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Napsin-A and AMACR are superior to HNF-1β in distinguishing between mesonephric carcinomas and clear cell carcinomas of the gynecologic tract

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Abstract

Mesonephric carcinoma is a rare gynecologic neoplasm commonly mistaken for clear cell carcinoma, due to their overlapping morphologic features. Both tumors are negative for estrogen receptor (ER) and p16, magnifying this diagnostic dilemma. Recently, HNF-1β, a marker for clear cell carcinoma, has also been shown to be positive in mesonephric carcinomas. Other more recent markers for clear cell carcinoma, however, such as Napsin-A and AMACR, have not yet been studied in mesonephric carcinomas. Here, we examine HNF-1β, AMACR, and Napsin-A immunohistochemistry in 18 mesonephric and 55 endometrial/cervical clear cell carcinomas. HNF-1β was considered positive if nuclear staining was present in ≥70% of cells and ≥ moderate intensity; for Napsin-A and AMACR any cytoplasmic staining was considered positive (≥1%). H-scores were determined by multiplying the intensity score by proportion score. HNF-1β was positive in a substantial portion of mesonephric carcinomas (9/18, 50%; H-score 98) and clear cell carcinomas (34/55, 62%; H-score 163) and did not distinguish between the two entities (specificity: 50%; p-value of H-score: 0.08). Napsin-A and AMACR expression was significantly higher in clear cell [43/55 (62%) and 41/55 (75%), respectively] than mesonephric carcinomas [4/18 (22%) and 4/18 (22%) respectively], and helpful in this differential (specificity: 78% and 78%; p-values <0.05 for both). When Napsin-A and AMACR staining were seen in mesonephric carcinomas, staining was focal (≤ 5%), while staining in clear cell carcinomas was patchy/diffuse. In summary, Napsin-A and AMACR are helpful in distinguishing mesonephric carcinomas from clear cell carcinomas of the female genital tract, but HNF-1β is not.

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Keywords

mesonephric carcinoma; clear cell carcinoma; Napsin-A; AMACR; HNF-1β

INTRODUCTION

Mesonephric carcinomas are rare and aggressive[1,2] gynecologic neoplasms thought to arise from remnants of the embryologic Wolffian (also known as mesonephric) duct. Mesonephric carcinoma most frequently involves the cervix, where mesonephric remnants are common, but it can also develop within any structure that passes along the primitive mesonephric duct, including the ovaries, broad ligament, uterus and vagina[1,3].

Mesonephric carcinoma has many histologic patterns, which can vary within the same tumor and between cases, making the diagnosis incredibly difficult. The classic histologic patterns of mesonephric carcinoma are tubular, consisting of small back-to-back tubules lined by cuboidal epithelium and filled with intraluminal eosinophilic secretions, and ductal, consisting of larger glands lined by columnar epithelium and also referred to as the “pseudo-endometrioid” pattern[4,5]. Mesonephric carcinoma can also exhibit many other architectural patterns, including retiform, papillary, solid, spindled, and sex-cord like, and cytologic features, including hobnail cells and clear cells[4,6,7].

In the early stages of discovery, mesonephric carcinomas were not infrequently confused with clear cell carcinomas[8,7,9]. Between the 1940s and 1970s, tumors thought to represent mesonephric carcinoma were designated a variety of names, including “mesonephroma” and “clear cell adenocarcinoma of mesonephric origin”[9,10,11,12]. These tumors were made of “clear or hobnail” cells arranged in “cysts, tubules and solid masses”[7,9]. Due to their resemblance to renal cell carcinoma of the kidney, an organ which is partially derived from the mesonephric duct, many authors believed these tumors to be of mesonephric origin[10,9]. It was later explicated that a large subset of these tumors actually represented clear cell carcinomas of Mullerian origin, as many of these tumors were associated with endometriosis[9,11,12]. This period of discovery was also confounded by the use of DES (diethylstilbestrol) in pregnant women at the time, which had the inadvertent effects of increasing the rates of clear cell carcinomas affecting the gynecologic tract[13]. It is not surprising that clear cell carcinomas were misconstrued for mesonephric carcinomas. Both tumors affect the gynecologic tract (particularly the cervix), both are human papillomavirus (HPV) independent and both tumors can exhibit overlapping histologic features[14,15]. Similar to mesonephric carcinoma, clear cell carcinoma exhibits papillary, solid, and tubulocystic (small tubular) architecture, predominantly cuboidal cells, and cytologic hobnailing[15]. Distinction between the two tumors remains, even in present day, very challenging. This problem is further complicated by their shared immunohistochemical profile. Estrogen receptor (ER) and p16, two of the most commonly used immunohistochemical markers in the diagnosis of adenocarcinomas of the cervix, are negative in both tumors[1,16–19,20,21,22].

