Original Article

An Evaluation of Special AT-rich Sequence-binding Protein 2 Expression in Primary Epithelial Tumors and Metastatic Tumors of the Ovary

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Abstract

Background: Ovarian cancer is the second most common gynecologic cancer in women. Differential diagnosis between primary and metastatic neoplasms can be problematic in some cases. The special AT-rich sequence-binding protein 2 (SATB2) is a nuclear matrix-associated protein that is important for growth and development. SATB2 has been shown to be a sensitive and highly specific marker for colorectal carcinomas (CRCs). SATB2 expression has also been reported in lung, breast, pancreas, renal, laryngeal, esophageal carcinomas and bone cancers. In this study, we aimed to evaluate SATB2 expression in primary epithelial and metastatic ovarian tumors and determine its significance in differentiating between subtypes. **Material and Methods:** The study group comprised 148 cases of primary epithelial tumor and 29 cases of metastatic ovarian tumor. Immunohistochemical analysis was performed by applying SATB2 on paraffin blocks. **Results:** SATB2 expression was identified in 54.5% of mucinous carcinomas, 51.7% of endometrioid carcinomas, 18.2% of high-grade serous carcinomas, 17.9% of borderline mucinous tumors, 6.7% of borderline serous tumors, and 51.7% of metastatic ovarian tumors. SATB2 expression did not show specificity for any of the subgroups. Metastatic ovarian tumors originating from the colon, breast, upper gastrointestinal tract, and appendix also showed SATB2 expression at different rates. All of the metastatic CRCs showed SATB2 positivity. **Conclusion:** It must be considered that primary carcinomas and metastatic carcinomas may manifest varying levels of SATB2 expression with different intensity and extensiveness. Extensive and strong SATB2 expression indicates metastatic colon carcinoma, consistent with the literature. Further comprehensive studies are needed in order to investigate SATB2 specificity for different subtypes.

Keywords: *Metastatic, ovarian tumor, primary, special AT-rich sequence-binding protein 2*

Introduction

Ovarian cancer is the sixth most common cancer in women and the seventh most common cause of cancer-related death worldwide.[1] It is also the second most common gynecologic cancer.[2] In general, the disease is more prevalent in industrial countries with low parity. The prevalence rates of ovarian cancer increase with age.[3]

Malignant ovarian tumors are categorized in three main histopathologic tumor groups of different etiology, biology, and clinical behavior. These are: surface epithelial-stromal tumors, sex cord-stromal tumors, and germ cell tumors. Surface epithelial-stromal tumors, which are generally called "ovarian carcinomas," constitute 95% of all ovarian cancers.[4]

It is difficult to determine the rates of metastatic disease in the ovaries; however, they are thought to constitute 6%–7% of all ovarian cancers.[5] It is crucial to establish a differential diagnosis between primary and metastatic tumors because their prognoses and treatments are completely different. The macroscopic, microscopic, and immunohistochemical (IHC) characteristics are fundamentally important in the differential diagnosis of these tumors, but all of these characteristics may overlap in certain cases, making a definitive histopathologic diagnosis impossible.[6]

Special AT-rich sequence-binding protein 2 (SATB2) is a novel DNA-binding protein and nuclear transcription factor of 733 amino acids.[7-9] SATB2 is related to gene transcription and the rearrangement of chromatin.[10,11]

Previous studies have demonstrated that SATB2 plays an important role in brain development, craniofacial modeling, and osteoblast differentiation.[12-16]

How to cite this article: Oz E, Bozdag Z, Tepe NB, Bayramoglu Z, Dizibuyuk OF, Karakok M. An evaluation of special AT-rich sequence-binding protein 2 expression in primary epithelial tumors and metastatic tumors of the ovary. Clin Cancer Investig J 2019;8:57-63.

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Access this article online

Website: www.ccij-online.org

DOI: 10.4103/ccij.ccij_26_19

Quick Response Code:

IHC studies have shown that SATB2 is strongly expressed not only in the normal and neoplastic osteoblastic tissue, but also in the normal colorectal and appendiceal epithelia.[17] Furthermore, SATB2 is related to stem cell development.[18] It has been shown that loss of or low expression of SATB2 is a sign of malignant behavior and poor prognosis in colorectal cancer.[19] Since the discovery of SATB2 in 2003,[15] there has been a rapid increase in the number of studies investigating the role of this protein.[8-10] Evidence on its relationship with cancer has been gradually accumulating. Colorectal, head and neck, and bone cancers have been associated with SATB2 expression.[20,21] Recent studies have generated controversial results concerning the role of SATB2 in colorectal, breast, laryngeal, and oral carcinomas.[22-25]

The present study aims to determine SATB2 expressions in paraffin-embedded tissue samples of patients operated for primary epithelial ovarian tumors and metastatic ovarian tumors using the IHC staining metho and to evaluate the significance of SATB2 expression for differential diagnosis between subtypes of epithelial tumors and between primary and metastatic tumors.

