Ann Ist Super Sanità 2015 | Vol. 51, No. 1: 52-59
DOI: 10.4415/ANN_15_01_09

Pathologic diagnosis of malignant mesothelioma: chronological prospect and advent of recommendations and guidelines

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Abstract
Malignant mesothelioma (MM) is rare and difficult to diagnose. Its identification depends upon pathological investigation (cyto-histological assessment and immunohistochemistry) supported by clinical and radiological evidence. In the last decade, the standardization of diagnostic methods has become a major focus of debate among pathologists and clinicians. This has led to the writing of guidelines and recommendation for the diagnosis to achieve the goal of a standard diagnosis. In this article, a chronological view relating to the pathological diagnosis of MM is presented together with a review of guidelines and recommendations.

Key words
- mesothelioma
- guidelines
- pathology
- diagnosis

INTRODUCTION

Malignant mesothelioma (MM) is a rare cancer derived from the lining cells of serosal cavities. The pleura site outnumbers the peritoneum. Its identification depends upon pathological investigation supported by clinical and radiological evidence. To date, the approach to the diagnosis is based on cytological and histological assessment and ancillary testing. The diagnosis can be very complex because MM is known for its composite epithelial/mesenchymal patterns, its phenotypic variability from case to case, and its aptitude to mimic other cancers (particularly adenocarcinoma) or benign/reactive processes.

Experienced pathologists can identify the majority of cases beyond doubt. However, given the low frequency of this malignancy non-experienced pathologists may only encounter 1-3 cases a year in their routine, irrespective of his/her experience. The failure to identify MM or, *viceversa*, the misdiagnosis of MM in case of metastasis has major implications at the individual level, and at public health level (bias in incidence and mortality estimates). Also, the diagnosis of MM carries important medico-legal implications, mainly related to compensation issues. In the last two decades, the improvement standardization of diagnostic methods has become a major focus of debate among pathologists and clinicians at local, and international level. This has led to the writing of guidelines and recommendation for the diagnosis to achieve the goal of a standard diagnosis.

In this article, a chronological perspective approach relating to the pathological diagnosis of MM is presented together with a review of guidelines and recommendations. The role of immunohistochemistry and cytology is also briefly discussed. In closing, a focus on the Italian experience is provided. In Italy, asbestos was widely used in many industries until the end of the 1980s and a nationwide surveillance system of MM incidence, the National Mesothelioma Register (ReNaM) (http://www.ispesl.it/renam/Index.asp) is operating since 1993. Based on the literature in English as main language, basic textbooks or book sections and relevant peer-reviewed articles were taken into account as reference types.

PATHOLOGIC DIAGNOSIS OF MALIGNANT MESOTHELIOMA – CHRONOLOGY

Since the seminal paper by Wagner *et al*. in 1960 [1], growing evidence of increased prevalence of MM in persons exposed to asbestos stimulated interest in the diagnosis of serosal tumors (*Table 1*). In standard pathology textbooks, however, there was almost no mention that this entity even existed. The identification of this cancer was a diagnosis of exclusion, after "painstaking" post-mortem investigation of all organs to exclude a primary neoplastic growth elsewhere [2].

During the 1970s, pathologists were progressively capable to make a diagnosis of MM on the basis of histology (hematoxylin-eosin stained sections), mucin histo-

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Table 1
Pathological diagnosis of mesothelioma – Chronology

