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GATA4 is diagnostically useful for distinguishing primary ovarian mucinous carcinomas from metastatic colorectal adenocarcinomas to the ovary

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Summary. Aim. Determining the primary origin of an ovarian mucin-producing carcinoma can be challenging at times because some metastases of primary colorectal origin may exhibit gross, microscopic, and/or immunohistochemical features that overlap with those of primary ovarian mucinous carcinomas (OMCs). We hypothesized that GATA binding protein 4 (GATA4) might be a novel, useful marker for differentiating primary OMCs from metastatic colorectal adenocarcinomas to the ovary.

Methodology. For comparison with the usefulness of other markers (special AT-rich sequence-binding protein 2 (SATB2) and caudal type homeobox 2 (CDX2)), we elucidated the expression profiles of GATA4 in OMCs, colorectal non-mucinous adenocarcinomas (CNMACs), and colorectal mucinous adenocarcinomas (CMACs) using immunohistochemistry.

Results. We confirmed GATA4 expression (H-score ≥50 points) in 93%, SATB2 in 0%, and CDX2 in 64% of 14 OMCs. GATA4 was expressed in 13%, SATB2 in 90%, and CDX2 in 93% of 30 CNMACs. GATA4 was expressed in 20%, SATB2 in 73%, and CDX2 in 100% of 30 CMACs.

Conclusion. The expression of GATA4 in a mucus-producing ovarian tumor strongly supports it being a primary OMC rather than a metastatic colorectal carcinoma: GATA4 expression indicates OMC and SATB2 expression indicates colorectal adenocarcinoma. However, three cases of colorectal adenocarcinoma were GATA4-positive and SATB2-negative, so the GATA4/SATB2 marker combination is not absolute for determining the primary site. Further research for more markers is necessary to find the ideal combination.

Key words: GATA4, Ovarian mucinous carcinoma, Colorectal non-mucinous adenocarcinoma, Colorectal mucinous adenocarcinoma, Immunohistochemistry

Introduction

Determining the primary origin of an ovarian mucin-producing carcinoma can be challenging at times because some metastases of primary colorectal origin may exhibit gross, microscopic, and/or immunohistochemical features that overlap with those of primary ovarian mucinous carcinomas (OMCs) (Moh et al., 2016). Although, the best treatments for each type of tumor may be quite different. Mitry et al. showed a marginal statistical significance in favor of adjuvant chemotherapy with a 5-fluorouracil bolus-based regimen after complete resection of colorectal cancer metastases. Therefore, adjuvant chemotherapy after curative resection of metastases from colorectal cancer may be considered, which shows that it is critical to determine the type of ovarian tumor that was surgically removed, a primary OMC or metastatic colorectal tumor (Mitry et al., 2008). It is important to determine the organs of origin to provide the best operative method, chemotherapy, and radiotherapy for treatment. Furthermore, recent advances in targeted therapies have increased the need for accuracy in the determination of origin organs.

Currently, special AT-rich sequence-binding protein 2 (SATB2) is one of the most useful markers of colorectal origin determination in metastatic cancers. Evaluation of primary extraovarian tumors showed the highest incidences of SATB2 staining among primary colorectal adenocarcinomas (71%), primary appendiceal low-grade mucinous neoplasms (100%), and primary appendiceal high-grade adenocarcinomas (100%) (Moh et al., 2016). Also, our previous study revealed that 97% of colorectal non-mucinous adenocarcinomas (CNMACs) and 87% of colorectal mucinous adenocarcinomas (CMACs) were positive by SATB2 immunostaining (Mochizuki et al., 2018). However,

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Abbreviations. SATB2, special AT-rich sequence-binding protein 2; OMC, ovarian mucinous carcinoma; GATA4, GATA binding protein 4; CDX2, caudal type homeobox 2; CNMAC, colorectal non-mucinous adenocarcinoma; CMAC, colorectal mucinous adenocarcinoma.

those results indicate that even SATB2 has limitations in determining a colorectal origin.

