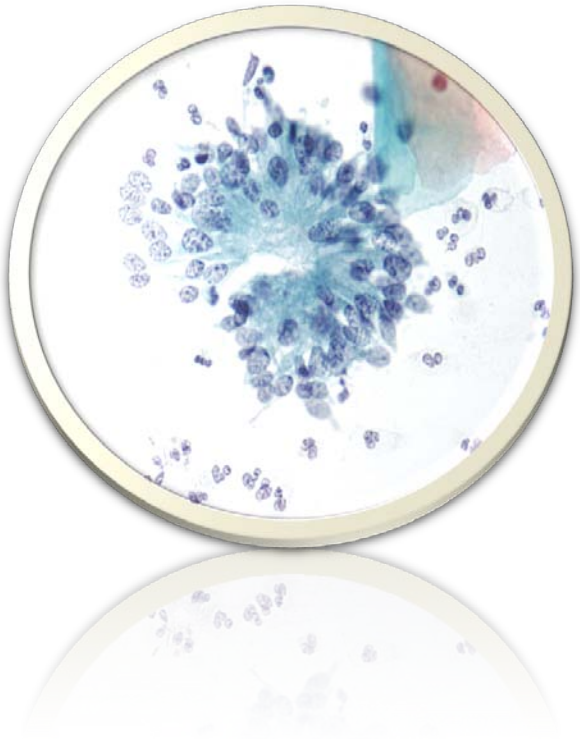
CITOLOŠKA DELAVNICA

OB UVEDBI NOVE NAPOTNICE, KI BO USKLAJENA S KLASIFIKACIJO PO BETHESDI

19. – 20. november 2010

ZBORNIK



Sekcija za citopatologijo, Slovensko zdravniško društvo

Državni program ZORA, Onkološki inštitut Ljubljana

Inštitut za patologijo, Medicinska fakulteta Univerze v Ljubljani

CITOLOŠKA DELAVNICA OB UVEDBI NOVE NAPOTNICE, KI BO USKLAJENA S KLASIFIKACIJO PO BETHESDI

Ljubljana, 19. – 20. november 2010

ZBORNIK

Izdajatelj

Onkološki inštitut Ljubljana

Zaloška 2

1000 Ljubljana

http://www.onko-i.si/

UVODNIK

Spoštovane citopatologinje, citopatologi, presejalke in presejalci,

V drugi izdaji Evropskih smernic za presejanje raka materničnega vratu (2008) je priporočena uporaba klasifikacije sprememb materničnega vratu po Bethesdi, ki jo uporabljajo v številnih državah Amerike in se vse bolj uveljavlja tudi v Evropi. Z novo terminologijo, ki smo jo začeli uporabljati leta 2006, smo se Bethesdi že približali, s spremembami, ki jih uvajamo sedaj, pa želimo odpraviti še nekaj zadnjih razlik. Razloga za prehod na Bethesdo sta predvsem poenotenje in primerljivost rezultatov z mednarodnimi.

Delavnico smo organizirali zato, da bi bil prehod na novo klasifikacijo lažji, pa tudi zato, da bomo imeli priložnost skupaj pregledati nekatere zapletene probleme pred katerimi se bomo znašli. Z Bethesdo med patološke spremembe na ploščatih celicah uvajamo skupino atipičnih ploščatih celic, pri katerih ne moremo zanesljivo izključiti ploščatocelične intraepitelijske lezije visoke stopnje. To entiteto bo na delavnici predstavila strokovnjakinja iz Anglije, Amanda Herbert. S pomočjo izbranih primerov, ki smo jih iz različnih slovenskih citoloških laboratorijev izbrale organizatorice delavnice, pa bomo na delavnici predstavili in natančno opisali žlezne spremembe po posameznih kategorijah.

Delavnica je sestavljena iz teoretičnega in praktičnega dela. Pripravile smo tudi Atlas žleznih sprememb, ki vam bo, upamo, pomagal pri ocenjevanju in razvrščanju ploščatoceličnih in žleznih sprememb v stare in nove kategorije.

V imenu strokovnega in organizacijskega odbora vam želim prijetno in koristno strokovno druženje,

Ana Pogačnik

PROGRAM DELAVNICE

Petek, 19. november 2010

13.30–14.00	*Registracija*
14.00–14.10	*Pozdravni nagovori*
14.10–14.55	**ASC-H, atypical squamous cells, cannot exclude high-grade squamous intraepithelial lesion (HSIL)** *Amanda Herbert*
14.55–15.15	*Odmor za kavo*
15.15–18.00	Citološka delavnica **ASC-H, atypical squamous cells, cannot exclude high-grade squamous intraepithelial lesion (HSIL)** *Amanda Herbert*

Sobota, 20. november 2010

9.00–9.45	**Spremembe na žleznih celicah** *Margareta Strojan Fležar, Veronika Kloboves Prevodnik, Ana Pogačnik, Alenka Repše Fokter, Vivijana Snoj*
9.45–10.00	**Izpolnjevanje citološkega izvida BMV po Bethesdi** *Ana Pogačnik, Margareta Strojan Fležar, Alenka Repše Fokter, Vivijana Snoj*
10.00–13.00	Citološka delavnica: **Spremembe na žleznih celicah** *Margareta Strojan Fležar, Veronika Kloboves Prevodnik, Ana Pogačnik, Alenka Repše Fokter, Vivijana Snoj*
13.00–13.15	*Zaključek*

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ASC-H, atypical squamous cells, cannot exclude high-grade squamous intraepithelial lesion (HSIL)

Amanda Herbert, Guy's & St Thomas' NHS Foundation Trust

Introduction

Atypical squamous cells, cannot exclude high-grade SIL (ASC-H) cannot be considered without understanding the background to the meaning of 'atypical', [or 'borderline' in the British Society for Clinical Cytology (BSCC) system used in the UK, see footnotes], and without taking account of the occasional difficulty in distinguishing squamous from glandular cells.

