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ORIGINAL ARTICLE

PAX2, PAX8 and CDX2 Expression in Metastatic Mucinous, Primary Ovarian Mucinous and Seromucinous Tumors and Review of the Literature

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Abstract Ovarian cancer is the most common cause of gynecologic cancer death. Both morphologically and immunohistochemically, metastatic mucinous tumors are the best mimickers of mucinous ovarian tumors; its pathogenesis still remains a mystery. PAX2 and PAX8 immunohisyochemistries are useful for differentiating numerous primary tumour types from metastatic ones. There are few studies in literature about PAX expressions in mucinous and seromucinous tumors. None of these are takes into account the histologic type (whether it is seromucinous or mucinous) or the metastatic origin. With this purpose hematoxylin and eosine slides of ovarian mucinous and seromucinous tumors were re-evaluated and one block was chosen for each case. The study included 76 ovarian mucinous and seromucinous tumors of the ovary reported in Hacettepe University department of pathology between 2000 and 2013. Tissue microarray (TMA) was designed from the chosen blocks, PAX2, PAX8, CDX2 immunostains was preformed to the TMA slides. As a result, most of the metastatic cases were negative for PAX2 (91.2 %) and PAX8 (86.3 %), many were diffusely and strongly positive for CDX2 (68.2 %). Seromucinous tumors were devoid of CDX2 expression; but all cases (except one) displayed strong and diffuse positivity with PAX8. In other words differing from mucinous tumors, seromucinous tumors show strong PAX8 positivity–similar to serous tumors. This study shows that PAX8 and CDX2 could be useful in differentiating primary mucinous from metastatic tumor. Furthermore unlike the homogeneity in seromucinous tumors for PAX8 and CDX2 mucinous tumors shows heterogeneity with different expression patterns.

Keywords PAX2 · PAX8 · Mucinous ovarian tumor · Mucinous ovarian carcinoma · Borderline seromucinous tumor

Introduction

Primary ovarian mucinous carcinomas represent 3 % [1] of ovarian carcinomas while metastatic ovarian carcinomas constitute approximately 7 % [2] of all ovarian tumors. Though they are rare, depending on the similar histological and immunophenotypical appearance, distinction between them is still challenging field of routine pathology practice. There are many studies in the literature indicating how to differentiate metastatic tumors from primary ones. Majority of the reports are agreed that the true diagnosis depends on the evaluation of classical immunomarkers (CK7, CK20, CK19, CDX2, WT-1, B-cathenin, etc.), gross examination and clinical features [3, 4]. Although morphological and immunophenotypical information is documented, there is still some mucinous tumors that cannot be definitively classified as primary and metastatic regardless of multidisciplinary aspects.

Recently, new mullerian markers (PAX2 and PAX8) are documented as useful markers to differentiate mullerian mucinous tumors from non-mullerian tumors [5–7]. PAX is a transcription factor, belonging to a paired box gene family that regulates embryonic development of kidney, mullerian organs, and thyroid. This transcription factor has a crucial role for normal function of related organs. Deletion in PAX8 expression results in lack of endometrium, poor development of the myometrium, but normal function of fallopian tubes, cervix, and vagina.

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Table 1 Details of immunohistochemical antibodies

Antibody	Manifacturer	Clone/Catalog Number	Dilution	Antigen Retrival
PAX2	GeneTex	GTX 62120	1/500	ER2 (EDTA)
PAX8	Biocare	API 438 AA	Ready-To-Use	ER2 (EDTA)
CDX2	Biocare	PM 226 AA	Ready-To-Use	ER2 (EDTA)

*ER indicates Epitop Retrival solution

Ovarian mucinous tumor pathogenesis is still a mystery. To elucidate the pathogenesis, new theories have been developing. Theories for this content are summarized below:

