Human Pathology (2020) 105, 1–8

ELSEVIER

Human PATHOLOGY

www.elsevier.com/locate/humpath

Original contribution

The potential utility of GATA binding protein 3 for diagnosis of malignant pleural mesotheliomas☆,☆☆,☆☆☆

Sarita Prabhakaran M.D [b], Ashleigh Hocking PhD [b], Chankyung Kim MBBS [a], Matthew Hussey BSc [a], Sonja Klebe MD, PhD, FRCPA, FFSc [a,b,*]

[a] *Department of Surgical Pathology, SA Pathology at Flinders Medical Centre, Adelaide, South Australia, SA 5042, Australia*
[b] *Department of Anatomical Pathology, College of Medicine and Public Health, Flinders University, Adelaide, South Australia, SA 5042, Australia*

Received 29 July 2020; revised 24 August 2020; accepted 24 August 2020

Available online 2 September 2020

Keywords:
GATA3;
Immunohistochemistry;
Mesothelioma;
Sarcomatoid;
Desmoplastic mesothelioma

Summary Malignant pleural mesothelioma is associated with asbestos exposure and poor outcomes. The usefulness of immunohistochemistry for diagnosis of sarcomatoid mesothelioma, especially the desmoplastic type, is limited, and more effective markers are required. GATA binding protein 3 (GATA3) has been suggested as a diagnostic marker for sarcomatoid mesothelioma. The potential usefulness of GATA3 for prognostication and its clinical and pathological correlations in different subtypes of mesothelioma have not been evaluated. We investigated the immunohistochemical labeling and associations for GATA3, BRCA1-associated protein 1 (BAP1), and Ki67 labeling in three major histological types of pleural malignant mesotheliomas. We examined 149 clinically annotated malignant mesotheliomas and assessed associations of GATA3 expression with clinical variables and prognosis. In addition, we labeled 10 cases of fibrous pleuritis with GATA3, all of which were negative. GATA3 was positive in 75 of 149 (50%) mesotheliomas, with the highest incidence of labeling seen in the sarcomatoid subtype (73%), compared with the biphasic (50%) and epithelioid (40%), mesotheliomas. A total of eight desmoplastic mesotheliomas showed labeling with GATA3. Patients whose tumors had sarcomatoid histology showed poorer survival than those with the other subtypes ($p < 0.001$), but overall GATA3 labeling did not have a statistically significant association with survival ($p = 0.602$). There was no association of GATA3 labeling and BAP1 status or Ki67 index. Our study includes the largest cohort of mesotheliomas that has been labeled for GATA3 to date. GATA3 is a useful marker for sarcomatoid mesothelioma, including the desmoplastic subtype. Discordance in

☆ Part of this study was published in Pathology (2020) Vol 52, S78

☆☆ Competing interestsS.K. prepares medicolegal reports for the courts of Australia on the diagnosis of lung disease, outside the submitted work. The other authors report no other conflicts of interest in this work.

☆☆☆ Funding/Support: This research was funded by the Professor Douglas Henderson AO bequest fund.

* Corresponding author. Department of Surgical Pathology, SA Pathology at Flinders Medical Centre, Adelaide, South Australia, Australia.
E-mail addresses: sarita.prabhakaran@flinders.edu.au (S. Prabhakaran), ash.hocking@flinders.edu.au (A. Hocking), chankyung.kim@sa.gov.au (C. Kim), matthew.hussey@sa.gov.au (M. Hussey), sonja.klebe@sa.gov.au (S. Klebe).

https://doi.org/10.1016/j.humpath.2020.08.005

GATA3 and BAP1 labeling of epithelioid and sarcomatoid components in the biphasic subtype is not uncommon.

1. Introduction

Malignant mesothelioma is a rare, but aggressive, cancer that arises most commonly in the pleura and also in the peritoneum, pericardium, and tunica vaginalis. Most cases are secondary to exposure to asbestos. The median survival is less than a year in untreated patients.

Immunohistochemical (IHC) markers are used for diagnosis, but their utility is limited in sarcomatoid/desmoplastic subtypes [1−4]. Given the prognostic and therapeutic implications, additional markers for sarcomatoid mesotheliomas would be useful.

GATA binding protein 3 (*GATA3*) plays a role in controlling gene expression and is also involved in oncogenesis [5]. GATA3 expression has been variably associated with prognosis in different malignancies [6,7].

BRCA1-associated protein 1 (BAP1) is a tumor suppressor gene involved in regulation of cell cycle, growth, and response to DNA damage. It is used to differentiate reactive mesothelial cells from malignant mesotheliomas [8]. BAP1 loss is more frequent in epithelioid and biphasic (45−81%) mesothelioma than in the sarcomatoid subtype (0−63%) [9], and loss of BAP1 favors a diagnosis of mesothelioma over adenocarcinoma [10]. Similar to GATA3, its impact on prognosis is conflicting in different tumors and even reported as variable in mesothelioma [9,11].

