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The Significance of BRCA-associated Protein (BAP1) and Calretinin Expression in Malignant Pleural Mesothelioma and Non-small Cell Lung Carcinoma: An Immunohistochemical Study

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ABSTRACT

Background: Malignant pleural mesothelioma (MPM) and non-small cell lung carcinoma (NSCLC) are common diseases with rising incidence, patients have different prognosis and are treated differently, and thus it is very important to diagnose these malignancies properly. This differential diagnosis is not easy. The aim of this work is to evaluate the role of BRCA-associated protein (BAP1) and calretinin in the differentiation between mesothelioma and non-small cell lung carcinoma. ***Methods:*** BRCA-associated protein (BAP1) and calretinin were assessed by immunohistochemistry in 44 lung paraffin blocks, malignant pleural mesothelioma (22 cases) and non-small cell lung cancer (22 cases). ***Results:*** BAP1 expression was observed in 20/22(90.9%) of cases of non small cell lung carcinoma, while only 8/22 (36.4%) of malignant pleural mesothelioma showed positive BAP1 immunoreactivity. There was a statistically significant difference in BAP1 expression between non-small lung carcinoma and malignant pleural mesothelioma (p value = 0.001)**.** Calretinin expression was observed only in 3/22 (13.6%) of cases of non-small cell lung carcinoma, while 18/22 (81.8%) of malignant pleural mesothelioma showed positive calretinin immunoreactivity. There was a statistically significant difference in calretinin expression between non-small lung carcinoma and malignant pleural mesothelioma (p value< 0.001). BAP1 has sensitivity of 90.9%, specificity of 63.6%, predictive value positive (PVP) of 71.4% and predictive value negative (PVN) of 87.5%. Calretinin has sensitivity of 81.8%, specificity of 86.4%, PVP of 85.7% and PVN of 82.6%. ***Conclusion:*** BAP1 and calretinin IHC can be used with other immunohistochemistry panel to differentiate between malignant pleural mesothelioma and non-small lung carcinoma.

Keywords: Malignant Pleural Mesothelioma, Non-small Cell Lung Carcinoma, BRCA-associated Protein (BAP1), Calretinin, Immunohistochemistry

INTRODUCTION

Malignant pleural mesothelioma (MPM) is one of the most common malignant tumors of the pleura, which arises from its lining cells. They are mostly diagnosed in middle aged men exposed to asbestos in their workplace [(1).]

The incidence of MPM has been increasing worldwide over the past 20 years with an expected peak in Europe in (2020). The U.S.A reached its peak incidence in 2004 .More than 14,200 mesothelioma cases are diagnosed all over the world every year [(2).]

Malignant pleural mesothelioma is an aggressive tumor characterized by high resistance to conventional therapy and poor prognosis with a median survival rate about 2 years after diagnosis .The poor prognosis is most probably due to difficulty of accurate diagnosis until the progression of the disease to advanced stages [(3).]

Non small cell lung carcinoma (NSCLC) represents 80-85% of all lung carcinomas which

is considered the most common cause of cancer-related death worldwide (9.2% of all tumors**)** **(4).**
Lung cancer and MPM patients have different prognosis and are treated differently, thus it is very important to diagnose these malignancies properly. This differential diagnosis is not easy, because MPMs, in particular the epithelial subtype –which represents about 70% of all MPMs– can show a morphology similar to that of NSCLC and lung carcinosarcomas. Spindle cell carcinomas can have morphology similar to biphasic and sarcomatoid MPM **(5).**
However, these malignancies can show either conflicting IHC results, with both types can be positive or negative in the same tumor, or showing only a fraction of tumor cells as positive. Accordingly, there are still until nowadays a large number of MPMs that are misdiagnosed **(6, 7).**
BAP1 is a component of the ubiquitin proteasome system (UPS), located on chromosome 3p2, a region which is deleted in several cancers like mesothelioma, cutaneous and uveal melanoma **(8).**
BAP1 is suggested to be a tumor suppressor gene, which has a role in the regulation of cell cycle, differentiation, gluconeogenesis, apoptosis and the DNA damage response **(9).**
Calretinin is a 29-k D calcium-binding protein, which is expressed normally in neurons of the central and peripheral nervous system. An increasing number of studies have shown the ability of this protein as a biomarker for the diagnosis of MPM **(10).**
In this work, we aim to evaluate the role of BRCA-associated protein (BAP1) and calretinin in the differentiation between mesothelioma and non-small cell lung carcinoma.