Endometriosis may have a role in pathogenesis of the seromucinous tumors. 30 % to 57 % of endometriosis related tumors (clear cell, endometrioid type) shows ARID1A tumor suppression gene mutation [8, 9]. Loss of ARID1A immunoexpression is seen in 33 % of borderline seromucinous tumors [10]. 8 % of teratomas contain benign, borderline and malign mucinous tumor [11, 12]. This relatively frequent concurrence is considered as mucinous tumors were originated from teratomas. Lastly Kell et al highlights "microsatellite polymorphism analysis showed some mucinous carcinomas arise from female gametes and thus are of germ cell origin" [13]. Some mucinous tumors may be derived from teratomas. Mucinous tumors are also frequently accompanied by Brenner tumors. It is thought if extensive sectioning is done to mucinous cyst adenomas, many of them will contain foci of Brenner component. It is proposed that mucinous tumors frequently contain Walthard nests that are frequently located at the paratubal region. It is speculated that Brenner tumors and mucinous tumors have the same histogenesis; both are derived from microscopic Walthard regions [14]. 75 % of mucinous ovarian tumors show KRAS mutation. Moreover mucinous cyst adenoma, borderline and carcinoma foci in the same tumor show KRAS mutations at the same codon (codon 12 and 13). It means that cyst adenoma borderline and carcinoma has developmental sequence [15]. A proteoglycan called LGAL4 (galactin 4) expressed in mucinous borderline and carcinoma cases are contrarily negative in cyst adenoma. Therefore this proteoglycan could be responsible for early development of mucinous tumor [16].

The aim of this study is to suggest a new beneficial marker for mucinous ovarian tumor workup to differentiate metastatic and primary ones and propose an idea which may be helpful to find a way out of this puzzling pathogenetic problem.

Material and Methods

Case Selection

Seventy-six cases of mucinous (borderline, primary and metastatic) and seromucinous tumors were identified from surgical pathology files of the Hacettepe University Pathology Department from 2000 to 2013. The cases that were without paraffin block or that has insufficient data were eliminated from the study. All the selected ones were routine in-house cases. All slides of all cases were re-classified according to the current clinical-radiological data, co-biopsies, up-to-date knowledge and literature. According to the current classification criteria [17], 46 metastatic mucinous tumors, 8 seromucinous borderline tumors, 15 mucinous borderline tumors and 7 primary mucinous adenocarcinomas were included. Primary source for metastatic tumors were searched. Ten cases out of 46 metastatic tumors, primary tumor was not determined. Those 10 cases were classified in metastatic group based on their morphology, multiple field involvement, laterality and poor prognosis.

Preparation of TMA's (Tissue Microarray) and Immunomarkers

Formalin fixed and paraffin embedded tissue sections were reviewed to identify representative areas of the tumor and to acquire the cores of the microarray analysis. One block was chosen and for each case and 3 cores of 1 mm in diameter were collected from the most proliferative and chaotic area by using Advanced Tissue Arrayer (Ata 100). 16 cases (48 tissue) were placed in a TMA block. Different tissues (thyroid and tuba uterina) were included to create TMA map, which guided the array reading. Four μm sections were obtained from each TMA for immunohistochemistry.

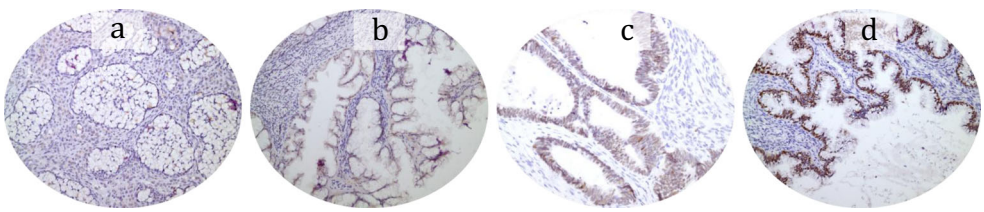

Fig. 1. Evaluation of intensity (20×): Intensity of staining graded between 1 and 3 **1a:** Grade 1 intensity. **1b**: Grade 1 intensity: staining that can barely seen. **1c**: Grade 2 intensity: staining intensity between 1 and 3. **1d**: Grade 3 intensity: strong dark nuclear positivity

