A Combined Morphologic and Molecular Approach to Retrospectively Identify KRAS-Mutated Mesonephric-like Adenocarcinomas of the Endometrium

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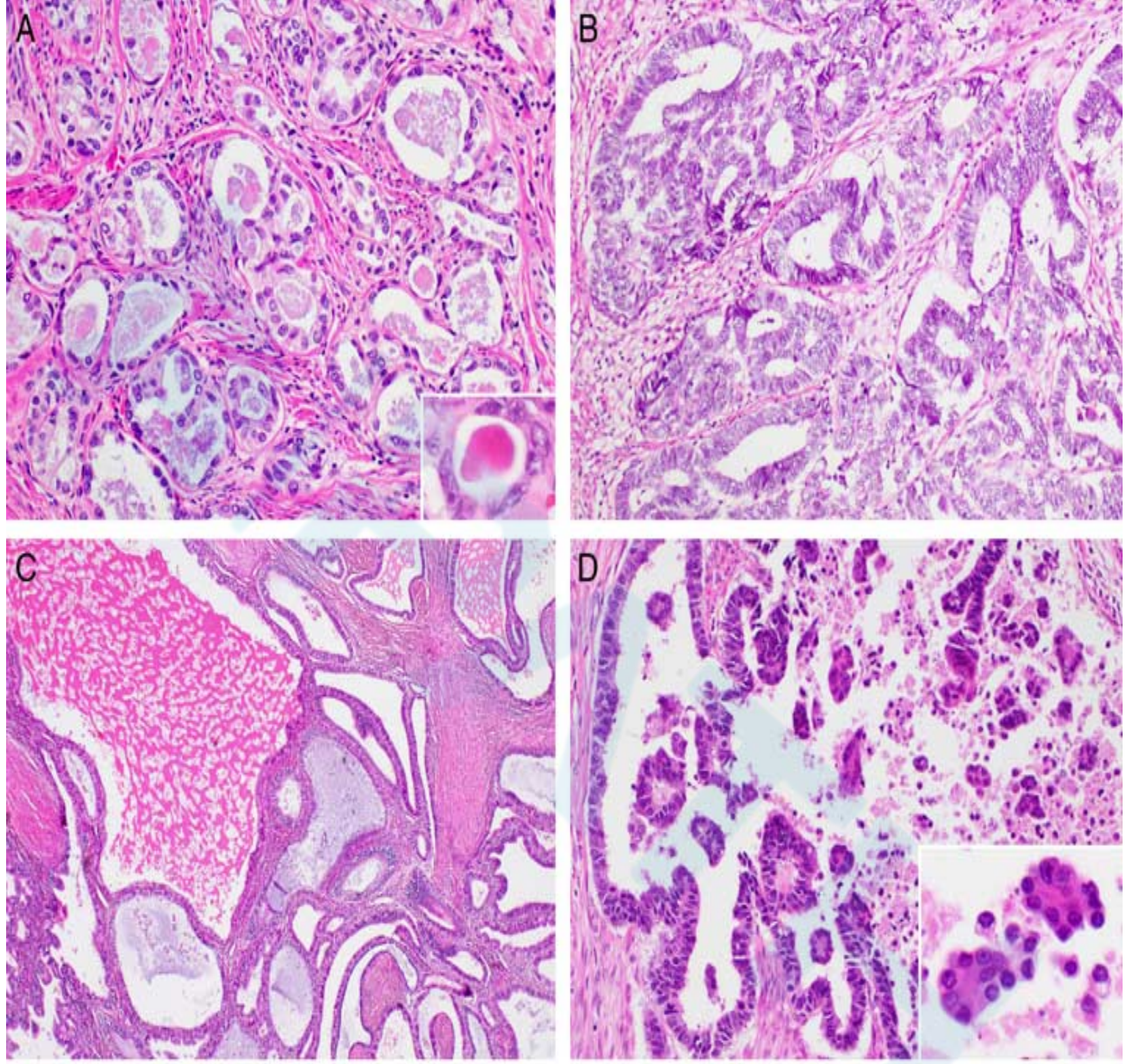
Background

- Mesonephric carcinomas are rare, aggressive tumors often associated with mesonephric hyperplasia/remnants and most commonly occur in the cervix.
- They have also been reported in the uterine corpus, often located deep in the myometrium and sometimes without endometrial involvement.
- An unusual subset of endometrial carcinomas, mesonephric-like adenocarcinomas, share morphologic, immunophenotypic, and molecular attributes with mesonephric carcinomas.

