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Mesothelin, the Best Tumor Marker for Mesothelioma

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ABSTRACT

Introduction: *Malignant Pleural Mesothelioma (MPM) is a rare and aggressive disease with limited treatment options and a poor prognosis.*

Patients and Methods: *Patients typically present with pleural effusion, dyspnea, and chest pain. The initial diagnostic procedures include chest X-ray, CT scans, and pleural fluid cytology. MPM is usually diagnosed at an advanced stage. Mesothelin levels were evaluated. Patients included 2 control groups: healthy individuals (n = 355) and oil refinery workers (n = 283), compared to acute MPM (n = 135): mild mesothelin levels (1.5–40 nm, n = 63) and very high mesothelin levels (40–201 nm, n = 72). Mesothelin levels were measured using Fujirebio Diagnostics kits (Malvern, PA), which were FDA-approved for mesothelioma monitoring in 2007. VEGF and IL-6 levels were also assessed using kits of R&D Systems.*

Results: *The results demonstrate a clear correlation between MPM and significantly elevated mesothelin levels compared to the control groups. A significant decrease in mesothelin levels was observed in patients who responded to treatment over three and six months, while non-responders exhibited increasing mesothelin levels. Rising mesothelin levels were associated with disease recurrence. Parallel biomarker trends were observed: IL-6 and VEGF levels showed a similar pattern.*

Conclusions: *We have shown that mesothelin is the best tumor marker for MPM, indicating response to therapy, enabling early detection of recurrence and allowing immediate therapy to improve survival.*

Keywords
MPM, Tumor Markers, Early detection, Treatment response.

Introduction
Malignant Plural Mesothelioma (MPM) is a rare aggressive disease with a limited treatment response and poor prognosis, overall, 5 years survival rates is estimated as less than 10%. The worldwide MPM incidence is around 7 per Million in Europe. Exposure to Asbestos and chronic inflammation, are suggested to be initial risk factors [1,2].

Patients with MPM, usually present with symptoms of pleural effusion, including dyspnea and chest pain. The initial diagnostic procedures involve chest x-ray, CT and pleural fluid cytology. However, Mesothelioma is often diagnosed already in an advanced stage. Obviously, early diagnosis and immediate interventions are needed to improve disease outcome. Therefore, there is a critical need for reliable and non-invasive tools to improve the diagnosis as early as possible [3-5].

The challenges of mesothelioma diagnosis are two-fold: 1. distinguishing mesothelial cells from metastatic malignant other carcinoma (as Lung Ca).

Also-Identification of new Biomarkers, suggested to be not invasive methods and not expensive, are important and needed for

early detection, introducing more specific treatments, finding new targets for MPM treatments and improving survival [6,7].

Available serum markers, include: SMRP, Mesothelin, Osteopontin (OPN), Fibulin 3, HMGB. OPN and Mesothelin high or increasing levels, indicate MPM. Serum Mesothelin, previously referred to MSLN, is most recently used to diagnose. The initial diagnostic procedure involves chest X-ray, C.T. and pleural fluid cytology. In addition, TM as Mesothelin, was approved in 2007 by the FDA8.

Materials and Methods

Mesothelin levels were evaluated in 2 groups of Controls: Healthy controls n=355 and in Oil Refineries - subjects n=283 as having high predisposition to mesothelioma, (see Figure 1).

Those levels were compared to 2 groups of Acute Mesothelioma patients: in a group where mild Mesothelin levels ranged between 1.5-40 nm (n=63), and in an acute group of Mesothelin consisting of very high levels - Mesothelin 40-201 nm (n=72), with a total of 135 acute Mesothelioma patients, (see Figure 2).

Follow-up of patients and changes in Mesothelin levels, (see Figures 3, 4 and 5A).

In some patients, we also evaluated additional Biomarkers such as VEGF and IL-6, as shown in (Figure 5B).

Significant elevations in Mesothelin levels, were parallel to those of high VEGF and IL-6 levels.

Mesothelin levels were evaluated by kits from Fujirebio Diagnostics, Malvern, PA, approved for Mesothelioma monitoring by the FDA, in 2007. VEGF and IL-6 levels, were evaluated by kits purchased from R&D Systems Inc. USA, used according to the manufacturer's instructions.