HNF-1β was identified as a useful marker for clear cell carcinoma of the gynecologic tract in 2003[23], and has been subsequently validated in many studies[21,24,20,22,25]. HNF-1β is a homeobox transcription factor that plays a role in glucose homeostasis, anti-apoptosis and

the embryologic development of urogenital organs[23,26]. Unexpectedly, HNF-1β was also found to be positive in a subset of mesonephric carcinomas[17]. Subsequent to HNF-1β, additional markers for clear cell carcinoma have been reported, which include Napsin-A[27,24,21,20,28,22] and AMACR (alpha-Methylacyl-CoA racemase, p504S)[29,24]. Napsin-A is an aspartic protease, better known for its role in processing pulmonary surfactant in the lung and was initially discovered in studies exploring napsin's ability to separate primary and metastatic tumors in the lung[30,31]. AMACR (p504s) is an enzyme involved in the oxidation of branched chain fatty acids and is better known for its diagnostic role in separating prostatic adenocarcinoma from normal prostatic tissue, discovered via gene expression profiling (cDNA microarrays)[32]. Its usefulness in the diagnosis of clear cell carcinomas of the gynecologic tract was sparked by the detection of AMACR in clear cell carcinomas of the bladder/urethra[29].

To the best of our knowledge, no studies have compared the expression of HNF-1β, Napsin-A and AMACR in mesonephric carcinomas. Given the common confusion between mesonephric carcinomas and clear cell carcinomas, the goal of our study was to compare the usefulness of HNF-1β, Napsin-A and AMACR in separating clear cell carcinomas and mesonephric carcinomas in the gynecologic tract.

MATERIALS AND METHODS

Study Cases

Cases were acquired from the anatomical pathology archives of Vancouver General Hospital (VGH) and Memorial Sloan Kettering Cancer Center (MSK). All gynecologic tumors were identified by searching the pathology intranet database (1986–2018). All mesonephric neoplasms were reviewed by a gynecologic subspecialty pathologist (LH, KP). Diagnoses made on prior biopsy by the primary pathologists were also recorded if available.

Tissue Microarrays

Hematoxylin and eosin (H&E) stained slides of endocervical and endometrial clear cell carcinomas were reviewed by a gynecologic subspecialty pathologist (LH, BTC). A slide with representative tumor was selected from each case. The area of tumor was circled on the slide and corresponding formalin-fixed paraffin embedded (FFPE) tissue block. Duplicate 0.6 mm cores were taken from each case for tissue microarray (TMA) construction.

Immunohistochemistry

Immunohistochemical stains were performed on 4-μm thickness whole tissue sections for the mesonephric neoplasms and on TMA sections for the clear cell carcinomas. This was done using the Ventana Discovery XT and Ventana Benchmark XT systems (Ventana Medical Systems, Tucson, AZ) following manufacturer recommendations. Sections were cut onto charged glass slides, air dried for 10 minutes and baked at 60°C for 10 minutes. Cell conditioning solution CC1 (Ventana), heat induced antigen retrieval (37°C for 32 minutes) and Ventana XT Optiview DAB detection kit was used for all antibodies.

The following immunohistochemical stains were performed: HNF-1β, Napsin-A, and AMACR. At VGH, the rabbit polyclonal HNF-1β antibody (catalogue number HPA002083) was obtained from Sigma, while at MSK the mouse monoclonal antibody (clone: CLO374; catalogue number: AMAB90733) was obtained from Sigma. At both VGH and MSK the mouse monoclonal Napsin-A antibody (clone: 1p64; catalogue number: NCL-L-NAPSINA) was obtained from Leica. At VGH, the rabbit AMACR antibody (clone 13H4; catalogue number GA060) was obtained from DAKO, while at MSK the AMACR antibody (clone: 13H4; catalogue number: Z2001L) was obtained from Zeta Corp. All immunohistochemical stains were performed at VGH with the exception of the exception of 6 slides (HNF-1β for 4 cases, Napsin-A for 1 case, AMACR for 1 case), which were done at MSK. To assess concordance, 3 unstained slides were available and re-stained at VGH, which showed complete concordance with the results obtained from MSK.

Nuclear staining was considered positive staining for HNF-1β and cytoplasmic staining for Napsin-A and AMACR. For each stain, staining was quantified based on the percentage of tumor cells staining: negative (0%); focal (1% to 25%); patchy (26% to 49%); diffuse (≥50%), as well as the intensity of staining: 0 = none, 1+ = weak, 2+ = moderate, 3+ =strong. Modified histoscores (H-score) were calculated by multiplying the proportion of cells staining and the intensity, yielding H-scores between 0 to 300.