Period	Year (ref)	Authors' field	Major area under discussion
1960s	1960 [1]	Pathology	Description of mesothelioma cases with crocidolite exposure
	1967 [2]	Pathology	Diagnosis of mesothelioma is a diagnosis of exclusion (after exclusion of a primary cancer elsewhere)
1970s			Diagnosis is made on the basis of histology (hematoxylin-eosin stained sections) and mucin histochemistry
	1977 [7]	Commission of the European Communities on the Public Health Risks of Exposure to Asbestos	Set up Mesothelioma Registries in accordance with criteria as agreed upon by a "panel" of pathologists (designated as Mesothelioma Panel) that had as one of its basic objectives the standardization of the pathological diagnosis of mesothelioma
1980s			Multi-technical approach with the employment of histochemical and ultrastructural studies, as well as "negative" imunostaining for carcinoembryonic antigen (CEA), a "positive" carcinoma marker
	1983 [8]	Council of the European Communities	Council directive: Member States shall keep a register of recognized mesothelioma cases
1990s			Rapid growth in the application of immunohistochemistry
	1992 [6]	Pathology	Reliable diagnosis to be based on stringent criteria (gross appearance, histology, histochemistry, immunohistochemistry and electron microscopy)
	1999 [16]	Pathology	Pathology Panels of the WHO
2000s			Urgency of improving and standardizing diagnostic methods – establishment of guidelines (see Table 2)
	2004 [22]	Pathology	WHO classification of tumors of the pleura*
	2006 [23]	Pathology	Pathology of MM by the International Mesothelioma Panel

*A new edition is in press (expected March 2015).

chemistry [3], and less rigorous exclusion of alternative tumors. In the mid-1970s, the ultrastructure of MM was described [4], and this proposed as a contribution tool to the diagnosis [4, 5]. In 1975, as part of a cohort mortality study for asbestos insulation workers, Irving J. Selikoff (1915-1992) the principal figure since the early 1960s in establishing a causal relationship between exposure to asbestos and excess of mortality rates, invited his colleague Yasunosuke Suzuki – at Mount Sinai Hospital in New York – to evaluate autopsy and biopsy samples obtained from deceased insulation workers. Professor Suzuki, the last member of the "Selikoff generation" (he passed away in 2011), initiated his systematic survey of MM cases that were confirmed as definite or probable in the diagnostic certainty by Suzuki himself, based on gross appearances, histology, histochemistry and electron microscopy [6]. In 1977, a report of a working group of experts for the Commission of the European Communities on the Public health risks of exposure to asbestos pointed out that the incidence of MM was underreported because many pathologists did not recognized the diagnosis [7]. The Commission recommended to set up Mesothelioma Registries in accordance with criteria as agreed upon by a "panel" of pathologists (designated as Mesothelioma Panel) that had as one of its basic objectives the standardization of the pathological diagnosis of mesothelioma.

In 1983, the Council of the European Communities adopted the directive that Member States shall keep a register of recognized MM cases [8]. To assist in the establishment of MM registries, an atlas was prepared for the Commission of the European Communities in 1985 [9]. During the 1980s, it was highlighted the importance of a multi-technical approach to the pathological diagnosis of MM with the employment of histochemical and ultrastructural studies [10]. In parallel, it was provided evidence of the usefulness immunohistochemistry as an aid in the differential diagnosis of MM [11] that included "negative" staining for carcinoembryonic antigen (CEA), a "positive" carcinoma marker. The AFIP Atlas of Tumor Pathology on Tumors and pseudotumors of the serous membranes turned out one of the major reference textbook among pathologists [12]. Additional important reference were chapters in textbooks relating to pulmonary pathology [13] or to asbestos-related diseases [14].

In the 1990s, after the rapid growth in the application of immunohistochemistry, the AFIP Atlas was updated [15]. Moreover, WHO Pathology Panels promoted and proposed the adoption of a uniform diagnostic terminology to classify mesothelial tumors [16], and many new books (and new editions) dealing with MM dedicated specific sections on the pathology of MM [17-19]. As well, pathologists were required to provide a reliable diagnosis of MM based on stringent criteria that included gross appearance, histology, histochemistry, immunohistochemistry and electron microscopy [20].