GATA3 was initially used for identifying breast and urothelial carcinomas, but recent studies suggest its use for diagnosis of mesothelioma, especially sarcomatoid mesothelioma, including desmoplastic mesothelioma [12−15]. Miettinen et al. [14] showed 37 of 64 (58%) mesotheliomas were positive for GATA3. Berg and Churg [12] and Terra et al [15] have earlier showed GATA3 IHC labeling in 19 of 19 (100%) and 63 of 64 (98%) sarcomatoid mesotheliomas with the L50-823 GATA3 antibody clone. Labeling was not specific for sarcomatoid mesothelioma as these studies also reported labeling in sarcomatoid carcinomas (2/13 [15%] and 15/32 [47%], respectively) [12,15]. Data are inconsistent with Davis et al [16] reporting no labeling with the same antibody clone in 13 cases of epithelioid, 1 case of biphasic, and 1 case of sarcomatoid mesothelioma. These three studies together account for GATA3 labeling in 82 sarcomatoid mesotheliomas. The prognostic significance of labeling of GATA3 has not been evaluated in mesothelioma.

Sarcomatoid mesothelioma, especially of the desmoplastic variant, predicts poor survival and can be difficult to diagnose [3,4]. Sarcomatoid mesotheliomas may closely resemble other sarcomatoid tumors such as monophasic synovial sarcoma, solitary fibrous tumor, epithelioid sarcoma, and sarcomatoid cancer that are part of the differential diagnosis of pleural mesotheliomas, particularly the sarcomatoid subtype [1]. Most sarcomatoid/desmoplastic pleural mesotheliomas are strongly positive for cytokeratins, whereas most sarcomas are keratin negative. However, there are some keratin-positive sarcomas, such as angiosarcoma and monophasic synovial sarcoma, that make diagnosis difficult, and caution is advised [17]. In addition, the differentiation between desmoplastic mesothelioma and benign conditions such as fibrous pleuritis can be challenging. The presence of spindled cells around fat spaces could be mistaken for invasion and therefore assumed malignant [2]. GATA3 is not expected to label benign proliferations in the pleura including fibrous pleuritis [18]. Hence, there is a need for a marker that can aid in diagnosis by differentiating sarcomatoid/desmoplastic mesotheliomas from the aforementioned pathologies.

We here investigate the usefulness of GATA3 immunohistochemistry for diagnosis and prognosis of epithelioid, sarcomatoid (including desmoplastic), and biphasic mesothelioma and correlate with labeling for BAP1 and Ki67, as the mitotic count has been associated with GATA status and prognosis [19]. We also assessed GATA3 labeling in fibrous pleuritis and discordance in IHC labeling among the epithelioid and sarcomatoid components of biphasic mesotheliomas.

2. Materials and methods

2.1. Patient recruitment

A cohort of 149 patients was recruited, diagnosed at the Department of Anatomical Pathology at Flinders Medical Centre between the years of 1991 and 2013. Patients were included based on the histological diagnosis of pleural mesothelioma, availability of adequate tissue blocks, and clinical follow-up information. Tissue from 10 benign fibrous pleuritis cases was also retrieved. Diagnostic clinical procedures of cases were performed in a National Association of Testing Authorities, Australia (NATA)-approved laboratory using Quality assurance program (QAP)-validated tests. Work was approved by the Southern Adelaide Clinical Human Research Ethics Committee (approval number: HREC/19/SAC/28).

2.2. IHC analysis

All IHC labeling was performed on a Ventana Benchmark Ultra; Ventana, Tucson, AZ, USA Immunostainer.

The primary antibody to GATA3 was from Cell Marque (Rocklin, CA) mouse anti-GATA3 (clone L50-823) diluted 1:50, BAP1 (sc-28383; Santa Cruz Biotechnology, Texas, USA) at 1:100, Podoplanin (D2-40) (Cell Marque) at 1:25, Ki67 prediluted rabbit monoclonal antibody (clone 30-9, Ventana, Tucson, AZ) and the Ventana UltraView DAB detection kit.

2.3. Histological scoring

Slides were independently reviewed by 2 pathologists. A score from 0 to 3 was assigned for diffuseness of tumor nuclei staining (0 = <1%, 1 = 1–25%, 2 = 25–50%, 3 = >50%). Intensity was scored as 0 for no labeling, 1 for weak labeling, 2 for moderate labeling, and 3 for strong labeling. Diffuseness and intensity scores were added to provide a maximum score of 6, with scores of 2 and higher denoting positive GATA3 IHC labeling selected from the core with the highest value [12,20].

BAP1 was defined as positive (retained) if there was nuclear labeling in any number of tumor cells. For Ki67, a cutoff of 25% labeling was used to define high and low labeling as described previously in the study by Pillai et al [21].

