Napsin A, Hepatocyte Nuclear Factor-1-Beta (HNF-1 β), Estrogen and Progesterone Receptors Expression in Arias-Stella Reaction

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This study was presented in part at the 106th Annual Meeting of the United States and Canadian Academy of Pathology, San Antonio, TX.

Arias-Stella reaction (ASR)

- Pseudoneoplastic glandular response, first described by Javier Arias-Stella in 1954 as atypical endometrial changes associated with the presence of chorionic tissue

- Characterized by enlarged glands with abundant clear or eosinophilic cytoplasm and vacuolization associated with hyperchromatic, pleomorphic and smudged nuclei - "hobnail" appearance

- Frequently occurs as a reaction in the endometrium of women of reproductive age with intrauterine / extrauterine pregnancy and gestational trophoblastic disease

- Described also in extraendometrial sites: endocervix, fallopian tube, endometriosis (cervix, ovarian, peritoneal, subcutaneous, umbilica, urinary bladder), paraovarian and paratubal cysts, vaginal adenosis, ovarian germinal inclusion cysts, luteal cysts of puerperium and gestation and even in some ovarian mucinous neoplasms

Arias-Stella reaction (ASR)

- The finding of Arias-Stella effect in secretory endometrium is not diagnostic of intrauterine (even extrauterine) pregnancy

- Rarely can be seen in nonpregnant patients on hormonal therapy (oral contraceptives, ovulation inducing drugs and hormone replacement therapies and phytoestrogens)

- Nuclei of ASR cells enlarge because of DNA polyploid contents; aneuploidy is absent

- No need for treatment since it is a benign condition that usually regresses post partum

Microscopic (histologic) description

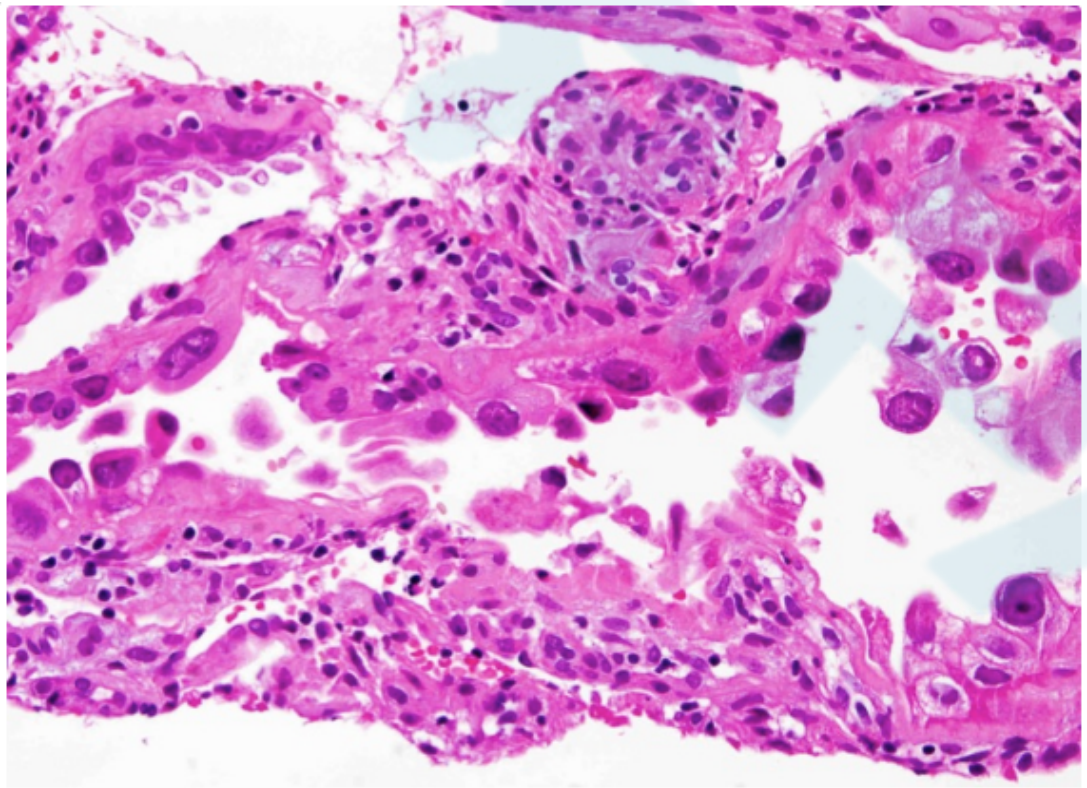
Dr. Arias-Stella classified the histologic variants into five types:

- *Minimal atypia*: characterized by mild nuclear enlargement
- *Early secretory pattern*: marked nuclear enlargement, subnuclear and supranuclear vacuoles
- *Secretory or hypersecretory pattern*: enlarged nuclei and intense and diffuse cytoplasmic vacuolization
- *Regenerative, proliferative or nonsecretory pattern*: nuclei with a vesicular configuration with glands showing no / minimal secretory activity
- *Monstrous cell pattern*: nuclei show giant and bizarre forms with homogenous chromatin and frequent pseudoinclusions