The terms atypical or borderline should only be used for cases in which there is genuine doubt as to whether the changes are reactive or neoplastic – or, to be more precise, whether they are reactive, neoplastic or squamous intraepithelial lesion (SIL). The definition of atypical and borderline are virtually identical in the Bethesda system (TBS),[1] the EU recommendations for terminology,[2] and the original[3] and revised BSCC terminology.[4]

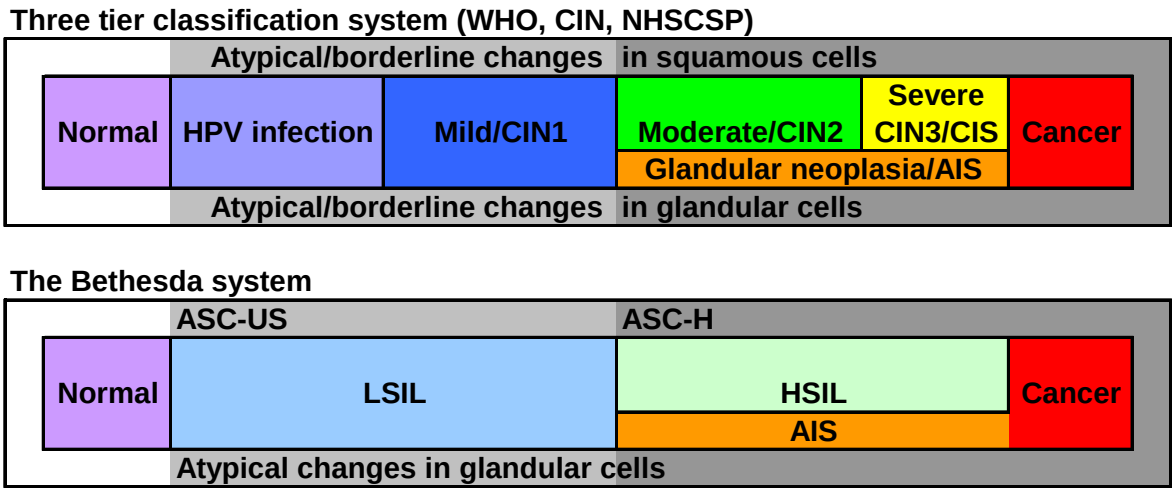
All these systems recommend that atypical squamous cells of undetermined significance (ASC-US)[1] and ASC-H[2] should be reported sparingly and their use limited. Every time ASC-US or ASC-H is reported cytologists should consider the alternative diagnoses of negative, LSIL[3], HSIL[4] and occasionally cancer. Especially with ASC-H cytologists should also consider whether the cells might be glandular (usually endocervical or endometrial) rather than squamous in origin.

In the UK borderline changes often include some cases of koilocytosis in addition to the abnormalities described as ASC-US in TBS, and many Pap smears with other less

[1] ASC-US, borderline changes in squamous cells, not otherwise specified (NOS) (BSCC)
[2] ASC-H, borderline changes in squamous cells, high-grade dyskaryosis not excluded (BSCC)
[3] LSIL, mild dyskaryosis (BSCC) or mild dysplasia
[4] HSIL, moderate and severe dyskaryosis (BSCC) or moderate and severe dysplasia/carcinoma in situ

diagnostic features suggesting human papillomavirus (HPV) get reported as ASC-US. The BSCC has proposed that koilocytosis should be included with LSIL,[4] which was the original intention of their terminology,[2] so the BSCC system (see footnotes) is translatable into TBS as recommended in the European guidelines.[2]

Conceptual categorisation of cytological findings in a Pap smear of the uterine cervix (Figure 1, taken from the EU guidelines[2]):



Rationale of atypical / borderline reports

- ASC-US, ASC-H and atypical glandular cells (AGC) represent a 'grey area' that acts as a buffer between normality and abnormality.
- Specificity is improved by limiting their use to avoid false positives.
- ASC and AGC improve sensitivity by avoiding false negatives.
- Atypical/borderline changes are a function of every screening system that requires high sensitivity.

Essential differences between ASC-US and ASC-H

Most ASC-US borders on LSIL/HPV[5] and is therefore usually seen in mature squamous cells.[1-4] The category was retained in TBS 2001 because it had been shown to be associated with approximately 10% of high-grade cervical intraepithelial neoplasia (CIN) on biopsy.[6]

From the outset of defining borderline changes in the UK, it was recognized that there was a difference between equivocal changes "bordering on mild dyskaryosis" (LSIL/mild dysplasia) and those that were equivocal for "more severe abnormalities" in which referral for colposcopy and biopsy was indicated.[3] It had been known for many years that borderline changes may harbour high-grade CIN lesions or even cancer.[7]

ASC-H has been justified as a separate category because it is significantly more likely than ASC-US to represent high-grade CIN.[8,9,10] However, ASC-H should only apply to about 5-10% of total ASC reports[2] and tends to involve immature squamous metaplastic cells.

- Most (but not all) ASC-US involves mature squamous cells so its differential diagnosis is usually between LSIL/HPV and normal/reactive/hormonal change.
- Some ASC-US represents changes that are probably benign/reactive/hormonal when it is thought that colposcopy is not indicated and repeat after treatment or time might help (the 'missing' ASC-probably benign category).
- Most ASC-H involves immature metaplastic cells or their mimics, so its differential diagnosis is between HSIL/cancer and normal/reactive/hormonal change.

Avoiding the overuse of atypical / borderline reports

Specificity is improved (avoiding false positives) by asking the following questions before reporting ASC-US or ASC-H:

- Are the changes recognizable as reactive, hormonal or metaplastic?
- Would a repeat after specific treatment or time interval help?
- Have their differential diagnoses (often among causes of potential false negatives) been excluded?

Rational answers to these questions, if necessary in consultation with a colleague, should reduce ASC/borderline reports, including ASC-H, to a manageable level and avoid floundering in the "ASCUS swamp".[11] Additionally, rates of ASC-US, ASC-H, LSIL and HSIL should be monitored and compared with local and national standards as a method of quality control.

Normal reactive, hormonal and metaplastic changes

"Numerous variants of benign cellular findings have been described and need not be reported if they do not imply an increased risk of neoplasia. These include hormonal patterns (post-partum or atrophic), repair changes, microglandular hyperplasia, tubo-endometrioid metaplasia, tubal metaplasia, sampling of the lower uterine segment, irradiation changes or alterations due to inflammation or the presence of an intrauterine contraceptive device (IUD) and benign glandular cells occasionally seen in post-hysterectomy specimens (Tambouret 1998). As long as they are recognized as such they need not be reported."[2]

As will be explained in the workshop, this is easier said than done and the final sentence is clearly important: *as long as they are recognized as such.*

Reactive, hormonal and metaplastic changes (potential false positives)

All the changes mentioned above are among those that could be described as 'potential false positives' and the key to avoiding them lies in familiarity with the full range of benign/reactive/hormonal changes, which pathologists and trainees should make sure they get plenty of chance to see.

- Their differential diagnoses (potential false negatives) are equally if not more important (i.e., in terms of sensitivity) and should affect the reporting of these changes as well as clinical management.

Hormonal patterns (post-partum or atrophic): When oestrogenisation is low, the cells have a relatively high nuclear/cytoplasmic (N/C) ratio and tend to form cohesive sheets. In the great majority of cases, careful attention to nuclear detail allows a distinction to be made between sheets of poorly oestrogenised normal cells, and sheets of HSIL, which is the differential diagnosis. The latter cells usually stand out as a separate population with coarsely granular chromatin and irregular nuclear margins, whereas normal atrophic cell sheets are of uniform shape and size throughout the smear.