MATERIAL AND METHODS

Material: The present work is a retrospective study carried out on 44 lung paraffin blocks that were previously diagnosed as malignant pleural mesothelioma (22 cases) and non-small cell lung cancer (22 cases), collected from the Pathology Department, Faculty of Medicine, Zagazig University and National Cancer Institute in Egypt in the period from May 2015 to October 2017. Clinical data were obtained from the referral clinical reports. The selected specimens were obtained by surgical excision (17 cases) and core biopsy (27 cases), and were classified according to WHO 2015 classification of lung tumors **(11).** Each case in the study was stained by routine H&E stain to evaluate the diagnosis. Cases that underwent chemo or radiotherapy or metastatic cases to lung or pleura were excluded.

Immunohistochemistry: The procedure of immunohistochemical staining was carried out according to streptavidin–biotin immuno-peroxidase method (Dako-Cytomation, Glostrup, Denmark). Sections were cut at 3–5 µm thickness from formalin-fixed-paraffin blocks, mounted on positively charged slides followed by xylene removal of paraffin, thereafter, rehydrated by ascending grades of alcohol. Then, sections were heated in buffered citrate (pH 6.0) for 20 minutes, and washed by PBS (pH 7.3). Endogenous peroxidase activity was stopped using 6% H2O2 in methanol. Then, the slides were incubated overnight with mouse monoclonal antibodies against BRCA associated protein 1(BAP1) (Santa Cruz Biotechnology, Texas, USA, sc-28383; diluted 1:3000) and rabbit polyclonal antibody against Calretinin: (Biocare Medical, USA; diluted 1:100). After PBS rinsing, slides were immersed in a biotin-conjugated secondary antibody (Lab vision Corporation, Fermont, USA). The chromogen used was DAB, while Mayer's hematoxylin was used as a counter stain, and then the slides were washed with distilled water and PBS. Positive and negative controls were stained at the same staining setting with the studied cases: Hepatocellular carcinoma and nerve tissue were used as positive control for BAP1 and Calretinin respectively, while negative controls were done using the same tissue with omission of the primary antibody. The study is complied with the guidelines of research ethics committee of Zagazig University Hospitals.

Assessment of immunohistochemistry:

1- BRCA associated protein 1(BAB1) immunostaining: The BAP1 staining was considered positive when the granular brown nuclear labeling was seen in any number of

tumor cells, regardless of background cytoplasmic reactivity [(12)].

2- Calretinin immunostaining: Calretinin were accepted as positive when nuclear and/or cytoplasmic reactivity was seen in more than 10 % of the tumor cells. The intensity of staining for calretinin even nuclear or cytoplasmic or both was scored as mild (1) (10-20% tumor cells were stained), moderate (2) (20-50% tumor cells were stained), or strong (3) (>50% of tumor cells were stained) [(13)].

STATISTICAL ANALYSIS

All data were collected, tabulated and statistically analyzed using SPSS version 19. Continuous Quantitative variables were expressed as the mean ± SD & median (range), and categorical qualitative variables were expressed as absolute frequencies (number) & relative frequencies (percentage). Continuous data were checked for normality by using Shapiro Walk test. Student's t-test was used for the comparison between 2 groups of normally distributed data. Categorical data were compared using Chi-square test. Validity of the screening tests (BAP-1, Calretinin) were assessed in the terms of sensitivity, specificity, predictive value positive, predictive value negative and accuracy.