Materials and Methods

The samples included in this study were obtained from the archives of Gaziantep University's Pathology Department and belonged to the time period between 2004 and 2017. The study group comprised 148 cases of primary epithelial tumor and 29 cases of metastatic ovarian tumor. All hematoxylin and eosin-stained preparations of these cases were reassessed based on the 2014 WHO classification. Paraffin blocks of the preparations that contained the largest epithelial tumor component were selected, and immunohistochemical (IHCal) analysis was performed by applying SATB2 on the sections prepared from these blocks. The total number of 148 primary epithelial ovarian tumor cases included: 33 high-grade serous carcinomas, 5 low-grade serous carcinomas, 2 non-invasive low-grade serous carcinomas, 30 borderline serous tumors, 29 endometrioid carcinomas, 5 clear cell carcinomas, 5 malignant Brenner tumors, 11 mucinous carcinomas, 28 borderline mucinous carcinomas, and 29 metastatic ovarian carcinoma. A total of 29 metastatic ovarian tumor cases comprised 8 colorectal adenocarcinomas, 5 breast carcinomas, 15 adenocarcinomas with upper gastrointestinal tract (GIT) origin, and 1 carcinoma with appendiceal origin.

The IHC antibody to SATB2 (rabbit monoclonal antibody EP281, Cell Marque, USA), was studied using an automated immunohistochemistry-staining device (Ventana, Bench Mark Ultra Auto-Stainer, USA).

Nuclear staining for SATB2 was considered positive if more than 1% of tumor cells were positive. Normal colon tissue was used as a positive control.

Assessment of immunoreactivity

In the assessment of IHC SATB2 expression, preparations were evaluated in terms of expression intensity in the tumor cells and the extensiveness of expression. Only nuclear expression was considered as positivity. Colon epithelium tissue and colon adenocarcinoma were used as external controls. Based on other studies on SATB2 in the literature, the degree and intensity of expression were evaluated.[26] According to these studies, expressions were assessed as weak, moderate, or strong based on the intensity of expression in the colon epithelium. The extensiveness of expression in the tumor tissue was scored between 0 and 4. Accordingly, expression was assessed as 0 if there was no staining, 1(+) if there was expression in 1%–25% of the tumor cells, 2(+) if there was expression in 26%–75% of the tumor cells, and 3(+) if there was expression in more than 75% of the tumor cells.

Statistical analysis

Descriptive statistics were presented as numbers and percentages. The relationships between categorical variables were determined using the Chi-square test, while pair-wise relationships were determined using Fisher's Exact Test. SPSS version 22 (SPSS Inc., Chicago, USA). package program was used for analyses. $P < 0.05$ was accepted as statistically significant.

Results

Six of our 33 high-grade serous carcinoma cases showed 1(+) SATB2 expression. Five out of six cases where positive expression was observed demonstrated moderate expression, while 1 demonstrated weak expression.

None of the five low-grade serous carcinoma cases demonstrated SATB2 expression.

None of the two noninvasive low-grade serous carcinoma cases demonstrated SATB2 expression.

Two of the 30 "borderline" serous carcinoma cases demonstrated 1(+) SATB2 expression. Among the cases that showed positive expression, 1 demonstrated weak expression, while 1 demonstrated moderate expression.

Positive SATB2 expression was observed in 15 of the 29 endometrioid carcinoma cases. Ten of the cases that showed positive expression were assessed as 1(+), while 5 of them were considered 2(+). Out of 10 1(+) cases, 1 demonstrated strong, 8 moderate, and 1 weak expression, while 2 of the five 2(+) cases showed strong- and 3 showed moderate-level expression.

Six of the 11 mucinous carcinoma cases demonstrated positive SATB2 expression. Out of 6 cases with positive expression, 4 showed 1 (+) expression with 1 strong-intensity, 1 moderate-intensity, and 2 weak-intensity expressions, while the other 2 demonstrated 3 (+) strong expression.

