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Pleural effusion hyaluronic acid as a prognostic marker in pleural malignant mesothelioma

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ABSTRACT

Background: Malignant mesothelioma (MM), a primarily asbestos-induced tumour, has a poor prognosis, with over-all 5-year survival less than 5%. Tumour biomarkers are being intensely investigated in MM as aids to diagnosis and prognosis. Hyaluronic acid (HA) is produced in MM but its role in prognostication remains uncertain.
Materials and methods: HA concentrations were determined in matching serum and pleural effusion of 96 MM patients, 26 lung cancer patients and 42 patients with benign effusions resulting from infectious, cardiac, renal, liver and rheumatoid diseases and compared to the current 'best practice' biomarker, mesothelin. Liver and kidney function were determined for each patient. Diagnostic accuracy was determined by area under the receiver operator characteristic curve (AUC) analysis following logistic regression modelling. Difference in survival between groups was determined by both log-rank test and Cox proportional hazards regression modelling.
Results: For effusion HA, the AUC (IQ range) was 0.89 (0.82–0.94) and for effusion mesothelin, it was 0.85 (0.78–0.90). Serum HA was not diagnostically useful. A combined measure of effusion HA, and serum and effusion mesothelin had an AUC of 0.92 (0.86–0.96), which was significantly higher than effusion mesothelin alone. Effusion HA had a biphasic distribution in MM patients, dichotomised at a concentration of 75 mg/L. The median survival of MM patients with high effusion HA was 18.0 (13.7–22.4) months, significantly longer than those with low HA effusion levels (12.6 months (8.4–16.8), $p = 0.004$). Serum HA, and effusion and serum mesothelin were not significant prognostic indicators.
Conclusion: This study demonstrates that a combined biomarker panel has greater diagnostic accuracy than effusion mesothelin alone, and that significant prognostic information is provided by effusion HA.
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1. Introduction

Malignant mesothelioma (MM) is an asbestos-induced cancer which is difficult to diagnose and has a median post-diagnosis survival of less than 12 months. This poor survival may be related to the late clinical diagnosis of the disease [1,2].

Hyaluronic acid (HA) is a large polysaccharide made predominantly by fibroblasts and is present in MM pleural effusions [3–7]. HA is rapidly removed from the circulation by the clearance receptor stabilin-2 [8], and has a plasma half-life of 2.5–5 min [9,10]. Despite being a recognised feature of MM, the role of HA in diagnosis and prognostication remains uncertain.

Soluble mesothelin was identified as a specific serum biomarker for MM in 2003 [11] and is also elevated in MM effusions [12]. Mesothelin is the best characterised biomarker for MM however, recent meta-analysis found sensitivity was too low for early diagnosis and suggested further biomarker research be undertaken [13]. To determine if the sensitivity of the mesothelin biomarker for MM could be improved by the incorporation of effusion and serum HA we undertook this study in matching serum

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Table 1
Patient demographics and biomarker concentrations in serum and pleural effusion.

Group	Histology	No.	Age	Male/female	Serum mesothelin (nM)	Serum HA (ng/mL)	Effusion mesothelin (nM)	Effusion HA (mg/mL)
MM	Epitheloid	53	69 (10)	86/10	2.1 (3.2)$^{\#\#}$	46.0 (157.8)	29.3 (52.5)$^{**,\#}$	62.4 (73.6)$^{**,\#\#}$
	Sarcomatoid	2						
	Biphasic	9						
	Not specified[a]	32						
Lung Cancer	Adenocarcinoma	13	70 (12)	20/6	1.0 (1.1)	17.4 (78.5)	7.1 (18.2)	12.7 (19.7)
	Non-small cell	8						
	Small cell	3						
	Mixed small and large	2						
Benign		42	68 (13)	26/16	1.2 (1.3)	34.0 (117.8)	4.5 (5.9)	8.7 (12.1)

Results for the number of patients (No.) are reported as median and interquartile range in parenthesis.
Adjusted p value reported for independent samples median test for benign group *cf* MM ($^{**}p < 0.001$, $^{*}p < 0.02$); and for lung cancer group *cf* MM ($^{\#\#}p < 0.001$, $^{\#}p < 0.02$).
[a] MM patients in whom histology was 'not specified' were diagnosed based on effusion immunocytology as described in Section 2.

and pleural effusions. As there is increasing interest in biomarkers as prognostic indicators in MM and HA concentration has been reported to correlate with survival [14] and disease progression [15] the prognostic value of the two biomarkers in MM was also examined.