RESULTS

Clinicopathological parameters:

The present study included 44 cases (22 cases of lung carcinoma and 22 cases of pleural mesothelioma); all were studied for BAP1 and calretinin immunohistochemical expression. The age of the studied cases ranged between 49 and 82 years with mean age of 66.5. The majority of the studied group were males (72.7%) and the remaining 27.3 % were females. The 22 studied malignant pleural mesothelioma cases included 14 cases (63.6%) of epithelioid type, 5 cases (22.7%) of biphasic type and the remaining 3 cases (13.6%) were of sarcomatoid type.The 22 studied non-small cell lung carcinoma included 13 (59.1%) adeno-carcinoma type, 7 cases (13.1%) squamous cell carcinoma and the remaining 2 cases (9.1%) were large cell carcinoma.(Table 1)

Immunohistochemical results:

1. Immunohistochemical results of BAP1: BAP1 expression was observed in 20/22 (90.9%) of cases of non small cell lung carcinoma, while only 8/22 (36.4%) of malignant pleural mesothelioma showed positive BAP1 immunoreactivity. There was a statistically significant difference in BAP1 expression between non-small lung carcinoma and malignant pleural mesothelioma (p value = 0.001) (Table 2). There was no statistically significant difference between different groups of malignant pleural mesothelioma patients as regarding BAP1 IHC expression. (p= 0.979)(Table 3). Also, there was no statistically significant difference between different groups of non-small cell carcinoma patients as regarding BAP1 IHC expression (p=0.240)(Table 4)

2. Immunohistochemical results of calretinin: Calretinin expression was observed only in 3/22 (13.6%) of cases of non small cell lung carcinoma, while 18/22 (81.8%) of malignant pleural mesothelioma showed positive calretinin immuno-reactivity. There was a statistically significant difference in calretinin expression between non-small lung carcinoma and malignant pleural mesothelioma (p value< 0.001) (Table 5) .There was no statistically significant difference between different groups of malignant pleural mesothelioma as regarding calretinin expression. (p= 0.052) (Table S1). Also, there was no statistically significant difference between different groups of non-small cell carcinoma as regarding calretinin IHC expression (p=0.362) (Table S2)

3. Sensitivity and specificity of BAP1 and Calretinin in diagnosis of malignat pleural mesothelioma and non-small cell lung carcinoma: BAP-1 has sensitivity of 90.9%, specificity of 63.6%, PVP of 71.4% and PVN of 87.5%.(Table S3). Calretinin has sensitivity of 81.8%, specificity of 86.4%, PVP of 85.7% and PVN of 82.6 %.(Table S4).

Table (1): Clinicopathological parameters of the studied cases

Characteristics		
Age (years)		
Mean ± SD (Range)	66.5 ± 8.77 49 - 82	
Sex		
Female Male	12 32	27.3 72.7
Types	**Numbe r.**	**Percent**
Malignant pleural mesothelioma Epitheloid Biphasic Sarcomatoid **Non-small cell carcinoma** Adenocarcinoma Squamous cell carcinoma Large cell carcinoma	22 14 5 3 22 13 7 2	50 % 63.3 22.7 13.6 50% 59.1 31.8 9.1

Table (2) : Comparison of BAP1 IHC expression among the studied cases

Variable	**Non-small cell carcinoma (n=22)**		**Malignant pleural mesothelioma (n=22)**		χ^2	**P value**
	No	**%**	**No**	**%**		
BAP-1:						
Positive Negative	20 2	90.9 9.1	8 14	36.4 63.6	**14.481**	**0.001 (S)**

Table (3): Comparison of BAP1 IHC expression among the malignant pleural mesothelioma studied cases

Variable	**Biphasic (n=5)**		**Epithelioid (n=14)**		**Sarcomatoid (n=3)**		χ^2	**P value**
	No	**%**	**No**	**%**	**No**	**%**		
BAP-1:								
Positive Negative	2 3	40 60	5 9	35.7 64.3	1 2	33.3 66.7	0.043	0.979 (NS)

Table (4): Comparison of BAP-1 IHC expression among the Non-small cell carcinoma studied cases

Variable	Adeno carcinoma (n=13)		Large cell carcinoma (n=2)		Squamous cell carcinoma (n=7)		χ^2	P value
	No	%	No	%	No	%		
BAP-1:								
Positive	12	92.3	1	50	7	100	5.50	0.240
Negative	1	7.7	1	50	0	0		(NS)