Background

- Mesonephric-like adenocarcinoma can also show a variety of histologic patterns including tubular, glandular, spindled, solid, and papillary. Eosinophilic, colloid-like, secretions are occasionally present in tubules.
- Some cases of mesonephric-like adenocarcinoma show areas of solid growth, comprised of spindle cells, mimicking carcinosarcoma.
- In contrast to mesonephric carcinomas of the cervix, mesonephric-like adenocarcinomas of the uterine corpus are not associated with mesonephric remnants.



A, Tubular pattern. The tubules are lined by a single layer of cuboidal cells and possess intraluminal eosinophilic material (inset).
B, Glandular pattern. The endometrioid-like glands are lined by several layers of columnar epithelium.
C, Glandular pattern. Some glands are cystically dilated and irregular in shape.
D, Papillary pattern. Note the intraluminal papillary projections and floating micropapillary tufts (inset).

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Background

- Recognizing this variant of endometrial carcinoma is challenging given their morphologic overlap with endometrioid carcinoma, serous carcinoma, and/or carcinosarcoma.
- Mesonephric-like adenocarcinomas have an immunophenotype that is identical to mesonephric carcinoma and distinct from other types of endometrial carcinoma. They are often positive for TTF-1,GATA-3, CD10 (luminal staining), and calretinin, and are negative for ER and PR.
- GATA-3 is a relatively sensitive and specific marker for mesonephric lesions; however, staining in mesonephric carcinomas may be weak and/or patchy, and demonstrate an inverse staining pattern with TTF-1.

Background

- Molecularly, both mesonephric-like adenocarcinoma and mesonephric carcinomas are characterized by KRAS mutations, microsatellite stability, and frequent gain of chromosome 1q.
- Molecular profiling of endometrial carcinomas has led to categorization into 4 molecular groups (POLE ultramutated, microsatellite instability [MSI] hypermutated, copy number low, and copy number high).
- KRAS mutations are seen in ~ 18% of endometrioid endometrial carcinomas, often associated with MSI and/or other common alterations seen in endometrial carcinoma, such as PTEN, PIK3CA, and PIK3R1 mutations

Background

- In this study, we used a rational combined molecular and morphologic approach to retrospectively identify cases of KRAS-mutated mesonephric-like endometrial adenocarcinomas. Identification of this unusual variant will allow for further study and assessment of clinical significance, and it is likely not as rare as currently reported.

MATERIALS AND METHODS

- The Institutional Review Boards of Brigham and Women's Hospital and Dana Farber Cancer Institute approved this study.
- Endometrial carcinomas with canonical KRAS mutations were identified from a database of 570 endometrial carcinomas.
- Representative slides were reviewed for histopathologic parameters, including tumor subtype, grade, and squamous and mucinous differentiation.
- Immunohistochemistry
- Targeted MPS

  MSI/MSS and the mutation status of KRAS and PTEN were recorded.

MATERIALS AND METHODS

TABLE 1. Clones, Dilutions, and Suppliers of Antibodies Used for Immunohistochemical Stains

Antibody	Clone	Dilution	Supplier
CD10	56C6	1:20	Cell Marque, Rocklin, CA
Chromogranin A	LK2H10	1:4000	ThermoScientific, Waltham, MA
ER	SP1	1:40	Fisher Scientific, Hampton, NH
GATA-3	L50-823	1:500	Biocare Medical, Pacheco, CA
WT-1	6F-H2	1:75	Dako, Carpinteria, CA
p63	4A4	1:100	Biocare Medical, Pacheco, CA
PAX-8	polyclonal	1:1000	Proteintech Group, Rosemont, IL
PR	PgR636	1:200	Dako, Carpinteria, CA
Synaptophysin	27612	1:100	Leica, Buffalo Grove, IL
Thyroglobulin	NB100-65184	1:500	Novus, Littleton, CO
TTF-1	8G7G3/1	1:500	Dako, Carpinteria, CA