2.4. Statistical analysis

Cohen's kappa was used to evaluate the inter-rater variation between the two pathologists' GATA3 scores computed using SPSS version 23, (IBM Corp, Armonk, NY) software. Survival was calculated as the number of months between diagnosis and death of the patient or last follow-up in the case of patients still alive. If a patient was still alive at the last follow-up, cases were censored. The statistical association between clinicopathological characteristics and GATA3 expression was analyzed using the chi-square test or Fisher's exact test (two-tailed test). Differences in survival were calculated using the Kaplan-Meier method, and a log-rank test was used to evaluate statistical differences. Univariate and multivariate analyses were performed using a Cox proportional hazards model to assess the influence of each variable on survival. A p value of less than 0.05 was considered to indicate statistical significance. Age, sex, and histological subtype were included in the multivariate model as they are universally accepted prognostic factors in malignant mesothelioma. Statistical analyses performed in this study were conducted using SPSS, version 23, software.

3. Results

3.1. Patient characteristics

Tumor tissue from 100 patients was assessed on Tissue microarray (TMA) sections (4 cores of 1 mm each to reach concordance with the results from whole sections) [22], whereas whole sections of the remaining 49 patients' tissues were examined. There were 87 epithelioid, 40 sarcomatoid, and 22 biphasic pleural mesotheliomas. Of the sarcomatoid mesotheliomas, eight were classified as desmoplastic. Table 1 summarizes the patient characteristics for the cohort. The mean survival time for all patients in this cohort was 15 months, and individually, the mean survival was 19, 12, and 8.6 months for the epithelioid, biphasic, and sarcomatoid subtypes, respectively.

Table 1 Patient information.

Variables	n (%)
Total cases in TMA	149 (100%)
Age at diagnosis, median years (range)	74 years (47–97)
Gender	
Male	110 (74%)
Female	39 (26%)
Histological subtype	
Epithelioid	87 (58%)
Sarcomatoid	40 (27%)
Biphasic	22 (15%)
Ki-67 expression	
Lower than 25% (low)	38 (41%)
Higher than 25% (high)	55 (59%)
BAP1 IHC expression	
Retained	70 (60%)
Loss	47 (40%)
GATA3 IHC expression	
Present	75 (50%)
Absent	74 (50%)

Abbreviations: BAP1, BRCA1-associated protein 1; GATA3, GATA binding protein 3; IHC, immunohistochemical; TMA, tissuemicroarray.

3.2. Immunohistochemistry

GATA3 IHC positivity was seen in 75 of 149 (50%) mesotheliomas (Fig. 1A-C), with an incidence of 73%, 50%, and 40% among the sarcomatoid, biphasic, and epithelioid mesotheliomas, respectively (Table 2). A κ value of 0.82 indicated good agreement between pathologists. GATA3 labeling was heterogenous in some of the tumors, with some cells showing weak or no labeling and others revealing good nuclear labeling. All 8 desmoplastic subtypes showed high expression of GATA3, with 4 of these 8 attaining scores higher than 4. We checked for the incidence of expression of D2-40 in the sarcomatoid mesotheliomas as this antibody is often used in the diagnostic workup of these tumors. We have found that 20% of the sarcomatoid mesotheliomas in the TMA and 28% in the full sections label with D2-40, which is in line with previous reports [23]. We detected concordant labeling of GATA3 in both histological components of the biphasic subtype in 17 of 22 (77%) and discordance in 5 of 22 (23%) mesotheliomas (Table 3). Sections with fibrous pleuritis did not reveal any labeling with GATA3, except among

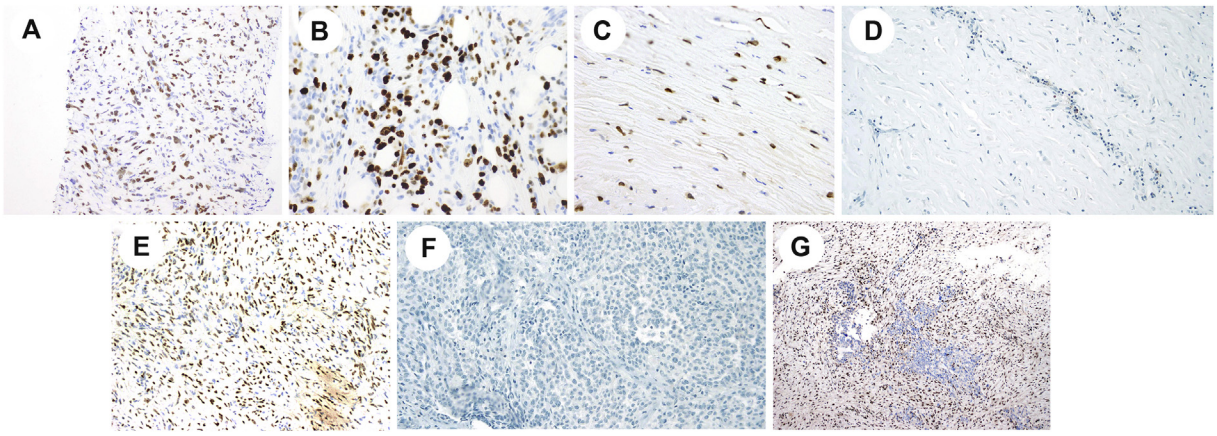

Fig. 1 IHC expression in pleural mesothelioma and fibrous pleuritis. GATA3 IHC expression in (A) sarcomatoid, (B) epithelioid, and (C) desmoplastic sarcomatoid (all positive IHC expression) and (D) fibrous pleuritis (negative IHC expression). BAP1 IHC expression in (E) sarcomatoid (retained expression), (F) epithelioid (loss of expression), and (G) biphasic (discordance) mesothelioma (magnification, ×200). BAP1, BRCA1-associated protein 1; GATA3, GATA binding protein 3; IHC, immunohistochemical.