In contrast, patients not responding to therapy, correlated to increased levels of Mesothelin (see Figure 4).

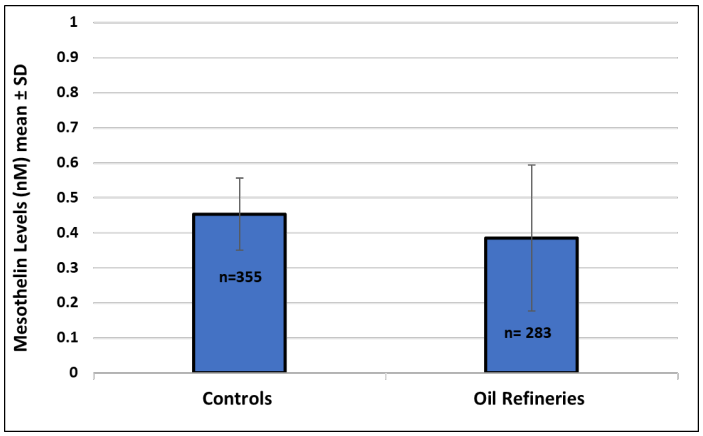


Figure 1: Mesothelin levels in Controls.

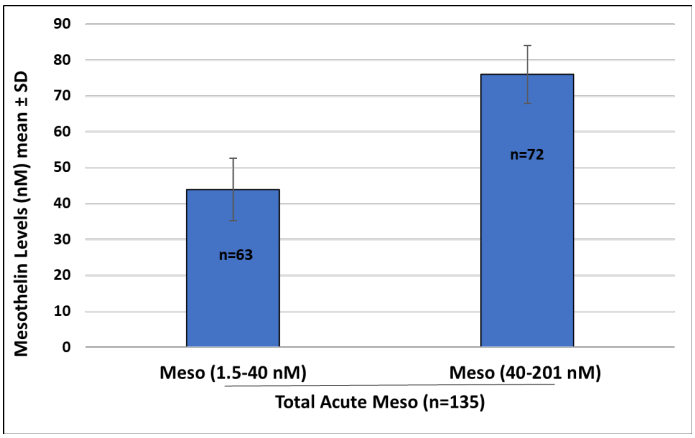
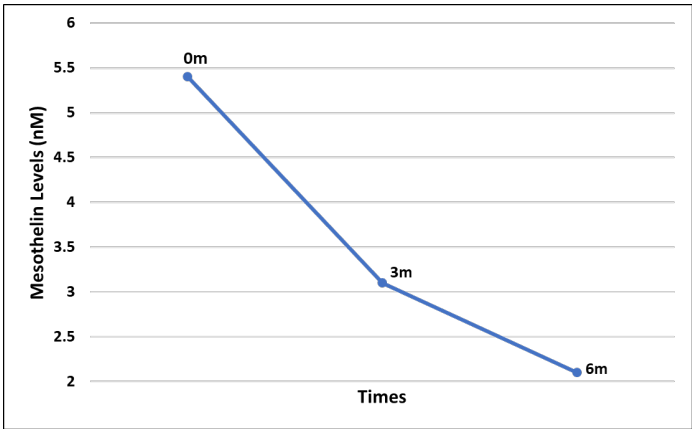


Figure 2: Mesothelin levels in acute Mesothelioma.

Mesothelin levels decreased significantly in responding patients to therapy, during 3 and 6 months (see Figure 3).