These hormonal changes are seldom associated with nuclear abnormalities unless there is some degree of concomitant inflammation, in which case coarsening of chromatin, hyperchromasia and some irregularity of nuclear outline may occur. When this is associated with cytoplasmic orangeophilia, which is commonly seen in atrophic smears, the changes can mimic HSIL. In these instances, a borderline/ASC-US report with a recommendation for repeat after local oestrogen treatment may occasionally be justified, but ASC-H should be reported if the changes are thought to be suspicious but not diagnostic of HSIL.

Repair changes: Regeneration and repair may be easy to recognize, and we are specifically advised not to report them as such, but there are some instances when the changes are very much less obvious and may even be suspicious of neoplasia. As in a case in the workshop wrongly reported as ?glandular neoplasia, which could not safely

have been reported as negative and would have been better reported as ASC-H (avoiding a false positive).

Microglandular hyperplasia: MGH is unlikely to be confused with HSIL, and the differential diagnosis of these hyperplastic cells, half way between endocervical and immature metaplastic cells, tends to be glandular neoplasia. Smooth nuclear membranes, prominent nucleoli and cohesive cell groups characterise MGH but the differential diagnosis (various types of glandular neoplasia are potential false negatives) must be considered before reporting it negative; and in practice it is seldom diagnosed accurately on cytology alone and likely to be reported as AGC.

Tubo-endometrioid metaplasia (TEM) and tubal metaplasia (TM): The key to recognising these entities lies in noticing ciliated cells (or terminal bars) on cells with eccentric nuclei (TM) and their association with regular sheets of glandular cells with stromal tails (TEM). Both are potential false positives. TM on its own may be confused with HSIL (particularly CIN2) if the cilia are inconspicuous or absent, but the large, usually round nuclei lack the irregular chromatin pattern of dyskaryosis. TEM may be confused with CGIN (AIS) or CIN3 (look for separated dyskaryotic cells).

TEM and endometriosis (which looks similar) are often seen after LLETZ or cone biopsies. If mistaken for neoplasia, this may lead to unnecessary additional treatment, which should be avoided in view of its association with adverse pregnancy outcome. [12] Some form of atypical/borderline report recommending investigation is indicated in cases of genuine uncertainty (AGC or ASC-H).

Sampling of the lower uterine segment: LUS presents as similar problem to TEM, and has the same clinical association of being seen post-treatment (due to the shortened cervix). Regular nuclei, lacking the abnormal chromatin pattern of high-grade dyskaryosis and the absence of separated severely dyskaryotic cells help in its recognition; and distinction from hyperchromatic crowded groups and microbiopsies of CIN3 (potential false negatives). ASC-H and colposcopy may be indicated when in doubt.

Irradiation changes: These can mimic recurrent squamous cell carcinoma, which should only be suspected when a severe nuclear abnormality (severe dyskaryosis) is seen in viable cells, along with either i) a high N/C ratio, ii) intracytoplasmic keratinisation (dyskeratosis), iii) tissue fragments (microbiopsies) or iv) all three. Irradiation change is associated with copious, often vacuolated cytoplasm and the nuclear change can mimic mild and moderate dysplasia. Clinical follow-up and examination of treatment is more important than cytology in all except obviously malignant smears, which should be reported as such. ASC-H could be used occasionally.

Alterations due to inflammation: Before the BSCC defined the borderline category and provided illustrations for its use,[13] the term "inflammatory smear" (broadly equivalent to Pap class II) was often used to describe nuclear abnormalities that were thought not to be dyskaryotic (SIL/dysplasia/class III). Such smears probably included many changes that would now be classified as borderline (ASC or AGC) but also included changes that ought to have been recognized as HSIL or even cancer.

In any form of inflammation, with or without a recognisable cause, there is a variable inflammatory cell exudate (usually polymorphs), which may obscure (on conventional smears) or replace (LBC) the cells. The cells frequently show a "shift-to-the-left" as a manifestation of increased turnover, resulting in an excess of active immature metaplastic squamous cells. In most instances these cells will be recognisable as reactive and need not be reported but sometimes the chromatin may be coarsely granular and the nuclear membranes somewhat irregular in outline. Nucleoli are usually present but may be less distinct if the chromatin is coarsened.

In these cases a report of atypical or borderline may be given, usually ASC-US if the changes are thought on balance to be consistent with the degree of inflammation, and repeat may be recommended after investigation and treatment of any infection found. As these changes are often in immature metaplastic cells, a judgement should be made as to whether there is a possibility of their being HSIL rather than reactive, in which case ASC-H may be appropriate.

Trichomonas vaginalis may be associated with striking inflammatory changes as described above, which may mimic dyskaryosis/dysplasia. After treatment, reactive changes should resolve and dyskaryosis, if present, should look more obvious. It is seldom necessary to report these as ASC-H (unless the TV is not noticed, as in a case in the workshop) although some end up being reported as ASC-US.

The presence of an intrauterine contraceptive device (IUD): The typical features should be recognised (avoiding a false positive diagnosis) by the association of isolated hyperchromatic endometrial cells, reactive 'bubble-gum' endocervical cells with uniform nuclei and prominent nucleoli, with or without relevant clinical information about an IUD. However, the isolated endometrial cells may mimic 'sparse severely dyskaryotic cells' (potential false negative) if the complete picture is not seen, but should not show the irregular chromatin pattern of severe dyskaryosis. If in doubt, ASC-H could avoid a potential false negative or false positive diagnosis.

Lymphocytes and histiocytes: Both these normal types of cells may mimic HSIL (potential false positives). Follicular cervicitis should be recognised by the typical chromatin pattern of lymphocytes, the mixture of large and small cells and the presence of tingible-body macrophages. Histiocytes (with certain oral contraceptives and 'exodus' post-menstruation smears) may be misleading and mimic separated dyskaryotic cells of HSIL, especially when the cytoplasm is orangeophilic. In our experience these are occasional causes of false positive primary screening assessments, but are not represented in any of our cases of ASC-H.

Immature metaplastic cells: Last but not least are immature squamous metaplastic cells, which are an expected feature of negative conventional smears and LBC preparations and are therefore not mentioned in the list of 'reactive/hormonal/hormonal changes' in the EU guidelines quoted above. However, debate on the website prior to the BSCC terminology conference in 2001 demonstrated that distinguishing immature squamous metaplasia from dyskaryosis was one of the most difficult areas of cervical cytology,[4] described in one response as the "greatest cognitive dilemma". The distinction seems to be particularly difficult with ThinPrep.

Even in the absence of features suggesting inflammation or repair, as discussed above, metaplastic squamous cells may show hyperchromatic clumped chromatin, mimicking dyskaryosis/SIL (the distinction between immature metaplasia and CIN2 being the main problem). The cytoplasm is usually relatively normal, its borders well demarcated, often with "pulled out" strands between adjacent cells and hyaline, often amphophilic cytoplasm. In ThinPrep, the nuclear membrane is pronounced and even in outline, while in dyskaryosis the membrane is thinner, but irregular and often 'bulging'. If HSIL is suspected, the smear should be classified as ASC-H and colposcopy recommended.