Table 2 GATA3, BAP1, and Ki67 distribution among subtypes of pleural malignant mesothelioma.

Total score	Total	Epithelioid	Sarcomatoid	Biphasic
GATA3 immunohistochemistry				
0–1	74	52 (60%)[a]	11 (27%)	11 (50%)
2–6	75	35 (40%)	29 (73%)	11 (50%)
BAP1 status				
BAP1 loss	47	36 (59%)	4 (12%)	7 (32%)
BAP1 retained	70	25 (41%)	30 (88%)	15 (68%)
Ki67				
Low	38	18 (36%)	9 (43%)	11 (50%)
High	55	32 (64%)	12 (57%)	11 (500%)

BAP1 results were available only in 117 cases.
Ki67 results were available only in 93 cases.
Abbreviations: BAP1, BRCA1-associated protein 1; GATA3, GATA binding protein 3.
[a] Percentages indicated are calculated for individual histology subtypes.

inflammatory cell infiltrates (Fig. 1D). BAP1 IHC loss was identified in 47 of 117 (40%) mesotheliomas distributed among 36 of 61 (59%) epithelioid, 4 of 34 (12%) sarcomatoid, and 7 of 22 (32%) biphasic subtypes. (Fig. 1E–G). As expected, BAP1 loss was higher in the epithelioid subtype than in other histologies. Within the biphasic group, concordance between the histological components in IHC labeling was seen in 82% and discordance in 18% cases. Ki67 discordance was seen only in 2 biphasic mesotheliomas, wherein labeling was observed only in the epithelioid component (Table 3).

3.3. Clinicopathological correlations of GATA3

There was a statistically significant association of positive GATA3 expression with the sarcomatoid subtype ($p = 0.003$) compared with other subtypes. No associations were found with GATA3 positivity and gender ($p = 0.327$), age at diagnosis ($p = 0.805$), and Ki67 ($p = 0.417$). BAP1 retention was associated with GATA3 positivity ($p = 0.045$) (Table 4). This may be an indication of the histological subtype because BAP1 loss was associated with an epithelioid phenotype ($p < 0.001$). Ki67 labeling was not associated with either subtype ($p = 0.408$) (not shown).

3.4. GATA3 and survival analysis

GATA3-positive cases had a trend to better prognosis (although not statistically significant), with a median survival of 12 months compared with 10 months for all tumor types ($p = 0.602$) (Fig. 2A). The sarcomatoid subtype

Table 3 GATA3 and BAP1 distribution among 22 biphasic pleural malignant mesotheliomas.

Antibodies	Concordant IHC results		Discordant IHC results	
	E & S retained	E & S loss	E loss & S retained	E retained & S loss
BAP1 immunohistochemistry	15	3	3	1
GATA3 immunohistochemistry	6	11	4	1
Ki67	0	0	0	2

Abbreviations: BAP1, BRCA1-associated protein 1; E, epithelioid; GATA3, GATA binding protein 3; IHC, immunohistochemical; S, sarcomatoid.

Table 4 Correlations of GATA3 with clinicopathological parameters in malignant mesothelioma.

Variables	Total	Positive	Negative	*p* value
	149	75	74	
Age at diagnosis (median age = 74 years)				
<74 years	74	38 (51%)	36 (49%)	0.805
>74 years	75	37 (49%)	38 (51%)	
Ki-67				
High	55	20 (36%)	35 (64%)	0.417
Low	38	17 (45%)	21 (55%)	
NA	56	NA	NA	
BAP1 immunohistochemistry				
Loss	47	16 (34%)	31 (66%)	0.045
Retained	70	37 (53%)	33 (47%)	
NA	32	NA	NA	
Gender				
Male	110	58 (53%)	52 (47%)	0.327
Female	39	17 (44%)	22 (56%)	
Histology				
Epithelioid	87	35 (40%)	52 (60%)	
Sarcomatoid	40	29 (73%)	11 (27%)	0.003[a]
Biphasic	22	11 (50%)	11 (50%)	

Results not available in 32 cases for BAP1 immunohistochemistry and 56 cases for Ki-67.
Abbreviations: BAP1, BRCA1-associated protein 1; GATA3, GATA binding protein 3.
[a] Significant values.

Table 5 Univariate analysis for prognostic indications in malignant mesothelioma.