On the other hand, most ovarian serous and endometrioid tumors express paired box 8 and often express estrogen receptors. These are known gynecological primary broad tumor markers. Nevertheless, these markers are known to be low in OMCs (Vang et al., 2006; Chu et al., 2011; Schmoeckel et al., 2018). GATA binding protein 4 (GATA4) belongs to the GATA family of zinc finger transcription factors and is located at 8p23.1. In humans, it plays a key role in embryogenesis and cardiac development, and mutations can lead to heart disease due to an abnormal fold or other embryogenic failures in heart development (Li et al., 2018). GATA4 is expressed in endodermal derivatives including visceral and parietal endoderm, intestinal epithelium (particularly in the proximal gut), stomach, adrenal gland, lung, liver, ovary, and testis (Ayanbule et al., 2011). There are few studies on GATA4 expression in OMCs or colorectal adenocarcinomas. Cai et al. (2009) showed that GATA4 expression was positive in 11 out of 12 cases of OMCs, whereas Haveri et al. (2008) found that the mucosa of the terminal ileum, colon, and rectum generally lacked GATA4 protein, and GATA4 was not present in any of the 12 colon carcinoma samples studied.

We hypothesized that GATA4 might be a novel, useful marker for differentiating primary OMCs and metastatic colorectal adenocarcinomas to the ovary. This study aims to clarify GATA4 expression in OMCs, CNMACs, and CMACs and compare its usefulness with SATB2 and caudal type homeobox 2 (CDX2) using immunohistochemistry.

Materials and methods

Materials

We collected 14 OMCs (confluent/expansile invasive pattern, 10 cases; infiltrative/destructive pattern, 4 cases), 30 CNMACs, and 30 CMACs obtained surgically at the University of Yamanashi Hospital (Table 1). Medical history and clinical examination (computed tomography/magnetic resonance imaging/positron emission tomography/endoscopic examination) had not indicated the possibility of metastasis from other organs in the cases of OMC, CNMAC, and CMAC, and the pathological diagnosis of these tumors followed the *WHO Classification of Tumours* (Nagtegaal et al., 2019; Vang et al., 2019). Two pathologists (K.M. and I.T.) independently reviewed hematoxylin and eosin-stained slides blinded to the original pathological diagnosis. The Research Ethics Committee of the Faculty of Medicine, University of Yamanashi approved this study (approval number: 2756).

Immunohistochemistry

Sections 4-μm thick were cut from formalin-fixed, paraffin-embedded tissue blocks that were dewaxed and rehydrated. This was followed by immunohistochemical staining performed on representative slides. GATA4 (EPR26718-103, Abcam, Cambridge, UK, dilution 1:100) and SATB2 (EPNCIR130A, Abcam, Cambridge, UK, dilution 1:600) were used as the primary antibodies. We performed antigen retrieval through heat treatment by autoclaving at 121°C for 10 min in Antigen Retrieval solution pH 9 (Nichirei Biosciences, Tokyo, Japan). After inhibiting endogenous peroxidase, we used a positive control (GATA4, ovary; SATB2, colon) to perform the primary antibody reaction. CDX2 (EP25, Leica Biosystems, Tokyo, Japan, ready USE) was used as the primary antibody. We performed antigen retrieval through heat treatment by autoclaving at 121°C for 10 min in Solution for Antigen Activation (LSI Medience Corporation, Tokyo, Japan). After inhibiting endogenous peroxidase, we used a positive control (colon) to

Table 1. Clinicopathological characteristics of patients with OMC, CNMAC and CMACs.