In the 2000s, it emerged the urgency of improving and standardizing diagnostic methods. Case series with pathological analysis of hundreds of MM cases were available [21]. In 2004, it was released the WHO classification of tumors of the pleura [22]; this book provides

an international standard for pathologists: diagnostic criteria, pathological features and all recognized MM variants including ICD-O codes were described. A new edition of the WHO classification of tumors of the pleura is being in press at the present (4th edition; expected March 2015). In 2006, the International Mesothelioma Panel published a volume on the pathology of MM [23] providing information about recent advances in methods for diagnosing this tumor; as well, it was available the third update of the AFIP Atlas [24]. In the same period, several books were published involving groups of specialists; these volumes have sections devoted to MM pathology [25, 26]. Very recently a monograph book on MM has been released delivering a concise, updated review of the pathological characteristics of this malignancy, WHO classification, mimicking conditions, and immunohistochemistry [27].

PATHOLOGIC DIAGNOSIS OF MALIGNANT MESOTHELIOMA – GUIDELINES AND RECOMMENDATIONS

A systematic analysis of peer-reviewed articles regarding guidelines and recommendations for the pathological diagnosis of MM was performed in the PubMed electronic database. The search was conducted using the following search terms: mesothelioma AND diagnosis, and *mesothelioma* AND *guidelines* OR *recommendations* in the advanced search page, encompassing the period 1960 to May 2014. Additional exploration included the term *guideline* in the specific search field "publication type". Inclusion was confined to relevant papers in English and relevant non-English articles with English abstracts. Articles dealing with guidelines and/or recommendations restricted to the radiological diagnosis or the treatment of MM were excluded.

Data from each study were extracted and organized into a summary table (*Table 2*). References refer mainly to pleural MM. These papers are written by clinicians or by a multidisciplinary team of experts or by societies with interest in the field of MM, with the aim for guidance in various sectors including pathological diagnosis; others studies are entirely dedicated to the pathological aspects of diagnosis.

The first articles appeared in the late 1990s. In France, the product of a collaborative project by the Federation Nationale des Centres de Lutte Contre le Cancer (FNCLCC) [28] was the pronouncement that diagnosis should be based on multiple thoracoscopic

Table 2
Basic studies on pathological diagnosis of MM based on PubMed Search of the terms mesothelioma (title) AND recommendations (title) OR guidelines (title) OR as publication type (guidelines)

Year	Publication type	Reference	Authors' Country	Topic	Update
1998	FNCLCC Practice guidelines	[28][1]	France	Standards, options and guidelines	2001 [32][1]
1999	CAP Practice guidelines	[29][2]	USA	Protocol for examination of specimens	
2001	BTS Consensus Development Conference	[30][1]	UK	BTS Standards of Care Committee Statement including pathological diagnosis	2007 [31][1]
2005	ESMO Guidelines	[33][1]	Europe	Recommendations on diagnosis	2007 [34][1] 2008 [35][1] 2009 [36][1] 2010 [37][1]
2007	ADASP Practice guidelines	[38][2]	USA	Recommendations for the reporting	-
2009	IMIG Consensus Development Conference	[39][2]	USA, Canada, France, UK	Guidelines for pathologic diagnosis	2013 [40][2]
2010	ERS/ESTS guidelines	[41][1]	Europe	Recommendation for the management with a pathological point of view	-
2011	Consensus Development Conference	[66][1]	Italy	First Italian Consensus Conference: expert opinions	
2013	ADRI Review article on guidelines	[42][1]	Australia	Guidelines for the diagnosis	-
2013	Consensus Development Conference	[43][1]	Italy	Second Italian Consensus Conference on pleural MM: recommendations on management with a summary of pathology evidence	2015[3]

[1] Reference relevant to all health personnel with an interest in the field
[2] Reference relevant to pathologists
[3] Third Italian Consensus Conference (www.aiom.it)
National Mesothelioma Register (ReNaM)
Federation Nationale des Centres de Lutte Contre le Cancer (FNCLCC)
College of American Pathologists (CAP)
British Thoracic Society (BTS)
European Society for Medical Oncoloogy (ESMO)
International Mesothelioma Interest Group (IMIG)
European Respiratory Society and the European Society of Thoracic Surgeons (ERS/ESTS)
Asbestos Diseases Research Institute (ADRI)
Association of Directors of Anatomic and Surgical Pathology (ADASP)

biopsies and immunostains (cytokeratin, EMA, vimentin, CEA, and Leu-M1). In 1999, it was developed a document by the College of American Pathologists (CAP) as a tool to assist pathologists in the diagnostic process for the examination of specimens from patients with pleural MM. Use of this protocol (checklist) was intended to be entirely voluntary [29]. Immunohistochemistry and electron microscopy were considered "important adjuncts to routine microscopic evaluation" but no other details were given.