Covariate	*p*
Age (relative to the median age of 74 years)	0.286
Gender	0.009
Subtype	<0.001
Ki67	0.27
GATA3 IHC result	0.608
BAP1	0.995

Abbreviations: BAP1, BRCA1-associated protein 1; GATA3, GATA binding protein 3; IHC, immunohistochemical.

(irrespective of IHC labeling) had worse survival, with a median of 5.5 months compared with 15 and 8.5 months in patients with the epithelioid and biphasic subtypes, respectively ($p < 0.001$) (Fig. 2B). A difference in survival between the histological subtypes based on GATA status was not seen. Women overall had better prognosis in line with the published data [24]. Interestingly, women whose tumors were labeled with GATA3 had significantly better median survival of 24 months than men with GATA3 IHC labeling (9 months) ($p = 0.031$) (Fig. 2C). Ki67 was not significantly associated with survival ($p = 0.258$) (data not shown).

Univariate analysis using the Cox proportional hazards model for multiple factors such as age at diagnosis, gender,

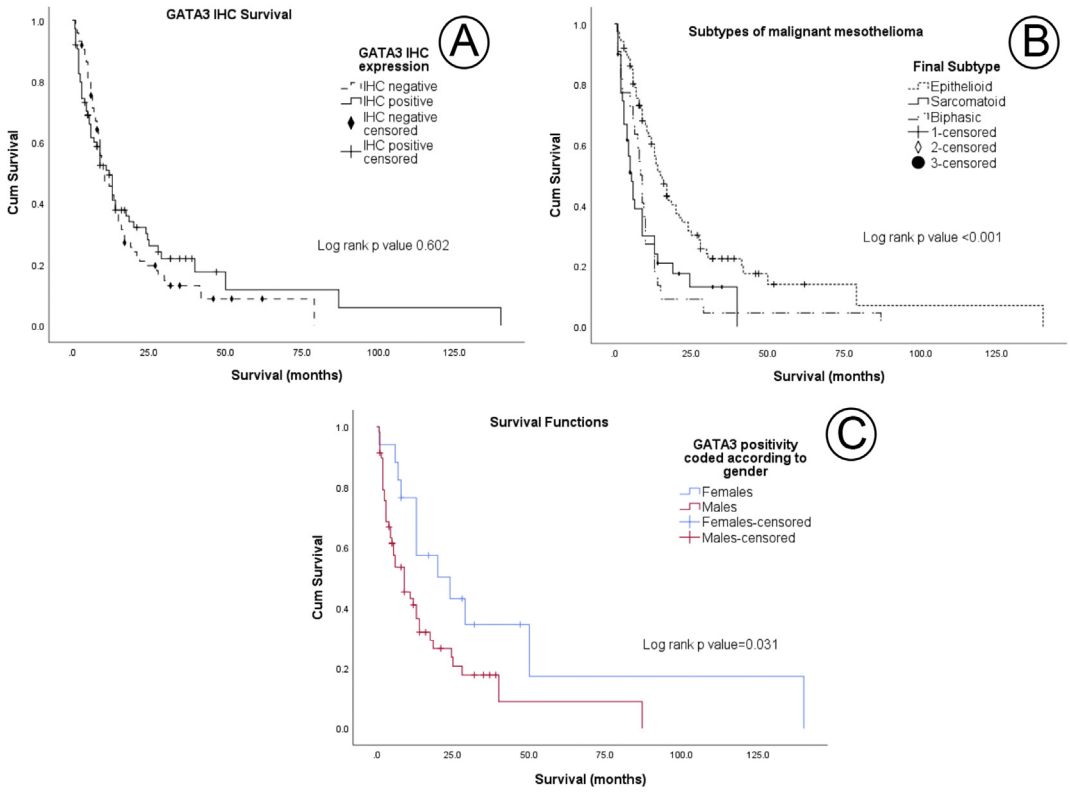

Fig. 2 Kaplan-Meier survival curves for (A) GATA3 IHC expression, (B) histological subtypes, and (C) GATA3 positivity in both genders. GATA3, GATA binding protein 3; IHC, immunohistochemical.

Table 6 Multivariate analysis for prognostic indications in malignant mesothelioma.

Variables	HR	*P*	95% CI
Gender			
Female	1.0 (reference)		
Male	1.483	0.124	0.897−2451
GATA3 (immunohistochemistry)			
Low	1.0 (reference)		
High	0.788	0.304	0.501−1.241
Subtype			
Epithelioid	1.0 (reference)		
Sarcomatoid	2.61	0.01*	1.493−4.565
Biphasic	1.788	0.042*	1.021−3.131
BAP1 (immunohistochemistry)			
Retained	1.0 (reference)		
Loss	1.334	0.211	0.849−2.096

The symbol * denotes variables that were associated with poor survival by multivariate analysis.
Abbreviations: BAP1, BRCA1-associated protein 1; CI, confidence interval; GATA3, GATA binding protein 3; HR, hazard ratio.