Statistical Analysis

For the calculation of binary classification test performance (sensitivity, specificity, negative predictive value (NPV), positive predictive value (PPV)), the stains were categorized into positive or negative. For Napsin-A and AMACR, any cytoplasmic immunohistochemical staining was considered positive (any tumor cells staining ≥1%). For HNF-1β immunohistochemical stain was considered positive only if staining was seen in ≥70% of cells and at least moderate intensity, as previously described[33]. Test scores for each marker were determined using an online statistical calculator (https://www.medcalc.org/calc/diagnostic_test.php) and using clear cell carcinoma as the test reference.

RESULTS

Clinical and Histologic Features of Study Cases

A cohort of 73 cases were examined that included 18 mesonephric neoplasms from various sites (8 cervical mesonephric carcinomas, 3 cervical mesonephric carcinosarcomas, 5 endometrial mesonephric-like carcinomas, and 2 pelvic masses) and 55 pure clear cell carcinomas from various sites (5 cervical, 50 endometrial). Thirteen mesonephric neoplasms have been described in a previous study[6].

The clinicopathologic features of patients with mesonephric neoplasms are summarized in Table 1. Patients with mesonephric neoplasms ranged in age from 30 to 75 years (mean age: 58 years). Information on stage was available for 16 tumors, and 8 of these (50%) were diagnosed at stage pT2 or above. The most common presenting symptoms were abnormal uterine bleeding and postmenopausal bleeding. The most common histologic patterns were tubular, papillary, and ductal (Figures 1–2). Biopsy diagnosis was available in 13 of 18

cases. The diagnosis of mesonephric carcinoma was not made on any of the prior biopsy sampling (Table 1). Mesonephric carcinomas were confused for endometrioid carcinoma (7 of 13 cases), clear cell carcinoma (1 of 13 cases), mixed endometrioid and serous carcinoma (1 of 13 cases), endometrial hyperplasia (1 of 13 cases), moderate to poorly differentiated cervical adenocarcinoma (2 of 13 cases), and Mullerian carcinosarcoma (1 of 13 cases).

The resection specimens in three cases were initially diagnosed as mixed cell carcinomas; two mixed endometrioid and mesonephric carcinomas, and one mixed mesonephric, clear cell and endometrioid carcinoma. Additional immunohistochemical stains were performed (ER and, in some cases, Napsin-A). All tumors were negative for ER, including the endometrioid-like areas. The tumor with a questionable clear cell carcinoma component was negative for Napsin-A. Given these findings, these three tumors were re-classified as pure mesonephric carcinomas.

Immunohistochemical Findings

The immunohistochemical findings are summarized in Tables 2-3 and Figures 3–4. HNF-1β showed staining in 9 of 18 cases (50%) of mesonephric carcinoma (1 endometrial, 7 cervical, and 1 pelvic mass) (Table 1). Eight of the 18 had staining in ≥70% of cells and at least moderate intensity. Fifty of 55 (91%) clear cell carcinomas demonstrated staining for HNF-1β, and 34/55 (67%) exhibited staining in ≥70% of cells and at least moderate intensity. The H-score for HNF-1β was higher in clear cell carcinoma compared to mesonephric carcinoma (163 vs 98), but was not statistically significant (p=0.08) (Figure 3). The specificity and PPV of HNF-1β for separating clear cell carcinoma from mesonephric carcinoma was 50% and 79% (Table 2).

Napsin-A showed focal positive staining in 4 of 18 (22%) mesonephric cases (2 endometrial, 2 cervical). The staining was intense (3+) in 3 of the 4 cases, but all focal or patchy (1%, 1%, 5% and 20% of tumor cells) in proportion. Napsin-A showed staining in 43 of 55 (78%) cases of clear cell carcinoma (4 focal, 15 patchy, 24 diffuse)(Figure 3). The H-score of Napsin-A was statistically higher in clear cell carcinoma compared to mesonephric carcinoma (59 vs 4) ($p<0.001$) (Figure 3). The specificity and PPV of Napsin-A for separating clear cell carcinomas from mesonephric carcinomas was higher than that for HNF-1β, 78% and 92% respectively (Table 2). If we set a cut-off of Napsin-A staining at 10%, which has been proposed previously[34], the specificity and PPV increases to 95% and 98% respectively.

