial decision to eliminate the space within the pleura, diagnose the condition, and start pleurodesis, a palliative measure for malignant pleural effusions that stops the effusion from recurring. The inability to remove all of the pleural fluid because of the distance apart among pleura's many locations and the undependable lung are the two main contraindications of pleurodesis.[73] To prevent the effusion from recurring, a symphysis between the parietal and visceral pleura needs to be established. A significant inflammatory reaction is triggered by talcum powder instillation, which ultimately leads to a well-organized fibrinous pleuritis in the pleural cavity. Mesothelial cells are crucial at this point.

The substantial destruction of the outermost layer of the mesothelium comes first, followed by the effectiveness of chemical pleurodesis, which sets off an inflammatory cascade suitable for forming collagen fibers that would result in pleural symphysis. Chemokines including interleukin 8, TNF alpha, VEGF (vascular endothelium transformation factor), PDGF (platelet-derived development factor), bFGF (fundamental fibroblasts growth component), translating growth hormone beta, and MCP1, are released by damaged mesothelial cells and set off the inflammatory cascade. The activation of fibrinolysis and fibrinogenesis is balanced at the same time. Because angiogenetic stimulation should enhance the development of pleural fluid and so render pleurodesis ineffective, angiogenesis is likewise coordinated amongst stimulants as well as regulation.[73] An essential component of chemical pleurodesis is inflammatory conditions. A histiocytic as well as granulomatous reactivity to an external element is brought on by the talc. This reaction was verified in an animal model where the administration of nonsteroidal anti-inflammatory medicines failed talc pleurodesis.[74] The literature has long established that chronic Tumorigenesis as well as the progression of malignancies at all phases depend on inflammatory processes, which stimulate the protons in the cogenetic circuit. It has been demonstrated that the stimulation of interleukins 6, 17, and 11 stimulates the development of cancer cells, especially in certain conditions such as hypoxia along with oxygen deprivation.[75] Research showed that interleukin 11 promotes fibroblast growth factor-beta with rectal cancer of the colon, leading to tumor expansion along with evasion of the immune system.[75,76] Although talc pleurodesis is a recognized palliative treatment for MPM, it may accelerate the development of disorders like AMH and MIS that are malignant. Its application to the management of mesothelial hyperplasia and MIS is, in fact, still up for discussion. In these situations, selecting the optimal course of treatment may be aided by an accurate multidisciplinary discussion. Pleurodesis may be the final option for benign or perhaps malignant pleural effusions that have not shown any benefits from indwelling pleural catheters, according to Blintcliffe et al.[77] However, in vitro findings imply that keeping a pleural effusion going may aid in the survival and growth of cancer cells.[78,79] With a typical duration of five years, the progression time for MIS is defined as ranging from twelve to ninety months.[80]

Conclusion

After five years, MPM is an uncommon illness that has a

significant death rate. The prognosis is still dismal even if there has been significant progress in recent years regarding patients' therapy possibilities. To reach a definitive diagnosis, a thoracoscopic biopsy remains the most effective procedure. Currently, surgery, radiation, and chemotherapy are used in a multimodality strategy; however, innovative, specialized treatments, including ICI, have demonstrated promising results. There are still a lot of unanswered questions regarding its preinvasive versions, such as AMH and MIS. In particular, there are several contentious areas in MIS management, and AMH doesn't offer any precise instructions for relevant follow-up. Therefore, the primary objective of potential speculative investigation to identify the optimal program of therapy ought to aim to improve our awareness of all preinvasive lesions as well as how they progress into cancer. although there remains plenty of time to go until persons suffering from MPM can recover, more research might be the answer.

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