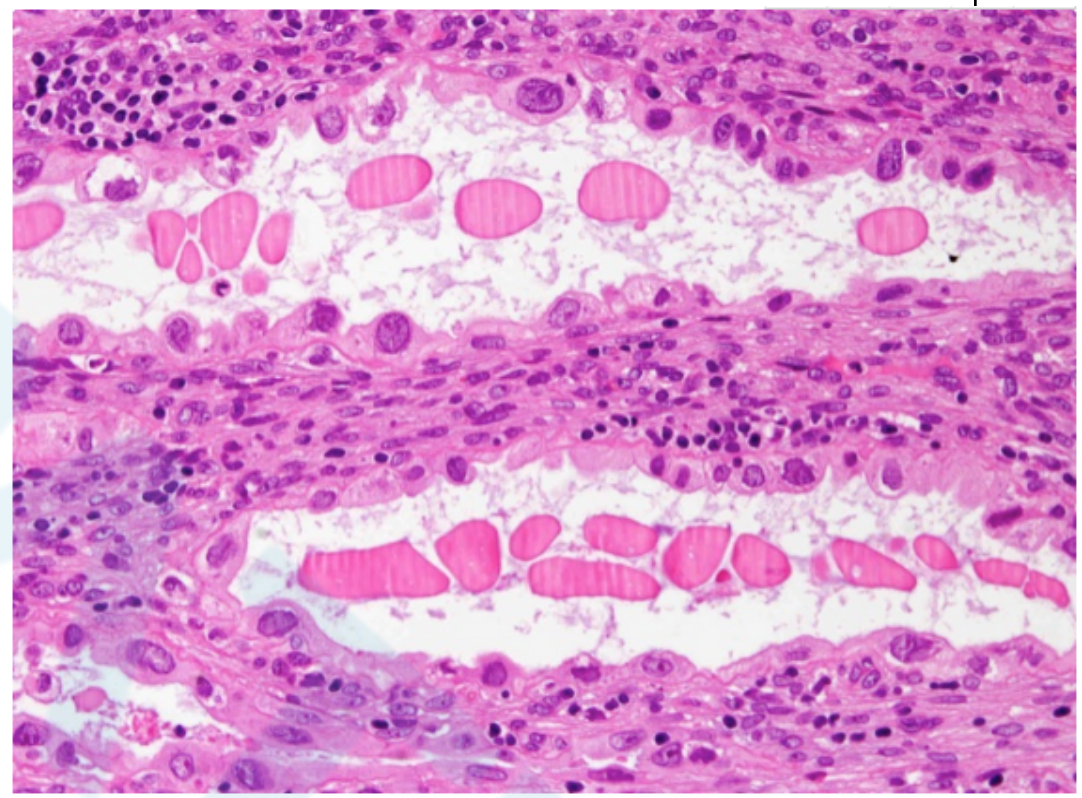
Adv Anat Pathol 2002;9:12

- Two subtypes may potentially mimic clear cell carcinomas
- “early secretory” and “secretory/hypersecretory” patterns: prominent clear and hobnail cells and intraglandular papillary change; Cells in the “secretory/hypersecretory” pattern may also have pyknotic nuclei and smudged nuclear chromatin

- Patterns without clear cell change include the “minimal atypia” pattern, the “regenerative, proliferative or nonsecretory” pattern; “monstrous cell” pattern



Arias-Stella change with nuclear enlargement, rather normal N/C and intense subnuclear and supranuclear vacuoles with absence of mitosis or apoptosis along with Intraglandular papillary epithelial tufts. Stromal decidualization is also visible.



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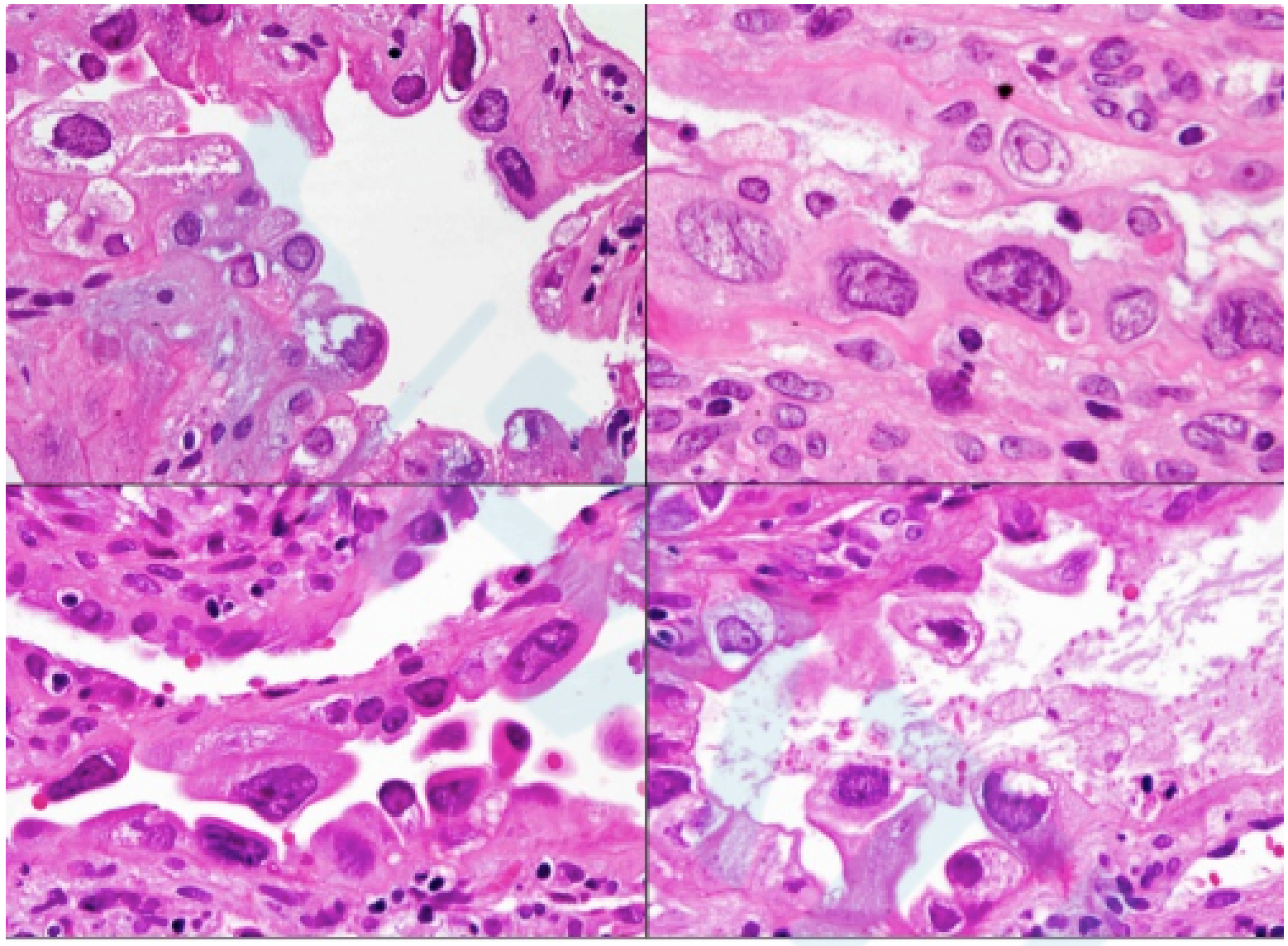
Contributed by Ayse Ayhan, M.D., Ph.D.



Hobnail growth pattern as well as nuclei with a vesicular configuration while glands showing no / minimal secretory activity discernible in the combination picture. In the upper right image, monstrous cell pattern with giant, bizarre nuclei with homogenous chromatin containing nuclear pseudoinclusion is visible.