AMACR showed focal positive staining in 4 of 18 mesonephric cases, all 4 were cervical. Staining intensity was moderate to strong (2+ to 3+) but proportion was focal to patchy (1%, 5%, 5% and 20% of cells) (Table 1). AMACR showed staining in 41 of 55 (75%) cases of clear cell carcinoma (9 focal, 10 patchy, 22 diffuse). The H-score of AMACR was statistically higher in clear cell carcinoma compared to mesonephric carcinoma (81 vs 2, $p<0.001$, Figure 3). The specificity and PPV for AMACR was very similar to that for Napsin-A (78% vs 78%, and 92% vs 91%, respectively) (Table 2).

There was no correlation between HNF-1β, Napsin-A and AMACR staining and morphologic pattern in the mesonephric carcinomas.

DISCUSSION

In our study, we examined HNF-1β, Napsin-A and AMACR immunohistochemistry in a series of 18 mesonephric carcinomas from various gynecologic sites and 55 endometrial and cervical clear cell carcinomas. Our results show that Napsin-A and AMACR are comparable, and that both are superior to HNF-1β in distinguishing between mesonephric carcinomas and clear cell carcinomas of the female genital tract.

Traditionally, before the advent of positive markers, clear cell carcinoma was diagnosed by its "negative phenotype" including lack of immunoreactivity for ER[24]. HNF-1β was the first "positive" marker identified for the diagnosis of ovarian clear cell carcinoma, and in the first cardinal study by Tsuchiya *et al.*, it was shown to be very sensitive and specific, with staining in 95% of clear cell carcinoma and only 2% of non-clear cell carcinomas[23]. Subsequent studies of clear cell carcinomas involving other gynecologic sites reiterated that, with few exceptions, HNF-1β is good marker for distinguishing clear cell carcinoma from serous and endometrioid carcinoma[21,22,28,20,19,18,35]. In the gynecologic tract, HNF-1β has also been shown to be positive in usual-type endocervical carcinomas, gastric-type endocervical carcinomas, ovarian clear cell tumors and ovarian yolk sac tumor[18,19,24,36] thus its usefulness is not global and is limited to context-specific scenarios. In the scenario of clear cell carcinoma versus mesonephric carcinoma, we found that HNF-1β was not useful, as it was positive in 39% of mesonephric carcinomas and 62% of clear cell carcinomas. Our findings align with the observations noted by Kenny *et al.*[17]. In their study, 3 of 8 (38%) mesonephric carcinomas were positive for HNF-1β and all 3 cases showed diffuse (≥50% of cells) staining. The only other report of HNF-1β is in a case report of a mesonephric-like carcinoma of the uterine corpus, which was negative for HNF-1β[16].

In the past few years, Napsin-A has been identified as a good immunohistochemical marker for clear cell carcinoma of the gynecologic tract, showing expression in 56% to 93% of endometrial[27,21,20,22], 82% to 93% of ovarian[24,20,22] and 70% to 71% of endocervical[22,28] clear cell carcinomas. Napsin-A has been reported to have superior specificity to HNF-1β[20,24]. Our study showed that Napsin-A was a helpful marker in distinguishing mesonephric and clear cell carcinomas, with a specificity of 78%. Napsin-A staining was very focal in 3 of the 4 mesonephric carcinomas that were positive, and was predominantly patchy/diffuse in clear cell carcinomas. If a diagnostic threshold for Napsin-A is set at ≥10% of cells, which was done previously by Yamashita *et al.*[34], the specificity increases to 95%. To the best of our knowledge, this is the first report of Napsin-A staining in mesonephric carcinomas.

AMACR expression has been reported to occur in up to 7% of endometrial carcinomas[37] and up to 7% of ovarian carcinomas[38], but the histotypes were not listed. Noske *et al.*[39] examined two cohorts of ovarian carcinoma (n=136 and n=252) and found AMACR staining in 11.8% and 5.4%, respectively. In the first cohort there was no correlation between AMACR staining and histologic subtype, but in the second cohort, AMACR expression was significantly related to the endometrioid and clear cell histotypes[39]. In 2013, Fadare *et al* performed a larger study where they evaluated the expression of AMACR in a series of 49 endometrial clear cell carcinomas, 13 endometrial serous carcinomas, and 49 endometrial

endometrioid carcinomas and showed AMACR to be highly sensitive (75%) and specific (79%) for the diagnosis of endometrial clear cell carcinoma[29]. This group also investigated the expression of AMACR in ovarian clear cell carcinomas, and found that, in this subset of tumors, it was highly specific (99%) but relatively less sensitive (82%) compared to Napsin-A and HNF-1β[24]. In our study, the findings for AMACR were very similar to that of Napsin-A. AMACR staining was seen in 4 out of 14 (22%) of mesonephric carcinoma, but tended to be focal, while staining in clear cell carcinomas was seen in 75% of cases and were more likely to be strong and diffuse. The specificity was the same as Napsin-A, 78%. There has been only one case report, documenting AMACR staining in a mesonephric carcinoma of the cervix[40]. In this report, the curettage was misdiagnosed as clear cell carcinoma due to the presence of papillary, glandular, tubular, hobnail cells and clear cells. The finding of adjacent mesonephric remnants and a pseudoendometrioid pattern that was ER negative, prompted the diagnosis of mesonephric carcinoma. This tumor was positive for AMACR and HNF-1β, and negative for Napsin-A.