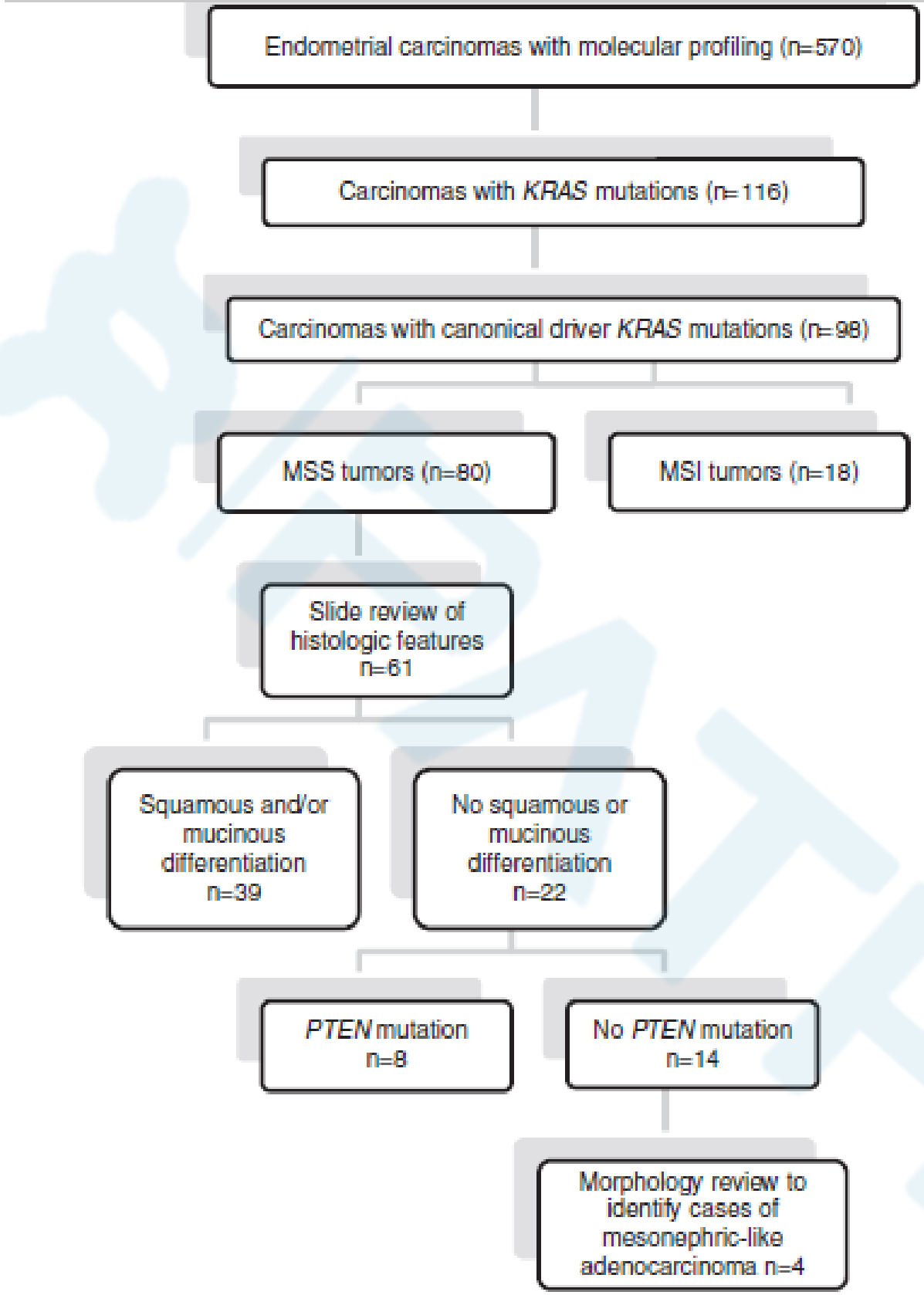

FIGURE 1. Algorithm used to identify cases of mesonephric-like adenocarcinoma amongst a cohort of endometrial carcinomas.

RESULTS

TABLE 2. Tumor Histotype, Microsatellite Status, and Histologic Features of Endometrial Carcinoma With Canonical *KRAS* Mutations

	n (%)	
	MSI (n = 18/98 [18%])	**MSS (n = 80/98 [82%])**
Histotype and grade		
Endometrioid	17/18 (94)	58/80 (72)
Grade 1	6/17 (35)	42/58 (72)
Grade 2	10/17 (59)	13/58 (22)
Grade 3	1/17 (6)	3/58 (5)
Serous	0	7/80 (9)
Carcinosarcoma	0	10/80 (12)
Mixed	0	3/80 (4)
Dedifferentiated carcinoma	1/18 (6)	0
Poorly differentiated carcinoma	0	2/80 (2)
Histologic features		
Mucinous differentiation	10/15 (67)	29/61 (48)
Squamous differentiation	9/15 (60)	23/61 (38)
Neither squamous nor mucinous differentiation	3/15 (20)	22/61 (36)
FIGO stage		
IA	10 (56)	39 (49)
IB	1 (6)	11 (14)
II	1 (6)	4 (5)
III	4 (22)	13 (16)
IV	0	6 (7)
Not staged	2 (11)	7 (9)

RESULTS

- The majority of these tumors were endometrioid (n=75, 77%).
- Most of these endometrioid tumors were grade 1(n=48, 64%).
- Half of the tumors were FIGO stage IA.
- Of the KRAS-mutated, MSS cases with morphology review, 39/61 (64%) had squamous and/or mucinous differentiation.

