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Contribution of BAP1 loss and *p16 (CDKN2A)* deletion analysis to the definitive diagnosis of mesothelioma in effusion cytology

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Abstract. – OBJECTIVE: The cytological diagnosis of mesothelioma is a controversial issue, and definitive diagnosis often requires ancillary tests. The aim of this study was to investigate the contribution of BRCA1-associated protein (1) (BAP1) loss and *p16 (CDKN2A)* homozygous deletion (HD) on the early diagnosis of mesothelioma in effusion fluids.

MATERIALS AND METHODS: Between 2019-2022, 21 pleural and peritoneal fluid samples diagnosed with atypical mesothelial proliferation in our institution were included in the study. The slides of the cases that underwent BAP1 immunohistochemistry (IHC) were retrieved from the archive and re-examined. Homozygous deletion (HD) of *p16 (CDKN2A)* was investigated by the fluorescence *in situ* hybridization (FISH) method in cell blocks of cytology samples. At least 100 atypical mesothelial cells were counted in each case, and the HD threshold value was >10%.

RESULTS: The mean age of the cases was 63.47 years (34-90 years), female/male ratio was 3/1. Of the pleural mesothelioma cases, 16 were epithelioid, 2 were biphasic, and 1 were sarcomatoid. Two cases were diagnosed with peritoneal well-differentiated papillary mesothelioma (WDPM). BAP1 loss was observed in 11 (69%) of 16 cases. HD deletion of *p16 (CDKN2A)* was seen in 11 (58%) patients with FISH. The HD threshold value was 10-20% in 6 of the cases, 30-50% in 3 cases, and above 90% in 2 cases. While HD deletion was observed in *p16 (CDKN2A)* in all biphasic and sarcomatoid cases (n=3), no deletion was observed in peritoneal WDPM (n=2). Positivity was observed with at least one method in 12 (86%) of 14 pleural mesotheliomas who underwent both BAP1 IHC and *p16 (CDKN2A)* FISH. Due to technical reasons, the FISH signal could not be obtained in two cell blocks, so no results could be obtained.

CONCLUSIONS: Asbestos exposure in areas where mesothelioma is endemic and/or the presence of proliferating mesothelial cells in cytological examination are important clues for diagnosis. In controversial cases, BAP1 IHC should be the first step in an ancillary test. Although the FISH method applied to cell blocks has cytology-specific limitations and difficulties, investigating the *p16 (CDKN2A)* deletion with FISH in selected cases will contribute to the diagnosis.

Key Words:
Mesothelioma, immunohistochemistry, BAP1, FISH.

Introduction

Mesothelioma[1], a tumor originating from serous surfaces, frequently involving the pleura, and having a low response to treatment, is seen as endemic in the Southeastern Anatolia region of Turkey. The first clinical finding of pleural mesothelioma in patients is pleural effusion, with a rate of 54-89%. However, cytological diagnosis of mesothelioma by morphological examination alone is a controversial issue, and there are publications[2] reporting that its sensitivity is 30-75%. The cytological features of benign reactive mesothelial cells overlapping with malignant mesothelial cells and the technical failure to show stromal invasion reduce the sensitivity rate[3]. For this reason, repeated cytological samples or large pleural resections, which are a highly invasive procedure, are usually performed for final diagnosis. In order to prevent tumor spread, radiotherapy is applied after sampling, so both surgery and radiotherapy-related complications and patient costs increase, hospital stays are prolonged, and the chance of early diagnosis of the patient decreases[4,5].

The accepted definitive diagnostic criterion of mesothelioma is identifying tumor invasion into the fat and muscle tissues through histopathological examination of biopsy or resected specimens. Yet, in certain instances, even extensive resection samples might not reveal such invasions[4]. Consequently, recent recommendations advocate for ancillary tests alongside morphological assessments

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to enhance the diagnostic sensitivity of effusion cytology in potential mesothelioma cases[6].