Characteristics	Tumor type		
	OMC (n=14)	CNMAC (n=30)	CMAC (n=30)
Gender, n			
Male	-	15	13
Female	14	15	17
Age			
Mean (years)	58	68	71
Range	28-79	45-86	27-89
Location			
Cecum	-	0	4
Ascending colon	-	9	6
Transverse colon	-	4	7
Descending colon	-	0	1
Sigmoid colon	-	14	5
Rectum	-	3	7
Left ovary	5	-	-
Right ovary	9	-	-
Size			
Mean (mm)	160	47	58
Range	65-300	17-120	20-105
*pT-Category**, n			
pT1 13	0	1	
pT1a	8	-	-
pT1b	0	-	-
pT1c	0	-	-
pT1c1	4	-	-
pT1c2	1	-	-
pT1c3	0	-	
pT2 1	6	2	
pT2a	1	-	-
pT2b	0	-	-
pT3 0	15	21	
pT3a	0	-	-
pT3b	0	-	-
pT3c	0	-	-
pT4 -	9	6	
pT4a	-	7	5
pT4b	-	2	1

OMC, ovarian mucinous carcinoma; CNMAC, colorectal non-mucinous adenocarcinoma; CMAC, colorectal mucinous adenocarcinoma. *Evaluated according to the 2017 TNM classification.

perform the primary antibody reaction. We used the N-Histofine Simple Stain MAX PO (MULTI) (Nichirei Biosciences, Tokyo, Japan) with diaminobenzidine as a chromogen and a light counterstain with hematoxylin to perform immunohistochemistry. Two pathologists (K.M. and I.T.) simultaneously reviewed immunostained sections using a double-headed light microscope.

We used the H-score as our immunohistochemical evaluation system. This was calculated by summing each gradation of staining intensity (0-3) by the percentage of area stained at that intensity. These results were then classified into the H-score with 0=0 to 49 points, 1=50 to 99 points, 2=100 to 199 points, and 3=200 to 300 points. We also defined sections scored 1, 2, or 3 as positive and sections scored 0 as negative (Specht et al., 2015).

Statistical analysis

We used Fischer's exact test to evaluate differences between the OMC and CNMAC/CMAC samples regarding the immunohistochemical staining of GATA4. A p-value of less than 0.05 indicated statistical significance. Statistical analysis was conducted with IBM SPSS Statistics version 22 (IBM Corp., Armonk, NY, USA).

Results

GATA4 immunostaining in OMCSs, CNMACs, and CMACs

Table 2 summarizes GATA4 immunostaining patterns. GATA4 expression in 14 OMCs showed that 7% classified as 0, 21% as 1, 71% as 2, and 0% as 3 (Fig. 1B). GATA4 expression in 30 CNMACs showed that 87% classified as 0, 3% as 1, 10% as 2, and 0% as 3 (Fig. 2B). GATA4 expression in 30 CMACs showed 80% classified as 0, 7% as 1, 13% as 2, and 0% as 3