Why is there no category for ASC-probably reactive, to avoid over-investigation and treatment of all these potential false positives?

The reason, as for AGC, is that the differential diagnosis tends to be HSIL or even cancer, so repeat cytology may be inappropriate. Our cancer audit cases include occasional cases in which 'borderline changes' were not repeated as recommended, or not investigated when persistent; these patients might not have ended up with cancer if the changes had been reported as ASC-H (or AGC) in the first place and colposcopy recommended. Nevertheless, we reserve the right to ask for repeat cytology (see above) in some of these instances when we genuinely 'favour reactive changes' rather than HSIL or cancer but cannot be sufficiently certain to report to issue a negative report (favouring sensitivity over specificity).

- Repeat cytology should only be recommended when repeat after an appropriate time interval (post-partum cases) or treatment (TV or atrophic vaginitis) is likely to help.
- Likelihood of compliance with recommendations for repeat cytology should be taken into account.
- Colposcopy for ASC-H (and AGC) should be expected to include some 'probably benign' cases, and treatment should be decided after multidisciplinary case discussion, slide review (cytology with or without histology) and, if available, high-risk HPV testing.

Avoiding the overuse of ASC-H for recognizable HSIL and cancer

In practice, now the category exists, it is more often used as a cautious report of HSIL (or even cancer) rather like 'C4' is used for 'suspicious of malignancy'. However, as it defines 'atypical/equivocal' changes, it should be more like 'C3'. The numbers of

ASC-H reports should be few enough to allow consultation with colleagues before reporting and discussion at multidisciplinary meetings before treatment is decided. If too many obvious HSIL cases are reported as ASC-H, it loses its value as a buffer against potential false negatives and false positives. Reporting rates of ASC-H and HSIL should be monitored for laboratories and individual pathologists.

ASC-H need not be used for obvious HSIL and cancer if screeners and pathologists are familiar with the following unusual types of high-grade cytology, many of which represent 'potential false negatives' that have been mentioned above in the differential diagnosis of reactive/hormonal/ metaplastic changes.

Potential false negatives

Most are well-recognised types of HSIL (high-grade dyskaryosis), which should not be missed as long as cytologists are familiar with them. A significant proportion of HSIL cytology falls into these groups so pitfalls abound – it is important for cytologists (non-medical and medical) to be familiar with these entities, which will be illustrated in the workshop.

All these abnormal cells may be sparse (conventional or LBC) or partly obscured with exudate or blood (in conventional cytology).[14] False negative smears usually have fewer cells than true positives, which places them at risk for being missed.[15,16]

- **Small cell dyskaryosis**[17] – differential diagnosis includes endometrial cells, histiocytes and lymphocytes (see above)
- **Sparse dyskaryotic cells** – differential diagnosis includes IUCD change (see above)

- **Pale cell dyskaryosis** – distinction from immature squamous metaplasia depends on the character of the cytoplasm as well as the nuclear membrane and chromatin.[4,17]
- **Microbiopsies** – may be overlooked at low-power[14] but high-power should enable abnormal chromatin to be recognised. Differential diagnosis includes reactive endocervical cells, LUS and TEM.
- **Syncytial dyskaryosis** (also known as large pale cell dyskaryosis) - recognised by the chaotic arrangement of cells and abnormal chromatin pattern with more cytoplasm than usual.[18] Differential diagnosis – reactive endocervical cells and glandular neoplasia.
- **Bland dyskaryosis** (recently described in LBC preparations) - also characterised by chaotic arrangement of cells with abnormal chromatin.[4,19] Differential diagnosis: reactive endocervical cells.
- **Dyskaryosis in the presence of inflammation**, often in suboptimal smears partly obscured by exudate or blood (HSIL or cancer). [14] Differential diagnosis: repair, endocervicitis (reactive metaplastic and/or endocervical cells).
- **Small keratinising cells** may have degenerate nuclei without overt dyskaryosis – search elsewhere for cells that are more typical of HSIL. Differential diagnosis: normal atrophic cells and LSIL.
- **Glandular neoplasia** is less common, easy to miss and can be difficult to distinguish from reactive endocervical cells.
- **Other forms of neoplasia** may involve the cervix – watch out for endometrial carcinoma, ovarian carcinoma, direct spread from bladder or rectum, metastasis from breast and lymphoma – all of which are rare except endometrial carcinoma.

In our experience, as reflected in the workshop cases, ASC-H is most often associated with:

i) Inflammation (endocervicitis vs CIN2-3 or cancer)

ii) immature squamous metaplasia (reactive vs CIN2)

iii) hyperchromatic crowded cell groups (e.g., TEM, LUS vs CIN3)

Cases are usually discussed beforehand with colleagues and always at multidisciplinary meetings. About half are HSIL.

Borderline changes save lives

Borderline/atypical reports cause considerable anxiety to patients and may lead to unnecessary treatment. Nevertheless, many potential false negatives and potential false positives fall into categories that could usefully be reported as ASC-H, and investigated so that appropriate management can be undertaken. The pitfalls and look-alikes described in this workshop are common sources of error and cannot always be avoided. A significant minority of CIN2, CIN3 and early screen-detected cancer is found on investigation of ASC-H, AGC or persistent ASC-US indicating that their follow-up is important.[8,9,10] ASC-H and AGC assessments were over-represented in slide review of women with cancer who had previous low-grade cytology reports in a recent cancer audit at Guy's & St Thomas'[20] and, as in the Slovenia audit, the smears were often suboptimal.[14]

ASC-H slide sets

The slide sets contain cases reported as ASC-H as well as examples of their differential diagnoses (actual and potential false positives and false negatives) and some "unknowns" whose diagnosis will be provided at the end of the workshop.

In all cases ask yourself these questions:- Is it negative? Is it LSIL? Is it HSIL or cancer? Am I genuinely uncertain and cannot exclude HSIL?