In summary, in their classic forms, mesonephric and clear cell carcinoma are readily distinguished from each other, but present diagnostic challenges when they show overlapping morphology, particularly on small biopsies. In this study, we found that none of the 13 mesonephric carcinomas had an accurate diagnosis of mesonephric carcinoma made on biopsy. Immunohistochemistry is therefore a valuable tool in distinguishing between these two neoplasms. While HNF-1β, Napsin-A and AMACR have all been shown to be expressed in a variety of different tumor types across the body, these markers can be extremely helpful in specific diagnostic situations. In the scenario of mesonephric carcinoma versus clear cell carcinoma, Napsin-A and AMACR are helpful markers but HNF-1β is not.

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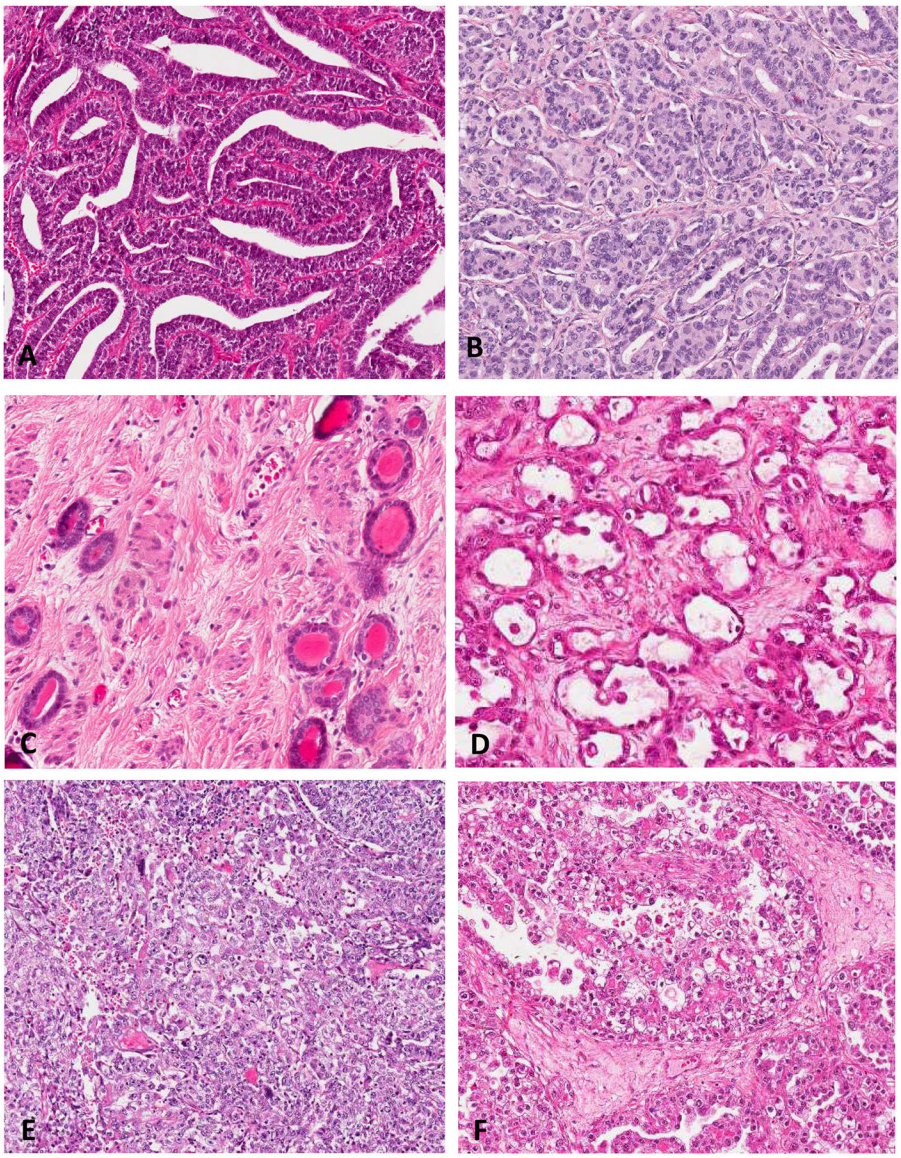

FIGURE 1.