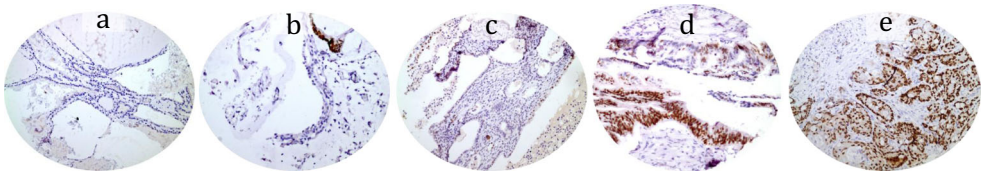

Fig. 2. Evaluation of distribution (20×): Staining distribution was graded semi-quantitatively based on the percentage of positive staining tumor cells. **2a**: Grade 1 distribution: 0–5 % of tumor cells are positive **2b**: Grade 2 distribution: 5–25 % of tumor cells are positive **2c**: Grade 3 distribution 25–50 % of tumor cells are positive **2d:** Grade 4 distribution 50–75 % tumor cells are positive **2e**: distribution 5 75–100 % of tumor cells are positive

PAX2, PAX8 and CDX2 expressions were evaluated via immunohistochemistry. Immunohistochemical antibody clone names, sources, dilutions and antigen retrieval details were listed in Table 1. Adjustment of PAX2 and PAX8 dilution was tested till the dark and nuclear staining were achieved in tubal secretory and basal cells. The same procedure was implemented for CDX2 in colonic adenocarcinoma tissue. The sections were kept in incubator at 70 °C for 30 min. They were then brought to an automated stainer (Leica-Bond-Max).

Interpretation and Scoring of Immunohistochemistry

Nuclear expressions of PAX2, PAX8 and CDX2 were considered positive staining reactions. 3 tissues from each case were scored according to the staining intensity and percentage.

1. Staining intensity was graded according to the darkness of staining. Intensity of staining graded between 1 and 3 (**1:** staining that can barely seen, **2:** staining intensity between 1 and 3, **3:** strong nuclear positivity as in control tuba uterina blocks). Fig. 1a-d demonstrates intensity interpretations.
2. Staining distribution was graded semi quantitatively based on the percentage of positive staining tumor cells. Grade was between 1 and 5 (1: <5 %, 2: 5–25 %, 3: 25–50 %, 4: 50–75 %, 5: 75–100 %). Fig. 2a-e demonstrates distribution interpretations.
3. The staining "score" was calculated by multiplication of those two grades (intensity and percentage of staining). The staining score was between 1 and 15.

Statistical Analysis

Chi-square test was used for qualitative values that cannot be attributed by numerically (intensity). Numerically given values were analyzed with Mann-Whitney U-test. When the group number was more than 2, then Kruscall-Wallis test was used. All the data was analyzed in SPSS 20 pocket program. For positive/negative predictive, sensitivity and specificity values MedCalc Version 12.7.7 was used.

Results

Clinical and Macroscopic Findings

30 out of 76 cases included in the study were primary tumors while 46 of them were metastatic mucinous tumors. Average age of the cases was 47 while the average age of seromucinous

Table 2 Clinical features of the cases

Diagnosis	Number of Patient and percentage (%)	Age	Ovary Diameter	Bilaterality
Metastasis	46 (60.6 %)	**Av**: 48 **Max**:92 **Min**:21	**Av**: 9 **Max**:25 **Min**:2	38 (82.6 %)
BOT-SM	8 (10.5 %)	**Av**: 30,5 **Max**:48 **Min**:22	**Av**:11,42 **Max**:20 **Min**:5	2 (25 %)
BOT-M	15 (19.7 %)	**Av**: 55 **Max**:87 **Min**:21	**Av**: 17 **Max**:28 **Min**:6	0 (0 %)
CA	7 (9.2 %)	**Av**: 52 **Max**:65 **Min**:40	**Av**: 15,6 **Max**:22 **Min**:9	1 (14 %)
Total	76 (100 %)	-	-	41 (100 %)

*BOT-SM (Borderline seromucinous), *BOT-M (Borderline mucinous), *CA (primary mucinous adenocarcinoma)

borderline tumors was 30.5. Age, tumor diameter and laterality details of the patients in the study were listed in Table 2. Seromucinous tumors were observed at younger ages compared to other primary mucinous tumors ($p = 0.02$). Although it was statistically insignificant, it was found that they were frequently more bilateral than the other primary tumors and had smaller tumor diameters ($p > 0.05$).

Endometrial adenocarcinoma was found only in 2 cases. Metastatic lymph node was observed in 14 cases, under the metastatic mucinous tumor group. Twenty-seven of the primary mucinous ovarian tumor cases were FIGO stage 1 (25 of them stage 1 A), while 3 cases were FIGO stage 2.