RESULTS

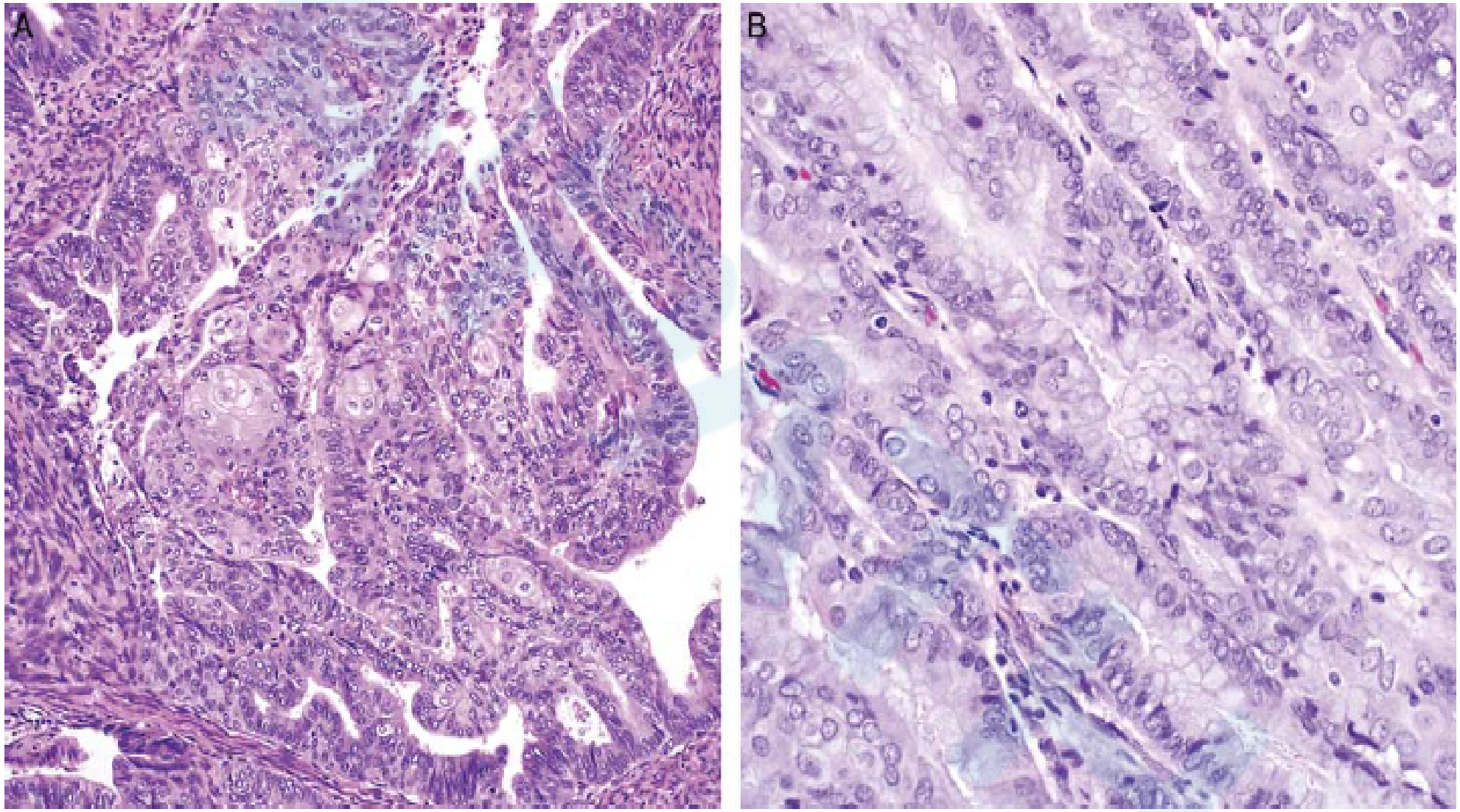

FIGURE 2. *KRAS*-mutated endometrioid adenocarcinomas frequently show areas of (A) squamous and (B) mucinous differentiation.

RESULTS

- 22 (36%) lacked these histotype defining features. Of these 22, 14 cases with a mesonephric-like adenocarcinoma-like molecular profile; these 14 cases underwent morphologic re-review. Of these 14 cases, 10 had morphology typical of: carcinosarcoma (4), serous (3), or endometrioid (3) carcinoma.