In 2001, a multidisciplinary statement on MM guidance (including pathological diagnosis) was offered by the British Thoracic Society (BTS) [30]. In 2007, an update statement was provided [31]. FNCLCC published an update as well on recommendation relating to MM diagnosis based on the publication of new data [32]. In 2005, the European Society of Medical Oncology (ESMO) Guidelines Task Force published the "Minimum clinical recommendations for diagnosis of malignant pleural mesotelioma" [33], and in the following years various revisions were released [34-37].

In 2007, the Associations of Directors of Anatomic and Surgical Pathology (ADASP) published detailed guidelines for the reporting of pleural MM [38]. Features optional for the final report ("specific institutional preference") included among others the results of any ancillary study (histochemical, immunohistochemical and electron microscopy). Although immunohistochemistry is routinely used to facilitate the diagnosis, ADSP does not prescribe a particular panel but recommends at least 2 positive mesothelial markers (calretinin, cytokeratins 5/6, D2-40 and WT-1) in conjunction with at least 2 or more negative mesothelial markers (*e.g.* CEA, TTF-1, Ber-EP4 and MOC-31).

In 2009, the International Mesothelioma Interest Group (IMIG) provided a consensus statement relating to practical, broad guidelines meant to be "a reference for the pathologist for diagnosis of MM" [39]. An update by the original contributors and other pathologists with expertise in the field was published in 2013 [40]. Authors of these articles are pathologists from North America (Canada and USA), United Kingdom and France. The most important recommendations are use of histological features (including subtyping) and immunohistochemical panels. Another major point is that antibodies need to be used reflect the differential diagnosis in each case: in the typical epithelioid MM, 2 mesothelioma markers and 2 carcinoma markers may be adequate to make a diagnosis; when there are unusual findings, additional markers should be used. It is affirmed the limited usefulness of cytology, histochemical stains, and electron microscopy. For sarcomatoid MM, cytokeratins (AE1-AE3, CAM 5.2 and cytokeratin 7) are recommended. The pathologist should always take the clinical, radiologic, and pathologic features into consideration, and get expert second opinion in difficult cases.

In 2010, the European Respiratory Society and the European Society of Thoracic Surgeons (ERS/ESTS) included in their guidelines for the management of pleural MM also a section relating to the pathological diagnosis with recommendations concerning the use of WHO 2004 classification, and that a diagnosis of MM should always include immunohistochemistry with the guidelines of IMIG [41].

The last publications referring to 2013 together with the IMIG update [40] are Guidelines of the Asbestos Diseases Research Institute (ADRI) by a team of experts in Australia [42] and Recommendations of the Pathology Committee of Second Italian Consensus Conference on pleural MM [43]. The Australian team states that a "tissue specimen" is necessary to evaluate the mesothelial phenotype and invasion, and immunoistochemistry is essential for the diagnosis and should include negative and positive markers. The combination and number of antigens to evaluate is dependent on the differential diagnosis with calretinin, WT-1 and podoplanin (D2-40) being the more specific positive markers.

Recommendations of the Italian pathology committee include the following: cytology is a diagnostic tool for experienced cytopathologists and immunohistochemistry should be based on the tumor subtype; for epithelial/mixed MM, 2 positive markers for mesothelium always including calretinin and 2 carcinoma markers one being CEA; for sarcomatous MM broad spectrum cytokeratin are first-line antibodies [43].