36 out of 46 metastatic mucinous adenocarcinomas consists of cases where primary origin was confirmed by biopsy (13, 13, 6, 2, 1 and 1 cases were originated from appendix, colon, stomach, pancreas, cervix and, small intestine respectively).

Immunohistochemical Findings

PAX2, PAX8 and CDX2 scores were listed in Table 3. Positive and negative predictive values of staining percentage, intensity and scores of PAX8 and CDX2 were calculated. Intensity, percentage and scores were found to be 75, 68, and 69 for PAX8, 65, 53, 67 for PAX2 and 85, 85, 82 for CDX2 respectively. Since they are very closed set of numbers for the same stain, hereafter only the "score" values are discussed in the manuscript. By that way results are simplified. Staining scores were between 1 and 15 and -for simplification- they were evaluated into 3 groups 1–5, 6–10, 11–15. Shedding or peeling was observed only in metastatic cases during staining procedure of TMA slides. Shedding was seen in 2 cases for PAX2, 3 cases for PAX8 and 4 cases for CDX2. Sensitivity scores for CDX2 to differentiate metastasis, PAX2 and PAX8 to differentiate primary tumor is 73.91, 80.2 82.61 respectively. Specificity scores for CDX2, PAX2 and PAX8 is 80, 60 and 60 respectively.

Metastatic Mucinous Ovarian Tumors 91.2 % of the metastatic mucinous tumor cases were in score "1–5" group for PAX2 while 86.3 % of them were in score "1–5" group for PAX8. On the other hand, for CDX2 expression 68.2 % of the metastatic tumors was in "10–15" score group.

Primary Seromucinous Type Ovarian Tumors All of the seromucinous tumors (except one) showed strong and diffuse nuclear positivity with PAX8 and all was CDX2 negative.

Primary Mucinous Ovarian Tumors 80 % and 66.7 % of the borderline mucinous tumors were in "1–5" score for group for PAX2 and PAX8 expression respectively. 85.7 % of primary mucinous adenocarcinomas were in "1–5" group for PAX2.

Table 3 PAX2, PAX8 and CDX2 score (multiplication of intensity and distribution grade results according to ovarian tumor diagnosis

Ovarian Tumor Diagnosis	PAX2 SCORE				PAX8 SCORE				CDX2 SCORE			
SKOR	1–5	6–10	11–15	TOTAL	1–5	6–10	11–15	TOTAL	1–5	6–10	11–15	TOTAL
Met	40 (91.2 %)	3 (6.4 %)	1 (2.4 %)	44* (%100)	38 (86.3 %)	4 (9.1 %)	2 (4.6 %)	44** (%100)	10 (23.2 %)	2 (4.6 %)	30 (68.2 %)	42*** (100 %)
BOT-SM	6 (75 %)	0 (0 %)	2 (25 %)	8 (100 %)	1 (12,5 %)	0 (0 %)	7 (87,5 %)	8 (100 %)	8 (100 %)	0 (0 %)	0 (0 %)	8 (100 %)
BOT-M	12 (80 %)	3 (20 %)	0 (0 %)	15 (100 %)	10 (66,7 %)	4 (26,7 %)	1 (6,7 %)	15 (100 %)	6 (40 %)	5 (33,3 %)	4 (26,7 %)	15 (100 %)
CA	6 (85.7 %)	0 (0 %)	1 (14.3 %)	7 (100 %)	2 (28.6 %)	4 (57.1 %)	1 (14.3 %)	7 (100 %)	4 (57.1 %)	1 (14.3 %)	2 (28.6 %)	7 (100 %)

Met (Metastasis), BOT-SM (Borderline seromucinous), BOT-M (Borderline mucinous), CA (primary mucinous adenocarcinoma)

*Shedding or peeling while staining procedure of TMA slides was observed in 3 cases

**Shedding or peeling was observed 3 cases

***Shedding or peeling was observed in 5 cases

Role of PAX2, PAX8 and CDX2 in Distinguishing Primary/Metastasis and Mucinous/Seromucinous *p* values obtained after statistical analysis were shown in Table 4. Accordingly, PAX2, PAX8 and CDX2 scores were statistically significant (this significance continues even when the seromucinous group expressing strongly PAX8 was removed).

