Mesothelioma as a Potential Environmental Disease - Medico-Legal Evaluation of Connection between Mesothelioma and Environmental Factors

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Abstract

Environmental diseases are caused by substance abuse, exposure to toxic chemicals, and physical factors of the environment. Environmental triggering factors on human life and the frequency, intensity, and duration of environmental and meteorological disasters have received an increasing public and social interest. Environmental factors may cause severe illnesses. Mesothelioma is a type of cancer that develops from the visceral or parietal mesothelium, and it has a well-known connection with environmental factors. Recently the World Health Organization established the new classification of pleural tumours. The histological classification of pleural malignant mesothelioma remains unchanged, the typing and the prognosis of the subtypes are more specified. Nowadays, even in countries that already banned asbestos use and production, past occupational exposure remains the cardinal root of mesothelioma mortality.

In this paper the authors present that the relationship between human health and stressful environment is a complex medical, social and public issue. The health impacts of environmental factors and events hinge on the vulnerabilities and recovery capacities of the natural environment and the local population.

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INTRODUCTION

Environmental diseases are a direct result from the environment. This includes diseases caused by substance abuse, exposure to toxic chemicals, and physical factors in the environment, like UV radiation from the sun, as well as genetic predisposition. Meanwhile, pollution-related diseases are attributed to exposure to toxins in the air, water, and soil. These health hazards may be found where people live, work, or play. Therefore all pollution-related diseases are environmental diseases, but not all environmental diseases are pollution-related diseases. Environmental diseases are non-communicable diseases, which are generally late-onset, appearing only after numerous toxic exposures. In recent years, however, the age of onset has been trending lower (Zeliger, 2015). Occupational diseases are multi-factorial conditions contracted primarily as results of exposure to different risk factors emerging from work activity [www.who.int]. These conditions are resulted from a variety of physical, chemical, biological, psychological factors which are present in the work environment. The recognition of the occupational diseases may be connected to compensation if it is obvious that there is a causal relationship between an occupational exposure and the disease [www.osha.europa.eu]. The realization of how much disease and ill health can be attributed to modifiable environmental risks can contribute to identifying opportunities for prevention and should add impetus to global efforts to encourage sound preventive measures through available policies, strategies, interventions, technologies and knowledge [www.who.int/quantifying_ehimpacts].

Forensic science is the application of science to criminal and civil laws. In addition to examine the deaths, the science of forensic medicine includes the examination of living persons in cases such as assault-injuries, insurance cases, or assessment of work ability as well. Health insurance is a practice or arrangement by which a company or government agency provides a guarantee of compensation for specified loss, damage, illness, or death in return for payment of a premium. Mesothelioma is a malignant tumour of the pleura that is strongly associated with asbestos exposure. It can be an occupational hazard, but it also can be an environmental disease despite of the ban of asbestos use. Without clarifying the cause of the disease, there is neither a correct insurance procedure nor compensation for the victim, and furthermore, required preventive measures cannot be initiated. Forensic and insurance medical practitioners play an important role in the evaluation of the connection between mortality and environmental factors.

THE PATHOPHYSIOLOGY OF MESOTHELIOMA

The mesothelium consists of a single layer of flattened to cuboidal cells forming the epithelial lining of the serous cavities of the body including the peritoneal, pericardial and pleural cavities. Malignant mesothelioma is a rare growth of mesothelial cells strongly associated with asbestos exposure. Mesothelioma can occur at any mesothelial layer such as the peritoneum or pericardium. The pleural layer is by far the most commonly affected, giving rise to malignant pleural mesothelioma, which is primarily linked to asbestos exposure. Its carcinogenicity is caused as the inhaled asbestos fibres cannot be eliminated by macrophages and, thus, they travel to the pleura through lymphatic pathways, producing a persistent inflammatory response (Gopar-

Nieto et al., 2016). In the beginning the tumour appears as a localized nodular lesion of the pleural cavity which can be various in size, often multifocal, forming multiple nodules starting with the parietal pleura. Pleural fluid shows after the appearance of the tumour, the tumour cells spread with the fluid in the pleural cavity and they make adherence on it. The involved lung is coated by a thick, sometimes gelatinous rind, the tumour often fills in the pleural cavity. With malignant pleural mesothelioma, there is a direct local invasion of the lymph nodes. Regional lymph node spread begins with the bronchopulmonary or hilar lymph nodes before moving to the carinal, internal mammary or peridiaphragmatic nodes. The pattern of nodal metastases is different from that seen in other type lung cancers. Overall, the involvement of lymph nodes in malignant pleural mesothelioma is not common. During its growth the mesothelioma infiltrates the muscles of the chest sometimes the skin, makes metastases to the lung, the lymph nodes, the contralateral pleura. Distant metastases can appear in the bones, adrenal glands, liver and brain. There is no evidence that alcohol, tobacco, or dietary intake is involved in malignant pleural mesothelioma (Jain and Wallen, 2018).

DEFINITION AND SUBTYPES OF MESOTHELIOMA

Mesothelioma is a type of cancer that develops from the visceral or parietal mesothelium. The most common area affected is the pleural mesothelium (75% of the cases). Less commonly (most of the remaining cases) the abdominal mesothelium and rarely the pericardial mesothelium or the tunica vaginalis testis may be affected (American Cancer Society, 2016; National Cancer Institute, 2018).