Please examine the nuclear variations from hypertrophied nuclei of ovoid or round shape with granular or vesicular viable chromatin, or hyperchromatic appearance, compact, pyknotic pattern as well as optically clear nuclei / nuclear pseudoinclusions; and cytoplasmic variations changing from abundant either densely eosinophilic or clear and vacuolated cytoplasm.

Contributed by Ayse Ayhan, M.D., Ph.D.

Napsin A

- Napsin A is an aspartic proteinase involved with the maturation of surfactant protein B in the lung

- Napsin A was initially described as a relatively specific marker for pulmonary adenocarcinomas, but it was subsequently found to also be expressed in papillary and clear cell renal cell carcinomas and breast carcinomas with apocrine features

- In the female genital tract, it stains clear cell carcinomas of ovaries and endometrium

- A positive result is clearly visible under low magnification and has become an important diagnostic marker for distinguishing ovarian and ECCCs from other carcinomas

HNF-1 β

- HNF-1 β is a member of the homeodomaincontaining superfamily of transcription factors

- Its expression is vital to normal embryonic processes and especially in the development and cell differentiation of urogenital organs

- In female genital tract malignancies, HNF-1 β is found to be overexpressed more frequently in clear cell carcinomas than nonclear cell carcinomas involving the ovaries, endometrium, and cervix

Napsin A; HNF-1 β

- a panel of immunostains consisting of ER, PR, napsin A, and HNF-1 β has been shown to be very useful in the diagnosis of ECCC, and especially in distinguishing it from endometrioid carcinoma with clear cell change

- When HNF-1 β and napsin A are used together, the sensitivity for diagnosing ECCC is 95.3%. When ER and PR are incorporated, the specificity is 100% when both of these markers are also negative

Design

- The diagnosis of endometrial clear cell carcinoma (ECCC) is challenging, the Arias-Stella reaction (ASR) is a well-known benign mimic

- A diagnostic difficulty may be encountered in small biopsies, such as in endometrial pipelle samples obtained from patients, when the only accompanying history is “abnormal vaginal bleeding.” The drug history or pregnancy status of the patient is sometimes unknown

- When abnormal glands lined by atypical clear cells are encountered in such biopsies, immunohistochemistry may sometimes be used to exclude clear cell carcinoma

- Fewer studies have addressed the immunohistochemical profile of ASR

MATERIALS AND METHODS

- Queen Mary Hospital, Hong Kong, between 2004 and 2017
- the approximate percentage of these glands involved by ASR were estimated semiquantitatively and stated as negative, focal (<50%), or diffuse (>50%)
- The histologic subtype of ASR according to Dr Arias-Stella's classification was determined as far as possible
- Any stromal decidual change, characterized by a presence of stromal cells with abundant amphophilic cytoplasm, was noted
- Gestational ASR, 40 cases；Nongestational ASR, 10 cases
- In 19 (38%), the reaction was extensive and involved >50% of the glands

- Napsin A (any granular brown staining in the cell cytoplasm); HNF-1β , ER, PR (brown staining of the nucleus)

- Two cases of non-neoplastic secretory phase endometrium were used for comparison. early secretory endometrium (prominent subnuclear vacuoles); mid-secretory endometrium (prominent luminal secretions and stromal edema)

- The intensity of staining was scored as: negative (0), weak (1+), moderate (2+), strong (3+); The extent of staining of was assessed and classified as negative (0), <50% (1+), and >50% (2+)

- By multiplying the intensity and extent scores, a histoscore, which ranged from 0 to 6, was generated

RESULTS---Gestational ASR(40)

- The median age of patients was 35 years (with a range of 18 to 43 y)

- 12，spontaneous miscarriage abortions and presented with passage of vaginal tissue mass； 23，first or second trimester abortions requiring uterine curettage； 5，endocervical polyps involved by endometriosis which were resected during an examination for abnormal vaginal bleeding during pregnancy

- In 9 cases (22.5%), the lesional cells were predominantly clear cells (early secretory or hypersecretory types); 8 cases (20%), the cells were predominantly columnar or showed hobnail change; 23 cases (57.5%) contained an admixture of clear and nonclear cells and further classification into specific ASR histologic subtypes was difficult

- A stromal decidual change was identified in 31 (77.5%)