Metastatic Mucinous Tumors Expressing PAX2 or PAX8 Contrary to the statistical significance of results and general tendency, some metastatic mucinous tumors expressed PAX2 or PAX8. 7 cases among all metastatic tumors were incompatible by demonstrating PAX2 or PAX8 expression. 3 of those were metastatic from appendix, 1 was from colon, 1 was from stomach and 2 of those were in the group with an unknown primary.

PAX8 Heterogeneity in Mucinous Tumors All mucinous/seromucinous tumor results were re-examined after the documentation of diffuse and strong PAX8 expression in seromucinous tumors (7 out of 8 seromucinous tumors) was completed. 7 of the mucinous tumors included in the study demonstrate more staining with PAX8 and 9 of them demonstrate more staining with CDX2. 6 mucinous tumors did not have any staining distribution and intensity to clearly demonstrate any CDX2 or PAX8 dominance.

Discussion

Since the first classification of epithelial tumors of ovary in the 19th century, remarkable progress has been achieved, and particularly significant changes were observed regarding the serous tumor pathogenesis. As to the present situation, it is stated that there is no entity as the epithelial ovarian tumor; its origin is tubal epithelial for serous tumors, endometriosis for endometrioid and clear cell tumors, transitional metaplasia in the tuba peritoneal junction – possibly – for mucinous tumors [18]. Moreover, testicle (a homologous organ of ovary) does not have "epithelial testicle tumor" is explained with the fact that males do not possess endometriosis and tuba uterina [18].

Considering the mucinous ovarian tumors, pathogenesis of the ovarian tumors is still a mystery. Researchers showed great interest in the matter based on the companion of mucinous epithelium with the other primary tumors of ovary (such as Brenner, teratoma, Sertoli-Leydig cell tumor including heterologous element) and the metastatic tumor's successful mimicry of the primary ovarian tumor. Since the first mucinous tumor excision of Dr. Ephraim McDowell [19], there has been important progress for pathogenesis and differential diagnose. After it was proven that most of the mucinous adenocarcinomas (previously known as the 10 % of all epithelial tumors) are the metastatic tumors to the ovary in many reported cases, it was revealed that primary mucinous adenocarcinomas are very rare tumor of the ovary (3 % of all ovarian tumor based on current statistics) [1].

To overcome the difficulty in diagnosis, new markers are arising each day to distinguish metastatic-primary mucinous tumor. It has been shown that primary-metastatic distinction can be possible with the combined evaluation of morphological, clinical and radiological data [[20]]. Recent studies have showed that the use of PAX2 and PAX8 immunomarkers are functional markers for revealing the origin of metastasis in many organs. For instance, they are useful to distinguish PAX8 positive tumors (kidney, primary or metastatic mullerian system tumors except mucinous tumors, thymus, and thyroid) from PAX8 negative tumors (adrenal, breast, gastrointestinal system, and lung, prostate) [6, 21, 22]. It is even a marker in routine practice to distinguish serous ovarian adenocarcinomas from breast adenocarcinomas or mesothelioma [6, 7]. There are limited studies in literature about PAX expressions in mucinous tumors. None of these takes the histologic type or the metastatic origin into account (whether it is seromucinous or mucinous). Review of the literature was listed in Tables 5 and 6.

The study is empowered by the fact that 78 % of the metastatic cases selected in the study have primary biopsy diagnosis proven with pathology report. The most important factor to relieve the pathologist during decision-making process for primary or metastatic in mucinous tumors is the existence of morphologically similar primary tumor, and it is important for reliability to have primary biopsy in many cases. When the results of the study are considered, it is seen that most of the metastatic cases (85–90 %) are negative with PAX2 and PAX8, while majority of them (68.2 %) show diffuse and strong reaction with CDX2. Results are statistically significant.