Table (5): Comparison of calretinin IHC expression among the studied cases

Variable	Non-small cell carcinoma (n=22)		Malignant pleural mesothelioma (n=22)		χ^2	P value
	No	%	No	%		
Calretinin:						
Positive	**3**	**13.6**	**18**	**81.8**	**20.49**	**<0.001**
+1:	2	66.7	2	11.1		**(HS)**
+2:	1	33.3	5	27.8		
+3:	0	0	11	61.1		
Negative	**19**	**86.4**	**4**	**18.2**		

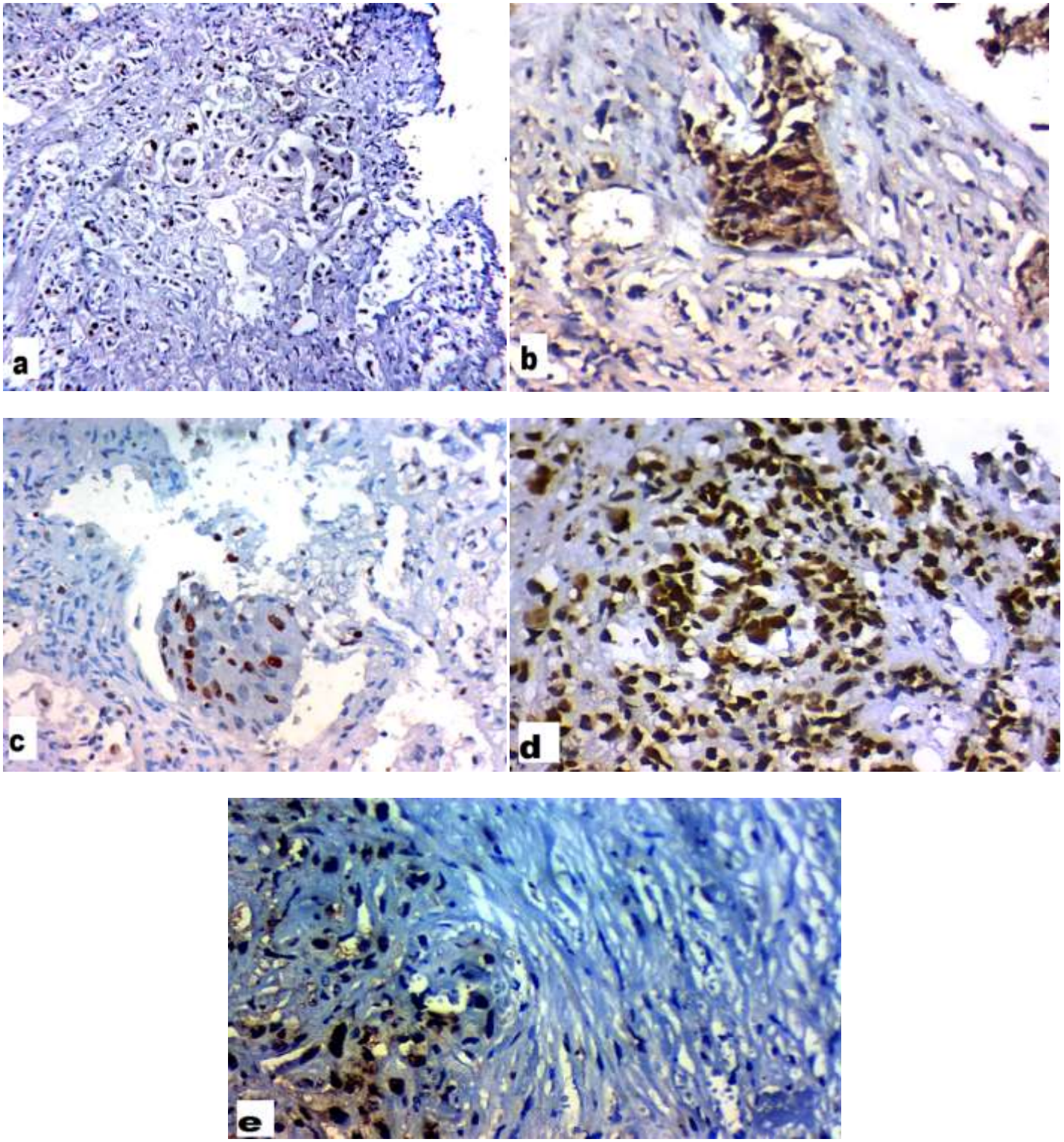

Figure 1: Immunohistochemical expression of BAP1: a) Moderately differentiated adenocarcinoma (NSCLC) showing positive nuclear BAP1 immunoreactivity.(Immunoperoxidase x200).b)Poorly differentiated adenocarcinoma (G III) (NSCLC) showing positive nuclear BAP1 immunoreactivity. (Immunoperoxidase x400) c) Squamous cell carcinoma (NSCLC) showing positive nuclear BAP1 immunoreactivity. (Immunoperoxidase X400). d) Large cell carcinoma (NSCLC) showing positive nuclear BAP1 immunoreactivity.(Immunoperoxidase X400). e) Biphasic mesothelioma showing positive BAP1immunoreactivity. (Immunoperoxidase X400).

