

Serum mesothelin and other biomarkers: what have we learned in the last decade?

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Abstract: In the last decade there is been much interest in noninvasive, economic and well-accepted diagnostic tests for screening of subjects exposed to asbestos, and in patients with malignant pleuric mesothelioma (MPM) for diagnosis or monitoring response to treatment. Several biomarkers have been suggested as tools for screening and early diagnosis of MPM. Currently, in patients with MPM, have been reported high levels of soluble mesothelin-related peptides (SMRP), plasmatic osteopontin (pOPN), vimentin, fibulin-3 and many others as promising marker for diagnosis, even their use in prevention monitoring is still discussed. In this type of disease, a key role could be played by miRNAs, which expression has been investigated in a large series of MPM to examine new pathways useful in diagnosis, prognosis and therapy. An altered expression of some proteins has been reported, useful as biomarkers, in comparative proteomic analysis of malignant pleural mesothelioma. New promising markers are nowadays under study and alone or better in combination, they'll be very helpful in diagnosing, monitoring mesothelioma patients or for screening of risk groups.

Keywords: Mesothelin; mesothelioma; biomarkers

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The relevance of the malignant pleuric mesothelioma (MPM) biomarkers

MPM is a highly aggressive tumor with a poor survival rate (1).

It is characterized by a long latency period in spite of its rapid, aggressive clinical outcome.

Therefore, effective preventive protocols may include very frequent instrumental diagnostic tests performed over a long period of time, i.e., decades, which may be neither economic nor ethical. Consequently, the use of early high sensitivity/specificity diagnostic markers is strongly recommended.

For screening and early diagnosis of MPM, new tools are

necessary, and several biomarkers have been suggested (2).

Presently, there are no useful tools for screening and early diagnosis of MPM, while clinical monitoring is based mainly on radiological tests. Moreover, evaluation of therapy response in MPM remains difficult, especially because of poor sensitivity and operator dependency of radiological assessment (3). In addition, in most cases relapse is characterized by a very rapid time course.

Several MPM biomarkers have been studied and some of them are still under investigation, these researches investigate serum, plasma and pleural effusions, especially using ELISA (4).

The value of tumor markers is more available to the clinician: it can only be useful if required and interpreted

taking into account the other information available to the clinical context.

An incorrect interpretation can trigger a series of diagnostic insights, even invasive, with stress and expenses that may not be justified.

Soluble mesothelin-related peptides (SMRP)

Mesothelin originates as a precursor of 71-kDa, then cutted into two mature proteins: megakaryocyte potentiating factor (MPF), secreted into the blood, and a cell surface glycoprotein (MW approximately 40 kDa) recognized by Chang and Pastan on 1992 in ovarian carcinomas (5), and then in malignant mesotheliomas, squamous-cell carcinomas and normal mesothelial cells (6).

SMRP are potentially a tumor marker for MPM. Many studies aimed to determine the differences in SMRP levels in patients with MPM versus patients with benign pleural disease or lung cancer (LC) or individuals formerly asbestos exposed; in other cases in patients with MPM before and after treatment.

Determination of serum SMRP has been proposed on 2003 by Robinson *et al.* as a marker for diagnosis of mesothelioma and monitoring disease progression on a relatively small group of subjects (7). Yet, SMRP dosage has been suggested to be a useful tool for screening asbestos-exposed individuals for early evidence of MPM and, possibly, LC.

Other studies (8-14) confirmed that serum SMRP was a promising marker for diagnosis, prognosis and clinical monitoring of MPM. High SMRP concentrations were detected in all the studies only in the epithelioid and mixed MPM.

Our data, in particular, provide the evidence that high SMRP dosage can be considered as an independent prognostic tool for patients with epithelioid MPM and suggest that this dosage could be useful both as a screening test for diagnosis (11), interpreted, of course, taking into account the other information available to the clinical context.

An important Individual patient data meta-analysis was performed by Hollevoet *et al.* (15). In symptomatic or high-risk individuals, this meta-analysis showed that a negative blood test for SMRP does not exclude MPM, even at a high-sensitivity threshold. On the contrary, a positive blood test for SMRP at a high specificity threshold leads to further diagnostic steps and could possibly help an earlier diagnosis.

The low false positivity indicated a high specificity as

well. The detection of elevated SMRP levels in asbestos-exposed subjects should induce the clinical consideration of the presence of MPM denotes. A lower probability of the presence of MPM in patients with normal SMRP levels can be considered due to the high negative predictive value of the method, but the limiting lower sensitivity cannot entirely excluded the presence of disease (16).

Several findings suggest that SMRP may be a useful tumor marker for detecting the progression of malignant mesothelioma and evaluating tumor response to treatment (17).

However, the poor sensitivity of mesothelin (35–50%) limits its value for diagnosis (18).