Although as our study showed positive/negative predictive values of staining distribution, intensity and "scores" of PAX8

Table 4 Statistical results of different combinations

Comparisons between ovarian tumor diagnosis	PAX2 score *p* value	PAX8 score *p* value	CDX2 score *p* value
All of the primary mucinous tumors VS Metastasis	0.000	0.000	0.000
BOT-SM VS (BOT-M + CA)	0.629	0.001	0.013
(BOT-M + CA) VS Metastasis	0.001	0.001	0.004

*BOT-SM (Borderline seromucinous), BOT-M (Borderline mucinous), CA (primary mucinous adenocarcinoma)

Table 5 PAX8 Expressions; Review of the English Literature

Study	Diagnosis	Number of PAX8 positive cases	Number of mucinous tumor in the study	Percentage of PAX8 positive cases to all mucinous cases (%)
Kobel et al. [23]	CA	2	31	6,4
Nonaka et al. [24]	CA	1	12	8,3
Ozcan et al. [7]	CA	4	10	4
Ozcan et al. [6]	BOT-M/C	3	13	23
Laury et al. [21]	CA	10	25	40
Chu P.G et al. [4]	CA	3	19	15
Tabrizi et al. [25]	CA	0	30	0

BOT-M (Borderline mucinous), CA (primary mucinous adenocarcinoma), C (Cystadenoma)

and CDX2 are very similar to each other combined evaluation of both staining distribution and staining intensity in routine practice may create more correct results.

Another interesting issue with respect to mucinous tumors is the "seromucinous type" tumor group. It has been found that this group is different than the mucinous tumors within the endometriosis related tumor group and shows ARID1 gene mutation [10, 26]. Lastly in WHO 2014 classification seromucinous tumors are not classified as a subtype of mucinous tumor; they are categorized as a distinct ovarian tumor. Additionally, textbooks include information that they are rare tumors, constitute 15 % of all borderline tumors, are observed at younger ages compared to other primary mucinous tumors, have a tendency [27] to become bilateral more often. In our case series, seromucinous borderline tumors make up the 34.7 % of all borderline mucinous tumor cases which is more than double of the expected number. Researches need to be conducted to understand whether they vary in different populations. No significant clinical difference was found compared to the other primary tumors with respect to being bilateral. It is also statistically significant that they were seen at younger ages than the other primary tumors which were compatible with the present literature.

None of the studies in the literature on the mucinous tumor and PAX expression, showed expression differences based on the type of mucinous tumor, mucinous or seromucinous. There was no attempt to put forward a pathogenetical mechanism based on PAX2 or PAX8 expressions. The results of the study revealed that seromucinous tumor had no CDX2 expression and that all cases (except 1) had strong diffuse positive with PAX8. That means, seromucinous tumors have a different staining pattern for PAX8 and CDX2 than and primary mucinous tumors (p = 0.000–0.013). Just like the pelvic serous tumors, they also express a mullerian marker PAX8.

We also see that mucinous tumors are not as homogenous as seromucinous tumors. One cluster of mucinous ovarian tumors (8 of them) expresses diffuse and strong PAX8, while the other cluster (9 of them) expresses diffuse and strong CDX2. Some mucinous tumors (6 of them) allow selecting neither CDX2 nor PAX8 dominance. This gives the idea that the mucinous tumors are heterogeneous tumors. As it is known that the seromucinous tumors are developed from a different pathway than the other primary tumors, our findings may indicate that the one cluster of the mucinous tumors has mullerian origin as the seromucinous tumors and even the serous tumors, that one cluster may develop as colon tumors (such as FAP and Lynch), and that one cluster may develop from a different pathway or from multiple pathways.

The restraining aspects of the study are the fact that only 76 cases are included in the study and immunohistochemistry is applied to TMA blocks. Even though it is attempted to select independent points for TMA preparation when dealing with this technique, it may not be realistic to give distribution information. In addition, truth of intensity results may be affected by the heterogeneity of the fixation periods of the tissues. Besides, the study is interesting as summarizing the literature about mucinous tumor's PAX2-PAX8 expressions. It is also promising for distinguishing primary and metastatic tumor and reveals the

Table 6 PAX2 Expressions; Review of the English Literature

Study	Diagnosis	Number of PAX2 positive cases	Number of mucinous tumor in the study	Percentage of PAX2 positive cases to all mucinous cases (%)
Tabrizi et al. [25]	CA	1	30	3,3
Ozcan et al. [6]	BOT-M/C	4	21	19
Ozcan et al. [6]	CA	0	9	0

BOT-M (Borderline mucinous), CA (primary mucinous adenocarcinoma), C (Cystadenoma)

diffuse and strong PAX8 expression in seromucinous borderline tumors, and may suggest an idea for pathogenesis. Findings are pioneers for future full section studies. Our study can be considered as a preliminary study of whole slide studies with wide series, to be done in comparison with the so far usual and conventional markers as CK7 and CK20.