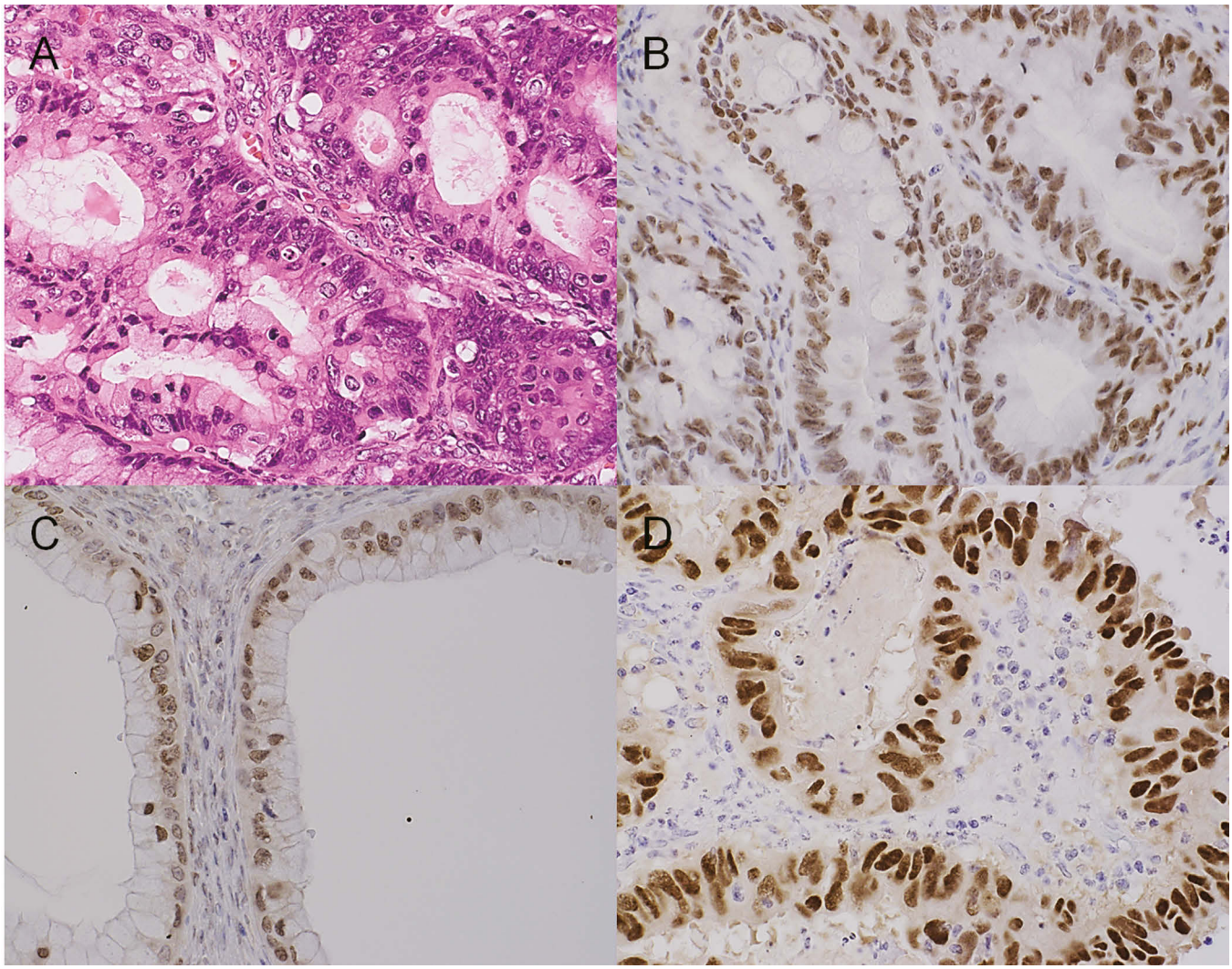

Fig. 1. Representative OMC **(A)**, exhibiting GATA4 immunoreactivity in tumor cell nuclei **(B)**, exhibiting SATB2 immunoreactivity in tumor cell nuclei **(C)**, and exhibiting CDX2 immunoreactivity in tumor cell nuclei **(D)**. x 400.

(Fig. 3B).

SATB2 immunostaining in OMCs, CNMACs, and CMACs

Table 3 summarizes SATB2 immunostaining patterns. SATB2 expression in 14 OMCs showed that 100% classified as 0, 0% as 1, 0% as 2, and 0% as 3 (Fig. 1C). SATB2 expression in 30 CNMACs showed that 10% classified as 0, 13% as 1, 10% as 2, and 67% as 3 (Fig. 2C). SATB2 expression in 30 CMACs showed that 27% classified as 0, 13% as 1, 20% as 2, and 40% as 3 (Fig. 3C).

Table 2. Expression of GATA4 in 14 OMCs, 30 CNMACs and 30 CMACs.

Tumor type	H-score (Classification)				*p*-value
	0	1	2	3	
OMC (n=14)	1	3	10	0	
CNMAC (n=30)	26	1	3	0	<0.001*
CMAC (n=30)	24	2	4	0	<0.001**

OMC, ovarian mucinous carcinoma; CNMAC, colorectal non-mucinous adenocarcinoma; CMAC, colorectal mucinous adenocarcinoma. *OMC vs. CNMAC. **OMC vs. CMAC.

Table 3. Expression of SATB2 in 14 OMCs, 30 CNMACs and 30 CMACs.