Benign subtypes

Benign tumours develop in the mesothelium, too. These tumours can be cured by surgical procedure and additional treatment is not needed often (American Cancer Society, 2016). *Localized fibrous tumour:* This benign subtype mostly develops on the visceral pleura, but solitary fibrosus tumour of the peritoneum can also occur. The localized fibrous tumours do not contain dysplastic mesothelial cells. 10% of these tumours are malignant. *Adenomatoid mesothelioma:* The adenomatoid mesothelioma starts to grow in the mesothelium of the reproductive organs. In male patients it often takes place on the epididymis. In female patients the tumor develops on the ovarian tubes. *Benign cystic mesothelioma:* This rare non-cancerous tumour often develops on the peritoneum.

Malignant subtypes

Malignant mesothelioma is an aggressive tumour which is mostly related to asbestos exposure. The disease occurs usually 30-40 years after the asbestos exposure (Salazar et al., 2018). The prognosis is poor, survival is approximately 10 months from the diagnosis. Mesothelioma grows from serosal mesothelial cells with three histological subtypes. Most of the malignant mesotheliomas show progressive diffuse local proliferation and aggressive invasion into the neighbouring tissue (Li et al., 2018). The diffuse forms can appear with nodules, plaques and sheets. Sometimes localized malignant mesotheliomas develop which are well localized from their envi-

ronment. The localized ones have better prognosis than the diffuse entity. Tumour cells can also reach the nearby lymph nodes, although the incidence of distant metastasis is rare. Mesothelioma is an incurable tumour with limited treatment options. According to the WHO classification there are the following malignant subtypes of mesothelioma in order of their prevalence (College of American Pathologists, 2017; American Cancer Society, 2016): *Epitheloid mesothelioma:* Approximately 50% of the cases are epitheloid mesotheliomas which have prominent papillo-tubular structures. It has better prognosis compared to biphasic and sarcomatoid subtype of mesothelioma (College of American Pathologists, 2017; American Cancer Society, 2016; Li et al., 2018). *Biphasic mesothelioma:* 30-40% of the mesotheliomas are biphasic. Biphasic means mixed, they should contain both epithelioid and sarcomatoid subtypes at least 10-10% of the tumour (College of American Pathologists, 2017; American Cancer Society, 2016). *Sarcomatoid or fibrotic mesothelioma:* The remaining 10% usually is sarcomatoid mesothelioma (College of American Pathologists, 2017). It has spindled cells and it is hard to differentiate sarcomatoid mesothelioma from fibrosarcoma. This subtype is the most aggressive malignant variant of the mesothelioma with the worst prognosis (Li et al., 2018). *Desmoplastic mesothelioma:* Desmoplastic mesothelioma is a minor subtype and considered as a variant of the sarcomatoid mesothelioma (College of American Pathologists, 2017). The diagnosis is difficult because of the histological picture of the tumour: it contains dense hyalinized fibrous stroma and few malignant cells (Sakai et al., 2018). The differential-diagnosis of sarcomatoid and desmoplastic malignant mesotheliomas from sarcomatoid carcinomas of the pleural lung metastases is difficult, because they can be morphologically similar and usually show positive test for pan-keratin (Berg et al., 2017).

Papillary mesothelioma

Well-differentiated papillary mesothelioma is also a minor subtype. This is a non-invasive papillary neoplasm and it has excellent prognosis and an indolent course. This tumour is usually appearing in young women without asbestos exposure, in male patients it is very rare but there are some examples in men, for example Bazine et al. have reported a case of a 36-year-old man (Bazine et al., 2017). It is difficult but important to differentiate it from morphologically similar epithelioid malignant pleural mesothelioma and papillary adenocarcinoma because they are more aggressive and have worse prognosis (Saha et al., 2018).

DIAGNOSIS

Symptoms of mesothelioma include dyspnoea which is the most common initial finding, seen in about 90% of patients, because of the presence of pleural effusion. Nonpleuratic chest pain, weight loss, appetite loss, cough, fatigue, and chest wall mass are nonspecific signs. Digital clubbing can be found in some cases (Jain and Wallen, 2018)**.** Early diagnosis of malignant mesothelioma is urgently needed because life expectancies and treatment options are limited in advanced stages of the disease. Malignant mesothelioma often presents with recurrent haemorrhagic or inflammatory effusions, which might mask the incipient stages of the disease and thereby delay the diagnosis and cytological tests of exudative and often haemorrhagic pleural fluid are often negative. Despite difficulties in recognizing the malignant cells present in those

early effusions, they are often the first available biologic material for diagnosis (Hjerpe et al., 2018). Radiographic abnormalities consist of nodular, irregular, unilateral pleural thickening and varying degrees of unilateral pleural effusion. Sixty percent of patients have right-sided disease, while only 5% have bilateral involvement. CT is the imaging method of choice for pleural mesothelioma because it allows the evaluation of the extent of the primary tumour, local invasion, lymphadenopathy, and extra-thoracic involvement.

The initial finding is often unilateral pleural effusion. Pleural plaques, some with calcifications, tend to be present in at least 20% of cases. Nodular and circumferential pleural thickening >1 cm is suggestive of pleural mesothelioma. The most common sites for metastasis of mesotheliomas are bone, liver, kidney, adrenal glands, brain, and lung parenchyma. FDG-PET/CT has become very useful to depict mediastinal, diaphragmatic, and chest wall invasion as well as any potential metastatic site in patients with pleural mesothelioma. Magnetic resonance imaging (MRI) is not routinely used for mesothelioma in most institutions, although it may provide information on chest wall or diaphragmatic extension (Aluja et al., 2018). Surgical intervention plays an important role in the diagnosis, staging and treatment of malignant pleural mesothelioma and can be applied with curative or palliative intent. The overall aim of surgery should be, as in any oncologic surgery, the macroscopic complete resection (MCR) of the tumour. Most importantly, the majority of patients with the diagnosis of malignant pleural mesothelioma should be appropriately staged and initially evaluated in a multidisciplinary setting, including medical oncology, radiation oncology, and surgery after histological diagnosis. Surgical staging, including determination of the histological subtype and lymph node status, as well as clinical staging with PET-CT scan and determination of cardiopulmonary reserve are crucial (Bueno et Opitz, 2018). Intraoperative fluorescence imaging (IFI) can improve real-time identification of cancer cells during an operation. Phase I clinical trials in thoracic surgery have demonstrated that IFI with second window indocyanine green (Tumor-Glow®) can identify subcentimeter pulmonary nodules, anterior mediastinal masses, and mesothelioma, while the use of a folate receptor-targeted near-infrared agent, OTL38, can improve the specificity for diagnosing tumours with folate receptor expression (Newton et al., 2018).