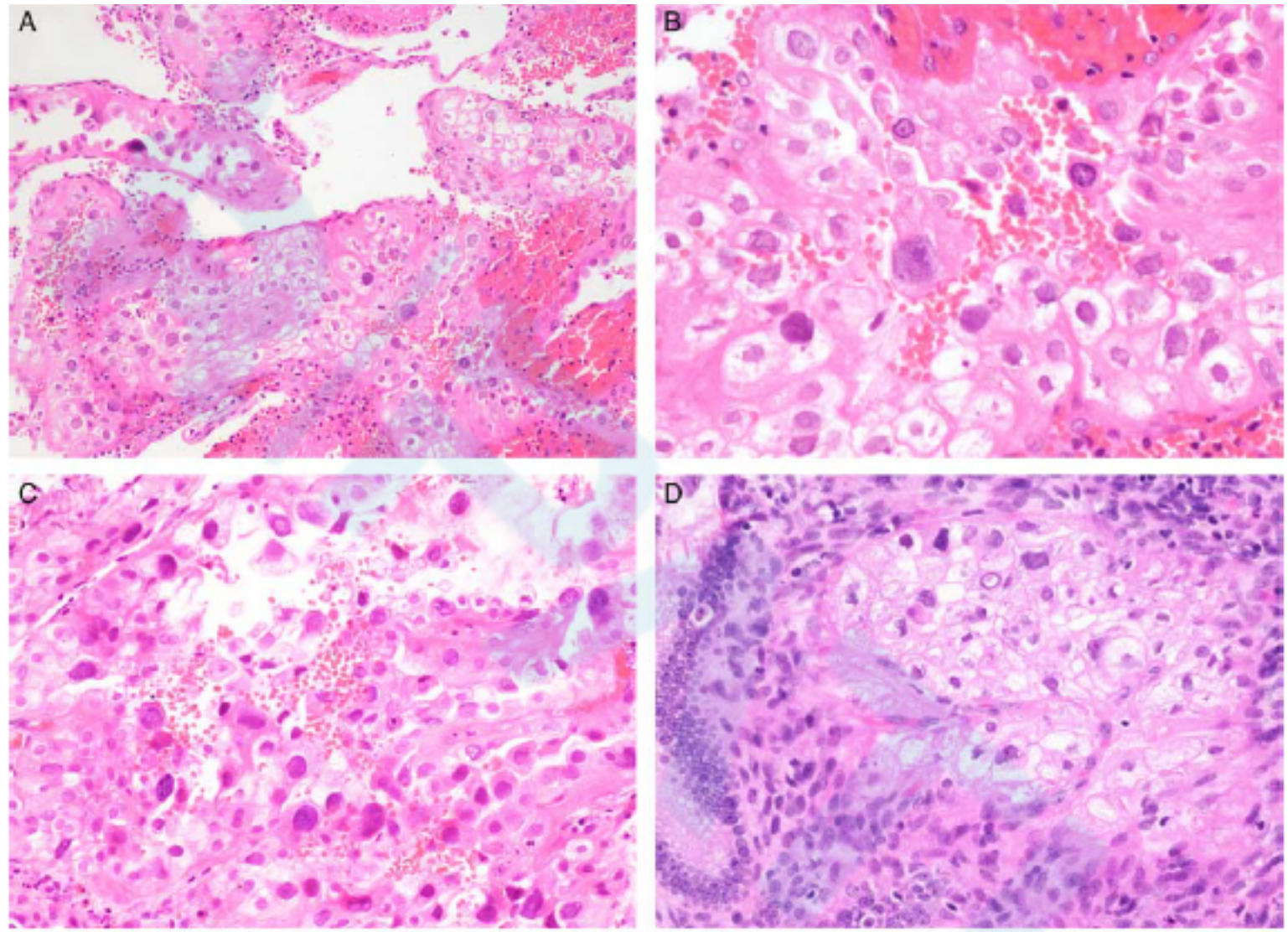


FIGURE 1. A–D, Gestational Arias-Stella reaction. A, The majority of cells in this case have abundant clear cytoplasm (secretory/hypersecretory pattern) (H&E). B, There is nuclear enlargement with smudged chromatin (H&E). C, An admixture of eosinophilic and hobnail cells (mixed pattern) (H&E). D, A cluster of glands involved by Arias-Stella reaction juxtapose to an uninvolved gland on the left (H&E).

RESULTS---Nongestational ASR(10)

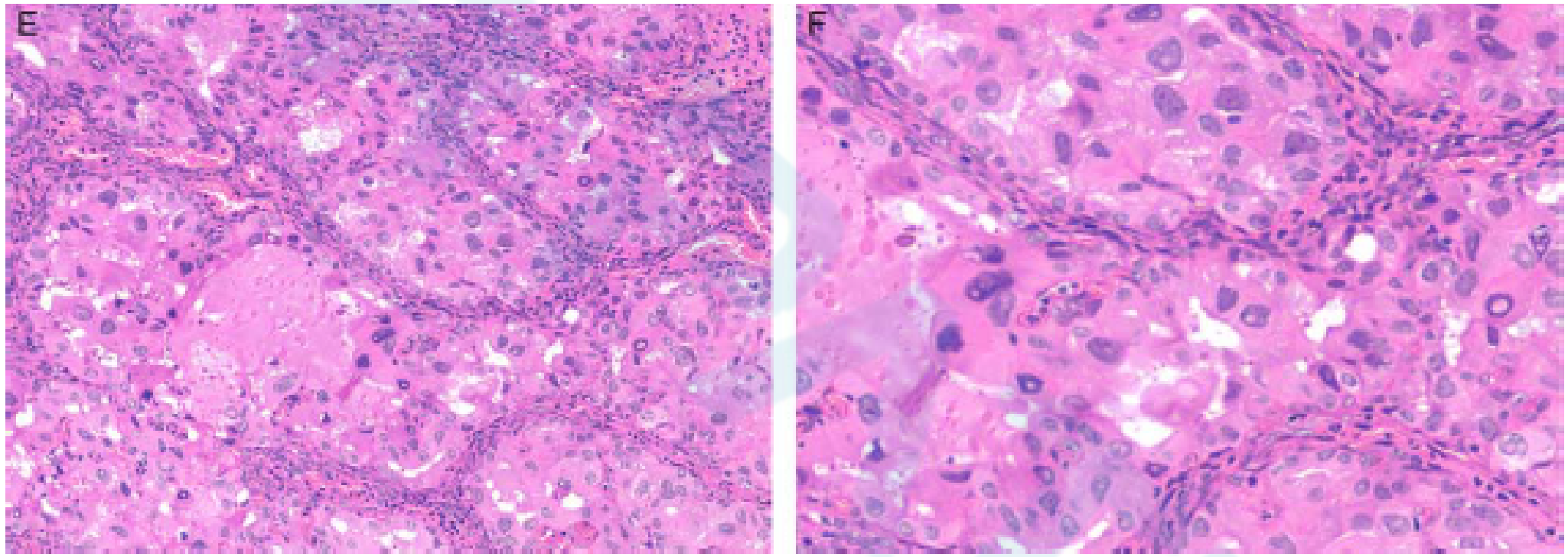


FIGURE 1. E and F, Nongestational Arias-Stella reaction (case 3). E, Cells are nonsecretory and have abundant eosinophilic cytoplasm (H&E). F, Nuclear chromatin are granular and with occasional pseudonuclear inclusions (H&E).

TABLE 1. Characteristics of Patients With Nongestational Arias-Stella Reaction

Case	Age (y)	Preexisting Conditions	Hormonal Drugs	Current Biopsy	Stromal Decidual Change	Napsin A Score	HNF-1β Score	ER Score	PR Score	Last Follow-up Sample
1	35	DUB	Medroxyprogesterone 10 mg, 7d	ASR and endometrial polyp	−	0	6	2	0	At 53 mo, proliferative endometrium
2	45	DUB	Levonorgestrel (mirena) 20 mcg, norethisterone 5 mg tds for 5 cycles	ASR and endometrial polyp	−	3	6	2	0	At 15 mo, progestogen effects only
3	39	Failed IVF and NAH	Norethisterone 5 mg tds for 6 cycles	ASR only	−	3	6	2	0	At 33 mo, progestogen effects only
4	36	NAH	Norethisterone 5 mg tds for 16 wks	ASR and persistent NAH	−	3	6	0	0	At 6 mo, persistent NAH
5	53	NAH	Levonorgestrel (mirena) 20 mcg for 4 mo	ASR only	+	3	6	2	0	At 12 mo progestogen effects only
6	48	NAH	Levonorgestrel (mirena) 20 mcg for 5 mo	ASR only	−	3	6	2	0	At 23 mo, progestogen effects only
7	37	Failed IVF, NAH and endometrial polyp	Levonorgestrel (mirena) 20 mcg for 4 mo	ASR and persistent NAH	−	3	6	2	0	At 20 mo, persistent NAH
8	46	AH	Levonorgestrel (mirena) 20 mcg for 5 mo	ASR and NAH	−	3	6	2	0	At 6 mo, grade 1 endometrioid carcinoma
9	39	AH (declined surgery)	Megestrol acetate 160 mg bd, norethisterone 5 mg tds and mirena for 3y	ASR and NAH	+	3	6	4	0	At 48 mo, progestogen effects only
10	36	Failed 3 cycles of IVF	Details of drugs not known	ASR and endometrial polyp	+	0	6	2	0	At 2 mo, ongoing IVF

AH indicates atypical hyperplasia; DUB, dysfunctional uterine bleeding; IVF, *in vitro* fertilization; NAH, nonatypical hyperplasia.