GATA3 IHC positivity, histological subtype, Ki67, and BAP1 showed that male gender and histology were significantly associated with poor survival in the cohort ($p = 0.009$ and $p < 0.001$) (Table 5). Multivariate analysis showed that the sarcomatoid and biphasic subtypes were independent prognostic markers of poorer survival ($p = 0.01$ and $p = 0.042$, respectively). GATA3 was not associated with prognosis overall ($p = 0.304$) (Table 6). BAP1 was not associated with survival in this cohort ($p = 0.995$) (data not shown).

4. Discussion

We showed GATA3 labeling in 50% (75/149) cases of our cohort of pleural malignant mesotheliomas. Previous reports suggest 58% of mesotheliomas (that included epithelioid and sarcomatoid mesotheliomas) can label with GATA3, as can synovial sarcomas (21%), epithelioid sarcomas (18%), leiomyosarcomas (8%), angiosarcomas (6%), and undifferentiated sarcomas (4%) [14]. Two other studies investigated GATA3 labeling in 19 and 64 sarcomatoid mesotheliomas [12,15]. Berg and Churg [12] found GATA3 labeling in 100% of sarcomatoid mesotheliomas, and Terra et al [15] found labeling in 98% sarcomatoid mesotheliomas. However, Davis et al [16] found no GATA3 labeling in 15 mesotheliomas that included 1 sarcomatoid mesothelioma. GATA3 IHC positivity in the epithelioid mesotheliomas in our cohort (35/87, ie, 40%) was within the reported range (33%) by similar studies [14,25].

The differential diagnosis of sarcomatoid mesothelioma includes primary chest wall sarcomas, eg, synovial sarcomas, epithelioid hemangioendothelioma, solitary fibrous tumors, angiosarcoma of the pleura, and metastatic tumors that mimic sarcomatoid mesotheliomas histologically [2]. Most sarcomatoid/desmoplastic mesotheliomas are strongly positive for cytokeratins, whereas nearly all sarcomas are keratin negative. However, there are some keratin-positive sarcomas, such as angiosarcoma and monophasic synovial sarcoma [17]. In addition, the diagnosis and differentiation of desmoplastic mesothelioma and fibrous pleuritis can be notoriously difficult [2−4]. Our study has shown labeling in 29 of 40 (73%) of sarcomatoid mesothelioma cases including those with desmoplastic sarcomatoid histology.

GATA3 IHC results reveal that it is highly sensitive but not very specific. Miettinen et al [14] showed labeling not only in 37 of 64 mesotheliomas but also in 2 of 30 angiosarcomas, 3 of 17 epithelioid sarcomas, 5 of 24 synovial sarcomas, and 2 of 49 sarcomatoid/undifferentiated sarcomas. Terra et al [15] showed labeling in 63 of 64 sarcomatoid mesotheliomas and 2 of 13 sarcomatoid carcinomas of the lung [14]. Howbeit, GATA3 can be used as an additional IHC marker as part of a panel wherein positive labeling in the relevant clinical context can support a diagnosis of sarcomatoid mesothelioma. It could also be crucial in differentiating fibrous pleuritis from the desmoplastic subtype as GATA3 did not label the cases with fibrous pleuritis we examined.

GATA3 mutations are predicted to influence protein production, depending on the location of the mutation, and are independent prognostic factors for overall survival [26]. Some mutant GATA3 proteins do not localize fully to the nucleus but are located at the cytoplasm, revealing a pattern of punctate expression [27]. This probably explains some of the heterogenous and granular staining we have seen with GATA3 expression in tissues that could affect the interpretation of IHC results.

A difference in survival between the histological subtypes based on GATA3 status was not seen. This could be attributed to the sample size of cases in our cohort. Perhaps, a larger study would reveal better prognosis for GATA3-positive sarcomatoid mesotheliomas. We also noted better prognosis for women whose tumors were labeled with GATA3. In view of the small number of women in our cohort, the prognostic significance of this marker is currently uncertain.

An abstract at the recent USCAP (2020) has shown 82% concordance and 18% discordance in GATA3 IHC expression within the components of biphasic mesotheliomas [28]. In our hands, there was 77% concordance and 23% discordance, respectively. The occurrence of discordance in GATA3 labeling in biphasic mesothelioma should not initiate a change in histological classification of these tumors.

BAP1 loss on IHC analysis favors a diagnosis of malignant mesothelioma over that of adenocarcinoma. Researchers have found differences in associations of survival with BAP1 loss, and some found an association with more favorable outcomes [8,11]. On the other hand, BAP1 loss

was not statistically associated with survival in other studies and also in our cohort [29].

We earlier found an association with poor prognosis in patients with both cytological and surgical specimens [30]. In the previous study, BAP1 loss was seen in 47 of 117 mesotheliomas (40%) and a higher proportion of epithelioid cases (77%). However, in this cohort, BAP1 loss was not associated with prognosis regardless of the subtype, and this could be due to inclusion of a high proportion of sarcomatoid mesotheliomas and the fact that for prognostic purposes, we accepted any positive labeling of BAP1 as retained. In addition, labeling in any component of the biphasic mesotheliomas was inferred as positive labeling.