The diagnosis of malignant pleural mesothelioma should always be the result of the microscopic examination of cytological or histological samples in the context of clinical, radiological and surgical findings. A cytopathological analysis of the pleural fluid supported by immunohistochemistry (IHC) is a screening test for malignant pleural mesothelioma and may help to differentiate between mesothelioma and other cancers. A differentiation between malignant pleural mesothelioma and a benign, reactive mesothelial proliferation in cytological samples is usually impossible since many of malignant pleural mesotheliomas lack the evident cytological features of malignancy. All recent guidelines agree that the most reliable method, a "gold standard", for establishing a definitive diagnosis of malignant pleural mesothelioma is a histological examination of a tissue biopsy sample, thus a histological confirmation of a cytological diagnosis is recommended in all patients in whom treatment is planned. For patients with suspected malignant pleural mesothelioma who present with a pleural effusion, American Society of Clinical Oncology (ASCO) advocates thoracentesis as an initial intervention. A surgical (thoracoscopic or open) pleural biopsy is preferred but if it is contraindicated, a core needle biopsy of an accessible lesion is acceptable.

A pathological report of a histological examination should concentrate on the diagnosis of malignant pleural mesothelioma but a histological subtype (epithelioid, sarcomatoid or biphasic) of a neoplasm should also be described due to its prognostic and predictive significance. A sarcomatoid subtype has the worst prognosis, often is resistant to chemotherapy, in addition surgery does not improve survival in patients with this histology. FDG PET-CT (fluorodeoxyglucose, positron emission tomography-CT) scanning is recommended by ASCO as an early assessment of the staging of American Society of Clinical Oncology especially for candidates for surgical treatment. PET-CT findings should be confirmed by biopsy and a microscopic examination to avoid false negative and false positive results. The assessment of the extent of the disease on the pleural surfaces requires a surgical exploration by video-assisted thoracoscopic surgery (VATS) and a potential mediastinal, hilar or supraclavicular lymph node involvement should be confirmed microscopically in samples obtained by EBUS/EUS-guides fine needle aspiration, mediastinoscopy or direct needle biopsy. An assessment of malignant pleural mesothelioma response to therapy requires tumour measurement according to modified Response Evaluation Criteria in Solid Tumours (RECIST) in chest CT. A pleural thickening should be measured perpendicularly to the chest wall or mediastinum in two sites at three different levels with at least a 1 cm interval of used transverse slices. A soft tissue window and 2.5 mm slice thickness are preferred (Malgorzata et al., 2018). When speaking of diagnostic biomarkers one must emphasize that the gold standard for malignant pleural mesothelioma diagnosis is by immunohisto- and cytochemistry. Malignant pleural mesothelioma progresses rapidly as the tumour spreads along the pleural surface to involve the pericardium, mediastinum, and contralateral pleura. The tumour may eventually extend beyond the thorax to involve abdominal lymph nodes and organs. Progressive pain and dyspnoea are characteristic. Local invasion of thoracic structures may cause superior vena cava syndrome, hoarseness, Horner syndrome, arrhythmias, and dysphagia. Paraneoplastic syndromes associated with mesothelioma include thrombocytosis, haemolytic anaemia, disseminated intravascular coagulopathy, hypercalcemia, and migratory thrombophlebitis.

Histological diagnosis

Histological subtypes

According to the 2004 WHO classification, there are three subtypes of mesothelioma: epitheloid, sarcomatoid and biphasic. Recently the World Health Organization published its new classification of the pleural tumours. The histological classification changed compared to the previous version. The histological classification of pleural malignant mesothelioma remains unchanged, the typing and the prognosis of the subtypes are more specified (British Thoracic Society, 2018). Epitheloid mesothelioma looks alike the histological appearance of adenocarcinoma. The tumour cells are cuboid, they make often tubular, papillary formations and acini. Papillary formations can invade the lumen of the cavities. Minor subtypes are microcystic, trabecular, decidual and sigillocellular (Kásler M., 2017). Sarcomatoid mesothelioma can be randomly spread or can form fascicles, which are stem cells or fibroblasts. The disposition of the tumour cells is often chaotic. They take place in myxotic stroma. This subtype of mesothelioma infiltrates the surrounding tissues. Inside the tumour sometimes differentiation to cartilage or bone tissue can appear (Kásler M., 2017). Biphasic mesothelioma contains both epitheloid and sarcomatoid components. According to the WHO classification at least 10-10% of both components must be present to the diagnosis of biphasic mesothelioma (Kásler M., 2017).

Diagnostical possibilities, difficulties of differential diagnosis

Differential diagnosis of the malignant pleural mesothelioma may be challenging because of the wide spectrum of the appearance of the tumour cells, malignant pleural mesothelioma often looks like epithelial and sarcomatoid malignancies. Tumour samples can be provided from the pleural fluid by aspiral cytology, thoracoscopy or Video-Assisted-Thoracic-Surgery (VATS). The sample is cytological or histological (Baas, et al., 2015; American Society of Clinical Oncology, 2018).