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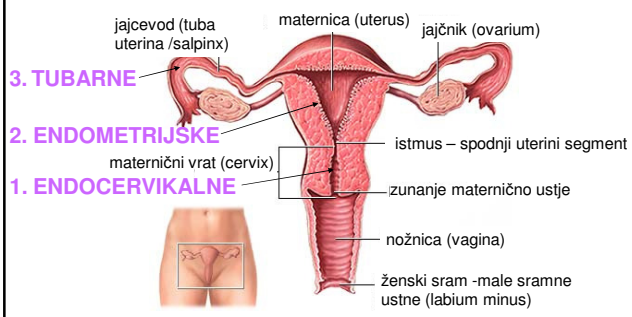
ŽLEZNE CELICE

BETHESDA:
Ne-neoplastične spremembe

Margareta Strojan Fležar
Inštitut za patologijo
Medicinska fakulteta Univerze v Ljubljani

Žlezne celice v BMV



Žlezne celice v BMV

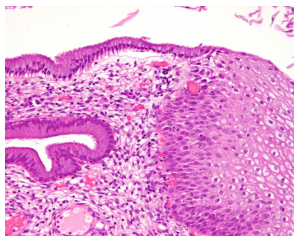
- Transfomacijska cona
- "junkcijska cona"

- Če v BMV ni metaplastičnih / endocervikalnih celic

⇩

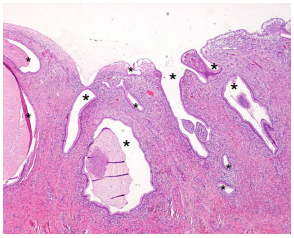
BETHESDA:

- BMV UPORABEN
- – pripomba o kakovosti BMV!!!



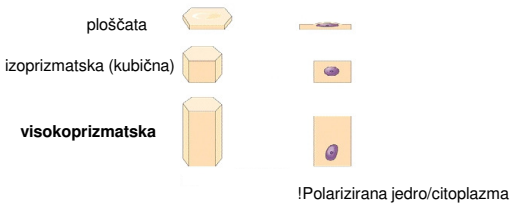
Endocervikalne žlezne celice - histologija

- Niso prave žleze
- Gubanje epitelija v stromo – kripte (*) (podobne sestavljenim žlezam)
- Sluznične gube "plicae palmatae"
- **Enoslojni cilindrični / visokoprizmatski epitelij**



Endocervikalne žlezne celice

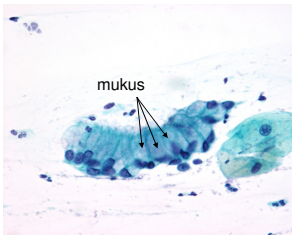
Cilindrične/ visokoprizmatske



!Polarizirana jedro/citoplazma

Endocervikalne žlezne celice

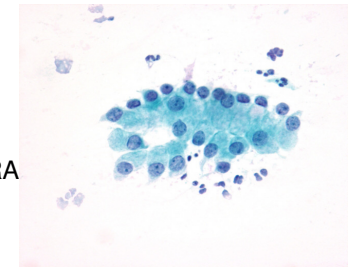
- Sekrecija – mukus v citoplazmo



- Lahko s cilijami na površini – v prvi fazi ciklusa

Endocervikalne žlezne celice

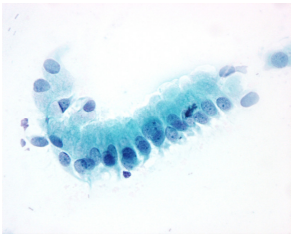
- Jedro (30% celice)
- Nežen, enakomeren kromatin, slabo vidna drobna jedrca
- Citoplazma nežna, se raztrga – GOLA JEDRA

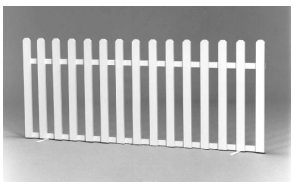


Endocervikalne žlezne celice - ureditev

- Posamične
- Trački
- Satast vzorec
- !Ni žleznih struktur (papil, acinov, rozet, žogic)

Endocervikalne žlezne celice - ureditev: trački

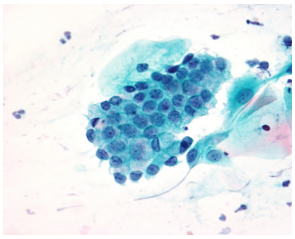




(angl. *picket fence, palisade*)

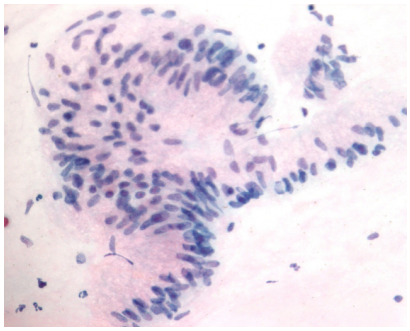
Urejena vrsta unimorfnih celic

Endocervikalne žlezne celice - ureditev: satovje



(angl. *honeycomb*)

Endocervikalne žlezne celice - artefakti: tanke celice



BETHESDA: Ne-neoplastične spremembe

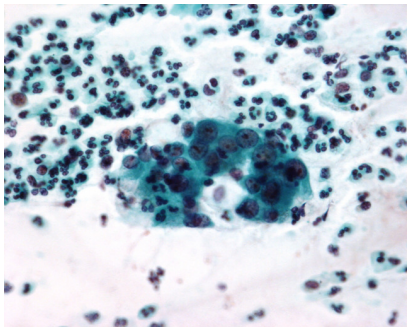
Reaktivne endocervikalne žlezne celice

- Pogoste
- Vzroki: hormoni, vnetja, polipi

BETHESDA: Ne-neoplastične spremembe
Reaktivne endocervikalne žlezne celice

- 2-D krpe
- Satovje ohranjeno
- Minimalno prekrivanje
- J/C polarnost
- ↑jedra (tudi 4-5x), hiperkromazija, jedrca (tudi makro!), ostanejo okroglo-ovalna
- Dvo/večjedrne (~herpes)
- Citoplazma dobro razmejena, bleda, cianofilna, lahko vakuole
- Vnetnice v ozadju
- DD: neoplastične celice, drugačna struktura skupin (3-D)!!!, podaljšana jedra, grob neenakomeren kromatin

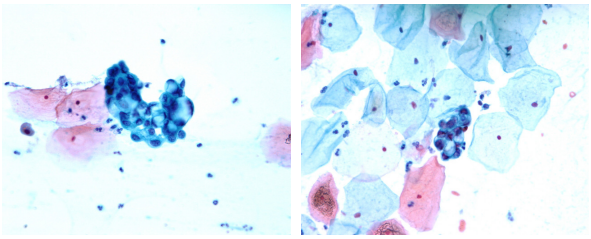
BETHESDA: Ne-neoplastične spremembe
Reaktivne endocervikalne žlezne celice



BETHESDA: Ne-neoplastične spremembe
Reaktivne endocervikalne žlezne celice pri IUV

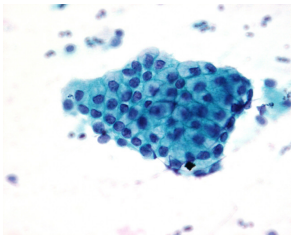
- Posamične c, skupki 5-15 c
- Čisto ozadje
- Citoplazma lahko vakuole
- Posamična ↑jedra, ↑J/C, hiperkromazija, jedrca
- Kalcifikacije
- KLINIČNI PODATEK!