RESULTS

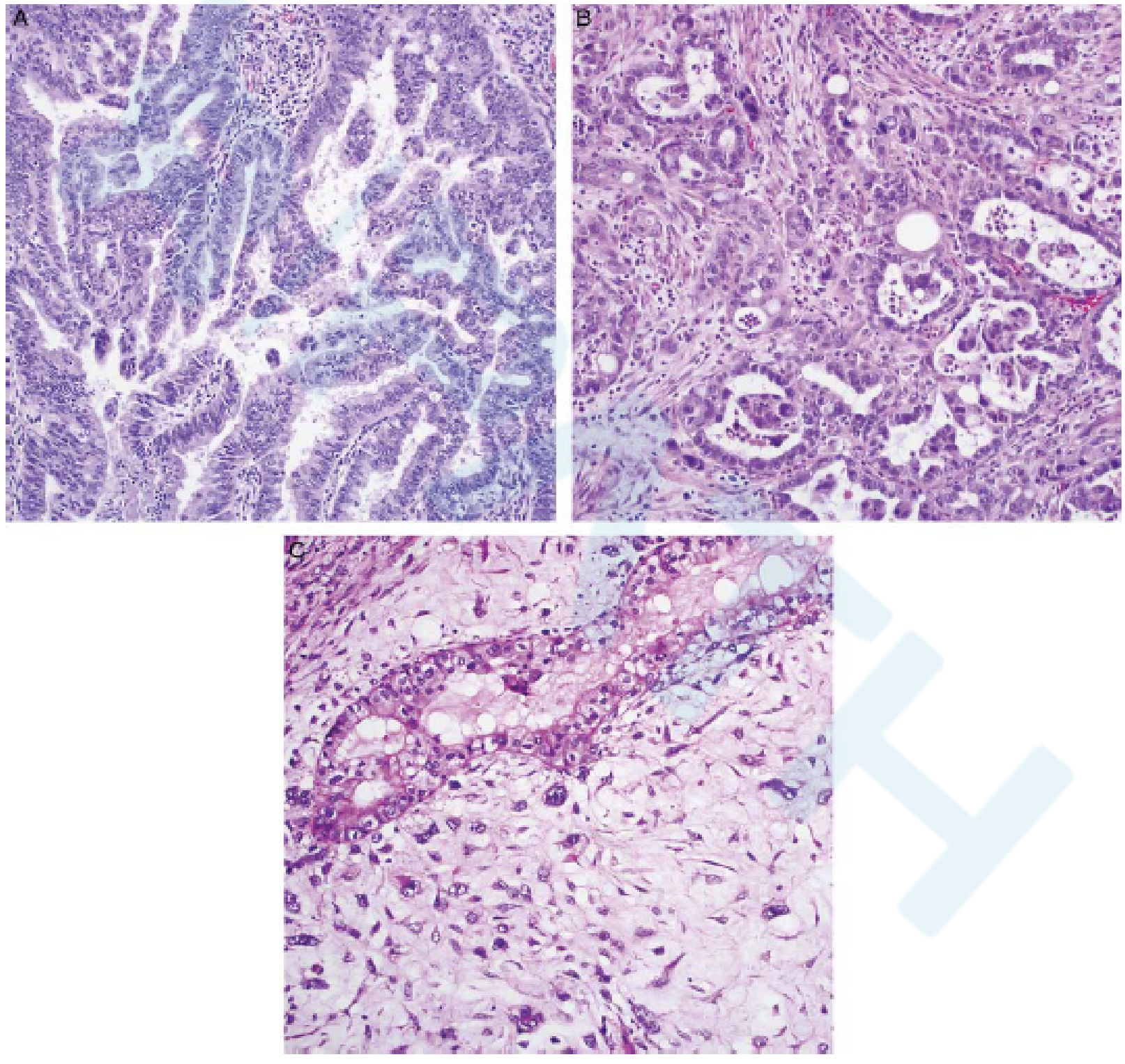

FIGURE 3. In addition to mesonephric-like adenocarcinoma, *KRAS*-mutated, MSS endometrial carcinomas may have other appearances, including (A) endometrioid, (B) serous, or (C) carcinosarcoma.

RESULTS

- In 4 cases, there was striking resemblance to mesonephric carcinoma, and thus were re-classified as mesonephric-like adenocarcinoma.
- The immunoprofiles were also in keeping with mesonephric-like adenocarcinoma.