Tumor type	H-score (Classification)				*p*-value
	0	1	2	3	
OMC (n=14)	14	0	0	0	
CNMAC (n=30)	3	4	3	20	<0.001*
CMAC (n=30)	8	4	6	12	<0.001**

OMC, ovarian mucinous carcinoma; CNMAC, colorectal non-mucinous adenocarcinoma; CMAC, colorectal mucinous adenocarcinoma. *OMC vs. CNMAC. **OMC vs. CMAC.

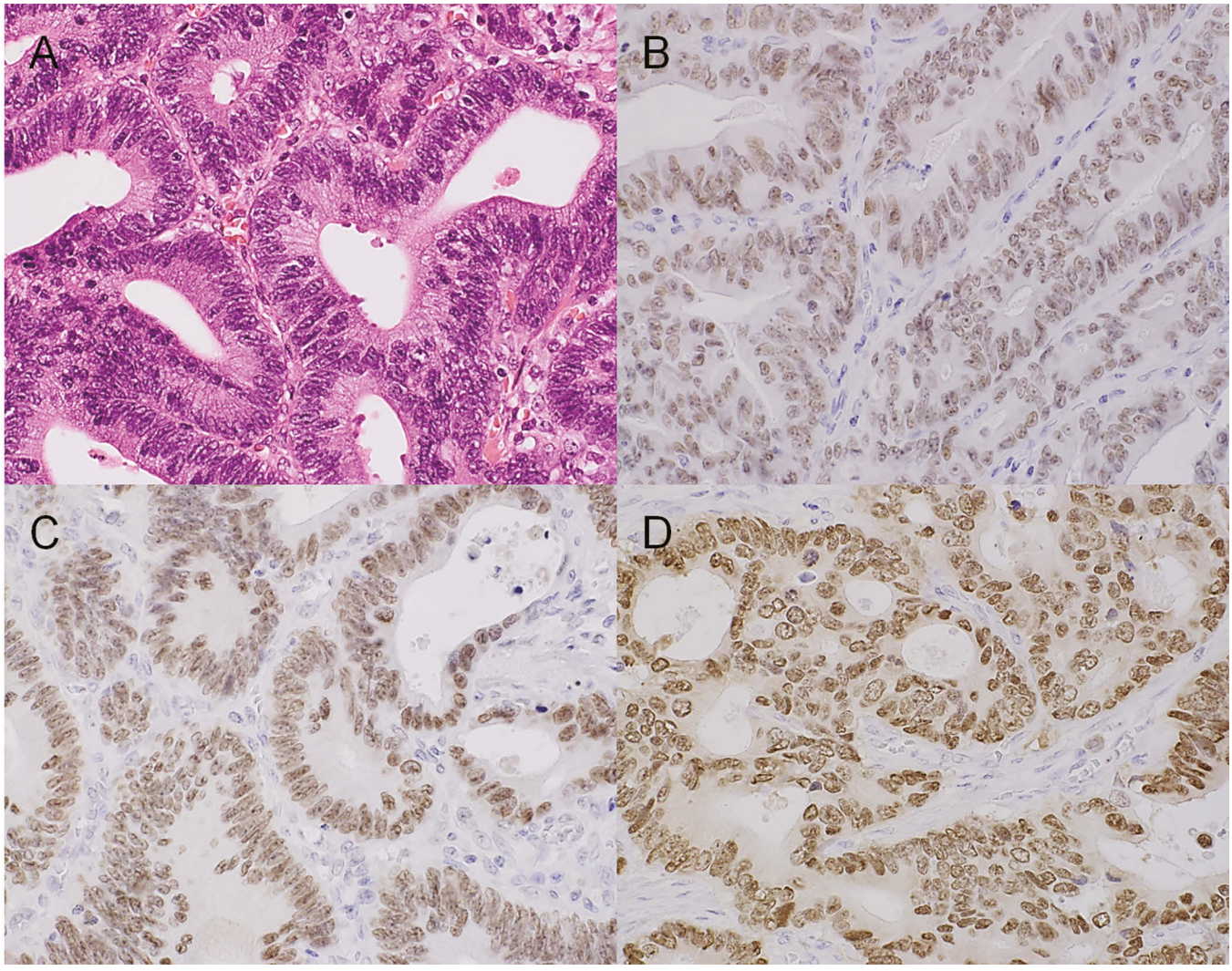

Fig. 2. Representative CNMAC **(A)**, exhibiting GATA4 immunoreactivity in tumor cell nuclei **(B)**, exhibiting SATB2 immunoreactivity in tumor cell nuclei **(C)**, and exhibiting CDX2 immunoreactivity in tumor cell nuclei **(D)**. x 400.