Cytological examination

Although the cytological examination of the pleural fluids is essential to the diagnosis of the mesothelioma, its effectivity depends on the examiner's experience and that's why its use is under discussion. But examination smears made from anticoagulated cytological samples which are taken from appropriate parts can lead to 75% sensitivity and cell block can be prepared to the diagnosis. The smears are stained by haematoxylin-eosin, Giemsa or Papanicolau. It is indifferent to the diagnosis. The epitheloid mesotheliomas show heterogeneous appearance and variant differentiation like adenocarcinomas, this fact means diagnostical problem by identifying the tumour. Diagnostical difficulties occur by its differential diagnosis from metastatic adenocarcinomas. Only a few sarcomatoid mesothelioma tumour cells are present in the pleural fluid and the diagnosis is barely possible. Many authors accept the cytological diagnosis when the clinical symptoms and the radiological imaging also confirm the diagnosis. The diagnosis is more certain if the cell block contains enough number of cells for the immunohistochemical and electron microscopic examinations. Other authors consider acceptable the diagnosis only if it is based on histological examination because the cytological examination has low sensitivity.

Histological examination of the pleural biopsy

Examination of the samples of biopsy is essential to make sure the pathologist examines malign tumour or active cell proliferation. In case of diagnosing malignity, the next step is differentiating primer tumour from a metastatic tumour. For this purpose, specific immunohistochemical examinations are carried out. By diagnosing mesothelioma, the special stains can be applied only to separate it from metastatic adenocarcinomas which secrete neutral mucin. The most commonly used staining methods are the digested PAS reaction and the alcian blue. The immunohistochemical examinations are widely used although their sensitivity and specificity are not complete (British Thoracic Society, 2018).

Immunohistochemistry

Immunohistochemical reagent is not available which is able to identify clearly the malignant mesothelium therefore immunohistochemical panel is used which is prepared by two aspects. The positive markers are the antibodies of the panel and they are specific to the mesothelial cells. Those antibodies which do not make reaction with the mesothelial cells are the negative markers. According to the current guidelines two positive and two negative antibodies are needed to establish a malignant pleural mesothelioma diagnosis, where calretinin is the only of the important histological markers that currently has been evaluated as a future circulating diagnostic biomarker. Mesothelin, like other tumour monitoring markers, like CEA or CA15-3 is useful only in patients where there is an elevation before treatment (Oluf, 2018). The most studied biomarker is mesothelin, characterized by a good specificity, but it has low sensitivity, especially for non-

epithelioid malignant mesothelioma. Other protein markers are Fibulin-3 and osteopontin which have not, however, showed a superior diagnostic performance. Recently, interesting results have been reported for the HMGB1 protein in a small but limited series. An increase in channel proteins involved in water transport, aquaporins, have been identified as positive prognostic factors in malignant mesothelioma, high levels of expression of aquaporins in tumour cells predict an increase in survival (Ledda et al., 2018). In spite of several candidate blood and pleural fluid biomarkers for malignant pleural mesothelioma diagnosis and prognosis, only mesothelin is an U.S. Food and Drug Administration (FDA) approved, commercially used clinical biomarker. As an adjuvant for diagnosis and monitoring it appears at least as useful as "classical" tumour markers e.g., CEA for colon cancer and CA-15-3 for breast cancer. Biomarkers for predicting response to systemic therapy, including chemotherapy and immunotherapy should be of high importance, as more than half of the patients are non-responders, only left with the toxicities. Finally, the role of biomarkers as drug targets may be very important, as several studies on mesothelin-based treatments as well as microRNA mimic of miR16 showed impressive responses and manageable side effects (Oluf, 2018). Of course, the evaluation of the results must be done only with the clinical and the morphological data together. The differentiation of the epitheloid mesotheliomas from lung or other distant organ adenocarcinomas is hard because of the above-mentioned difficulties of the differential diagnosis. The following entities can cause problems by differential diagnosis of sarcomatoid mesotheliomas: metastatic sarcomas, fibrotic inflammation, localized fibrous tumour or sarcomatoid carcinoma. Further diagnostic questions are raised by the pseudomesotheliomas.

PROGNOSIS

For malignant pleural mesothelioma, the histopathological subtype is one of the most important prognostic factors. Several immunohistochemical stains whose expressions have possible therapeutic implications have been identified in malignant pleural mesothelioma such as BAP1, mesothelin and PD-L1, nuclear grading in epithelioid malignant pleural mesothelioma is a strong and independent prognosis factor (Forest et al., 2018). Despite advances, the prognosis for most malignant pleural mesothelioma patients is grim; death is inevitable within 4 to 6 months. With treatment, some patients may survive 15 to 18 months. Rarely, 5-year survivals have been reported. The biggest problem is tumour recurrence, especially in patients managed with surgery. Patients undergoing surgery may have slightly longer survival, but they also develop many complications related to the procedure. These complications include arrhythmias, wound infection, deep vein thrombosis, air leak, respiratory failure, postoperative bleeding, and myocardial infarction. Poor prognostic factors include nonepithelial histology, poor performance status, age over 75, dyspnoea and chest pain on presentation, elevated lactate dehydrogenase and low haemoglobin on presentation, and weight loss (Jain and Wallen, 2018). Most patients die of respiratory failure and complications of local extension. Median survival time from onset of symptoms ranges from 4 months in extensive disease to 16 months in localized disease. Five-year survival is 5%. Tumours that are predominantly sarcomatoid are more resistant to therapy and have a worse prognosis, with median survivals of 1 year. Poor prognostic features include poor performance status, non-epithelioid histology, male gender, nodal involvement, elevated lactate dehydrogenase, high white blood cell count, low haemoglobin, and high platelet count (Cornett and Dea, 2013).