The median age of patients was 39 years (with a range of 35 to 53 y)

Medroxyprogesterone甲羟孕酮；Levonorgestrel (mirena)左炔诺孕酮/曼月乐；Norethisterone炔诺酮

Megestrol acetate醋酸甲地孕酮

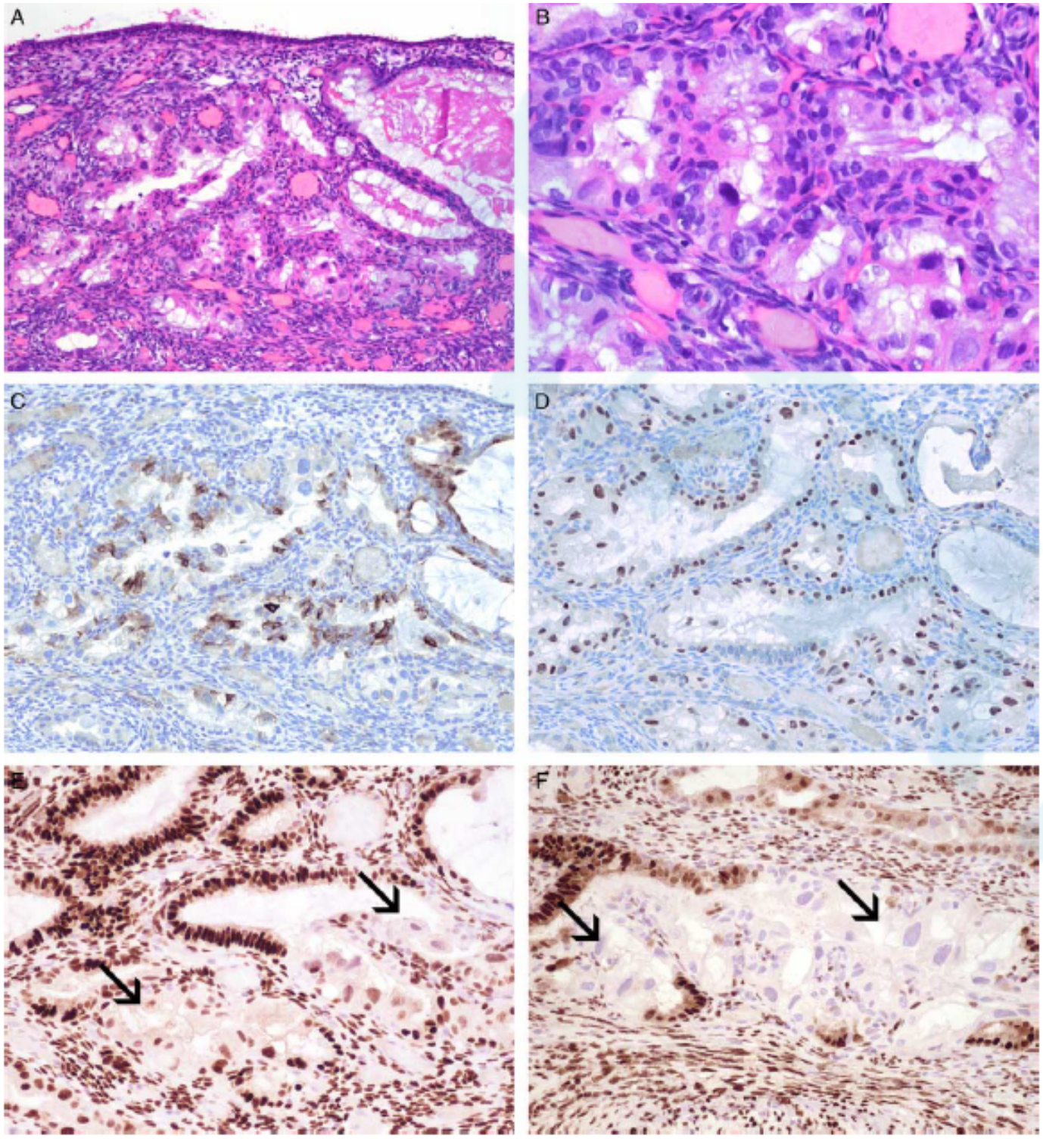


FIGURE 2. A–F, Nongestational Arias-Stella reaction in a patient treated with norethisterone for atypical endometrial hyperplasia (case 8).
A, The reaction involves the majority of glands in this field (H&E).
B, There are clear, eosinophilic and hobnail cells (H&E).
C, Napsin A shows granular cytoplasmic staining.
D, Hepatocyte nuclear factor-1 β stains the majority of cells.
E, The cells affected by Arias-Stella reaction show reduced or loss of staining for estrogen receptors (arrows).
F, There is a complete loss of staining for progesterone receptors (arrows).