CDX2 immunostaining in OMCs, CNMACs, and CMACs

Table 4 summarizes CDX2 immunostaining patterns. CDX2 expression in 14 OMCs showed that 36% classified as 0, 0% as 1, 36% as 2, and 29% as 3. (Fig. 1D). CDX2 expression in 30 CNMACs showed that 7% classified as 0, 3% as 1, 7% as 2, and 83% as 3 (Fig. 2D). CDX2 expression in 30 CMACs showed that 0% classified as 0, 0% as 1, 17% as 2, and 83% as 3 (Fig. 3D).

Table 4. Expression of CDX2 in 14 OMCs, 30 CNMACs and 30 CMACs.

Tumor type	H-score (Classification)				*p*-value
	0	1	2	3	
OMC (n=14)	5	0	5	4	
CNMAC (n=30)	2	1	2	25	0.001*
CMAC (n=30)	0	0	5	25	<0.001**

OMC, ovarian mucinous carcinoma; CNMAC, colorectal non-mucinous adenocarcinoma; CMAC, colorectal mucinous adenocarcinoma. *OMC vs. CNMAC. **OMC vs. CMAC.

Table 5. Expression of GATA4/SATB2 in 14 OMCs, 30 CNMACs and 30 CMACs.

Marker status*	Tumor type			*p*-value**
	OMC (n=14)	CNMAC (n=30)	CMAC (n=30)	
GATA4(+)/SATB2(+)	0	3	4	0.334
GATA4(+)/SATB2(-)	13	1	2	<0.001
GATA4(-)/SATB2(-)	1	2	6	1.000
GATA4(-)/SATB2(+)	0	24	18	<0.001

OMC, ovarian mucinous carcinoma; CNMAC, colorectal non-mucinous adenocarcinoma; CMAC, colorectal mucinous adenocarcinoma. *We defined 1, 2 or 3 classified specimens as positive and sections. classified 0 as negative by H-score. **OMC vs. CNMAC and CMAC.