BETHESDA: Ne-neoplastične spremembe
Reaktivne endocervikalne žlezne celice pri IUV (maternični vložku)



BETHESDA: Ne-neoplastične spremembe
Žlezne celice po histerektomiji

- Enake endocervikalnim
- Lahko pečatnocel. ali mucinozna metaplazija

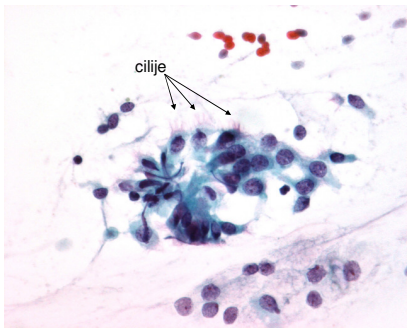


BETHESDA: Ne-neoplastične spremembe
NOVO!!! Tubarna metaplazija

- Cilindrične celice v skupkih ali psevdostratifikacija, gručanje
- Jedra: okroglo-ovalna, povečana, pleomorfna, hiperkromna
- Kromatin enakomeren, običajno ni jedrc
- ↑J/C
- Citoplazma: drobne vakuole, čašaste celice
- Cilije + terminalna plošča

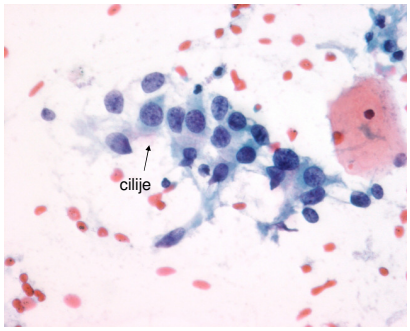
BETHESDA: Ne-neoplastične spremembe

NOVO!!! Tubarna metaplazija



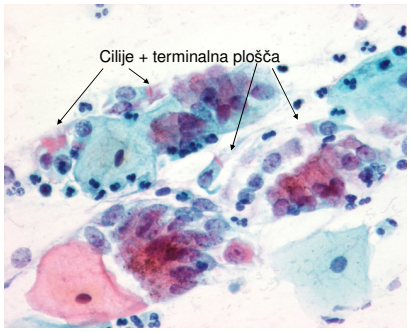
BETHESDA: Ne-neoplastične spremembe

NOVO!!! Tubarna metaplazija



BETHESDA: Ne-neoplastične spremembe

NOVO!!! Tubarna metaplazija



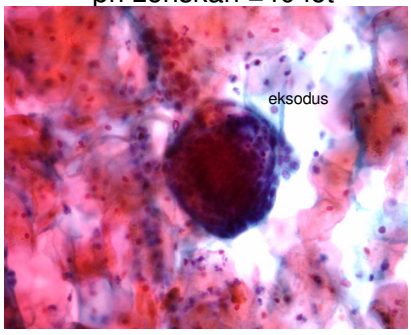
BETHESDA: Endometrijske celice v BMV
NOVO!!! - pri ženskah ≥40 let

- **Spontano odluščene**
- Žogice, redko posamične
- EM: žlezne+stromalne celice=histiociti
- Jedra: majhna, okrogla, velikost jedra intermed. c.
- Kromatin slabo pregleden (3-D skupki)
- Citoplazma: pičla, bazofilna, lahko vakuole
- Celične meje slabo vidne
- "eksodus" – 6-10 dan, prva polovica menstr. Cikla: "venci" zunaj žlezne, center stromalne c.
- 3-D skupki žleznih c.: majhne, nagnetene, degenerirana jedra, hiperkromna DD: CIS , pomoč - histiociti
- Vzroki: menses, polipi, hiperplazija

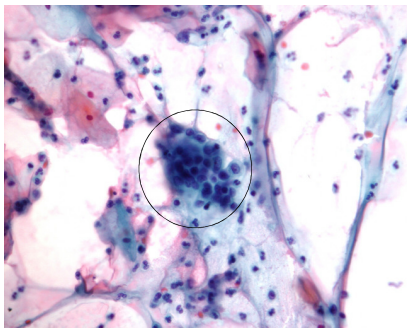
BETHESDA: Endometrijske celice v BMV
NOVO!!! - pri ženskah ≥40 let

- **Spontano odluščene**
- - prva polovica menstr. cikla 1. dan do 10-14. dan: prisotnost EM ustreza fazi menstr. cikla
- - izven faze menstr. cikla: anovulatorni ciklus, atrofija, post-partum, post-abortum, instrumentacija, IUV, endometrioza, tuboendometr. metaplazija, endometritis, piometra, leiomiomi, polipi, HNT, OHK, karcinom (pri 5% PM)
- - po menopavzi: benigen EM, hormonske spr., spremembe EM/uterusa
- priporočimo klinično korelacijo

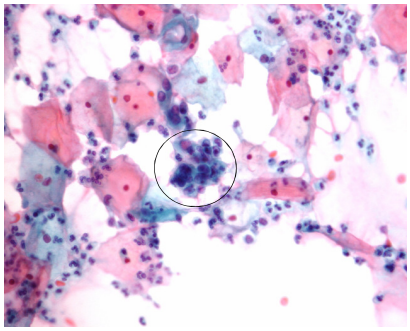
BETHESDA: Endometrijske celice v BMV
NOVO!!! - pri ženskah ≥40 let



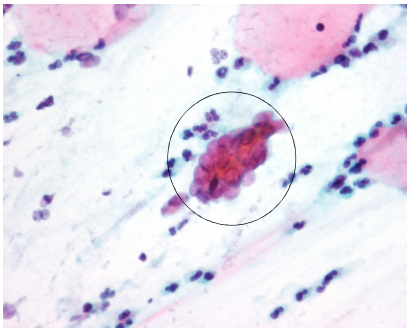
BETHESDA: Endometrijske celice v BMV
NOVO!!! - pri ženskah ≥40 let



BETHESDA: Endometrijske celice v BMV
NOVO!!! - pri ženskah ≥40 let



BETHESDA: Endometrijske celice v BMV
NOVO!!! - pri ženskah ≥40 let

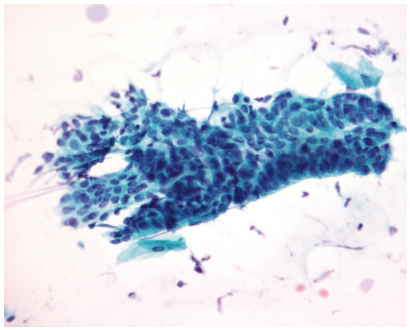


Opomba: Endometrijske celice v BMV

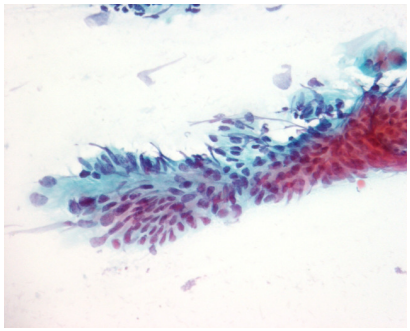
- **Neposreden odvzem brisa endometrija**
- Iz spodnjega uterinega segmenta (angl. LUS – lower uterine segment) – po konizaciji, previsok odvzem s krtačko
- Dvojna slika: EM stroma + žleze
- Gostocelični drobci, vretenaste celice, enostavne – razvejane tubularne žleze
- Mitoze / proliferacijska faza
- "globoke" stromalne c.: okrogle-vretenaste, majhna, ovalna jedra, zareze, pičla citoplazma