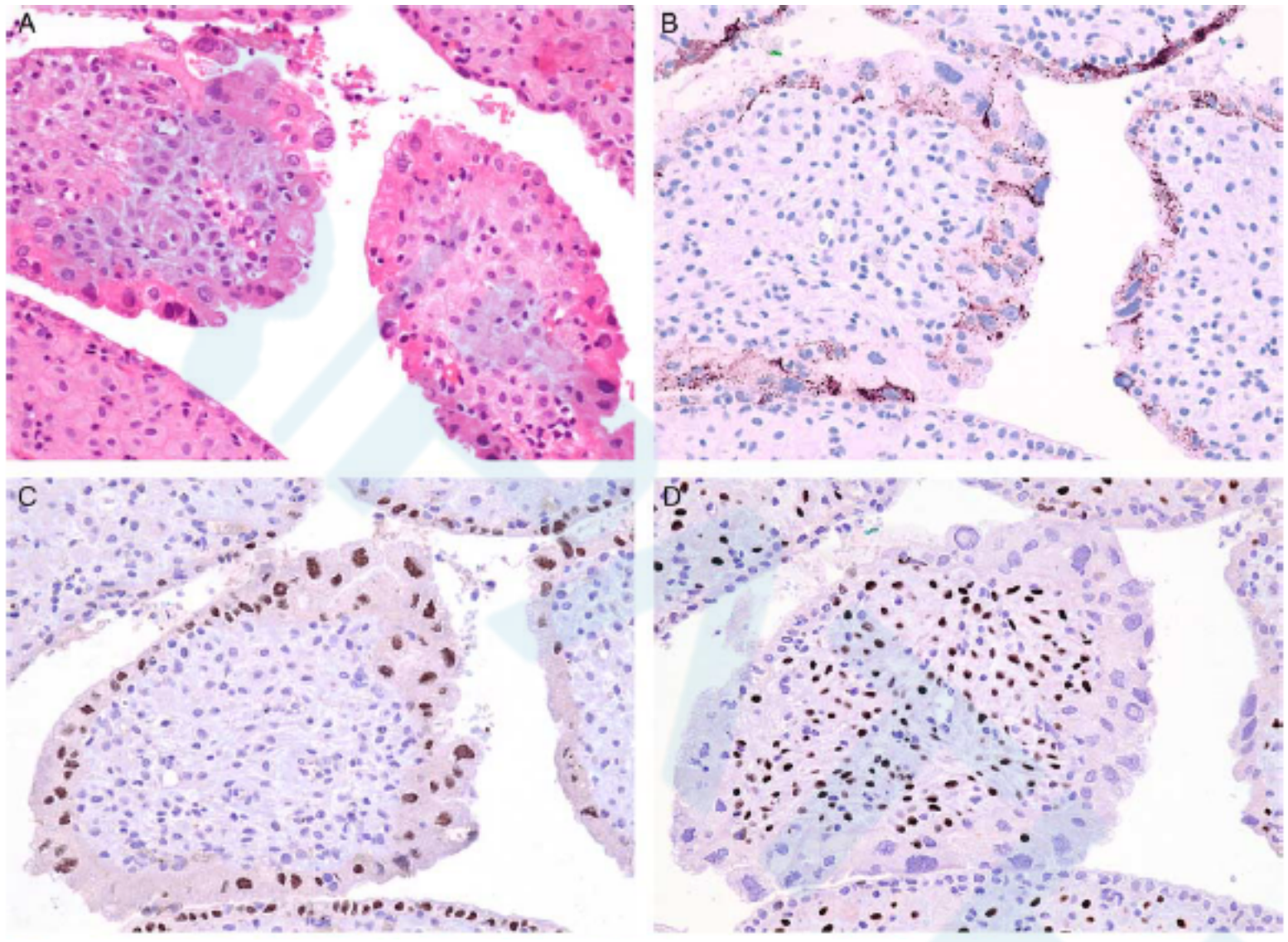


FIGURE 3. A–D, Arias-Stella reaction involving an endocervical polyp. A, The affected surface epithelial cells are eosinophilic, hobnail and clear. Prominent stromal decidual change is present. B, Napsin A stains most of the affected cells. C, Hepatocyte nuclear factor-1 β expression is strong and extensive. D, The affected surface epithelium is nonimmunoreactive for estrogen receptor. There is also complete loss of progesterone receptors expression (not shown).

TABLE 2. Napsin A, HNF-1β, ER, and PR Expression in Gestational and Nongestational ASR

	Gestational ASR (N = 40) (n [%])				Nongestational ASR (N = 10) (n [%])			
Histoscore	Naspin A	HNF-1β	ER	PR	Napsin A	HNF-1β	ER	PR
0	—	—	3 (7.5)	40 (100)	2 (20)	—	1 (10)	10 (100)
1	—	—	—	—	—	—	—	—
2	—	—	31 (77.5)	—	—	—	8 (80)	—
3	25 (62.5)	—	—	—	8 (80)	—	—	—
4	—	10 (25)	6 (15)	—	—	—	1 (10)	—
5	—	—	—	—	—	—	—	—
6	15 (37.5)	30 (75)	—	—	—	10 (100)	—	—

Napsin A was positive in all 40 (100%) gestational ASR and 8 of 10 (80%) nongestational ASR
In the majority of cases, staining was patchy and confined to one to several areas of a gland and involved many of the cells
All gestational or nongestational ASR were positive for HNF-1 β
ER expression was reduced in 37 (92.5%) and lost in 3 (7.5%) gestational ASR, and reduced in 9 (90%) and lost in 1 (10%) of nongestational ASR
None of the ASR in our series expressed PR

TABLE 3. Napsin A, HNF-1β, ER, and PR Expression Profile in ASR

	Gestational ASR (N = 40)	Nongestational ASR (N = 10)	Total (N = 50) (n [%])
Napsin A+, HNF-1β+, ER (reduced), PR−	37	7	44 (88)
Napsin A+, HNF-1β+, ER−, PR−	3	1	4 (8)
Napsin A−, HNF-1β+, ER (reduced), PR−	0	2	2 (4)

8% of cases had a immunoprofile of napsin A+, HNF-1 β +, ER− and PR−
88% were napsin A+, HNF-1 β +, ER (reduced), and PR−