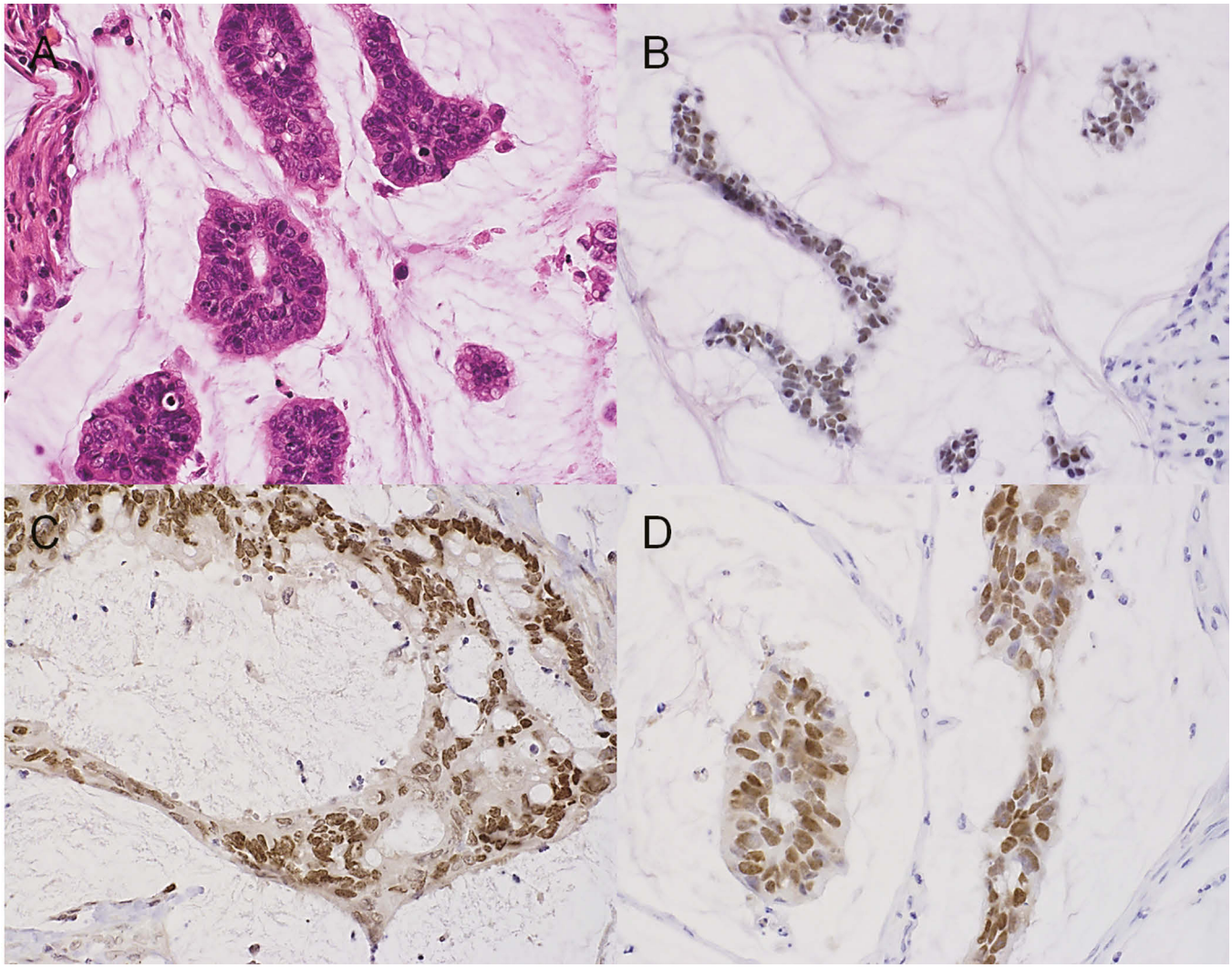

Fig. 3. Representative CMAC **(A)**, exhibiting GATA4 immunoreactivity in tumor cell nuclei **(B)**, exhibiting SATB2 immunoreactivity in tumor cell nuclei **(C)**, and exhibiting CDX2 immunoreactivity in tumor cell nuclei **(D)**. x400.

GATA4/SATB2 immunostaining in OMCs, CNMACs, and CMACs

Table 5 summarizes GATA4/SATB2 paired immunostaining patterns. GATA4 and SATB2 were both positive in 0% of the 14 OMCs, 10% of the 30 CNMACs, and 13% of the 30 CMACs. GATA4 was positive and SATB2 was negative in 93% of the 14 OMCs, 3% of the 30 CNMACs, and 7% of the 30 CMACs. GATA4 and SATB2 were both negative in 7% of the 14 OMCs, 7% of the 30 CNMACs, and 20% of the 30 CMACs. GATA4 was negative and SATB2 was positive in 0% of the 14 OMCs, 80% of the 30 CNMACs, and 60% of the 30 CMACs.