Five of the 28 "borderline" mucinous tumor cases demonstrated positive SATB2 expression. Two of these 5 cases were assessed as 1(+), while 3 were assessed as 3(+). While 1(+) cases showed weak expression, one of the 3(+) cases showed strong expression and the rest showed moderate and weak expression.

One of the 5 clear cell carcinoma cases demonstrated moderate level 1(+) positive SATB2 expression.

None of the five malignant Brenner tumor cases showed SATB2 expression.

Meanwhile, fifteen of the 29 cases in the metastatic tumor group demonstrated positive SATB2 expression. Positive expression was detected in all of the 8 cases with colorectal carcinoma (CRC). Seven of these eight cases manifested 3(+) expression with 6 strong-intensity and 1 weak-intensity expressions, and 1 case showed weak 1(+) expression. 1 (+) weak expression was observed in one out of the five breast carcinoma cases. Positive SATB2 expression was observed in 4 of the 15 cases with an upper GIS origin. Two out of these four cases demonstrated 3(+) strong, one 1 (+) moderate, and one 1 (+) weak expression. One case with an appendiceal origin showed 1 (+) expression [the data have been summarized in Table 1 and illustrated in Figure 1].

In general, the groups did not have any statistically significant relationships in terms of SATB2 expression ($P = 0.001$).

SATB2 positivity in endometrioid carcinoma cases (51.7%) was higher than high-grade serous carcinoma cases (18.2%) at a statistically significant level ($P = 0.007$). Furthermore, it was also higher when compared to "borderline" serous tumor cases (6.7%) ($P = 0.001$) and "borderline" mucinous tumor cases (17.9%) ($P = 0.012$) with statistical significance.

Cases of endometrioid carcinoma (51.7%) and mucinous carcinoma (54.5%) did not demonstrate a statistically significant difference in terms of SATB2 positivity rates ($P = 1.000$).

In endometrioid carcinoma cases (51.7%) and metastatic tumor cases (51.7%), the rates of SATB2 positivity were the same, but there was no statistically significant difference between these two groups ($P = 1.000$).

There was no significant difference between high-grade serous carcinoma cases (18.2%) and "borderline" serous tumor cases (6.7%) in terms of SATB2 expression ($P = 0.260$).

SATB2 positivity in high-grade serous carcinoma cases (18.2%) was lower than that in mucinous carcinoma cases (54.5%) at a statistically significant level ($P = 0.045$).

There was no significant difference between high-grade serous carcinoma cases (18.2%) and "borderline" mucinous tumor cases (17.9%) in terms of SATB2 expression ($P = 0.260$).

SATB2 positivity in high-grade serous carcinoma cases (18.2%) was lower than that in metastatic tumor cases (51.7%) at a statistically significant level ($P = 0.007$).

SATB2 positivity in "borderline" serous tumor cases (6.7%) was lower than that in mucinous carcinoma cases (54.5%) at a statistically significant level ($P = 0.002$).

There was no significant difference between "borderline" serous tumor cases (6.7%) and "borderline" mucinous tumor cases (17.9%) in terms of SATB2 expression ($P = 0.246$).

SATB2 positivity in "borderline" serous tumor cases (6.7%) was lower than that in metastatic tumor cases (51.7%) at a statistically significant level ($P = 0.001$).

SATB2 positivity in "borderline" mucinous tumor cases (17.9%) was lower than that in mucinous

Table 1: Sequence-binding protein 2 expression results of the tumors according to their extensiveness score

	Negative *n*	1+	2+	3+	Positive *n*, (%)
Primary epithelial tumors (*n*)					
High-grade serous carcinoma (*n*=33)	27	6	0	0	6 (18.2)
Low-grade serous carcinoma (*n*=5)	5	0	0	0	0
Noninvasive low-grade serous carcinoma (*n*=2)	2	0	0	0	0
Borderline serous tumor (*n*=30)	28	2	0	0	2 (6.7)
Endometrioid carcinoma (*n*=29)	14	10	5	0	15 (51.7)
Mucinous carcinoma (*n*=11)	5	4	0	2	6 (54.5)
Borderline mucinous tumor (*n*=28)	23	2	0	3	5 (17.9)
Clear cell carcinoma (*n*=5)	4	1	0	0	1 (20)
Malignant Brenner tumor (*n*=5)	5	0	0	0	0
Metastatic tumors (*n*)					
Colorectal adenocarcinoma (*n*=8)	0	1	0	7	8 (100)
Breast carcinoma (*n*=5)	4	1	0	0	1 (20)
Upper GIT (*n*=15)	11	1	1	2	4 (26.7)
Appendix (*n*=1)	0	1	0	0	1 (100)