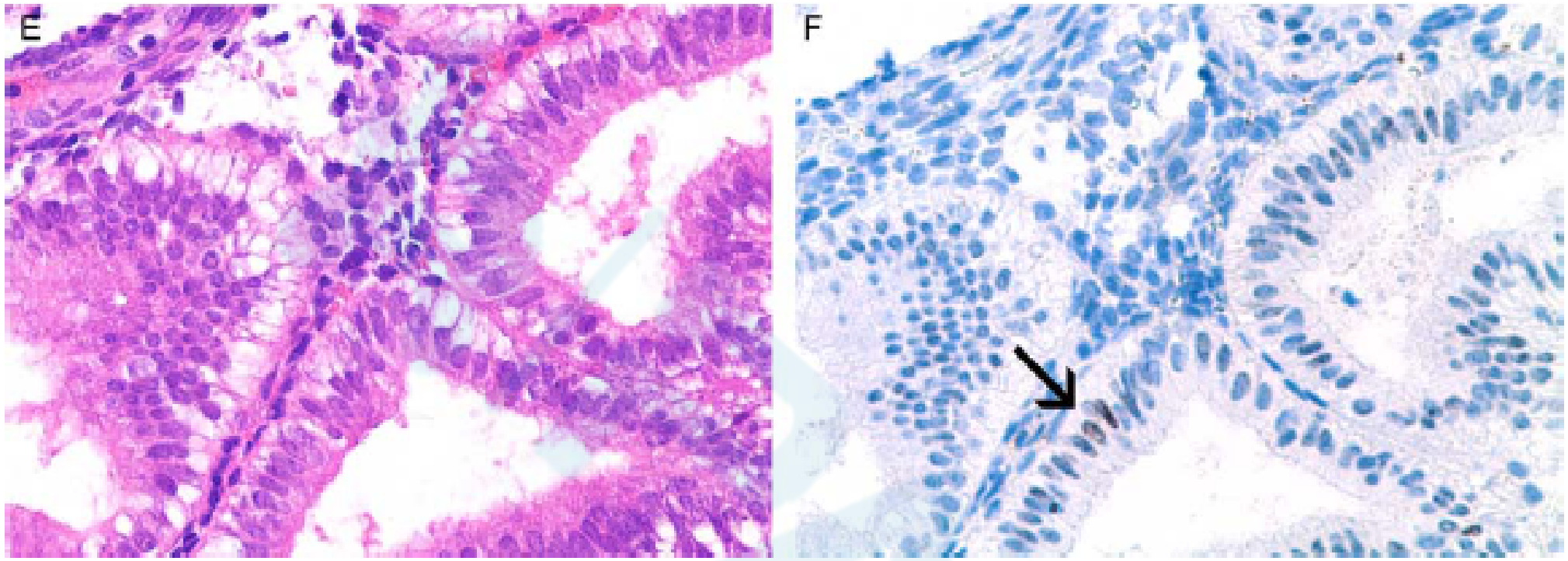


FIGURE 3. E–F, Early secretory phase endometrium (control case). E, There are prominent subnuclear vacuoles (H&E). F, Hepatocyte nuclear factor-1 β staining is confined to a few secretory epithelial cells (arrow) while napsin A is negative (not shown).

In both control cases of secretory endometrium, napsin A was negative
HNF-1 β was negative in the midsecretory phase endometrium, but focal and weak staining was found in the early secretory endometrium
Both ER and PR expression was not reduced or lost

DISCUSSION

- The results of our study have shown that the recently described clear cell carcinoma markers napsin A and HNF-1 β are also frequently expressed in ASR (96% and 100%, respectively)

- The diagnostic difficulty is further compounded by our results as a large number of ASR shows a similar immunoprofile to ECCC

- ASR may involve non-neoplastic epithelium but may also affect the glands in endometrial hyperplasia or carcinoma

- In these cases, obtaining additional clinical information (age, pregnancy, hormonal drugs) would be valuable

Differential diagnosis---Clear cell carcinoma

- 1% - 5% of all endometrial adenocarcinoma, a type II tumor (estrogen independent), arises from atrophic endometrium, similar to serous carcinoma
- Usually older, postmenopausal women
- High grade tumors (automatically FIGO grade III) with aggressive behavior

Clear cell carcinoma
Microscopic (histologic) description

- Papillary, tubular, tubulocystic or sheet-like architecture
- Large, clear to rarely eosinophilic cells with glycogen, distinct margins and hobnail cells
- May have colloid-like material in tubules
- Enlarged angulated nuclei with enlarged irregular nucleoli
- Benign endometrium is usually atrophic, not hyperplastic
- Positive stains: HNF1 β , NapsinA
- Negtive stains: ER, PR, P53(wild pattern)