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Compliance with Ethical Standards

Conflict of Interest We declare that we have no conflict of interest.

References

1. Seidman JD, Kurman RJ, Ronnett BM (2003) Primary and metastatic mucinous adenocarcinomas in the ovaries: incidence in routine practice with a new approach to improve intraoperative diagnosis. Am J Surg Pathol 27(7):985–993
2. Ulbright TM, Roth LM, Stehman FB (1984) Secondary ovarian neoplasia. A clinicopathologic study of 35 cases. Cancer 53(5):1164–1174
3. Lagendijk JH, Mullink H, Van Diest PJ, Meijer GA, Meijer CJ (1998) Tracing the origin of adenocarcinomas with unknown primary using immunohistochemistry: differential diagnosis between colonic and ovarian carcinomas as primary sites. Hum Pathol 29(5):491–497
4. Chu PG, Chung L, Weiss LM, Lau SK (2011) Determining the site of origin of mucinous adenocarcinoma: an immunohistochemical study of 175 cases. Am J Surg Pathol 35(12):1830–1836
5. Zhai QJ, Ozcan A, Hamilton C, Shen SS, Coffey D, Krishnan B, Truong LD (2010) PAX-2 expression in non-neoplastic, primary neoplastic, and metastatic neoplastic tissue: a comprehensive immunohistochemical study. Appl Immunohistochem Mol Morphol 18(4):323–332
6. Ozcan A, Liles N, Coffey D, Shen SS, Truong LD (2011) PAX2 and PAX8 expression in primary and metastatic mullerian epithelial tumors: a comprehensive comparison. Am J Surg Pathol 35(12):1837–1847
7. Ozcan A, Shen SS, Hamilton C, Anjana K, Coffey D, Krishnan B, Truong LD (2011) PAX 8 expression in non-neoplastic tissues, primary tumors, and metastatic tumors: a comprehensive immunohistochemical study. Mod Pathol 24(6):751–764
8. Jones JM, Cui XS, Medina D, Donehower LA (1999) Heterozygosity of p21WAF1/CIP1 enhances tumor cell proliferation and cyclin D1-associated kinase activity in a murine mammary cancer model. Cell Growth Differ 10(4):213–222
9. Wiegand KC, Shah SP, Al-Agha OM, Zhao Y, Tse K, Zeng T, Senz J, McConechy MK, Anglesio MS, Kalloger SE, Yang W, Heravi-Moussavi A, Giuliany R, Chow C, Fee J, Zayed A, Prentice L, Melnyk N, Turashvili G, Delaney AD, Madore J, Yip S, McPherson AW, Ha G, Bell L, Fereday S, Tam A, Galletta L, Tonin PN, Provencher D, Miller D, Jones SJ, Moore RA, Morin GB, Oloumi A, Boyd N, Aparicio SA, Shih Ie M, Mes-Masson AM, Bowtell DD, Hirst M, Gilks B, Marra MA, Huntsman DG (2010) ARID1A mutations in endometriosis-associated ovarian carcinomas. New Engl J Med 363(16):1532–1543
10. Wu CH, Mao TL, Vang R, Ayhan A, Wang TL, Kurman RJ, Shih Ie M (2012) Endocervical-type mucinous borderline tumors are related to endometrioid tumors based on mutation and loss of expression of ARID1A. Int J Gynecol Pathol 31(4):297–303
11. Okada S, Ohaki Y, Ogura J, Ishihara M, Kawamura T, Kumazaki T (2004) Computed tomography and magnetic resonance imaging findings in cases of dermoid cyst coexisting with surface epithelial tumors in the same ovary. J Comput Assist Tomogr 28(2):169–173
12. Ueda G, Sawada M, Ogawa H, Tanizawa O, Tsujimoto M (1993) Immunohistochemical study of cytokeratin 7 for the differential diagnosis of adenocarcinomas in the ovary. Gynecol Oncol 51(2): 219–223. doi:10.1006/gyno.1993.1276