Somatic mutations in the *BAP1* gene in mesothelioma and homozygous deletion (HD) in the *p16* (*cyclin-dependent kinase inhibitor 2A; CDKN2A*) gene are the most frequently detected changes in mesothelioma[7]. According to the literature, it has been documented[8] that the differentiation between malignant mesothelial proliferations and benign proliferations may be achieved with an almost perfect sensitivity of about 100% when the loss of BAP1 is identified using immunohistochemistry (IHC), and the determination of *p16* (*CDKN2A*) HD is conducted using fluorescence *in situ* hybridization (FISH).

In this study, we aimed to investigate the loss of BAP1 and *p16* (*CDKN2A*) deletion in the effusion samples previously diagnosed with atypical mesothelial proliferation to what extent it can contribute to cytopathology practice in the earlier diagnosis.

Materials and Methods

From 2019 to 2022, 21 pleural and peritoneal fluid samples diagnosed with atypical mesothelial proliferation were analyzed at our institution. Subsequent small biopsies or surgical resections were carried out on all these samples, and a mesothelioma diagnosis was confirmed upon the detection of genuine stromal invasion. Samples lacking a cell block, those insufficient in atypical mesothelial cells within the block, and those without histopathological sampling were omitted from the study. Demographic data and mesothelioma-type pathology reports were obtained. In the cytological examination, the slides of the cases that underwent BAP1 IHC were retrieved from the archive and re-examined. If the nuclear expression was lost in more than 50% of the atypical mesothelial cells, the result was considered 'positive'. Since nuclear expression was preserved in inflammatory cells, lymphocytes and histiocytes were used as internal controls[9].

In our study, FISH was applied to formalin-fixed, paraffin-embedded cell blocks prepared from effusion materials. Previously, H&E-stained sections of cell blocks were re-examined under a light microscope. Areas where atypical mesothelial cells were concentrated were selected. New blocks were prepared by taking 0.4 mm cores with a skin punch biopsy apparatus from the region, matching the selected area on the paraffin blocks, and 4 µm thick sections were taken. Then, the FISH procedure was completed using the ZytoLight SPEC CDKN2A/CEN9 Dual Color DNA FISH Probe (Bremerhaven, Germany) and the ZytoLight Tissue FISH deparaffinization and preparation kit. Slides were analyzed by fluorescence microscope (Axio Imager 2; Carl Zeiss Microscopy, Göttingen, Germany) and homozygous deletion of *p16* (*CDKN2A*) was investigated. Both chromosome 9 (CEN9) signals (in red) were observed, while the absence of *CDKN2A* signals (in green) was considered *p16* (*CDKN2A*) HD. At least 100 atypical mesothelial cells with clear borders were counted in each case, and the presence of *p16* (*CDKN2A*) HD in more than 10% of the cells was evaluated as positive[8,10].

Results

In the scope of this study, we meticulously assessed 21 effusion specimens. The subjects spanned an age spectrum from 34 to 90 years, with a median age of 63.47. The gender distribution manifested a female-to-male ratio of 3:1. Of the acquired samples, 19 originated from the pleural space, while 2 were drawn from the peritoneal area. Cytological evaluations uniformly identified each specimen with atypical mesothelial proliferation. Adhering to the histopathological criteria, the diagnoses were categorized as: epithelioid type mesothelioma (n=16), biphasic type mesothelioma (n=2), well-differentiated papillary mesothelioma (WDPM) (n=2), and sarcomatoid type mesothelioma (n=1).

BAP1 expression was evaluated by IHC in 16 effusion fluids, and loss of expression (positivity) was observed in 11 (69%) cases (Figure 1). BAP1 positivity was 73% (8/11) in epithelioid type and 100% in biphasic and sarcomatoid type. BAP1 was investigated in 1 patient with a diagnosis of peritoneal well-differentiated papillary mesothelioma (WDPM), and it was found to be negative.

p16 (*CDKN2A*) HD was seen in 58% (11/19) of FISH-studied cases (Figure 2). While *p16* (*CDKN2A*) HD was observed in all biphasic and sarcomatoid mesotheliomas (n=3), it was not observed in peritoneal WDPM cases (n=2) (Table I). The HD ratio of *p16* (*CDKN2A*) was 10-20% in 6 cases, 30-50% in 3 cases, and above 90% in 2 cases.