RESULTS

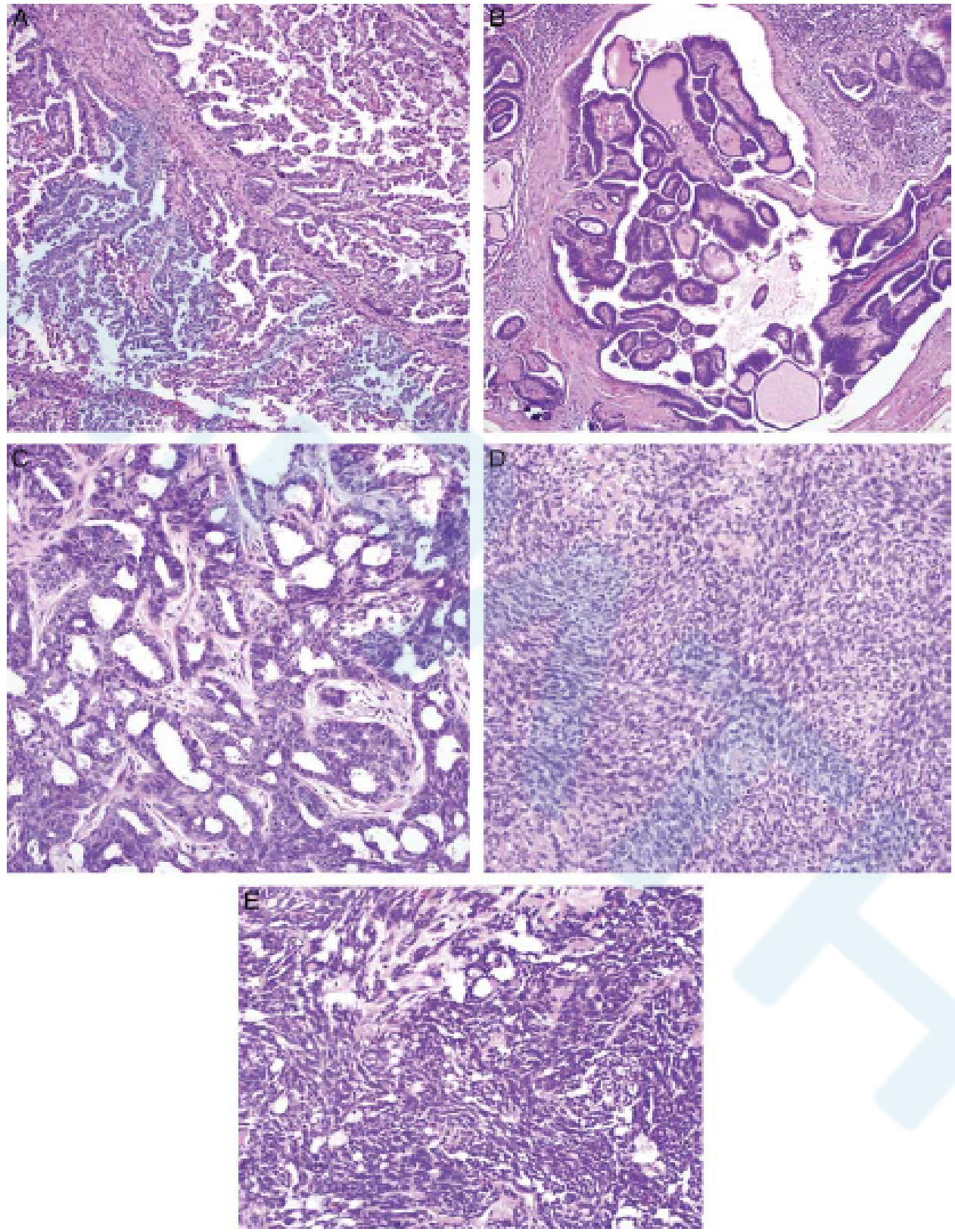

FIGURE 4. Mesonephric-like adenocarcinomas may show (A, B, cases 2 and 4, respectively) papillary, (C, case 1) glandular, and (D, case 1) spindle cell morphologies. In some cases, the patterns may intermingle, as in this case with tubules admixed with spindle cells (E, case 1).