The effects of liver and renal function on HA and mesothelin concentrations were assessed. Serum HA is elevated in liver disease, with the damaged liver failing to remove HA from circulation; HA is a component of some liver disease diagnostic test panels for this reason [16]. Mesothelin is excreted via the kidney so renal function is also important in mesothelin biomarker assessments.

2. Methods

2.1. Subjects

This was a study of patients who presented at Sir Charles Gairdner Hospital (Perth, Western Australia) with a pleural effusion clinically requiring pleurocentesis over the period 2003–2010. Patients provided informed written consent. Pleural effusions were centrifuged for 10 min at $400 \times g$ and the resulting supernatant was stored at −80 °C until assay. Blood samples were collected by routine venepuncture into BD Vacutainer serum tubes and allowed to clot for at least 2 h at room temperature, or at 4 °C overnight before processing. Blood samples were centrifuged at $400 \times g$ for 10 min then the serum was removed, aliquoted and stored at −80 °C until use. A total of 96 MM patients, 26 lung cancer patients and 42 patients with benign effusions resulting from infectious, cardiac, renal, liver and rheumatoid diseases (Table 1) were randomly selected from the Australian Mesothelioma Tissue Bank, a member bank of the Australasian Biospecimen Network which is supported in part by the Australian National Health and Medical Research Council. Samples were selected based on diagnosis and the presence of a serum sample collected within 1 week of the pleural effusion sample. Final diagnosis was made following review by experienced cyto-pathologists of immunocytological and biochemical features of the effusion [17–20], and clinical review of hospital records until death or censoring after a median of 10 months follow up (IQ range 7.5 months) to ensure diagnosis matched clinical presentation. This study was approved by the Human Research Ethics Committee of Sir Charles Gairdner Hospital.

2.2. Hyaluronic acid binding assay

HA was measured using the HA Test kit (Corgenix, Inc., Broomfield, CO) following the manufacturer's instructions and using the supplied HA standards. The manufacturer's upper limit of normal cut-off is 75 ng/mL in serum. The limit of detection of the assay was stated as 10 ng/mL; samples below the limit of detection were, for statistical purposes, assigned a value of 5 ng/mL.

2.3. Mesothelin assay

Mesothelin concentrations were determined using the MESOMARK™ assay (Fujirebio Diagnostics, Malvern, PA) following the manufacturer's instructions. Mesothelin concentrations were determined in duplicate from a standard curve performed on each plate and expressed as nM. A serum mesothelin value of ≥2.5 nM was considered positive for MM [21]. A cut-off value for pleural effusion mesothelin of 20 nM was previously established [12].

2.4. Liver function tests

A standard panel of liver function tests were performed using routine automated laboratory methods by PathWest Laboratory Medicine WA (Nedlands, Western Australia). These measures and their normal ranges in parentheses were: total protein (60–80 g/L), albumin (35–50 g/L), globulin (23–35 g/L), bilirubin (<20 μmol/L), gamma-glutamyl transferase (GGT; <60 U/L), alkaline phosphatase (35–135 U/L) and alanine transaminase (ALT; <40 U/L). Patients liver function was assigned as; "normal" if all tests were within the normal range; "abnormal without raised ALT or bilirubin" if any tests except for ALT or bilirubin were outside the normal range; and "abnormal – raised ALT or bilirubin" if either ALT or bilirubin were elevated.

2.5. Kidney function tests

Creatinine was measured by the Abbott Architect c16000 analyser® (Abbott Laboratories, Abbott Park, IL) using the Jaffe Creatinine method. Estimated glomerular filtration rate (eGFR) was then calculated using the Modified Diet in Renal Disease (MDRD) Formula [22]. Accordingly, patients were classified into Chronic Kidney Disease (CKD) stages: stage II – kidney damage with mild decrease in function and eGFR (60–89 mL/min/1.73 m^2), stage III – moderate decrease in eGFR (30–59 mL/min/1.73 m^2), stage IV – severe decrease in eGFR (15–29 mL/min/1.73 m^2) and stage V – kidney failure (<15 mL/min/1.73 m^2) [23].

2.6. Statistical analysis

Statistical analyses were performed using IBM® SPSS® statistics version 20 (Armonk, NY). The random sampling function in Microsoft Excel was used to select cases and controls for study. Summary results were reported as the median and interquartile range (IQR) and the patient groups were compared using the non-parametric NPTESTS procedure, with adjustment for multiple comparisons using the Dunn–Bonferroni method. Significance across the liver and kidney function ordinal scale groups was tested by the non-parametric Kruskal–Wallis test. Spearman's non-parametric correlation was used for comparing biomarkers. Receiver operator characteristic curve (ROC) analysis was used to

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