GIT: Gastrointestinal tract

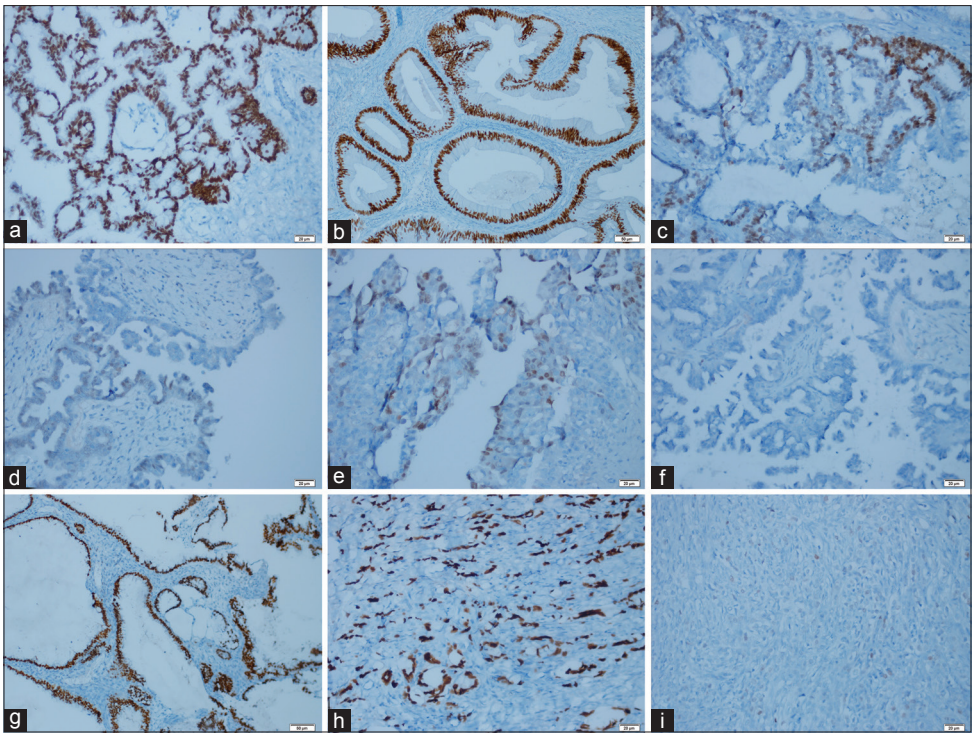

Figure 1: Special AT-rich sequence-binding protein 2 expression in primary and metastatic ovarian tumors. (a) Strong and diffuse (3+) special AT-rich sequence-binding protein 2 expression in mucinous carcinoma × 100, (b) Strong and diffuse (3+) special AT-rich sequence-binding protein 2 expression in borderline mucinous tumor ×100, (c) Moderate and 2(+) special AT-rich sequence-binding protein 2 expression in endometrioid carcinoma ×200, (d) Weak and 1(+) special AT-rich sequence-binding protein 2 expression in borderline serous tumor, ×200, (e) Moderate and 1 (+) special AT-rich sequence-binding protein 2 expression in high-grade serous carcinoma ×200, (f) Absence of special AT-rich sequence-binding protein 2 expression in low-grade serous carcinoma ×200, (g) Strong and diffuse (3+) special AT-rich sequence-binding protein 2 expression in metastatic colorectal carcinoma ×100, (h) Strong and diffuse (3+) special AT-rich sequence-binding protein 2 expression in metastatic upper gastrointestinal tract carcinoma ×100, (i) Weak and 1(+) special AT-rich sequence-binding protein 2 expression in metastatic breast carcinoma ×100

carcinoma cases (54.5%) at a statistically significant level ($P = 0.044$).

There was no statistically significant difference between the SATB2 positivity rates of mucinous carcinoma cases (54.5%) and metastatic tumor cases (51.7%) ($P = 1.000$).

SATB2 positivity in "borderline" mucinous tumor cases (17.9%) was lower than that in metastatic tumor cases (51.7%) at a statistically significant level ($P = 0.011$).