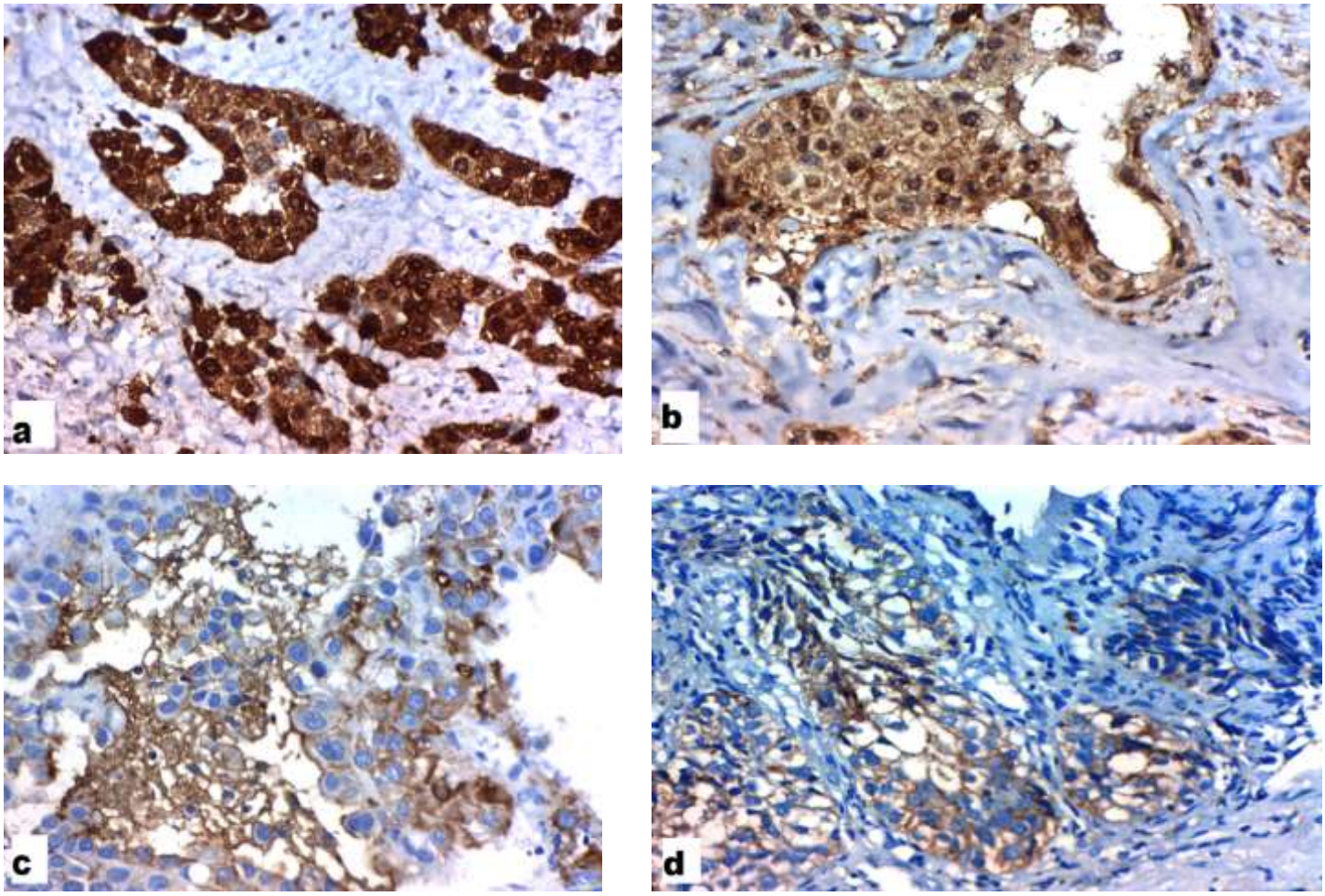

Figure 2: Immunohistochemical expression of calretinin :a) Malignant epithelioid pleural mesothelioma showing positive (+3) calretinin immunoreactivity. (Immunoperoxidase x 400). b) Biphasic mesothelioma showing positive (+2) immunoreactivity to calretinin IHC. (Immunoperoxidase x 400) c) Malignant epithelioid pleural mesotheliom showing positive (+1) cytoplasmic calretinin immunoreactivity. (Immunoperoxidase x 400) d) Squamous cell carcinoma (NSCLC) showing positive (+1) cytoplasmic calretinin immunoreactivity.(Immunoperoxidase X400).

DISCUSSION

Malignant pleural mesothelioma incidence represents less than 1 % of all cancers and they are mostly diagnosed in middle-aged men exposed to asbestos in their workplace [(1).] Non-small cell lung cancer, especially NSCLC advanced cases, is one of the leading worldwide sources of cancer-related death, and its accurate diagnosis is challenging [(5).]

BAP1 is a member of the ubiquitin C-terminal hydrolase subfamily of deubiquitinating enzymes, Somatic BAP1 mutations were detected in sporadic (i.e., non-familiar) MPM [(1),] making BAP1 the most commonly mutated gene in MPM.

In our study, nuclear BAP1was expressed in 90.9 % of Non- small lung cancer, while it was only expressed in 36.5% of malignant pleural mesothelioma. There was significant difference for BAP1 expression between non-small lung cancer and malignant pleural mesothelioma (p value = 0.001). This result was consistent to some how with **Carbone M. et al.,** [(6)] who studied BAP1 expression in 45 cases of non-small lung cancer and 35 cases of malignant pleural mesothelioma and showed that 45/45

(100%) of non- small lung cancer were positive for BAP1 while 13/35 (37%) of malignant pleural mesothelioma showed positivity for BAP1 expression.