THE GENETICS OF MESOTHELIOMA

Malignant pleural mesothelioma is primarily linked to asbestos exposure, with some suggesting that asbestos inhalation causes repeated pleural inflammation, interference with mitosis, activation of proto-oncogenes, and free radical production (Jain and Wallen, 2018). It is believed that particular genetic makeup or changes may make people more susceptible to this disease. Research shows that the loss of one copy of chromosome 22 is commonly seen in patients with malignant pleural mesothelioma. Other chromosomal anomalies that have been identified include deletions in chromosomal arms 3p, 1p, 6q, and 9p (Jain and Wallen, 2018). Besides that, additional genetic mechanisms have been implicated in the development of malignant mesothelioma in a subset of cases, including: germline BRCA1 associated protein-1 (BAP1) inactivation syndrome, structural gene rearrangements in Ewing sarcoma breakpoint region 1 or fused in sarcoma (FUS), and anaplastic lymphoma kinase (ALK) rearrangements (Hung and Chirieac, 2018). These alterations can be routinely identified by laboratory studies (fluorescence in situ hybridization testing for EWSR1/FUS and immunohistochemistry for BAP1 and ALK in patients with malignant mesothelioma, particularly those with atypical clinical presentation.

HISTORY OF MESOTHELIOMA

The earliest mention of pleural tumours was made in 1767 by a French pathologist, Lieutaud, who documented two such cases among 3000 autopsies. Various theories arose in the medical community about whether these pleural malignancies were primary or secondary in nature. Laennec was the first, who in 1819 claimed that these malignancies could arise directly from the pleura. In 1854 primary tumours of the peritoneum were described by Von Rokitanski, presumably these were the first recorded cases of peritoneal mesothelioma. The theories about the origin of cells from which these malignancies developed, were controversial in the medical community, initially the term ”pleuroma” was suggested, however later the term “mesothelioma” became widely accepted (Ribak et al., 1988). As -due to industrialization- the production and use of asbestos expanded, the effects of asbestos exposure became apparent. In 1935 Steven Gloyne was the first, who suggested a possible link between mesothelioma and occupational asbestos exposure in Britain. In 1943, Wedler published the first report about the connection between pleural malignancy and asbestosis among German asbestos workers. Despite of these observations, the association became conclusively recognized only in 1960, when Wagner described 33 histologically proven cases of pleural mesothelioma in South Africa, of which 28 persons had association with the Cape Blue asbestos field, among whom 4 people had direct occupational exposure to crocidolite. In 1964, Selikoff et al published their results of the New York Metropolitan area Asbestos Workers Union members: between 1942 and 1962, reported increased death rates from different types of cancer of the lung, bronchus and pleura among insulation workers exposed to asbestos (Selikoff et al., 1964; McDonald et al., 1996; Kratzke et al., 2018). The progressive ban of asbestos in developed countries was partly the consequence of the momentum initiated in 1964 in New York. 80% of mesothelioma cases are linked to asbestos burden (Kim et al., 2017). Asbestos exposure should be treated as a huge public health concern, although mesothelioma is rare, accounting for less than 1% of all forms of cancer (Shavelle et al., 2017). Due to its qualities, touted as “miracle mineral”,

asbestos has been widely used between the 1950s and 1980s, for different industrial purposes nearly in all western countries. Although based on the current data of International Ban Asbestos Secretariat, asbestos use has been banned in 65 countries worldwide and severely restricted in some other countries (USA), it still remained a threat, because it is still extracted and used in many states of Asia, South America, and Africa. While in the UK, USA and in Northern Europe asbestos production and its use decreased after 1970s, in some other parts of Europe its consumption deceased only one-two decades later. The European Union banned its use since 1999 (Marinaccio et al., 2018; www.ibasecretariat.org). Based on the estimations of WHO, globally 125 million people are exposed occupationally to asbestos (1.3 million people in the USA) (www.who.int).

EPIDEMIOLOGY

Mesothelioma mortality

Based on the estimations of the World Health Organization, worldwide 107,000 people die from mesothelioma, lung cancer and asbestosis annually (www.who.int). In Britain, mesothelioma death rates show a current peak: 0.75 % of male deaths, 0.13 % of female deaths in 2015, which until 2055 will decline (Gilham et al., 2018). Based on the extrapolation of Odgerel et al. - who used the reference data of 59 countries from the period 1994-2014 - the global burden of mesothelioma deaths is 38,400 per year (Odgerel at al., 2017).

Incidence of mesothelioma in the past, present and in the future

Between 1966-1972 the incidence of mesothelioma in Canada was 2.9 per million males and 1.4 per million females, whereas in the USA it was in 1972 2.7 per million males and 0.8 per million females (McDonald et al., 1996). Comparatively, in the last three years, based on available data of 59 country, mesothelioma mortality was 9.9 per million (Odgerel et al., 2017).