THE ROLE OF IMMUNOHISTOCHEMISTRY

It is well recognized that MM evade definitive characterization. There have been numerous attempts at trying to determine not only histological criteria but also ancillary testing guidelines [44]. Immunohistochemistry has emerged as the most commonly used supplementary procedure for its widespread availability. The antibody used depends on the histological subtype, the differential diagnosis, the site of the MM and the gender of the patient. It usually consists of a combination of "positive" and "negative" mesothelial markers (antibody panels, *Table 3*) [40]. In the typical case of epithelial MM, 2 mesothelioma markers and 2 carcinoma markers may be satisfactory. There are no established guidelines for the use of specific antibody panels. The selection of antibodies is related to the discretion of pathologists on the basis of which ones works the best in a given laboratory, journal publications, review articles and specialized textbooks.

Current recommendations follow the ongoing discovery of antibodies more specific for mesothelial cells and their commercial availability, since the late 1970ties. For example, the quite selective positive mesothelial marker calretinin was described in 1996 [45, 46] and its application in routine practice was realized after the late 1990s early 2000s.

Summary of the data encompassing the period 1979-2005 [47] documented that no single antibody is able to differentiate between adenocarcinoma and epithelioid MM by immunohistochemistry; the use of a small panel of antibodies with a high combined sensitivity and specificity is recommended. After that time, several articles have proposed an enormous variety of rapidly changing markers as ancillary testing in the diagnosis of MM [48-50]. For that reason, an increase use of immunostains has occurred in the past two decades in many

Table 3
Markers more often used in the diagnosis of mesothelioma

Epitheliod mesothelioma		Sarcomatoid mesothelioma	Markers differentiating mesothelioma *vs* reactive mesothelium[1]
Mesothelial markers	**Carcinoma markers**		
Calretinin	CEA	Cytokeratin 7	Desmin
Cytokeratin 5/6	TTF-1	Cytokeratin 8/18	EMA
HBME-1	CD15 (Leu-M1)	Cytokeratin CAM5.2	p53
Podoplanin (D2-40)	BG8	Cytokeratin AE1/AE3	GLUT-1
WT-1	B72.3	Cytokeratin MNF116	IMP3
Thrombomodulin	MOC31	Cytokeratin 34BetaE12	
	Ber-EP4	Vimentin	
	E-cadherin		

[1] FISH for deletion of p16/CDKN2A.

laboratories reflecting the acceptance of diagnostic panels, and the increasing availability of new antibodies [51]. Some investigators believe that single antibody or antibody pairs are equal or even better in efficacy when compared with more comprehensive pairs [44]. Others have validated minimal panels [52]. Recent reviews and update recommend compositions of panels of markers in various differential diagnosis [53, 54].

THE ROLE OF CYTOLOGY

Since most MM first present with effusions, cytological analysis represents the primary diagnostic approach. However, cytological diagnosis of MM is notoriously challenging and of variable sensitivity [55, 56]. Whether cytology should be an acceptable means of diagnosing MM is as yet controversial among pathologists. In spite of this, its role is relevant because cytology may be the only source of pathological material available. In the summary of the IMIG guidelines it is stated that "there is limited usefulness of cytology". However, the international community of cytopathologists has different consensus opinions and it is oriented in the reappraisal of this issue. An abstract entitled "Guidelines for cytopathologic diagnosis of malignant mesothelioma" has been discussed at the 2014 IMIG meeting (21-24 October 2014, Cape Town; http://imig2014.org/scientific-programme/) and an article submitted to *Cytopathology* has been accepted for publication. In the recent Italian consensus conference, the pathology committee recommended that cytology alone is a reliable diagnostic tool for "experienced cytopathologists", with immunocytochemical characterization [43].

THE ITALIAN EXPERIENCE

Among the initial articles by the Italian investigators, there are histological considerations and proposals about MM based on: morphological appearance in optical microscopy [57], epidemiological studies with reappraisal of histology with the purpose of confirming the diagnosis [58], surveys based on autopsy cases [59]. Later on there are interobserver variability studies to assess consistency of pathological diagnosis on standard hematoxylin-eosin stained slides [60] and on hematoxylin-eosin and immunostained slides [61]. In the early 1980s, two Italian pathologists contributed to the definition of the histogenesis of MM [62] and also investigated highly specific antimesothelial antibodies [63].