RESULTS

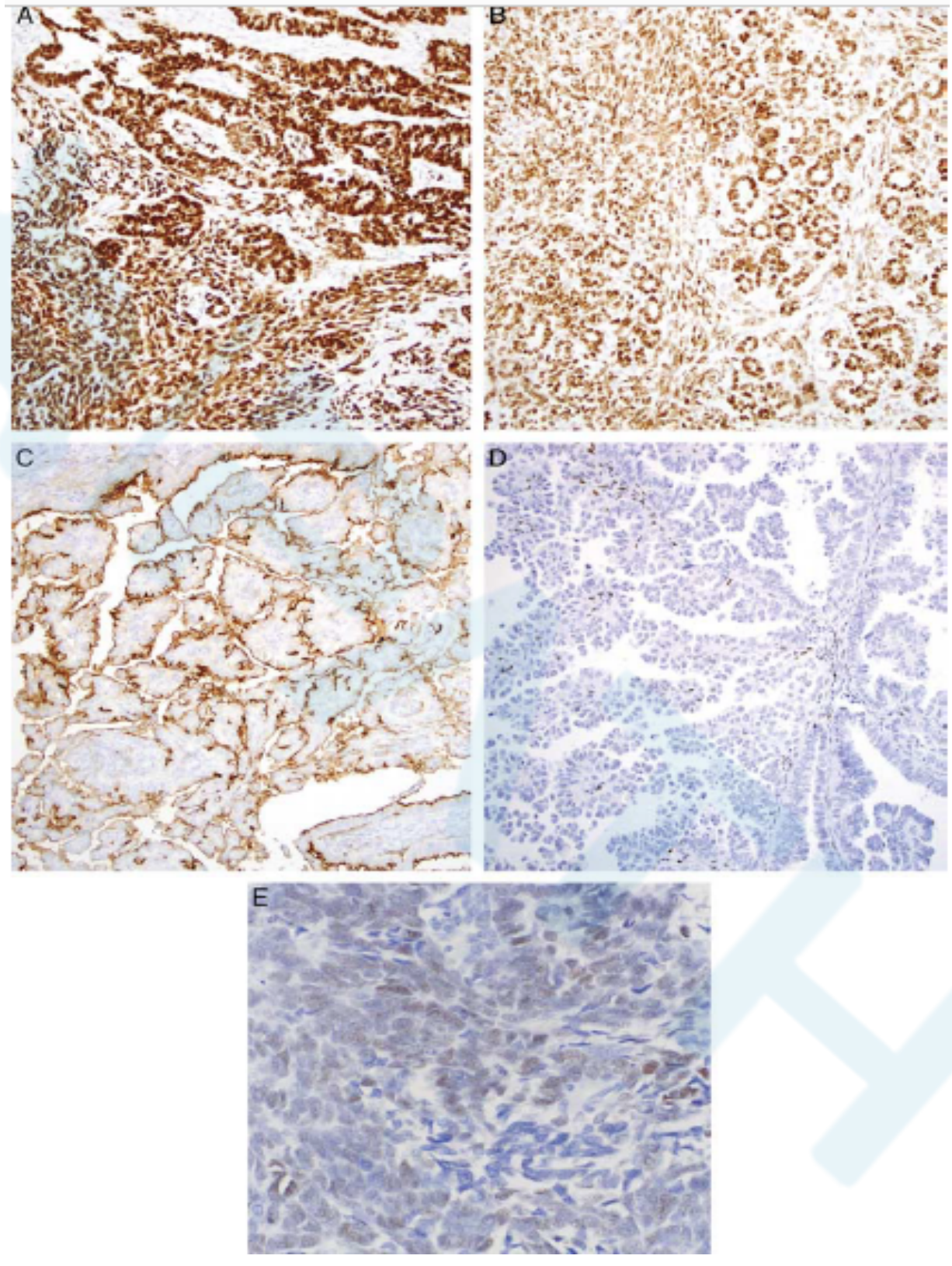

FIGURE 5. Mesonephric-like adenocarcinomas are usually positive for (A) PAX-8, (B) TTF-1, (C) CD10 (with luminal/apical staining), and negative for (D) ER. GATA-3 is also usually positive, and may show an inverse staining pattern with TTF-1. Case 1 showed diffuse staining with TTF-1 (B), but only focal staining with GATA-3 (E).

RESULTS

TABLE 3. Cases of Retrospectively Identified Mesonephric-like Adenocarcinoma, Their Original Diagnoses, Clinical Follow-up, and Molecular Features

Case	Original Diagnosis	Age (y)	FIGO Stage	Follow-up Period (y)	Outcome	Immunohistochemistry	DNA Variants	CNV
1	Carcinosarcoma	64	IB	12.5	AWD (lung metastases)	POS: TTF-1, GATA-3 (focal), CD10 (patchy, luminal), PAX8, ER (patchy, weak) NEG: PR, synaptophysin, chromogranin, p63	*KRAS* c.35G>C (p.G12A)	1p loss, 1q gain, 10p gain, 10q loss, 21 q loss
2	Endometrioid, grade 1	57	IA	1.6	NED	POS: TTF-1, CD10 (luminal), ER (heterogenous), PR (heterogenous) NEG: GATA-3 p53: wild-type	*KRAS* c.35G>T (p.G12V)	1p loss, 1q gain, 4p loss, 4q loss, 11p loss, 11q loss, 21q loss
3	Endometrioid, grade 2	58	IVB	2.5	AWD (local disease)	POS: p16 (patchy), TTF-1 (patchy), CD10 (patchy, luminal), Napsin A (scattered cells) NEG: ER, PR, GATA-3 p53: wild-type	*KRAS* c.35G>A (p.G12D) *PIK3RI* c.1351_1353delGAA (p.E451del)	1q gain, 11p loss, 11q loss, 13q loss, 17p loss, 22q loss
4	Endometrioid, grade 2	62	IIIC	8.4	DOD, with lung metastases	POS: PAX8, TTF-1 NEG: ER, PR, NapsinA, WT-1, chromogranin, synaptophysin, and thyroglobulin p53: wild-type	*KRAS* c.35G>T (p.G12V)	ND

AWD indicates alive with disease; DOD, died of disease; ND, not done; NED, no evidence of disease.