"povrhnje" stromalne c.: histiociti, posamične c., fižolasta-okrogla jedra, zmerno obilna, vakuolizirana citoplazma – exodus, pri spontano odluščenem EM

Endometrijske celice v BMV
Neposreden odvzem brisa endometrija

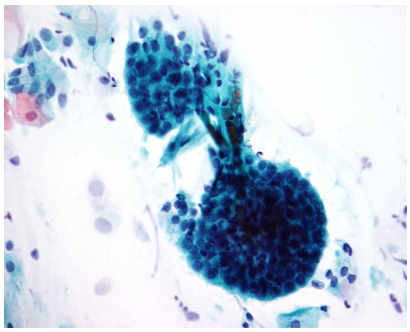


Endometrijske celice v BMV
Neposreden odvzem brisa endometrija



Endometrijske celice v BMV

Neposreden odvzem brisa endometrija



ŽLEZNE CELICE

BETHESDA:
Atipične žlezne celice, neopredeljene

Alenka Repše Fokter
SB Celje

Uvod

- Citološki pregled BMV – presejalni test za spremembe na ploščatih in žleznih celicah
- Namen: odkriti čim več “pravilno patoloških” BMV (občutljivost testa) in čim manj “napačno patoloških” BMV (specifičnost testa)

Uvod

- AŽC:
  -niso vedno žlezne
  -niso vedno atipične
- AŽC:
  -dovolj pogosto klinično tako pomembne, da jih je potrebno skrbno spremljati

Uvod

- Delež AŽC v literaturi: 0,1% do 2,5% (povprečno 0,4-0,5%)
- AŽC ► negativen follow up: 60% (15-80%)
- AŽC ► pomembne patološke spremembe: do 40%
  -bolj pogosto ploščatocelične (~75%) kot žlezne

Uvod

- Občutljivost Pap testa je pri ocenjevanju žleznih sprememb nižja kot pri ploščatih celicah zaradi problemov pri vzorčenju in interpretaciji
- AŽC, neopredeljene – slabša reproducibilnost, a kljub temu pomembna informacija pri odločanju o nadaljnjih diagnostičnih postopkih

Uvod

Citološka diagnoza	Histološka diagnoza
adenokarcinom	adenokarcinom
AIS	AIS
AŽC – verjetno neoplastične	negativno, **CGIN, AIS, CIN,** karcinom
AŽC - neopredeljene	?

Definicija

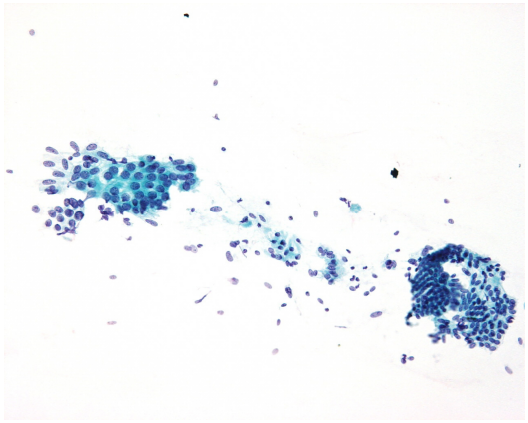
- Celična in jedrna atipija sta bolj izraženi kot pri reaktivnih spremembah, vendar celice nimajo značilnosti AIS.

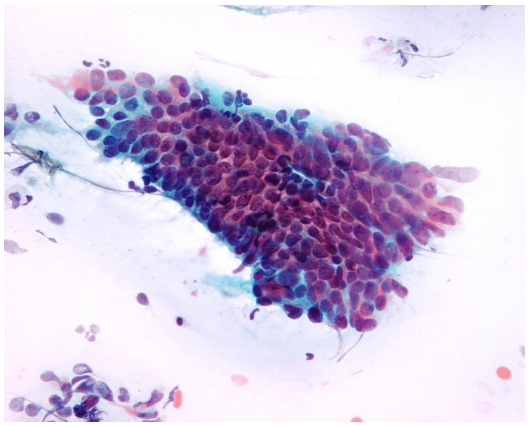
Citološke značilnosti

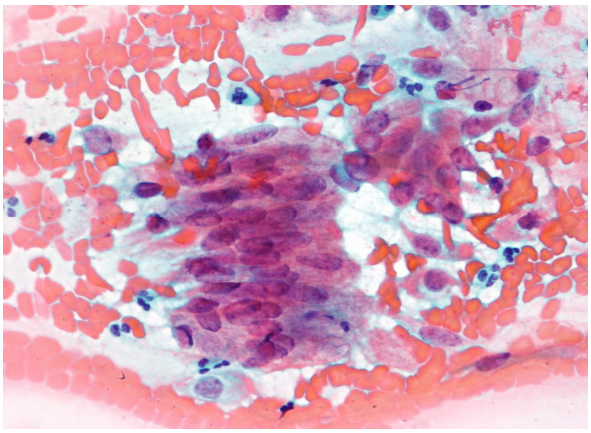
- Celice ležijo v skupinah in trakovih
- Prekrivanje jeder je neizrazito
- Jedra so povečana do 3x v primerjavi z jedri endocervikalnih celic
- Prisotna je blaga anizonukleoza in hiperkromazija

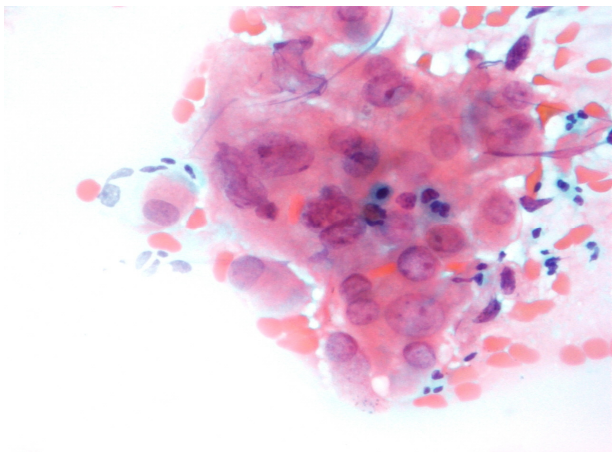
Citološke značilnosti

- Zelo redko so prisotne mitoze.
- Razmerje med velikostjo jeder in citoplazme je povečano v korist jedra.
- Meje med celicami so lahko ohranjene.