Classic morphologic patterns of mesonephric carcinoma: Ductal (A); Tubular (B); often associated with adjacent mesonephric remnants (C). Classic morphologic patterns of clear cell carcinoma: Tubulocystic (D); Solid (E); and Papillary (F).

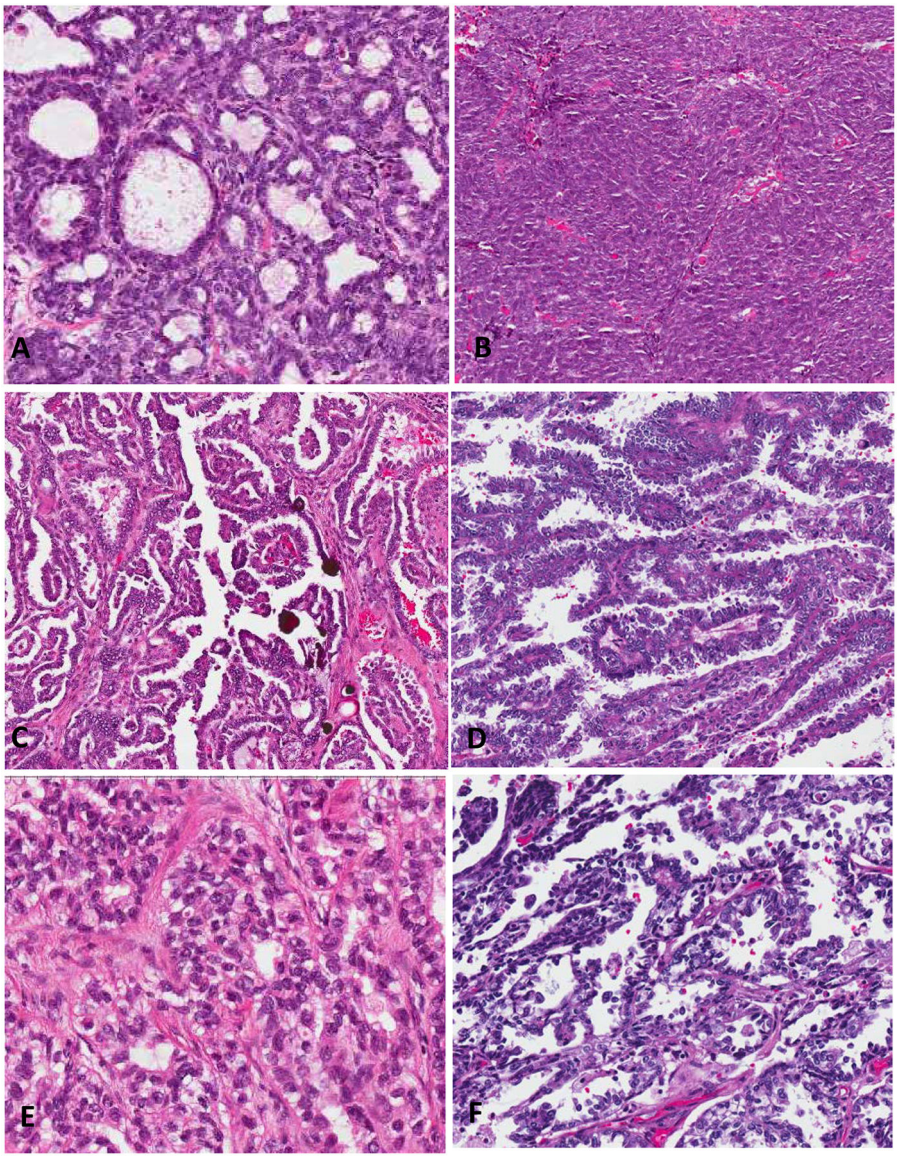

FIGURE 2.

Similar to clear cell carcinoma, mesonephric carcinoma can show Tubulocystic (A), Solid (B) and Papillary Areas (C-D) as well as cytologic clearing (E) and hobnailing (F).