13. Kerr SE, Flotte AB, McFalls MJ, Vrana JA, Halling KC, Bell DA (2013) Matching maternal isodisomy in mucinous carcinomas and associated ovarian teratomas provides evidence of germ cell derivation for some mucinous ovarian tumors. Am J Surg Pathol 37(8): 1229–1235
14. Seidman JD, Khedmati F (2008) Exploring the histogenesis of ovarian mucinous and transitional cell (brenner) neoplasms and their relationship with walthard cell nests: a study of 120 tumors. Arch Pathol Lab Med 132(11):1753–1760
15. Cuatrecasas M, Villanueva A, Matias-Guiu X, Prat J (1997) K-ras mutations in mucinous ovarian tumors: a clinicopathologic and molecular study of 95 cases. Cancer 79(8):1581–1586
16. Heinzelmann-Schwarz VA, Gardiner-Garden M, Henshall SM, Scurry JP, Scolyer RA, Smith AN, Bali A, Vanden Bergh P, Baron-Hay S, Scott C, Fink D, Hacker NF, Sutherland RL, O'Brien PM (2006) A distinct molecular profile associated with mucinous epithelial ovarian cancer. Brit J Cancer 94(6):904–913
17. Ronnett BM, Kajdacsy-Balla A, Gilks CB, Merino MJ, Silva E, Werness BA, Young RH (2004) Mucinous borderline ovarian tumors: points of general agreement and persistent controversies regarding nomenclature, diagnostic criteria, and behavior. Hum Pathol 35(8):949–960
18. Kurman RJ, Shih Ie M (2010) The origin and pathogenesis of epithelial ovarian cancer: a proposed unifying theory. Am J Surg Pathol 34(3):433–443. doi:10.1097/PAS.0b013e3181cf3d79
19. McMahon CP (2000) Ephraim McDowell, jane todd crawford, and the origins of oophorectomy. N C Med J 61(1):401–402
20. Pinto PB, Derchain SF, Andrade LA (2012) Metastatic mucinous carcinomas in the ovary: a practical approach to diagnosis related to gross aspects and to immunohistochemical evaluation. Int J Gynecol Pathol 31(4):313–318. doi:10.1097/PGP.0b013e31823f844d
21. Laury AR, Perets R, Piao H, Krane JF, Barletta JA, French C, Chirieac LR, Lis R, Loda M, Hornick JL, Drapkin R, Hirsch MS (2011) A comprehensive analysis of PAX8 expression in human epithelial tumors. Am J Surg Pathol 35(6):816–826. doi:10.1097/PAS.0b013e318216c112
22. Pickel H, Tamussino K (2003) History of gynecological pathology: XIV. Hermann johannes pfannenstiel. Int J Gynecol Pathol 22(3): 310–314. doi:10.1097/01.PGP.0000070844.85581.A1
23. Kobel M, Kalloger SE, Boyd N, McKinney S, Mehl E, Palmer C, Leung S, Bowen NJ, Ionescu DN, Rajput A, Prentice LM, Miller D, Santos J, Swenerton K, Gilks CB, Huntsman D (2008) Ovarian carcinoma subtypes are different diseases: implications for biomarker studies. PLoS Med 5(12):e232. doi:10.1371/journal.pmed.0050232
24. Nonaka D, Chiriboga L, Soslow RA (2008) Expression of pax8 as a useful marker in distinguishing ovarian carcinomas from mammary carcinomas. Am J Surg Pathol 32(10):1566–1571
25. Tabrizi AD, Kalloger SE, Kobel M, Cipollone J, Roskelley CD, Mehl E, Gilks CB (2010) Primary ovarian mucinous carcinoma of intestinal type: significance of pattern of invasion and immunohistochemical expression profile in a series of 31 cases. Int J Gynecol Pathol 29(2):99–107
26. Maeda D, Shih Ie M (2013) Pathogenesis and the role of ARID1A mutation in endometriosis-related ovarian neoplasms. Adv Anat Pathol 20(1):45–52
27. Blaustein A, Kurman RJ (2011) Blaustein's pathology of the female genital tract, 6th edn. Springer, New York, NY p 736–739