In 1996, a group of epidemiologists prepared the guidelines for the identification and definition of MM cases for their transmission from regional centers to the national mesothelioma Registry/ReNaM [64]. The update was released in 2004 [65]. A standard interpretative grid allows a breakdown of cases into classes or groups depending on the degree of diagnostic approximation. Consistency controls have been fixed, i.e. criteria and procedures aimed at assessing diagnostic uniformity through a critical revision of the diagnoses received or recorded. The case classification provides for 5 groups and several subgroups of decreasing levels of diagnostic certainty, in relation to the procedure and diagnostic certainty achieved: 1) MM that is certain; 2) probable MM; 3) possible MM; 4) MM "to be defined"; 5) not MM. The classification of cases is based on pathology reports and diagnostic imaging (confirmation of primary pleural or peritoneal neoplastic lesion and exclusion of alternative pathology), diagnosis of discharge of mesothelioma or similar assessment made by a clinician (MM probable and certain). The possible MM is characterized by indicative clinical and radiological data, in the absence of cyto-histological examinations.

In 2008, the First Italian Consensus Conference on pleural MM was held that included a section on biopathological evaluation [66] with specific indications. In 2011, at the Second Italian Consensus Conference on MM the pathology committee has proposed several recommendations, including as a first-line antibody battery two immohistochemical panels: 1) epithelioid/mixed MM (2 mesothelioma positive markers, one being always calretinin, and 2 carcinoma markers, one being CEA); 2) sarcomatoid MM (use of broad spectrum cytokeratin) [43]. In January 2015, at the Third Italian Consensus Conference on pleural MM (www.aiom.it), the pathologic committee discussed the challenges in the diagnosis of non-epithelial MM (sarcomatoid or biphasic variants), the guidelines for the cytological diagnosis of MM, and the need for standardized protocols for the pathology reporting of MM.

Table 4
Pathologic diagnosis of malignant mesothelioma: general recommendations from different pathologists worldwide (October 2014)

Guidelines are meant as a practical reference for the pathologists, not a directive	Adequate tissue samples in the typical context of clinical, radiological and surgical findings represent the gold standard for diagnosis	The first step in the diagnosis is the light microscopic examination of conventional stained preparations	Immunohistochemical panels are essential part to the diagnosis: they are dependent on the site of the tumor and the gender of the patient

In 2012, the Italian Ministry of Health published a volume dedicated to the asbestos-related diseases with a chapter relating to MM (www.quadernidellasalute.it/download/download/15-maggio-giugno-2012-quaderno.pdf).

CONCLUSIONS

Overall, general recommendations from different pathologists worldwide agree upon the following (*Table 4*): guidelines are meant a practical reference for the pathologists, not a directive. Adequate tissue samples in the typical context of clinical, radiological and surgical findings represent the gold standard for diagnosis. The first step in the diagnosis is the light microscopic examination of conventional stained preparations; immunohistochemical panels are essential part to the diagnosis; they are dependent on the site of the tumor and the gender of the patient, the phenotypic question (benign versus malignant; epithelioid vesus non-epitheliod MM) and on reagents available in a given laboratory.

MM is diagnosed both in laboratories with no specific expertise in MM pathology and in those with experience for the presence of an 'expert pathologist' in the field. Since the 1960s, MM review panels have been implemented in several countries to validate the pathologic diagnosis of MM. Nowadays, this diagnosis is still problematic. Agreement among panel members has been reported around [60] and above 70% [40]. The rarity of this cancer, its medico-legal issues for increasingly seek compensation and public health implications, and its prognosis in relation to histological subtype would deserve second expert opinion, particularly for difficult cases [67]. This implies a cost for the health system. However, appropriate referrals needs financial support that overall would be cost effective.

Conflict of interest statement

The authors declare that there is no conflict of interest. This research did not received a specific grant from any founding agency in the public, commercial, or no profit sectors.

Received on 30 October 2014.
Accepted on 4 March 2015.

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