Osteopontin (OPN)

OPN is a secreted glycoprotein that plays key roles in different biological processes, such as immunological regulation, cell-matrix interaction, cell migration and tumor development (19,20). The circulating OPN levels in serum are increased in several cancers, including MPM (21), in which serum OPN has been considered as a potential biomarker for early detection of the disease (22,23).

Our data suggest that confounding factors such as age, smoking habits and asbestos exposure do not influence plasma OPN and serum OPN. In addition to traditional radiological exams, plasma and serum OPN may be useful markers in the diagnosis of epithelial MPM. Furthermore, plasma OPN is more stable than serum OPN, and measurements of OPN in plasma are more reliable (23,24).

Other authors confirmed OPN as an effective marker for MPM diagnosis (22,25-28) and the utility as biological markers for the health surveillance of past-exposed patients (28). Nevertheless, further studies with a larger sample size and better design are needed to carefully assess the diagnostic power of this biomarker (25).

Fibulin-3

Human fibulin-3 is a secreted glycoprotein encoded by the epidermal growth factor (EGF)-containing fibulin-like extracellular matrix protein-1 (EFEMP-1) gene (29), and it could play a role in the regulation of MPM cell proliferation and migration. Fibulin-3 is produced in MPM but its role remains uncertain (30).

Several studies have investigated the diagnostic value of fibulin-3 for MPM and based on these fibulin-3 results a useful diagnostic marker for MPM (30-34).

Plasma fibulin-3 levels can distinguish healthy persons with exposure to asbestos from patients with mesothelioma. In conjunction with effusion fibulin-3 levels, plasma fibulin-3 levels can further differentiate mesothelioma effusions from other malignant and benign effusions (31).

Creaney *et al.* determined that fibulin-3 is increased in the plasma of MPM patients but at a lower diagnostic sensitivity than previously reported and inferior to that of SMRP in both plasma and effusions (32).

Other authors considered that the real use for serum fibulin-3 was for diagnosis in MPM but not for prognosis (30).

MicroRNAs (MiRNAs)

MiRNAs are short RNA non-coding sequences. In recent years, miRNAs expression involved in post-transcriptional regulation of gene expression in mesothelioma biology was found dysregulated both in cancer cells and sera, in patients affected by tumors of different histotypes, including MPM (35).

MiRNA are recently considered as diagnostic markers in different types of cancer. Preliminary analysis evidence miRNAs as possible markers for diagnosis and prognosis of MPM, and hypothesize new mechanisms for the therapy of this malignancy (35-48).

The histopathological subtypes were associated with the expression of miR-17-5p, miR-21, miR-29a, miR-30c, miR-30e-5p, miR-106a, and miR-143 and the reduction of the expression of two miRNAs (miR-17-5p and miR-30c) correlated with better survival of patients with sarcomatoid subtype (37).

Gee *et al.* studied the molecular differences between mesothelioma and lung adenocarcinoma by using miRNA microarrays (36).

Santarelli *et al.* proposed miR-126 as useful marker because significantly remained down-regulated in the malignant tissues compared with the normal tissues (38) and in serum (41) while Kirschner *et al.* confirmed the potential of miR-29c and miR-92a as candidate tumor markers and revealed that miR-625-3p was a promising novel diagnostic marker for MPM (39).

Bononi *et al.*, on the base of their studies, proposed as potential new MPM biomarkers three circulating up-regulated microRNAs, i.e., miR-197-3p, miR-1281 and miR-32-3p (35).

Micolucci *et al.* designated as “mesomiRs” (MM-associated miRNAs), a pool of deregulated circulating and tissue miRNAs; identified as biomarker useful for

MPM.

Data from previously exposed to asbestos and MPM subjects showed that the most promising candidates for a multimarker signature were circulating miR-126-3p, miR-103a-3p, and miR-625-3p in combination with SMRP (44).

De Santi *et al.* showed that in MPM the pattern of miRNAs expression is highly deregulated and that a 2-miRNA signature (Let-7c-5p and miR-151a-5p) can be considered as a useful tool for prognosis of MPM (45). Also miRNA-16 was directly related to MPM patient prognosis, suggesting its possible use as a prognostic marker in MPM patients (47).

The study of Cavalleri *et al.* suggests that plasmatic extracellular vesicles (EV)-associated miR-103a-3p and miR-30e-3p are able to discriminate MPM from subjects with past asbestos exposure (46).

Standardized validation studies are needed to assess clinical relevance of the MiRNAs, so as to move from the workbench to the clinic (44).

For screening use as biomarkers for monitoring of workers exposed to asbestos a better knowledge of miRNA signatures in MPM is still necessary to verify the contribution of specific miRNAs as early diagnostic biomarkers, also compared to different asbestos forms, exposure and subject work history (42).