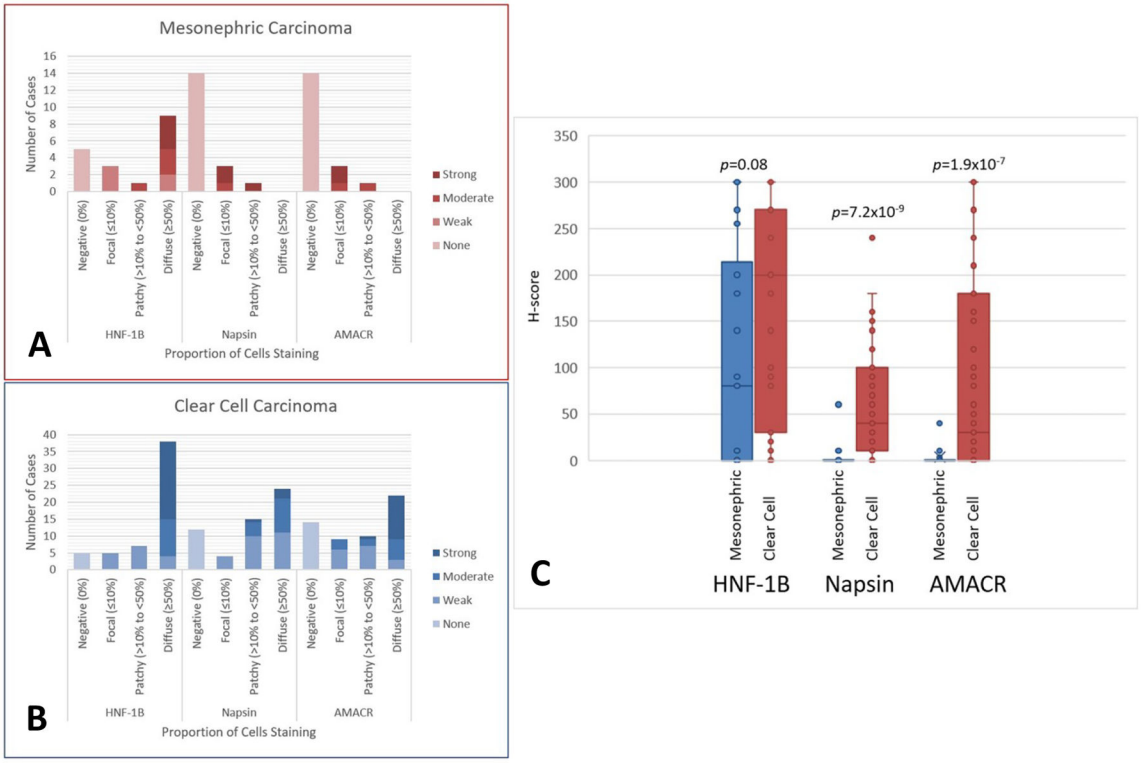

FIGURE 3.

Box plots demonstrating distribution of immunohistochemical staining in mesonephric carcinomas (A) and clear cell carcinomas (B). H-scores comparing mesonephric and clear cell carcinoma for each immunohistochemical marker.