Discussion

The GATA family of transcription factors is crucial to embryonic development, playing complex and widespread roles in cell fate decisions and tissue morphogenesis; its proteins are essential for the development of tissues derived from all three germ layers, including the skin, brain, gonads, liver, hematopoietic, and cardiovascular and urogenital systems (Tremblay et al., 2018). Although originally divided into hematopoietic (GATA1/2/3) and cardiac (GATA4/5/6) GATA factors, their function and expression patterns extend well beyond these tissues (Tremblay et al., 2018). Meanwhile, GATA3 is a transcription factor important in the differentiation of breast epithelia, urothelial, and subsets of T lymphocytes, which has been suggested as a useful evaluator of carcinomas of mammary or urothelial origin or metastatic carcinomas. It is also considered a useful marker in the characterization of renal and germ-cell tumors, mesotheliomas, and paragangliomas (Miettinen et al., 2014). GATA4 expression has been reported in carcinomas of some gastrointestinal organs, however, past reports have shown little to no GATA4 expression in colorectal carcinomas. Accordingly, GATA4 expression in carcinoma cells indicates that the origin is not the colorectal region (Bai et al., 2000; Karafin et al., 2009). Meanwhile, SATB2 immunostaining was observed in 0/17 primary OMCs and 24/32 (75%) metastatic colorectal adenocarcinomas to the ovaries; no SATB2 staining was observed in any ovarian metastasis of pancreatic, gastric, gallbladder, or endocervical origin (Moh et al., 2016), which shows that SATB2 expression in carcinoma cells is very useful for determining metastatic ovarian tumors of colorectal origin, with some limitations.

Positive GATA4 immunohistochemical expression appeared in 93% of the OMC, 13% of the ONMAC, and 20% of the CMAC samples. This might suggest that, after clinically limiting ovarian tumors to either primary ovarian or metastatic colorectal, the carcinomas without GATA4 immunoexpression were metastatic colorectal adenocarcinomas to the ovary as opposed to OMCs. Whereas carcinomas with GATA4 immunoexpression were OMCs as opposed to metastatic colorectal adenocarcinomas to the ovary. SATB2 expression occurred in 0% of the OMC, 90% of the ONMAC, and 73% of the CMAC samples. As a marker, GATA4 is comparable to SATB2 in distinguishing mucin-producing ovarian carcinomas from primary OMCs and metastatic colorectal adenocarcinomas. CDX2 was expressed in 64% of the OMC, 93% of the ONMAC, and 100% of the CMAC samples. Compared with GATA4 and SATB2, CDX2 is a slightly inferior marker for distinguishing mucin-producing ovarian carcinomas from primary OMCs and metastatic colorectal adenocarcinomas.

Because the treatment approach for primary OMCs is very different from metastatic colorectal adenocarcinomas, determining the type of ovarian tumor upon resection is essential. If metastatic colorectal adenocarcinoma to the ovary is mistakenly diagnosed as primary OMC, the subsequent clinical approach (treatment) is likely to be misdirected and inadequate. Although metastatic colorectal cancer remains incurable in most cases, survival has improved with advances in cytotoxic chemotherapy and targeted agents (Modest et al., 2019). In particular, there are many new targeted therapies for colorectal cancer: inhibitors of angiogenesis (bevacizumab, ramucirumab, and aflibercept), epidermal growth factor receptor-targeted therapies (cetuximab and panitumumab), BRAF mutation-targeted therapies (encorafenib and binimetinib), HER2 targeted-therapies (trastuzumab and lapatinib), an inhibitor of TRKA (entrectinib), and immunotherapies (pembrolizumab, nivolumab and ipilimumab) (Modest et al., 2019; Piawah and Venook, 2019; Doebele et al., 2020; Tabernero et al., 2021). Thus, in addition to conventional treatments (surgery, chemotherapy, radiation therapy, etc.), a novel treatment (molecular targeted therapy) has been developed. Consequently, a more accurate, appropriate, and precise pathological diagnosis must be made for patients to receive the maximum therapeutic benefit from treatment. The examination for GATA4 may also play a role in this process.

In conclusion, the expression of GATA4 in a mucus-producing ovarian tumor strongly supports that it is a primary ovarian mucinous carcinoma rather than a metastatic colorectal carcinoma. Basically, GATA4 expression indicates OMC and SATB2 expression indicates colorectal adenocarcinoma. However, in the present study, three cases of colorectal adenocarcinoma were GATA4-positive and SATB2-negative by immunohistochemistry; therefore, the combination of GATA4 and SATB2 is not a perfect marker combination for determining an ovarian tumor's primary site. Therefore, these immunohistochemical markers should be utilized in a correct clinicopathological context, and further research for more markers is needed to close this gap.

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