Based on the estimations, since 1990 until 2013 a huge rise (109.6%) of asbestos-related cancer incidence could be observed worldwide (Lemen et al., 2017). The incidence of malignant mesothelioma varied widely across countries. The highest incidence data were reported in developed, industrialized countries like UK, Belgium, and Australia overstepping 30 per 1 million inhabitants. Highest incidence worldwide was reported in the UK 3.6 per 100,000 in men and 0.7 per 100,000 in women. Lowest rates were reported from Japan and the Central European countries. Incidence in the USA was 1.94 per 100,000 for men and 0.41 per 100,000 for women while in Sweden it was 12 per 1 million inhabitants (Plato et al., 2016; Kim et al., 2017). In Iceland, based on the study of Tomasson et al. (2016), the incidence of mesothelioma increased between 1965 and 2014. In 2014 the rate reached 21.4 per 1 million among men and 5.6 per 1 million among women, while the mortality was 22.2 per 1 million among men and 4.8 per 1 million among women. In the last ten years the incidence in Iceland was higher than the reported rates in the neighbouring states (Tomasson et al., 2016). In the USA 3200 new cases of mesothelioma are diagnosed annually, the incidence tends to rise in the next two decades globally. The incidence among men is higher compared to women, probably because of more frequent occupational exposure (De Rienzo et al., 2016).

Influence of different factors on development of mesothelioma

Mesothelioma is more common in Caucasian and Hispanic races than in Asian, American or African people. Robert Shavelle et al. found that 92% of patients diagnosed between 1973 and 2011 with mesothelioma in the US pertained to Caucasian race (Shavelle et al., 2017). Reid et al. (2018) made a comparison of long term risks (with a follow-up more than 60 years) of non-occupational blue asbestos exposure in adults and children and found that those who were first exposed to crocidolite at Wittenoom as children (aged <15 years) although had greater estimated cumulative exposure than adults, presented significantly lower risk to develop mesothelioma than those who were first exposed to blue asbestos as adults (>15 years). This can be partly attributable to the fact, that children are more likely to have lower deposition in lower airways, due to their more efficient clearance mechanism and higher breathing rate. However, these children have more to live after the first exposure, than those firstly exposed as adults, so their lifetime risk may not be lower (Reid et al., 2018). Dragani et al. found that measures of asbestos body count and asbestos fibre count on surgically resected or post-mortem lung tissue (1982-2017) demonstrate that younger patients with heavier asbestos exposure were significantly more likely to develop mesothelioma at a younger age, than patients with low-level exposure (Dragani et al., 2018). Mesothelioma is diagnosed more often in patients older than 65 years, and due to its long latency period, only in 4% of the cases is diagnosed in persons under age 45 (Shavalle et al., 2017). Dimmer et al. published their observations in 2016 on 1625 patients diagnosed with malignant mesothelioma and found that the median age at diagnosis was 78 years, the youngest patient was 66, the oldest 103 years old, 78% of patients were men (Dimmer et al., 2016).

The dynamism of asbestos burden

Based on the study published in 2018 by Gilham et al., the sharply decreasing mean lung burden in the British birth cohorts among men and women with environmental exposure, born between 1940-1954 (17 f/mg) and 1975-1984 (0,7 f/mg), respectively, reflects the effect of cessation of amphibole use in the 1980s. The study reflects that average lung burden among men (after age 16) with occupational asbestos exposure, increased annually by about 2 f/mg between 1955 and 1980, and 0.1 f/mg per year after 1980, respectively, among plumbers, electricians and painters. Theoretically, if asbestos levels remained at that level, it is estimated from the current environmental amphibole exposure of 1 f/mg average lung burden that by age 30, a persisting lifetime mesothelioma risk (1 per 10,000) is likely to be across the whole British population (Gilham et al., 2018).

Different forms of asbestos exposure

Nowadays, even in countries that already banned asbestos use and production, past occupational exposure remains the cardinal root of mesothelioma mortality. Cessation of its use does not eliminate occupational exposure, once used in construction, still represents opportunity of exposure for workers in demolition, renovation and maintenance of buildings (Noonan, 2017), eventually for fire-fighters. In women attributable fragment to known origin of asbestos exposure is generally much lower than in men. In the USA, among patients with mesothelioma, 23% of women reported asbestos exposure compared to 58% of men (Kim et al., 2017). For women

a possible source of asbestos burden can be para-occupational exposure, which means lower asbestos burden than the occupational exposure (Marinaccio et al., 2018). Asbestos-exposed workers serve as a vector for the transport of fibres, generating para-occupational exposure, which is partly the source of exposure for family members of workers from a high-risk occupational environment, during handling the asbestos-contaminated clothes, contaminated household dust, etc. Lung burden due to para-occupational exposure among women diagnosed with mesothelioma respectively in men with moderate occupational exposure was in similar range (Noonan, 2017). A British case-control study including 622 patients diagnosed with mesothelioma and 1420 population-based controls found statistically significant two-fold greater risk for people younger than 30 with only para-occupational exposure, compared to the control group. Environmental-, residential exposure occurs via airborne emissions through asbestos process, natural disasters, disturbance of a natural asbestos deposit, residential proximity to the source of exposure etc. A multi-centre study presented that living within 2 kilometres of territories with high asbestos load (asbestos mines, asbestos-burdened industrial areas, etc.) was associated with a highly elevated risk for mesothelioma. Worldwide several geographic foci with discoveries of different types of naturally occurring asbestos (Corsica, Cyprus, Turkey, New Caledonia) have been related to elevated mesothelioma risk, characterized by lower F/M ratio compared to occupationally-exposed population, and younger age at diagnosis. This could reveal the growing importance of environmental exposure for mesothelioma risk (Noonan, 2017). The elevation in incidence of pleural mesothelioma tends to flatten after 45 years following the first exposure, but the excess risk doesn't disappear (Reid et al., 2014). Latency period from the first exposure until the diagnosis is usually 20-50 years (Tomasson et al., 2016), generally more than 35 years, so almost all recently diagnosed cases were firstly exposed to asbestos before 1980 (Gilham et al., 2018). Based on a study published by Reid et al. (2014), non-occupational asbestos exposure imply longer latency period, accordingly women tended to have longer latency period than men. Likely due to restrictions of asbestos use in Norway and in the United States in the 1970s, the incidence of mesothelioma showed a decline from 2005 among men. This rate didn't reduce yet in women, probably because the longer latency period (Reid et al., 2014).