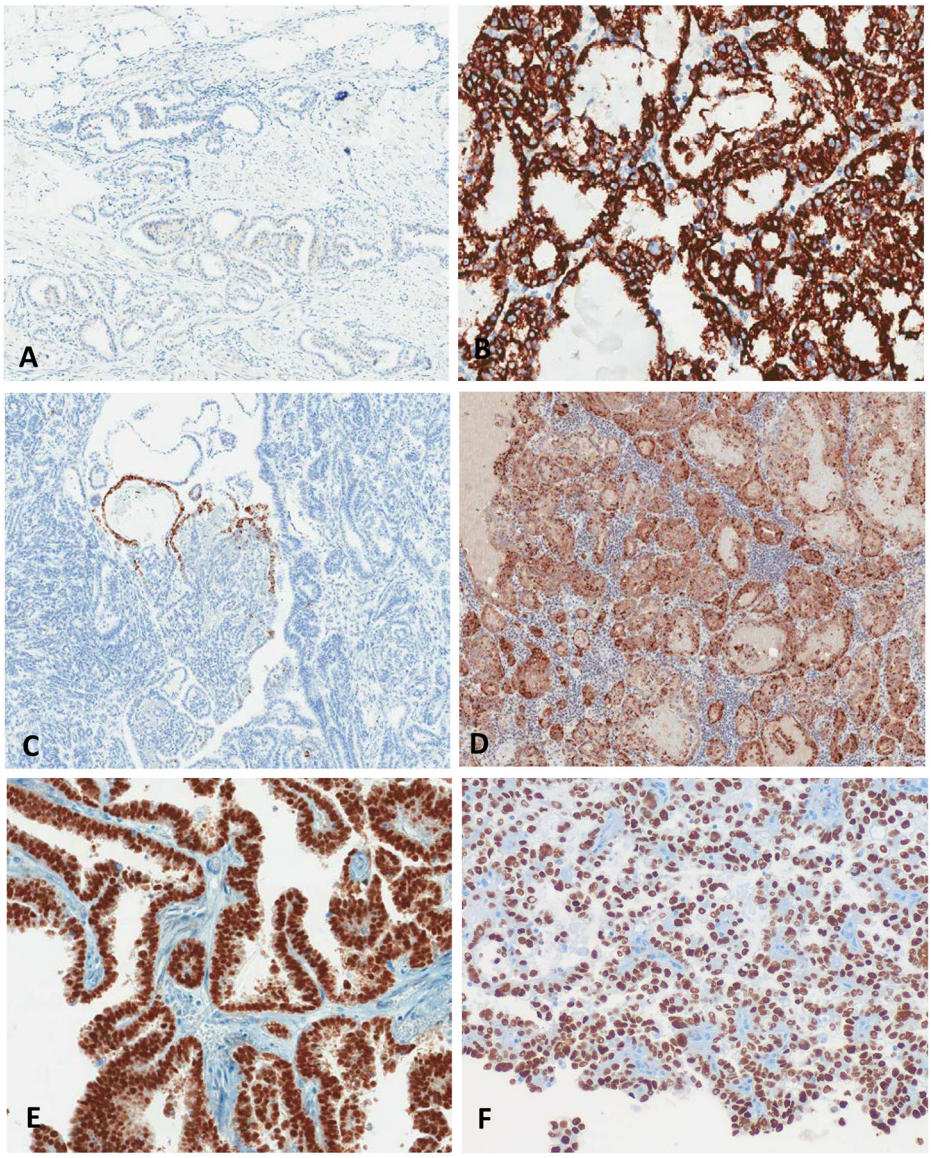

FIGURE 4.

Differential staining patterns in mesonephric carcinoma and clear cell carcinoma. Mesonephric carcinoma typically showed focal AMACR staining (A), focal Napsin A staining (C) and variable HNF-1β staining (E). By contrast, clear cell carcinoma usually showed diffuse AMACR (B) and Napsin A (D) staining, and variable HNF-1β (F) staining.

Table 1.

Summary of Clinical Features and immunohistochemical Findings in 18 Mesonephric Neoplasms

Case	Age	FIGO stage	Biopsy Diagnosis	Immunohistochemistry (Intensity; Proportion)		
				HNF-1β	Napsin-A	AMACR
Endometrial						
1	65	IVB	Clear cell CA	Negative	Negative	Negative
2	31	IIIA	Endometrioid CA, grade 1	Negative	+++; 1%	Negative
3	75	IB	Endometrioid CA, grade 2	+; 90%	+++; 1%	Negative
4	65	IA	Endometrioid CA, high-grade	Negative	Negative	Negative
5	65	IB	Endometrioid CA	Negative	Negative	Negative
Cervical						
6*	49	IIB	None**	Negative	Negative	Negative
7	78	IB1	Mixed endometrioid and serous	Negative	Negative	Negative
8	64	IB1	Endometrial hyperplasia	+++; 90%	Negative	Negative
9	50	IIIA	Endometrioid CA, grade 2	+++; 85%	Negative	+++; 1%
10	62	IIA2	Endometrioid CA, grade 1	+++; 100%	Negative	Negative
11*	59	IIB	Mullerian carcinosarcoma	+; 80%	Negative	Negative
12	43	IIB	Invasive endocervical adenocarcinoma, mod-poorly differentiated	++; 70%	+++, 20%	++, 5%
13	30	IB1	Invasive endocervical adenocarcinoma, poorly differentiated	Negative	Negative	+++, 5%
14	75	IB	Endometrioid CA, grade 3	Negative	Negative	Negative
15	----	----	None	++, 100%	Negative	Negative
16*	57	IB2	Unknown	++, 90%	+/++, 5%	++, 20%
Vaginal/Pelvic Mass						
17	66	III	None	+++; 100%	Negative	Negative
18	62	----	None	Negative	Negative	Negative

(+)Weak;

(++)Moderate;

(+++)Strong intensity staining

*Carcinosarcoma

**Thought to be a prolapsed cervical fibroid, therefore no biopsy was done

Table 2.

Immunohistochemical Staining and Test Performance of HNF-1β, Napsin-A, and AMACR in Mesonephric Carcinoma and Clear Cell Carcinoma[*].

Immunohistochemical stain	Mesonephric CA (n=18)	Clear cell CA (n=55)	Sensitivity	Specificity	PPV	NPV
HNF-1β+[**]	9/18 (50%)	34/55 (62%)	62%	50%	79%	30%
Napsin-A+	4/18 (22%)	43/55 (78%)	78%	78%	92%	54%
AMACR+	4/18 (22%)	41/55 (75%)	75%	78%	91%	50%

PPV, Positive predictive value; NPV, Negative predictive value

[*] Statistics were performed using clear cell carcinoma as the reference

[**] For HNF-1β, cases are considered positive if staining ≥70%, and at least moderate intensity