In conclusion, when all groups are considered, SATB2 expression was observed in the primary ovarian tumors, such as mucinous carcinomas and endometrioid carcinomas; however, the extensiveness and intensity of staining were generally observed to be low. All metastatic colon carcinoma cases demonstrated extensive and strong positivity.

Discussion

SATB2 is a novel DNA-binding protein and nuclear transcription factor with a lenght of 733 amino acids.[8-10] SATB2 is related to gene transcription and the rearrangement of chromatin. Previous studies have demonstrated that SATB2 plays an important role in brain development, craniofacial modeling, and osteoblast differentiation.[8]

In normal epithelial tissues, the SATB2 protein is expressed specifically in the nuclei of epithelial cells in the lower gastrointestinal (GI) tract. Among types of nonepithelial cells, it was expressed in certain lymphoid cells, germ cells in the testicles, and particular neurons of the central nervous system. The selective expression of SATB2 in the lower GI track suggested that it could function as a diagnostic marker for CRC. Therefore, this potential diagnostic biomarker was analyzed in numerous cases of CRC and other cancer types.[26] In a study, a total of 1882 cases, including a CRC case and 620 other (non-CRC) tumor cases were analyzed. It was demonstrated that, with a striking 85% positivity in all CRCs, SATB2 was a sensitive and extremely specific marker for CRC.[27]

The latest data show that SATB2 expression behaves like a tumor suppressor gene in various tumor types.[28] Liu *et al*.[23] showed that SATB2 downregulation in laryngeal squamous cell carcinomas was associated with the histological degree of the tumor, an advanced clinical stage, and tumor recurrence. Mansour *et al*.,[29] on the other hand, revealed that SATB2 behaved like a tumor suppressor gene in colorectal cancer through ERK5 inactivation.

As for ovarian tumors, there are only a limited number of studies related to SATB2. This study has examined

SATB2 expression in 148 primary epithelial ovarian tumors and 29 metastatic ovarian tumors. Among the total 148 primary epithelial ovarian tumor cases in the study, 33 were high-grade serous carcinomas, 5 were low-grade serous carcinomas, 2 were non-invasive low-grade serous carcinomas, 30 were "borderline" serous tumors, 29 were endometrioid carcinomas, 11 were mucinous carcinomas, 28 were "borderline" mucinous tumors, 5 were clear cell carcinomas, and 5 were malignant Brenner tumors. This study is the first in which SATB2 expression was assessed by comprehensively classifying primary epithelial ovarian tumors according to their histopathologic types.

In this study, SATB2 expression was detected in 18.2% (6/33) of the high-grade ovarian serous carcinoma cases and 6.7% (2/30) of the "borderline" serous tumor cases, while none of the 2 non-invasive low-grade serous carcinomas and 5 low-grade serous carcinoma cases showed SATB2 expression. Lin *et al*.,[7] in their large-scale study that involved gynecological and non-gynecological tumors, reported SATB2 expression in 1 (2.1%) of the 41 cases with ovarian serous carcinoma, the types and grades of which were not specified, 5 (3.8%) of the 131 cases with endometrial adenocarcinoma, and 5 of the 71 endocervical adenocarcinoma cases. In a study where they assessed SATB2 expression in colorectal and noncolorectal tumors, Dragomir *et al*.[26] reported focal expression with SATB2 in 15% of their 74 primary gynecological carcinoma cases, the localizations of which were not stated. However, details regarding these tumors were not provided. Magnusson *et al*.[27] detected SATB2 expression in 5 (3.3%) of their 153 ovarian cancer cases, the histological subtype, and degree of which were not specified. The reason for the low positivity rate in these studies that employed the tissue microarray method could be the limited number of tissues used in this method. In this study, however, we detected SATB2 expression in 35 (23%) of the total 148 primary epithelial ovarian tumors. This rate that we determined in our study is higher than those reported by other studies. A majority (71%) of the cases where positive expression was detected had a score of 1+ (1%–25% tumor cell staining).

In a study which employed the tissue microarray method, Moh *et al*.[17] did not detect SATB2 expression in any of the 72 cases with primary ovarian endometrioid adenocarcinoma or the 3 cases with endometrioid "borderline" tumors. In our study, we detected SATB2 expression in 15 (51.7%) of the 29 endometrioid carcinoma cases. This rate is very high compared to that reported in the Moh *et al*. study. Of the cases in this group that showed positive expression, 67% had a score of 1 (+), resembling primary epithelial ovarian tumors, which predominantly manifested 1 (+) staining.