Within the biphasic mesothelioma group, Schulte [28] identified 83% concordance and 17% discordance in BAP1 labeling. Our results were very similar, with 82% and 18%, respectively. Once again, discordance in labeling of BAP1 in different tissue components of biphasic mesotheliomas does not warrant a change in diagnosis. However, it is unclear whether these cases should be regarded as immunohistochemistry positive or negative as this could affect prognostication and further genetic referrals.

There was also no association of GATA3 expression with Ki67, which is intriguing as high GATA3 expression had been significantly associated with a higher mitotic count in soft-tissue sarcomas [19].

GATA3 expression as assessed by multivariate Cox regression analysis was not an independent predictor of survival. Similar conclusions have been reached in larger cohort studies of breast carcinomas [31−33].

Kaplan-Meier survival curves confirm that sarcomatoid mesotheliomas have poorer survival. Interestingly, tumors of 44% of the women in our cohort were labeled with GATA3, as opposed to 53% in men, and there was an association with better survival among women whose tumors were labeled for GATA3. It would be valuable to study GATA3 expression in a larger cohort of women with malignant mesotheliomas and document hormonal status to explore significant differences in survival.

5. Conclusion

In conclusion, all histological subtypes of malignant mesotheliomas can positively label with GATA3. Labeling was most common in the sarcomatoid subtype, at 73%, suggesting GATA3 may be a useful additional diagnostic marker for sarcomatoid mesotheliomas, especially desmoplastic mesotheliomas. GATA3 facilitates the differentiation of fibrous pleuritis from desmoplastic sarcomatoid mesothelioma. Discordance in labeling for GATA3 in different components of biphasic mesothelioma does not warrant reclassification of mesotheliomas especially when differentiating them from other histological mimics. GATA3 was not an independent prognostic marker for survival in pleural mesotheliomas.

Acknowledgments

The authors gratefully acknowledge the technical assistance rendered by Sarah Minns. S.K. contributed to conceptualization and design. C.K. and S.P. contributed to collection of data, analysis, and interpretation. A.H. and M.H. contributed to methodology. C.K., S.P., and S.K. contributed to manuscript writing. S.K. contributed to supervision.

References

[1] Galateau-Salle F, Churg A, Roggli V, Travis WD. World health organization committee for tumors of the P. The 2015 world health organization classification of tumors of the pleura: advances since the 2004 classification. J Thorac Oncol 2016;11:142−54.
[2] Husain AN, Colby TV, Ordonez NG, et al. Guidelines for pathologic diagnosis of malignant mesothelioma 2017 update of the consensus statement from the international mesothelioma interest group. Arch Pathol Lab Med 2018;142:89−108.
[3] Klebe S, Brownlee NA, Mahar A, et al. Sarcomatoid mesothelioma: a clinical-pathologic correlation of 326 cases. Mod Pathol 2010;23:470−9.
[4] Marchevsky AM, LeStang N, Hiroshima K, et al. The differential diagnosis between pleural sarcomatoid mesothelioma and spindle cell/pleomorphic (sarcomatoid) carcinomas of the lung: evidence-based guidelines from the International Mesothelioma Panel and the MESOPATH National Reference Center. Hum Pathol 2017;67:160−8.
[5] Wan YY. GATA3: a master of many trades in immune regulation. Trends Immunol 2014;35:233−42.
[6] Gonzalez RS, Wang J, Kraus T, Sullivan H, Adams AL, Cohen C. GATA-3 expression in male and female breast cancers: comparison of clinicopathologic parameters and prognostic relevance. Hum Pathol 2013;44:1065−70.
[7] Inoue S, Mizushima T, Fujita K, et al. GATA3 immunohistochemistry in urothelial carcinoma of the upper urinary tract as a urothelial marker and a prognosticator. Hum Pathol 2017;64:83−90.
[8] McGregor SM, Dunning R, Hyjek E, Vigneswaran W, Husain AN, Krausz T. BAP1 facilitates diagnostic objectivity, classification, and prognostication in malignant pleural mesothelioma. Hum Pathol 2015;46:1670−8.
[9] Farzin M, Toon CW, Clarkson A, et al. Loss of expression of BAP1 predicts longer survival in mesothelioma. Pathology 2015;47:302−7.
[10] Cigognetti M, Lonardi S, Fisogni S, et al. BAP1 (BRCA1-associated protein 1) is a highly specific marker for differentiating mesothelioma from reactive mesothelial proliferations. Mod Pathol 2015;28:1043−57.
[11] Luchini C, Veronese N, Yachida S, et al. Different prognostic roles of tumor suppressor gene BAP1 in cancer: a systematic review with meta-analysis. Genes Chromosomes Cancer 2016;55:741−9.
[12] Berg KB, Churg A. GATA3 immunohistochemistry for distinguishing sarcomatoid and desmoplastic mesothelioma from sarcomatoid carcinoma of the lung. Am J Surg Pathol 2017;41:1221−5.
[13] Lin F, Liu H. Immunohistochemistry in undifferentiated neoplasm/tumor of uncertain origin. Arch Pathol Lab Med 2014;138:1583−610.
[14] Miettinen M, McCue PA, Sarlomo-Rikala M, et al. GATA3: a multispecific but potentially useful marker in surgical pathology: a systematic analysis of 2500 epithelial and nonepithelial tumors. Am J Surg Pathol 2014;38:13−22.
[15] Terra S, Roden A, Yi E, Aubry C, Boland J. Utility of immunohistochemistry for MUC4 and GATA3 to aid in the distinction of sarcomatoid mesothelioma from sarcomatoid carcinoma. NEW YORK,