Positivity was observed with at least one method in 12 (85%) of 14 pleural mesotheliomas who underwent BAP1 IHC and FISH. While BAP1 positivity and *p16* (*CDKN2A*) HD were observed together in 7 of the cases (50%), only BAP1 pos-

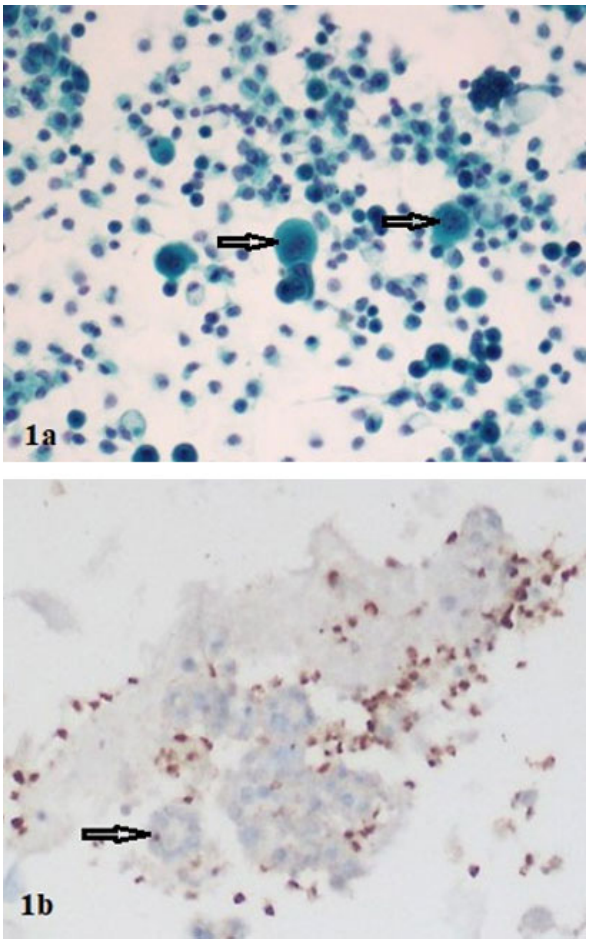

Figure 1. Cytomorphology and BAP1 immunohistochemistry. **a**, Atypical mesothelial cells in pleural fluid (Papanicolaou, objective x40). **b**, BAP1 loss in mesothelial cells. Background inflammatory cells with intact BAP1 (objective x40).