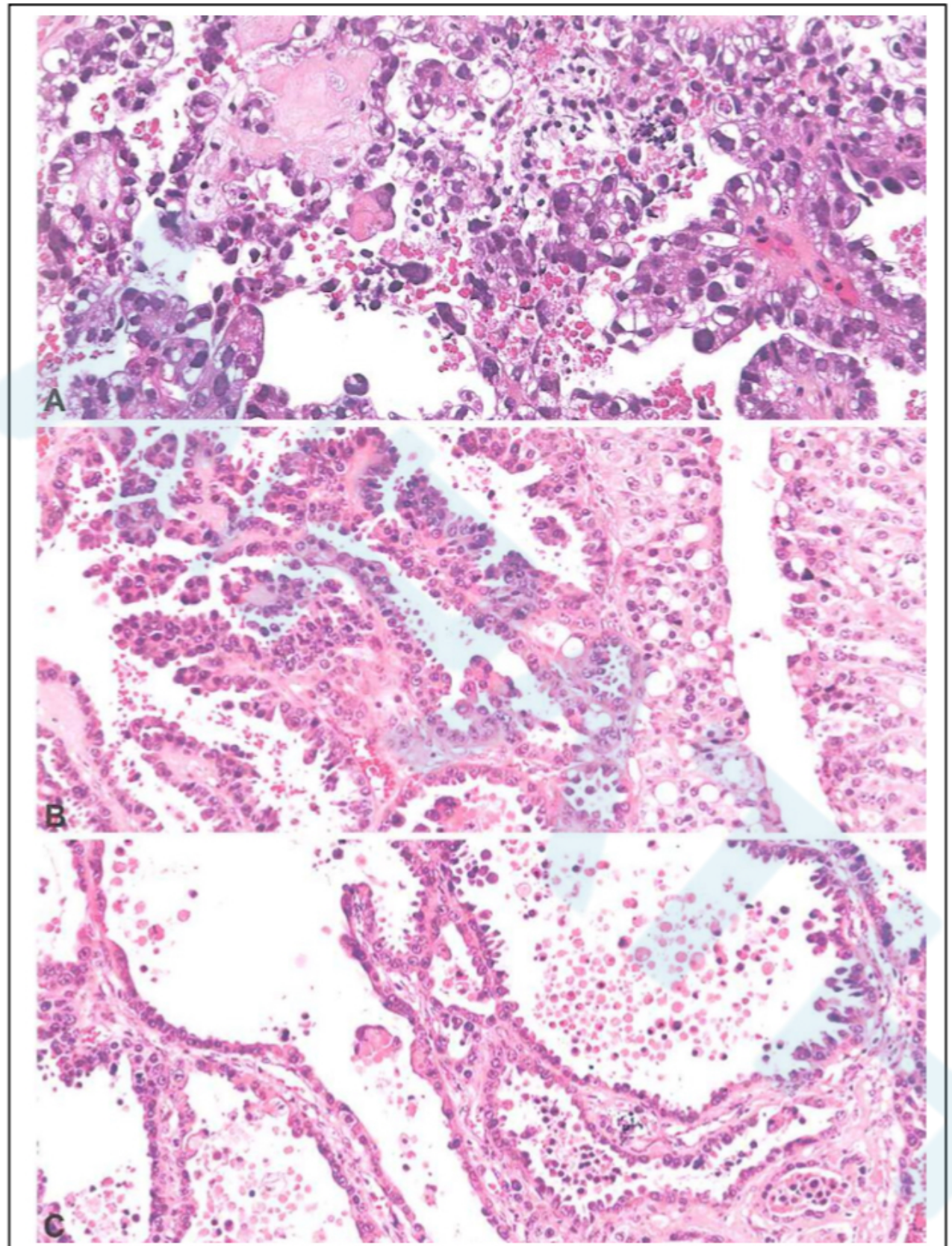


图 5.07 A 透明细胞癌。胞质透明，并可见鞋钉样细胞。乳头轴心透明变性。B 透明细胞癌，乳头状和实性结构。透明细胞的乳头（左）短而分支，纤维血管轴心透明变。胞质可透明、嗜酸性或呈鞋钉样。实性结构（右）中可见散在含有透明胞质空泡的细胞。C 透明细胞癌，管囊状结构。管囊状结构中常可见到鞋钉样细胞，表现为含有细胞核的顶部胞质突入腺腔。

	Arias-Stella reaction (ASR)	Clear cell carcinoma
age	reproductive aged women	postmenopausal woman
clinical history	pregnancy or hormone effect	a mass lesion
abundant clear or eosinophilic cytoplasm；“hobnail” cells		
histologic	glandular architecture	Papillary, tubular, tubulocystic or sheet-like architecture
glandular mitotic figures and apoptosis; (prominent nucleoli)	absence “smudged” nuclei	present
stromal decidual reaction	present	absence
desmoplasia and stromal invasion	absence	present
similar immunoprofile: ASR napsin A+, HNF-1 β +, ER (reduced), and PR− (88%)		

Arias-Stella reaction (ASR)

- Associated with: Pregnancy; Gestational trophoblastic disease; Oral contraceptives and ovulation inducing drugs; Postmenopausal women taking hormone replacement therapies; Phytoestrogen use

- Usually easy to recognize because it predominantly affects young and pregnant patients; however, it may occasionally raise concern for carcinoma if detected in nonpregnant or older patients

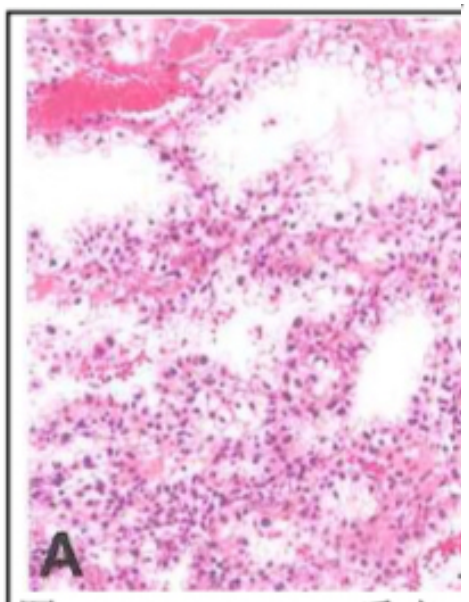
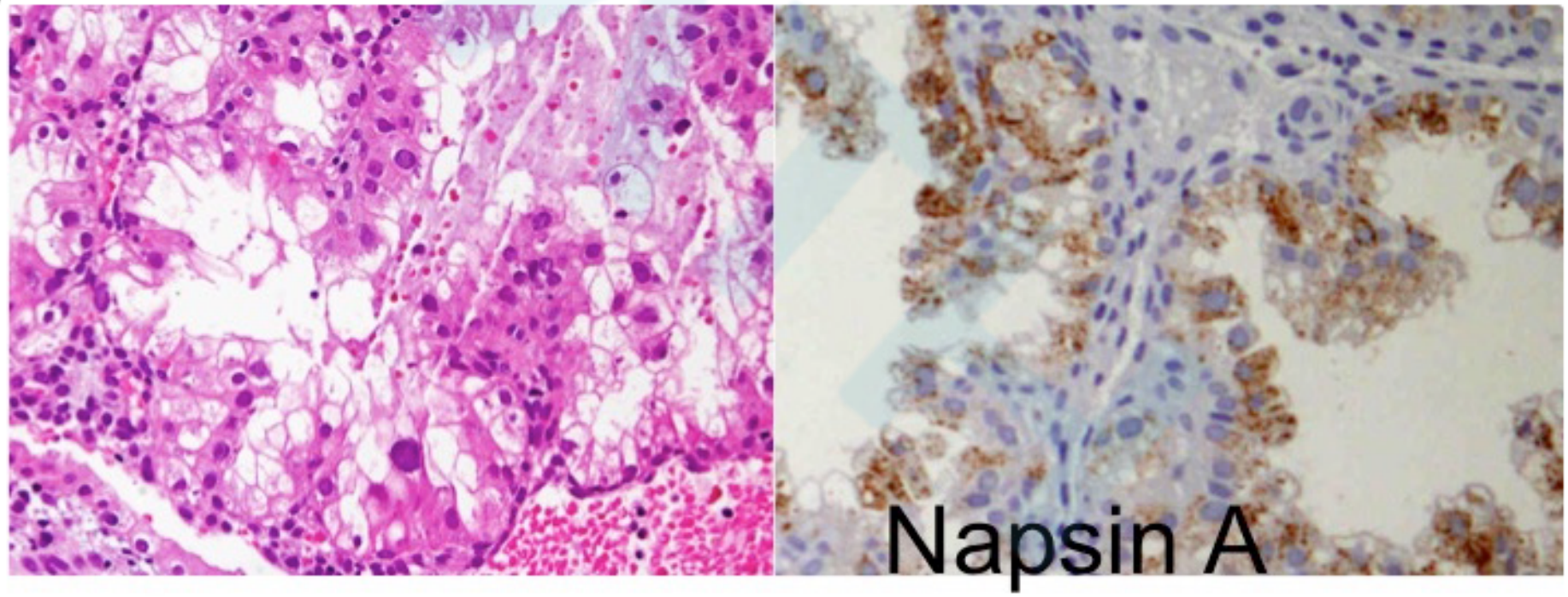


图 5.14 Arias-Stella 反应。
明细胞癌的管囊状结构。
核异型性类似于高级别肿



Napsin A positivity of Arias-Stella reaction.

Thank you for your attention!