Other biomarkers proposed

Many other indicators have been evaluated as biomarker for MPM [cytokines, serum thioredoxin-1 (TRX-1), CA125, CYFRA 21-1, IL6, HGF, desmin, IP10, vimentin, THSP2, circulating fibrinogen, etc.].

MPF is a 31-kDa secreted cytokine, originated from mesothelin cutting. When evaluated in serum of MPM patients and control subjects by ELISA, MPF levels were higher in MPM cases, with respect to healthy subjects, individuals with benign asbestos-related diseases, or LC patients (49,50).

C-C chemokine RANTES were found significantly associated with workers formerly asbestos exposed and MPM patients compared with healthy controls. Increased immune mediator concentrations were observed in the sera of the workers previously exposed to asbestos compared to controls for human fibroblast growth factor (FGF-b), vascular endothelial growth factor (VEGF), CCL5 (RANTES), CXCL10 (IP-10), CLEC11A (SCGF-b), CCL27 (CTACK), CCL11 (EOTAXIN), IL-5 and IL-6

($P < 0.001$). Levels of chemokines IP-10 and RANTES were associated with the severity of asbestos-related diseases. The immune proteins secreted by mesothelioma biopsies showed detectable levels of RANTES, VEGF, and IP-10 in MPM patients. A significant relationship between serum and pleural fluid concentrations was found for RANTES alone in the MPM cases (51).

In the progression of asbestos-related diseases some chemokines may have a prognostic role and can be useful for the health surveillance of workers with an occupational history of asbestos exposure, and patients affected by non-malignant asbestos-related diseases (52).

To differentiate patients with MPM from SPE, also serum sCD26 and DPPIV enzyme activity appear to be useful biomarkers. The prognosis of patients with MPM can be predicted by DPPIV activity in serum or pleural fluid (53).

The relationship between interleukin 6 (IL-6) levels and clinical parameters was studied by Nakano *et al.* in 25 patients with MPM (54).

IL-6 mRNA expression in the tumors and serum IL-6 levels was described also by Bielefeldt-Ohmann *et al.* (55).

Quite recently among some new serum markers differentially expressed in MPM and healthy subjects, have been found levels of IL6 statistically different between the studied groups (56).

Fitzpatrick *et al.* suggest involvement of the expression of cytokines and cytokine receptors *in situ* in MMP (57).

Serum TRX-1 (58) and circulating fibrinogen (59) are other reported serum biomarkers.

Combination or panel of serum biomarkers

The combination of multiple markers could be very useful to increase sensitivity and specificity in early diagnosis, monitoring e screening of MPM rather than the use of single markers.

Several panels of biomarkers have been suggested as tools for screening and early diagnosis, clinical monitoring, prognosis and screening of MPM (60-68). The combinations studied are multiple: 80HdG, VEGFbeta and SMRPs (60), miR-126, in association with SMRPs (61), serum concentrations of SMRP, CA125, and CYFRA21-1 (62), combination of serum SMRP and pOPN (27), combination of SMRP and miR-103a-3p (63,64), SMRPs, miR-126 and methylated thrombomodulin promoter, Met-TM (65), fibulin-3 and SMRP (66), combination of miR-132-3 and miR-126 (48), combination of six biomarkers

(SMRP-pOPN-IL6-vimentin-desmin-HGF) (56).

Conclusions

For diagnostic and prognostic purposes, to date, SMRP is the only biomarker approved by the FDA and suggested by several consensuses (66).

In accordance with the most advanced scientific papers and the most authoritative guidelines, this biomarker can be used, some sensitivity limits, as a diagnostic marker for evaluating follow-up therapy and as a prognostic indicator, at least in epithelioid mesotheliomas.

Helsinki criteria suggest that SMRP, pOPN, MPF, fibulin-3, quantitative miRNA expression and other may be useful as a follow-up tool in the treatment of malignancies and could be helpful in early clinical diagnosis. A major debate is whether early detection can improve treatment outcome. Actually no specific recommendations were made regarding these biomarkers for screening or other purposes (67).

Studies in recent years show that the use of markers panel, using also markers obtained evaluated by different approaches based on proteomics technology, greatly improves clinical diagnostic performance.

New promising markers are in the study and alone or better in combination and will be very helpful in diagnosing and monitoring mesothelioma patients.

Recently, a proteomic approach, screening of a large number of biomarkers, improves the diagnostic accuracy in different types of cancer, including MPM (68-70).

There are needed additional studies with more enrolled patients and better drawing to scrupulously assess the diagnostic power of all these biomarkers.

Probably the ongoing studies will allow, in the near future, more accurate MPM diagnosis and prognosis, earlier detection of MPM and helpful screening of people formerly exposed to asbestos (71).

In conclusion, the current status of MPM biomarkers is not satisfactory but encouraging due to emerging more sensitive and specific non-invasive biomarkers.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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