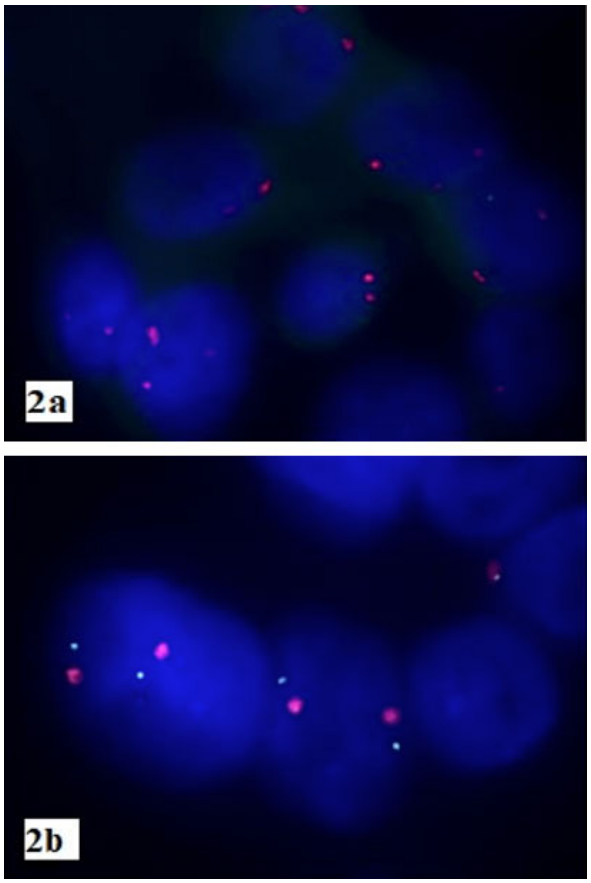

Figure 2. FISH analysis results of mesothelioma in pleural fluid. **a**, Mesothelioma cells with homozygous deletion of 9p21 by FISH with a *p16 (CDKN2A)* (green) and chromosome 9 (red)-specific probe (objective x100). **b**, *p16 (CDKN2A)* deletion-negative pattern in mesothelioma cells (objective x100).

itivity was found in 3 (21%) and only *p16* (*CDKN2A*) HD was detected in 2 (14%) cases. Both methods gave negative results in 2 cases (14%). No result could be obtained because FISH signal could not be obtained in two cell blocks due to technical reasons (Table II).

Discussion

In recent years, it has been recognized that when there is a loss of BAP1 and/or a homozygous deletion of the *p16* (*CDKN2A*) gene in small pleural biopsy and effusion samples from patients suspected of having mesothelioma, it almost definitively confirms the diagnosis[8,9]. Even though FISH analysis of *p16* (*CDKN2A*) HD provides more specific results than BAP1 IHC, it is costly, intricate, and demands specialized lab facilities. For cases that raise suspicions, initially integrating BAP1 IHC into cytological tests is a more practical approach. In our research, a 69% loss in BAP1 expression was found in effusion samples. The loss of BAP1 was 100% in biphasic and sarcomatoid types, but it was less pronounced in the epithelioid type. Published works[11-13] show BAP1 loss ranging between 57% and 83%, which is consistent with our findings.

Various studies[6,14,15] have indicated a higher prevalence of BAP1 loss in epithelioid mesothelioma than in biphasic and sarcomatoid types. In our collection of cases, the 2 biphasic mesotheliomas primarily exhibited epithelial characteristics, and only one case was of the sarcomatoid type. Despite the small sample size of these types, all 3 showed BAP1 loss, making it proportionally

Table I. Clinical and pathological data and *p16* (*CDKN2A*) FISH results of effusions diagnosed as atypical mesothelial proliferation.

Case	Age	Sex	Specimen type	Tissue diagnosis/type	BAP1 IHC[a]	*p16* (*CDKN2A*) FISH[b]
1	65	F	PF	Mesothelioma / Epithelioid	Negative	Positive
2	61	F	PF	Mesothelioma / Epithelioid	Negative	Negative
3	81	F	AF	Well differentiated papillary mesothelioma	Negative	Negative
4	35	F	AF	Well differentiated papillary mesothelioma	-	Negative
5	54	F	PF	Mesothelioma / Epithelioid	Positive	Positive
6	57	F	PF	Mesothelioma / Epithelioid	-	Positive
7	75	F	PF	Mesothelioma / Epithelioid	Positive	Positive
8	90	F	PF	Mesothelioma / Epithelioid	-	-
9	64	F	PF	Mesothelioma / Epithelioid	Positive	Positive
10	47	F	PF	Mesothelioma / Epithelioid	-	Positive
11	61	F	PF	Mesothelioma / Epithelioid	Negative	Negative
12	34	F	PF	Mesothelioma / Epithelioid	Positive	Negative
13	66	F	PF	Mesothelioma / Epithelioid	Positive	Negative
14	75	F	PF	Mesothelioma / Biphasic	Positive	Positive
15	54	F	PF	Mesothelioma / Biphasic	Positive	Positive
16	67	F	PF	Mesothelioma / Epithelioid	-	Negative
17	73	M	PF	Mesothelioma / Sarcomatoid	Positive	Positive
18	70	F	PF	Mesothelioma / Epithelioid	Positive	-
19	63	F	PF	Mesothelioma / Epithelioid	Positive	Positive
20	84	F	PF	Mesothelioma / Epithelioid	Negative	Positive
21	57	M	PF	Mesothelioma / Epithelioid	Positive	Negative