The most likely explanation of this result is that mutations of BAP1 are rare in non-small cell lung cancer while it is common event in malignant pleural mesothelioma: frame-shift mutations and deletions that would result in loss of BAP1 nuclear staining **(7).** And so there was statistically significant difference between both groups as regarding BAP-1 IHC expression.

In the present study, there was no statistically significant difference between different subtypes of MPM patients regarding BAP1 expression. This result consistent with Pulford et al. (12) concerning BAP1 expression in malignant pleural mesothelioma who found positivity in (39%) of epitheloid subtype, (38%) of biphasic subtype and (64%) of sarcomatoidsubype and also consistent with Carbone et al (6). Many other studies results showed similar ranges for BAP1 positivity in different subtypes, for epithelioid results range from (19-39%) while biphasic range from (38-67%), on the other hand sarcomatoid results showed different results with wide range from 30% to 100% making BAP1 results for sarcomatoid under trial.

Also in this work, there was no statistically significant difference in BAP1 expression between different subtypes of non-small lung cancer (P=0.240). However, Guo et al. (14) and Cigognetti et al. (15) reported that all cases of studied adenocarcinoma and squamous cell carcinoma of lung showed positive BAP1 staining.

Our results showed the high specificity of BAP1 loss for mesothelioma diagnosis, while BAP1 nuclear expression have high specificity for non small lung cancer (63.3%) with sensitivity of (90.9%) , it can also exclude 14 out of 22 patients without non small lung cancer as compared to the gold standered test.