Patient no. 1



Patient no. 2

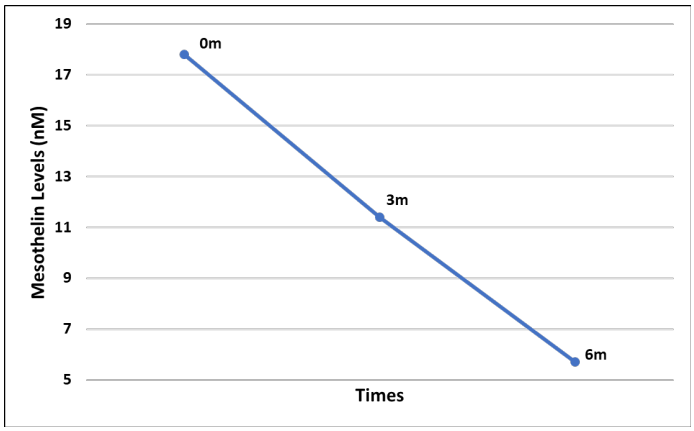
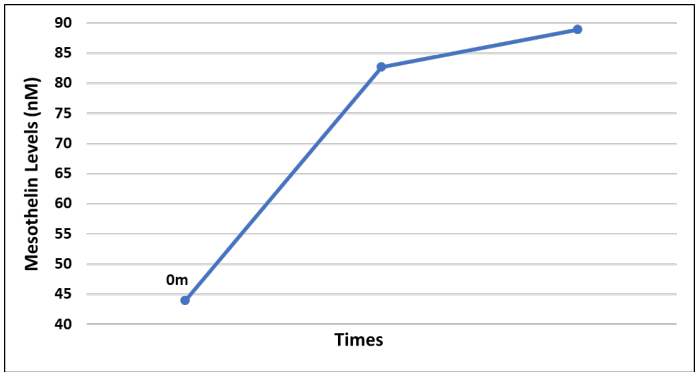


Figure 3: Response to therapy (decreases in Mesothelin levels).

Patient no. 1



Patient no. 2

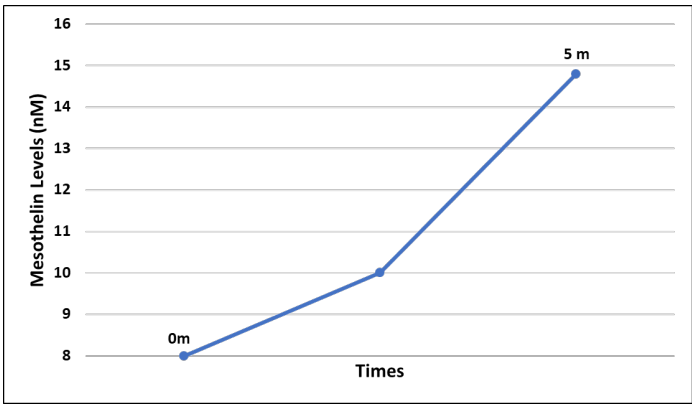


Figure 4: Non-response to therapy (Increases in Mesothelin levels).

Increasing Mesothelin levels, were correlated to non-response, then decreased during another type of therapy and during recurrence, there was an extreme increase toward ex, (see Figure 5a) Parallel to changes in Mesothelin.

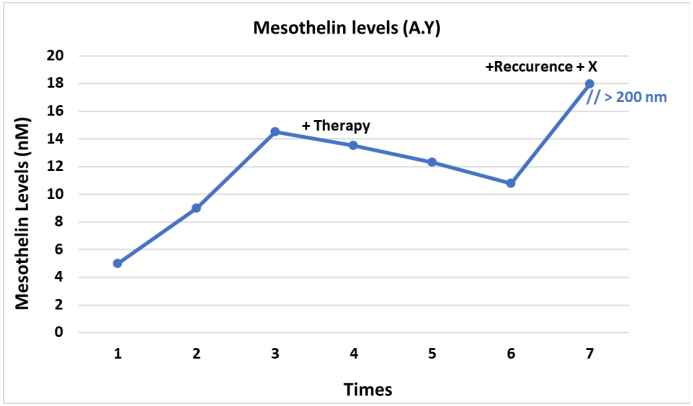


Figure 5A: Increases in Mesothelin levels in acute Mesothelioma.

levels, we found IL-6 and VEGF similar extreme increases (see Figure 5b).

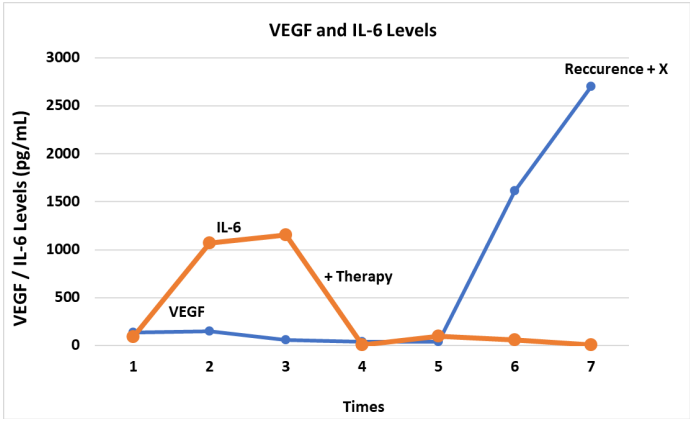


Figure 5B: Increases in other Tumor Markers in acute Mesothelioma.