Influencing factors of mesothelioma development

In Lombardy, the most industrialized region of Italy, where the largest number of men were employed in different industrial sectors using asbestos, in the period 2000-2012, 442 persons were diagnosed with malignant mesothelioma. 64.2 % of these patients were men, 35.8 % women. 73.6 % of the affected men was occupationally exposed to asbestos, this ratio among women was 38.2 %. However, compared to the statistics from other countries, where the number of men burdened with malignant mesothelioma was largely predominant, the proportion of affected women was much higher in Italy. This difference can be explained by the presence of asbestos in the textile industry and greater female workforce in industry. In this region between 2000 and 2012, the rate of mesothelioma cases increased annually by 3.6% in men, and 3.3% in women, respectively. Average number of malignant mesothelioma cases is still increasing in Lombardy among individuals older than 65 years while decreasing in the younger population (Mensi et al., 2016). In other countries, e.g. in the USA, the incidence rate of mesothelioma is higher among men than among women, probably due to higher rates of occupational exposure

among men compared to women, but this distribution differs in certain countries (Lemen et al., 2016). In Finland, between 1st January 2000 and 31st December 2012, median annual incidence of peritoneal mesothelioma was 4 cases per year (0.74 per million). Peritoneal mesothelioma was more frequent in men than in women (4.31 versus 2.62 new cases annually) (Salo, 2017). Based on the results of Plato et al. (2016), between 1961 and 2009, an excess risk of pleural mesothelioma was observed among Swedish women who worked in textile industry or as canning workers or cleaners. The proportion of mesothelioma in women was 21.1%. In this period an increased risk was perceptible in women for peritoneal mesothelioma (25.5%) compared to men (5.9%) of all mesothelioma cases (Plato et al., 2016). Italy represents one of the most affected European countries by mesothelioma, due to the fact that Italy was the main asbestos producer and one of the greatest consumers of the continent in the 20th century.

Marinaccio et al. (2018) published a study on 21,398 Italian malignant mesothelioma cases where pleural mesothelioma represented 93.3%, peritoneal and pericardial malignant mesothelioma represented 6.5% of the whole caselist. Among men, pleural mesothelioma had higher incidence (85%) compared to peritoneal mesothelioma (7%), and among women 73% was pleural and 18% peritoneal mesothelioma. Between 1993 and 2012 the gender ratio (F/M) for the malignant mesothelioma cases in Italy was 0.40, which presents a wider affection of women in mesothelioma, attributable to the higher female workforce participation in the industrial sector and to the relevance of non-occupational exposure. The female/male ratio among the newly diagnosed cases was 0.24 in Australia in 2014 while in France it was 0.27 between 1998 and 2008 and in South Korea 0.51 between 2001 and 2010. The latter likely is due to the high female workforce participation in asbestos textile factories, beyond the environmental asbestos burden. Mean age at diagnosis among women was higher than among men both with occupational and non-occupational exposure (Marinaccio et al., 2018). Kerger (2018) found much higher occurrence of occupational exposure in men compared to women. Based on his publication, in the USA the incidence of pleural mesothelioma in the 0-74 age group has decreased since the early 1990s among men and has increased for both genders in the people older than 75 years (Kerger, 2018). Based on the article published by Andujar et al. in 2016, the risk of malignant pleural mesothelioma was higher among occupationally exposed men, than in women with occupational exposure, contrary for non-occupational exposure. If both types of exposure were present, the risk in women became closer to the attributable risk of men. Results from the period 1994-2014 in different countries related to attributable risk of asbestos in malignant pleural mesothelioma, stratified by gender showed that the risk of occupational asbestos exposure for malignant pleural mesothelioma among men was 83.1% in Fance and 85% in the United Kingdom, respectively, while among women this attributable risk was lower: 41.7% in France and 22.5 % in the United Kingdom. In contrast, the attributable risk of non-occupational asbestos exposure in France among men was 20%, among women 38.7%, in the United Kingdom the attributable risk among men was 1.3%, and 16% in women, respectively (Andujar et al., 2016). Plato et al (2016) found that among Swedish men four identified occupations showed significant excess risk of both pleural and peritoneal mesothelioma: insulators, plumbers, painters and bricklayers. The highest risk of pleural mesothelioma was observed among insulators, most of the cases occurred among machinery fitters and -assemblers (Plato et al., 2016).

In the updated review and meta-analysis across 18 individual studies, published by Marsh et al (2017), a statistically significant elevated risk was observed for both residential and household exposures. A fibre-type potency response was found, chrysotile fibres not showing statistically elevated risk for mesothelioma (Marsh et al., 2017). However, it has been confirmed by the International Agency for Research on Cancer that all types of asbestos are carcinogenic for humans, particularly amphibole (Glynn et al., 2017; Marinaccio et al., 2018). A safe threshold hasn't been defined, below which there is no risk of malignant mesothelioma (Tomasson et al., 2016). Kharazmi et al. (2018) published a Swedish population-based study, using the Swedish FCD, and found no significant rise in risk of pleural mesothelioma for those who had positive familial history, but did not have occupational exposure compared to those with negative familial history of mesothelioma and without occupational exposure.