In support of our findings, genomic data from the TCGA collaboration on lung cancer showed that mutations of BAP1 are extremely rare in non-small cell lung cancer, loss of BAP1 nuclear staining were present in less than 1% of more than 400 lung adenocarcinomas and 178 SCC studied **(7).** Moreover, on June 2016, Andrici et al. (8) reported that out of 155 lung adeno-carcinomas and 72 lung SCC, only one had lost BAP1 expression. These Authors, quoting previous literature, noted: "this finding increases the specificity of loss of expression for BAP1 for the diagnosis of mesothelioma" (9). Although the paper by Andrici et al.(8) did not include a parallel analysis of MPM biopsies, their IHC results independently support our findings and conclusions. Together, these findings, justify including BAP1 in the panel of antibodies used to differentiate lung cancer from MPM.

Calretinin is a 29-kDa, calcium-binding protein involved in calcium signaling,and is strongly expressed in the neurons of the retina and sensory pathways **(16).** In the present study, calretinin was observed in 18/22 (81.8%) of cases of malignant pleural mesothelioma and in 3/22 (13.6%) of cases of non-small lung carcinoma .This results showed that there was highly significant difference between both groups as regarding calretinin IHC expression (P value < 0.001).

Several studies have demonstrated that calretinin is positive in most cases of malignant pleural mesothelioma and positive immunostaining ranged from 67% to 100% of MPM **(17- 19).**

In this work, there was no statistically significant difference in calretinin expression between different subtypes of malignant pleural mesothelioma (P=0.052). Other studies showed nearby results as Thapa et al. (18) who observed that 173/198 of epithelioid MPM were calretinin positive compared to 54/69 (78%) biphasic and 6/42 (14.2%) sarcomatoid, also Kushitani et al. (13) whose study was only on epithelioid subtype showed 33/36 (91.7%) positive calretinin staining.

These results make calretinin one of the most commonly used markers in the diagnosis of MPM because of its high sensitivity and specificity besides it is expressed in all

histologic types of MPM, in contrast with other highly sensitive mesothelioma markers, which are commonly expressed in the epithelioid component but not in the sarcomatoid component, As well, calretinin is one of the few antibodies that are much more frequently reactive in MPM than in non-small lung carcinoma.

In this work, there was also no statistically significant difference in calretinin expression between different subtypes of non-small lung carcinoma (P=0.362). These results are consistent with Mimura et al [17] who studied calretinin results on 66 cases of adenocarcinoma only 3 cases showed positivity for calretinin (4.5%) and Shain et al. studies showed 0% for both adenocarcinomas and non-small lung carcinomas. Similar results were observed by Kushitani et al.[13] as there were 15 out of 38 cases of non-small lung carcinoma showed positive calretinin (39.5%).

So finally, we can find that BAP1 was observed in 20/22 cases of non-small cell lung carcinoma and only 8/22 cases of MPM, so BAP-1 is able to correctly identify 20 out of 22 patients with non-small cell carcinoma (when the comparison is made with the gold-standard test; i.e., histopathological examination). It can also exclude 14 out of 22 patients without non-small cell carcinoma as compared to the gold-standard test and showed sensitivity of 90.9%, specificity of 63.6%, PVP of 71.4% and PVN of 87.5%.

Calretinin showed relatively high sensitivity (81.8%) as a positive marker for MPM. Besides, the specificity (86.4%) and diagnostic accuracy (84.1%) were sufficiently high, although the distribution of the reactive grade in non-small lung cancer was lower than that in MPM. Therefore, we found that calretinin is a marker often used in support of the diagnosis of MPM, is certainly a very sensitive MPM marker, but because it stains also a large proportion of squamous cell carcinoma and some adenocarcinomas it is insufficient, and the utility of calretinin for differentiation between them is limited. However, the combination of calretinin and other antibodies would be helpful.

Some factors might explain such discrepancies between different studies like: **i)** different sample size; **ii)** different study designs; **iii)** mixed tumor stages; **iv)** different criteria used to identify positive staining; **v)** different cut-off used to discriminate positive and negative cases; **vi)** different commercial antibodies used for the analysis, with the latter being the most important factor.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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None declared

Tables (S1-S4) are shown in the online supplement

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