RESULTS

- Two cases of mesonephric-like adenocarcinoma presented at a high stage (2 cases at stage I, 1 case at stage III, 1 case at stage IV).
- One patient (case 4) died of disease, and 2 patients (cases 1 and 3) were alive with disease (either distant metastases or local recurrence). Cases 1 and 4 were associated with lung metastases.
- Three cases of mesonephric-like adenocarcinoma had 1q gain.
- All 4 cases of mesonephric-like adenocarcinoma had activating mutations of KRAS. None of the KRAS-mutated mesonephric-like adenocarcinomas had mutations in PTEN, CTNNB1, or TP53.

DISCUSSION

- KRAS-mutated mesonephric-like adenocarcinoma is ~ 1% of all endometrial carcinomas and represents 5% of KRAS-mutated MSS endometrial carcinomas.
- It has been under-recognized in part because it has only recently been reported in the literature and there is some degree of morphologic overlap with endometrioid carcinoma, serous carcinoma, as well as carcinosarcoma.

DISCUSSION

- KRAS-mutated endometrioid tumors are generally associated with a longer disease-free survival compared with KRAS wild-type tumors.
- However, the small number of cases of mesonephric-like adenocarcinoma in this series appear to follow an aggressive course, suggesting that mesonephric-like differentiation may be a poor prognostic factor.
- Mesonephric-like adenocarcinoma appears to have a predilection for pulmonary metastases.

DISCUSSION

Morphologic feature of mesonephric-like adenocarcinoma

- The presence of tubules with eosinophilic secretions, a spindle cell component, or papillary architecture, frequently with hyalinized stroma but without the cytologic features of clear cell carcinoma such as cytoplasmic clearing or hobnailing.
- The presence of a variety of the architectural patterns described above in a tumor lacking squamous/mucinous differentiation without the striking cytologic atypia of a serous carcinoma should prompt consideration of mesonephric-like adenocarcinoma.
- Encountering an endometrial carcinoma with architectural and cytologic features reminiscent of low-grade serous carcinoma of the ovary should also prompt consideration of mesonephric-like adenocarcinoma.

DISCUSSION

Immunohistochemistry of mesonephric-like adenocarcinomas

- Mesonephric-like adenocarcinomas are usually positive for (A) PAX-8, TTF-1, CD10 and negative for ER. GATA-3 is also usually positive, and may show an inverse staining pattern with TTF-1.
- Both TTF-1 and GATA-3-positivity have been identified as adverse prognostic factors in endometrial cancer, and it is possible that some of these cases of TTF-1 or GATA-3 positive endometrial carcinomas represent mesonephric-like adenocarcinoma.

DISCUSSION

Differential Diagnosis

- KRAS-mutated endometrial carcinomas are most commonly of endometrioid morphology. They frequently have mucinous or squamous differentiation or MSI. They often positive for ER and PR.
- Uterine serous carcinoma (high grade) is characterized by an aberrant pattern of p53 staining, which is only rarely seen in mesonephric carcinomas and has not yet been described in mesonephric-like adenocarcinoma.
- Features that help differentiate mesonephric-like adenocarcinoma from carcinosarcoma are a lack of heterologous differentiation and wild-type p53 staining pattern. TP53 mutations are present in over 90% of carcinosarcomas. Furthermore, cases of carcinosarcoma with wild-type TP53 may have mutations in PTEN, demonstrate MSI.
- Clear cell carcinomas may also show tubular architecture and are often negative for ER/PR. However, clear cell carcinomas do not show spindle cell morphology, and mesonephric-like carcinomas do not demonstrate clear cell change or hobnail cells.

SUMMARY

- In this study, we demonstrated that KRAS-mutated MSS endometrial carcinomas lacking histologic features of endometrioid differentiation (ie, squamous/mucinous differentiation) are enriched for mesonephric-like adenocarcinomas.
- Mesonephric-like adenocarcinomas represent a previously under-recognized, but significant minority, of KRAS-mutated MSS endometrial carcinomas.
- The clinical significance of identifying mesonephric-like adenocarcinomas has yet to be firmly established, but they appear to behave aggressively.

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