Discussion

Malignant pleural mesothelioma (MPM) remains a highly aggressive malignancy characterized by late diagnosis, limited therapeutic options and poor overall survival. The lack of reliable, non-invasive biomarkers capable of supporting early diagnosis, differential diagnosis and longitudinal disease monitoring, represents a major unmet clinical need [8-10]. The present study provides clear evidence that serum Mesothelin fulfills many of these requirements and supports its role as the most informative tumor marker currently available for mesothelioma [5,6,11-13].

Our results demonstrate a clear and marked distinction between Mesothelin levels in patients with acute mesothelioma and those observed in both healthy controls and individuals with high occupational risk due to asbestos exposure [2-4,14,15]. Importantly, even among high-risk refinery workers, Mesothelin levels remained substantially lower than those observed in patients with established disease, highlighting the high specificity of Mesothelin elevation for active mesothelioma rather than asbestos exposure alone. This finding is especially clinically relevant, as asbestos-exposed populations represent a major target group for screening and early detection strategies [5,6,16-19].

Furthermore, stratification of patients according to Mesothelin levels revealed a wide dynamic range, with extremely elevated concentrations found in acute disease. This broad separation from control values underscores the potential diagnostic utility of Mesothelin and supports its use as a serum-based adjunct to imaging and cytological evaluation, particularly in cases where pleural fluid cytology is inconclusive or tissue sampling is challenging [19].

Beyond diagnosis, one of the most significant observations of this study is the strong correlation between longitudinal changes in Mesothelin levels and therapeutic response. Responding patients demonstrated a significant decline in Mesothelin levels at both 3- and 6-month follow-up, whereas non-responding patients exhibited persistently elevated or rising levels. These findings indicate that Mesothelin is not merely a static diagnostic marker but a sensitive indicator of tumor burden and treatment efficacy. Notably, rising

Mesothelin levels were associated with lack of response prior to overt clinical deterioration, suggesting potential value as an early marker of treatment failure [6,18].

The dynamic behavior of Mesothelin was further emphasized in patients undergoing changes in therapeutic strategy. In such cases, decreasing Mesothelin levels following treatment modification were observed, whereas disease recurrence was accompanied by extreme elevations. This pattern supports the use of Mesothelin as a reliable tool for real-time disease monitoring, early detection of relapse, and potentially for guiding therapeutic decision-making.

In addition, the parallel elevation of IL-6 and VEGF observed in patients with markedly increased Mesothelin levels provides insight into the biological processes underlying aggressive disease. IL-6 is a key mediator of cancer-related inflammation and immune dysregulation, while VEGF plays a central role in angiogenesis and tumor progression. The concurrent increase of these biomarkers with Mesothelin, suggests that high Mesothelin levels reflect not only tumor mass but also an activated inflammatory and angiogenic tumor microenvironment, characteristic of advanced or refractory mesothelioma. This coordinated biomarker response further strengthens the biological plausibility of Mesothelin as an integrative marker of disease activity.

When compared with other proposed serum biomarkers such as osteopontin, fibulin-3, and HMGB, Mesothelin offers several advantages, including regulatory approval, standardized assays, and consistent performance across diagnostic and monitoring settings. While other markers may provide complementary information, our data indicate that Mesothelin remains the most important and clinically actionable biomarker for mesothelioma at present [6,8,18-20].

In conclusion, this study reinforces Mesothelin as a highly sensitive and specific tumor marker for MPM, capable of distinguishing patients from both healthy individuals and high-risk populations. Its strong correlation with treatment response, resistance, and recurrence highlights its value for longitudinal monitoring. The observed association with IL-6 and VEGF further supports its relevance to disease biology and aggressiveness.

Collectively, these findings support the integration of serum Mesothelin measurement into routine clinical practice for diagnosis, follow-up, and management of patients with mesothelioma.

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