Those who had occupational exposure of asbestos with negative familial history of mesothelioma, had threefold greater risk for mesothelioma than those with negative family history and negative history of occupational exposure. People with a positive family history of mesothelioma and positive history of occupational exposure had 26 times greater risk of developing mesothelioma than those without family history of mesothelioma and negative history of occupational exposure. A positive interference was found between familial risk and occupational exposure on risk of developing pleural mesothelioma ($p < 0.001$) (Kharazmi et al., 2018). Mesothelioma still remains a disease of concern due to its long latency period. In the next two decades incidence of mesothelioma is expected to rise not only in developing countries, which are still extracting/using asbestos, but in the western countries too, where asbestos use is already banned (Napolitano et al., 2017).

CHEMISTRY AND HISTORY OF ASBESTOS

Asbestos is a mineral group which contains six natural silicate minerals. Ultrabasic magmatic rocks emerge during hydrothermal transformation, creating a scum, called serpentine. Asbestos is a fibrous odourless solid natural mineral which can be white, green, grey or yellow (PubChem Compound Summary, 2018). The asbestos fibres are composed of millions of microscopic fibrils that can be released by abrasion and other processes (Gee and Greenberg, 2002). Asbestos is divided in two classes, the serpentine type and the amphibole type (Alleman and Mossman, 1997).

Serpentine

The only member of the serpentine group is chrysotile. Chrysotile is the dihydrate of magnesium silicate, it contains curly fibres and it has two known forms, plated and fibrous and appears under the microscope as a white fibre. It is softer and more flexible than the members of the amphibole group. 95 percent of asbestos used in the world is chrysotile (PubChem Compound Summary, 2018; Alleman and Mossman, 1997).

It was used in the following products: Fire barriers, fireproof products including clothing for fire-fighters, pipe insulation, thermal insulation, floor tiles, chlor-alkali diaphragm membranes

by making chlorine, drywall compound, plaster, gas mask filters, vinyl floor tiles, sheeting, adhesives, roofing tars, felts, siding, and shingles, countertops, and pipes, acoustic ceilings, industrial and marine gaskets, brake pads and shoes, artificial snow, filters for removing fine particulates from chemicals and liquids.

Amphibole

Amphibole class minerals contain needle-like fibres. Amosite (brown asbestos), crocidolite (blue asbestos), tremolite, anthophyllite and actinolite are members of the amphibole class (PubChem Compound Summary, 2018; Alleman and Mossman, 1997). Amosite and crocidolite are the most common used minerals from the amphibole group. They were commodity for manufacturing: thermal and chemical insulations, asbestos cement pipe, sheets, ceiling tiles, and cigarette filter.

Mining

Mining of asbestos started more than 4000 years ago. Industrial mining began in the middle of the 19th century (Alleman and Mossman, 1997). The biggest mines were in Canada and the Russian Empire (later Soviet Union and Russia). In 2008-2009 and in 2014-2015 the world's biggest asbestos producers were Russia, China, Brazil, Kazakhstan and Canada, they mined 2 million tons per year together. They have large and moderate amount of reserves of asbestos, approximately 200 million tons (U.S. Geological Survey Mineral Resources Program, 2010; 2016).

Hungarian aspects

In Hungary in Dunabogdány the Csódi mountain contains asbestos as a mineralogical rarity. Asbestos processing factories used to be in Nyergesújfalu, Selyp and Budapest. Production and sale of asbestos products have been forbidden since 1st of January 2005 (Nyíregyházi Főiskola, 2009).

Recycling and substitutes

The use of asbestos in new constructions has been banned for safety and health reasons in a lot of developed countries. Although the manufacturing of asbestos products stopped, they are still present nowadays in the buildings. During the demolition of these buildings huge amount of asbestos gets into the air. The air pollution can be prevented by using water during demolitions. It is very important to destruct the buildings and handle the asbestos waste properly. Asbestos can be converted into harmless silicate glass by thermal decomposition. During the process the asbestos is heated to 1,000-1,250 ºC where a mixture of non-hazardous silicate phases is generated. Above 1,250 ºC silicate glass is produced. (Dixit, 1986) Industrial transformation of asbestos is using microwave thermal procedure which produces porcelain tiles and ceramic bricks (Gualtieri and Tartaglia, 2000). There is a method to degrade totally the chrysotile asbestos fibres where ultrasound and oxalic acid are used (Leonelli et al., 2006). Substitutes for asbestos are calcium silicate, carbon fibre, cellulose fibre, ceramic fibre, glass fibre, steel fibre, wollastonite, and several organic fibres, like aramid, polyethylene, polypropylene, and polytetrafluoroethylene. Several non-fibrous minerals or rocks, such as perlite, serpentine, silica, and talc are substitutes for products in which the reinforcement

properties of fibres are not needed. In the chlor-alkali industry, membrane cell technology is the only alternative to asbestos diaphragms (U.S. Geological Survey Mineral Resources Program, 2016).

CONCLUSION

Characterization of environmental risk factors is important to determine preventive strategies against the global environmental changes and the health effects. We concluded that greater attention needs to be placed on the social context of the environmental impact, the vulnerability and adaptation. Further investigations are essential to provide evidences between environmental effects and fatal outcomes. Regarding to the environmental factors and the climate change elements observed worldwide the environmental-related mortality has been recently represented a significant public interest. Effects of environmental factors represent a significant challenge for forensic pathologists to evaluate the cause of death and manner of death. Forensic pathologists provide valuable information about the manner of death after the autopsy has been performed. The environmental-related entity of fatal environmental accident might be considered among the classical types of manner of death categories in forensic medicine. The environmental factor-related death cases have an increasing importance in the evaluation of manner of death, and in the environmental death cases in forensic medicine.

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