In this study, SATB2 expression was detected at a rate of 54.5% (6/11) in mucinous carcinomas, which is one of the primary mucinous ovarian tumors, while this rate was 17.9% (5/28) in "borderline" mucinous tumors. Perez Montiel *et al*.,[6] in their study on ovarian tumors that demonstrated intestinal type mucinous epithelium with or without a teratoma component, did not detect SATB2 expression in any of the 51 cases of primary mucinous ovarian tumors not associated with teratoma. As for the teratoma-associated cases, 3 of the 4 cases showed diffuse and 1 showed focal SATB2 expression. Moh *et al*.,[17] detected SATB2 positivity at a rate of 4.5% (5/111) in all primary ovarian mucinous tumors, regardless of the teratoma component. When cases with a teratoma component were excluded, however, this rate dropped to 1% (1/97). Even though our study has fewer cases in this group, SATB2 expression was found to be significantly higher compared to both of these studies. Similar to our study, Perez Montiel *et al*.[6] assessed SATB2 expressions in paraffin-embedded whole tissue sections, while Moh *et al*.[17] worked with the tissue microarray method. As Perez Montiel *et al*.[6] did not provide detailed information on the histological types of mucinous tumors in their study, comparisons with this study were only possible in terms of numerical values.

In the present study, a higher rate of SATB2 expression was detected in the high-grade serous carcinoma cases (18.2%) compared to the "borderline" serous tumor cases (6.7%). There are no studies in the literature that have evaluated SATB2 expression in ovarian serous tumors and detailed the histological subtypes. In their study with 73 cases of clear cell renal cell carcinoma, Guo *et al*.[30] demonstrated that general survival increased in parallel to high SATB2 expression. In a study by Geng *et al*.[31] that included 203 esophagus squamous cell carcinoma cases, reduced SATB2 expression was suggested to have a relationship with pathological stage, recurrence, and prognosis.

According to studies in the literature, low SATB2 expression is associated with shorter survival, whereas high SATB2 expression is linked to longer survival times.[31-33] Our study's serous carcinoma findings contradicted these results. We detected higher rates of SATB2 expression in high-grade serous carcinomas compared to "borderline" serous tumors, which have a better prognosis. Similarly, in mucinous carcinoma cases, our study detected a higher rate of SATB2 expression compared to that in "borderline" mucinous tumor cases.

Perez Montiel *et al*.[6] reported SATB2 expression in 100% of their 20 cases with ovarian metastasis of colonic or appendiceal origins. In our study, all cases of metastatic ovarian tumors of colorectal adenocarcinoma origin demonstrated SATB2 expression. On the other hand, Moh *et al*.[17] showed SATB2 expression in 75% of the colorectal adenocarcinomas that metastasized to the ovary, 80% of low-grade appendiceal tumors, and 100% of high-grade appendiceal adenocarcinomas. The

findings of our study are consistent with not only these two studies, but also other comprehensive SATB2 studies of primary and metastatic colonic adenocarcinomas.[28] The appendiceal tumor case in this study demonstrated SATB2 expression.

Among metastatic ovarian tumors from noncolorectal primaries, this study detected SATB2 expression in 4 of the 15 cases of an upper GIT origin and 1 of the 5 breast carcinoma cases. In their study, Moh *et al*.[17] did not detect SATB2 expression in any of the 9 cases of gastric adenocarcinoma that metastasized to the ovary, while they showed expression in 2 of the 3 cases of nonspecific GI or pancreaticobiliary primaries. In a study by Perez Montiel *et al*.,[6] 4% of breast carcinoma cases showed weak focal SATB2 expression, while all pancreas and gastric carcinoma cases showed a negative reaction. The findings of our study in this group demonstrated similarities to other studies.

In this study, one of the five clear cell carcinoma cases demonstrated SATB2 expression. Meanwhile, five malignant Brenner tumor cases did not show any expression. The number of cases in this group was limited, and our literature review revealed no studies that have assessed expression in such tumors.

Conclusion

In conclusion, it must be considered that primary carcinomas and metastatic carcinomas may manifest varying levels of SATB2 expression with different intensity and extensiveness. Extensive and strong SATB2 expression indicates metastatic colon carcinoma, consistent with the literature.

Acknowledgments

This study was supported by the Scientific Research Projects Governing Unit (BAPYB) of Gaziantep University.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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