F, Female; M, Male; PF: pleural fluid; AF, abdominal fluid.
[a]Positive, Immunohistochemically, loss of BAP1 expression was detected; Negative, Immunohistochemically, no loss of BAP1 expression was detected.
[b]Positive, homozygous *p16/CDKN2A* deletion detected by FISH; negative, no homozygous *p16/CDKN2A* deletion detected by FISH.

more prevalent in the epithelioid type. WDPM is a non-invasive papillary tumor originating from mesothelial cells[16]. It is considered when diagnosing epithelioid mesothelioma with a papillary structure. A study by Lee et al[17], one of the few examining BAP1 expression in peritoneal WDPM, found BAP1 loss in 3 out of 8 cases. These specific cases also showed evidence of mesothelioma, either occurring simultaneously or subsequently. The absence of BAP1 was linked to malignancy. Notably, no BAP1 loss was found in any peritoneal WDPM cases, consistent with our findings. The study by Joseph et al[18] also reported negative results for all 6 cases they examined.

Table II. Comparison of BAP1 loss and Homozygous *p16/CDKN2A* deletion in pleural and peritoneal effusion.

	p16 (*CDKN2A*) FISH positive[b] n (%)	*p16* (*CDKN2A*) FISH negative n (%)	Total N (%)
BAP1 IHC positive[a]	7	3	10
BAP1 IHC negative	2	2	4
Total	9	5	14

IHC, Immunohistochemistry; FISH, fluorescence in situ hybridization
[a]Positive, Immunohistochemically, loss of BAP1 expression was detected; Negative, Immunohistochemically, no loss of BAP1 expression was detected.
[b]Positive, homozygous *p16/CDKN2A* deletion detected by FISH; negative, no homozygous *p16/CDKN2A* deletion detected by FISH.
BAP1 [BRCA1-associated protein (1)]

Loss of *p16* (*CDKN2A*), which is the most common genetic event observed in mesotheliomas, has been shown in approximately 22-74% of mesotheliomas by molecular studies[19]. Since the loss of *p16* (*CDKN2A*) can also be seen in metastatic carcinomas, it should be used in the pathology routine, not in the differential diagnosis of mesothelioma from metastases, but in the differentiation of benign reactive proliferations. In current guidelines[20,21], it is recommended to investigate the loss of *p16* (*CDKN2A*) with FISH in atypical mesothelial proliferations that cannot be diagnosed histopathologically or cytologically. The loss of *p16* (*CDKN2A*) detected in our series investigating the frequency of *p16* (*CDKN2A*) HD and its possible contribution to diagnosing mesothelioma cases in our region was within the rates reported in the literature by 58%. Loss of *p16* (*CDKN2A*) HD, which is reported[19,22] to be a poor prognostic marker, is observed more frequently in sarcomatoid and biphasic types, which are more aggressive types, compared to the epithelioid type. Wu et al[21] and Illei et al[23] reported loss of *p16* (*CDKN2A*) as 100% in sarcomatoid type, 87.5% and 84% in biphasic type, 55.6% and 69% in epithelioid type in their series. In our study, in accordance with the literature, a 57% loss of *p16* (*CDKN2A*) in epithelioid type was found in all of the biphasic and sarcomatoid type cases.