NY 10013-1917 USA: LABORATORY INVESTIGATION: NATURE PUBLISHING GROUP 75 VARICK ST, 9TH FLR; 2019.
[16] Davis DG, Siddiqui MT, Oprea-Ilies G, et al. GATA-3 and FOXA1 expression is useful to differentiate breast carcinoma from other carcinomas. Hum Pathol 2016;47:26–31.
[17] Ali G, Bruno R, Fontanini G. The pathological and molecular diagnosis of malignant pleural mesothelioma: a literature review. J Thorac Dis 2018;10:S276–84.
[18] Ramirez AS, Patel S, Liu Y, et al. Expression of GATA-3 in benign mesothelial cells. Am J Clin Pathol 2015;144. A093-A093.
[19] Haraguchi T, Miyoshi H, Hiraoka K, et al. GATA3 expression is a poor prognostic factor in soft tissue sarcomas. PloS One 2016;11: e0156524.
[20] Kjaer-Frifeldt S, Lindebjerg J, Brunner N, Garm Spindler KL, Jakobsen A. Limitations of tissue micro array in Duke's B colon cancer. APMIS 2012;120:819–27.
[21] Pillai K, Pourgholami MH, Chua TC, Morris DL. Prognostic significance of Ki67 expression in malignant peritoneal mesothelioma. Am J Clin Oncol 2015;38:388–94.
[22] Kao SC, Lee K, Armstrong NJ, et al. Validation of tissue microarray technology in malignant pleural mesothelioma. Pathology 2011;43: 128–32.
[23] Hinterberger M, Reineke T, Storz M, Weder W, Vogt P, Moch H. D2-40 and calretinin—a tissue microarray analysis of 341 malignant mesotheliomas with emphasis on sarcomatoid differentiation. Mod Pathol 2007;20:248–55.
[24] Taioli E, Wolf AS, Camacho-Rivera M, Flores RM. Women with malignant pleural mesothelioma have a threefold better survival rate than men. Ann Thorac Surg 2014;98:1020–4.
[25] Ordonez NG, Sahin AA. Diagnostic utility of immunohistochemistry in distinguishing between epithelioid pleural mesotheliomas and breast carcinomas: a comparative study. Hum Pathol 2014;45: 1529–40.
[26] Gaynor KU, Grigorieva IV, Allen MD, et al. GATA3 mutations found in breast cancers may be associated with aberrant nuclear localization, reduced transactivation and cell invasiveness. Horm Canc 2013; 4:123–39.
[27] Du F, Yuan P, Wang T, et al. The significance and therapeutic potential of GATA3 expression and mutation in breast cancer: a systematic review. Med Res Rev 2015;35:1300–15.
[28] Schulte J. Immunohistochemical biomarkers in biphasic malignant mesothelioma: a multi-institutional analysis. Abstracts from USCAP 2020: pulmonary, mediastinum, pleura, and peritoneum pathology (1869-1980). Mod Pathol 2020;33:1954.
[29] Singhi AD, Krasinskas AM, Choudry HA, et al. The prognostic significance of BAP1, NF2, and CDKN2A in malignant peritoneal mesothelioma. Mod Pathol 2016;29:14–24.
[30] Pulford E, Huilgol K, Moffat D, Henderson DW, Klebe S. Malignant mesothelioma, BAP1 immunohistochemistry, and VEGFA: does BAP1 have potential for early diagnosis and assessment of prognosis? Dis Markers 2017;2017:1310478.
[31] Gulbahce HE, Sweeney C, Surowiecka M, Knapp D, Varghese L, Blair CK. Significance of GATA-3 expression in outcomes of patients with breast cancer who received systemic chemotherapy and/or hormonal therapy and clinicopathologic features of GATA-3-positive tumors. Hum Pathol 2013;44:2427–31.
[32] Ni YB, Tsang JY, Chan SK, Tse GM. GATA-binding protein 3, gross cystic disease fluid protein-15 and mammaglobin have distinct prognostic implications in different invasive breast carcinoma subgroups. Histopathology 2015;67:96–105.
[33] Voduc D, Cheang M, Nielsen T. GATA-3 expression in breast cancer has a strong association with estrogen receptor but lacks independent prognostic value. Canc Epidemiol Biomarkers Prev 2008;17:365–73.