No loss of *p16* (*CDKN2A*) was observed in 2 peritoneal WDPM cases in our series. Similarly, it was reported that no loss of *p16* (*CDKN2A*) was found in the study of Lee et al[17], which included 5 cases.

Hamasaki et al[10] determined a 10% cut-off for the positivity of *p16* (*CDKN2A*) HD and suggested that cases with HD ≥30% showed a significantly worse prognosis. In our study, HD rate was ≥30% in 5/11 cases. However, since survival times were not evaluated, no comment could be made on the relationship between HD rate and prognosis. In the future, a large series comparing HD ratio and survival analyses will shed light on this issue.

In our lab, where we do not regularly use *p16* (*CDKN2A*) FISH for diagnosing mesothelioma, we believe it is essential to highlight certain aspects of the analysis process. One of the primary challenges in evaluating cell block sections using FISH is identifying mesothelial cells amidst inflammatory cells and cellular debris. For accurate results, we re-prepared small cell blocks from areas rich in atypical mesothelial cells. Only those cells with distinct features like large nuclei, clear nuclear boundaries, or discernible structural patterns were considered in the scoring process. Additionally, as Chevier et al[8] and Hamasaki et al[10] recommend, a minimum of 100 cells should be counted. This ensures we minimize the risk of false negatives due to scant cell presence and mitigate the influence of reactive mesothelial cell contamination.

BAP1 IHC should be used in clinically and radiologically suspicious fluids for mesothelioma, and if positive, it should be interpreted in favor of mesothelioma. In cases where it is negative, *p16* (*CDKN2A*) FISH should be applied, and if loss is detected, mesothelioma diagnosis should be made[6,9]. However, *p16* (*CDKN2A*) negativity does not rule out mesothelioma diagnosis, as seen in our study. In addition, Chevrier et al[8] reported that aggressive pleural or peritoneal sampling should be performed to detect *in situ* mesothelioma or early-stage invasive mesothelioma if the loss is observed in the effusion sample, even in one of the two methods in cases where no mass is detected clinically or radiologically.

Our study is the first series in which BAP1 loss and *p16* (*CDKN2A*) HD rates are investigated in the Southeastern Anatolia region of Turkey, where mesothelioma is endemic. It was observed that if these tests were performed on effusion samples diagnosed with atypical mesothelial proliferation, 86% of the cases could be interpreted as mesothelioma.

Limitations

This study presents several limitations. Firstly, the sample size is relatively small, particularly when considering the diverse subtypes of mesothelioma. This can limit the generalizability of the findings. Second, the study spanned a timeframe of three years, which may not be representative of potential shifts in diagnosis or prevalence. Third, while this study is the first in our endemic region, a comparison to other regions was not conducted. Fourth, technical challenges in FISH may have influenced results. Fifth, we did not evaluate survival times, preventing a prognosis linkage. Lastly, the approach was retrospective, lacking prospective follow-up and potential real-time interventions.

Conclusions

Early diagnosis of mesothelioma, which progresses with recurrent pleural effusion and whose diagnosis is usually made by tissue biopsies taken

by invasive procedures, is very important for the effectiveness of treatment. Asbestos exposure in areas where mesothelioma is endemic and/or the presence of proliferating mesothelial cells in cytological examination are important clues for diagnosis. In controversial cases, BAP1 IHC should be the first step in an ancillary test. Although it has cytology-specific limitations and difficulties, we think that *p16* (*CDKN2A*) FISH analysis applied to cell blocks in selected cases will contribute to the diagnosis.

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Conflict of Interest
The authors declare no conflict of interest.

Data Availability
The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' Contributions
Research concept and design: GA, SÖ. Data analysis and interpretation: GA. Collection and/or assembly of data: GA, SÖ. Writing the article: GA. Critical revision of the article: GA, SÖ. Final approval of the article: GA, SÖ.

Ethics Approval
All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee (Dicle University, decision No.: 260, date: 16.07.2020) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent
Written informed consent was obtained from all individual participants and/or their guardians.

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