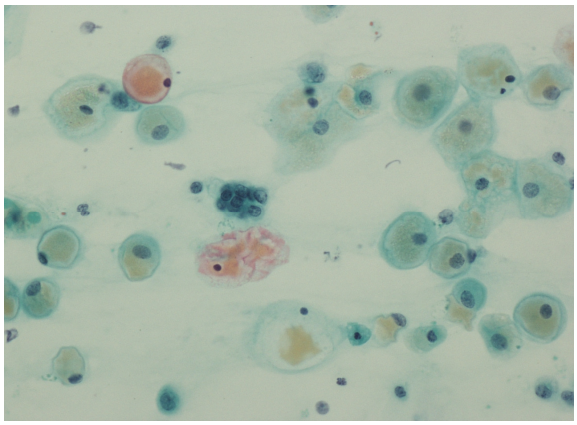


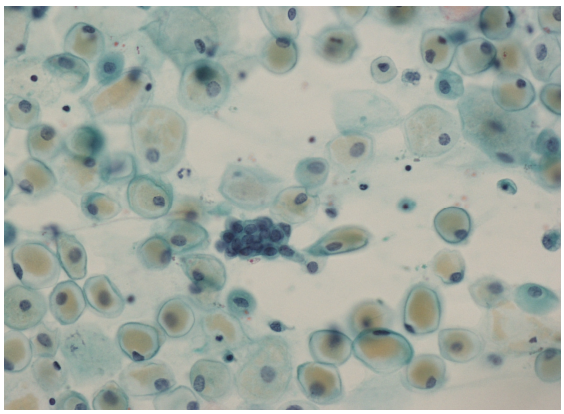
Atipične endometrijske celice

- Ležijo v majhnih skupinah (5 do 10 celic).
- Jedra so v primerjavi z normalnimi endometrijskimi celicami rahlo povečana.
- Vidni so lahko majhni nukleoli.

Atipične endometrijske celice

- Citoplazma je običajno slabo omejena, pičla, lahko vakuolizirana.
- Pri endometrijskih celicah ne ločujemo atipične, neopredeljene in atipične verjetno neoplastične, ker je reproducibilnost zelo slaba.

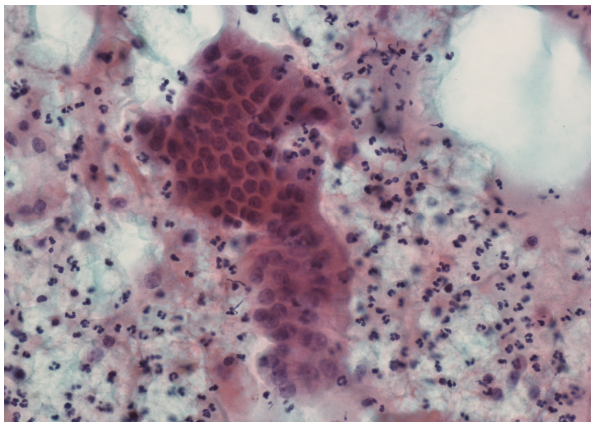




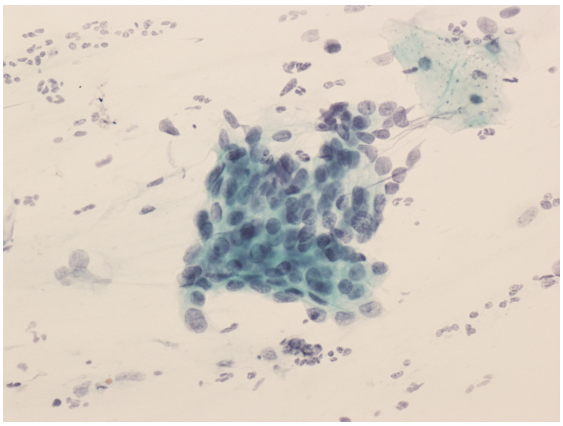
Histologija: hiperplastičen endometrijski polip

Diferencialna diagnoza

- Ne neoplastične spremembe
  -regeneracija
  -mehanski vpliv maternič nega vložka
  -tubarna metaplazija
  -"brush" efekt
  -artefakt po konizaciji ("cone biopsy artifact")
  -vpliv zdravljenja
  -…
- PIL visoke stopnje, karcinom



Tubarna metaplazija



CIN3

Zaključek

"AGC is for those times when you can't tell for sure what's going on, but you're worried about what you see."

(Richard M DeMay)

ŽLEZNE CELICE

BETHESDA: Atipične žlezne celice, verjetno neoplastične

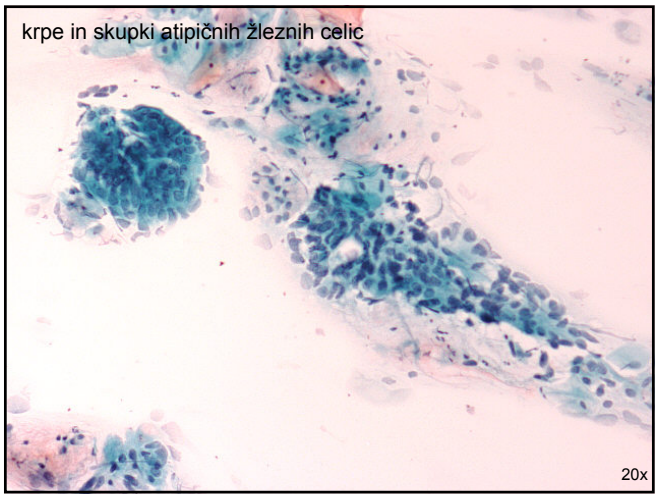
Veronika Kloboves Prevodnik
Onkološki inštitut Ljubljana

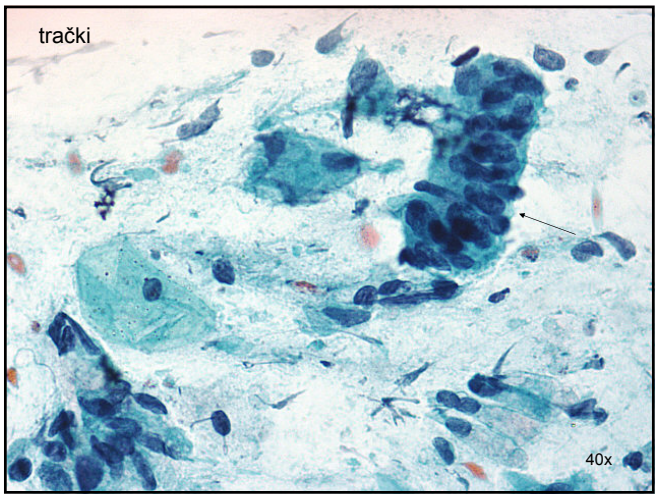
Definicija

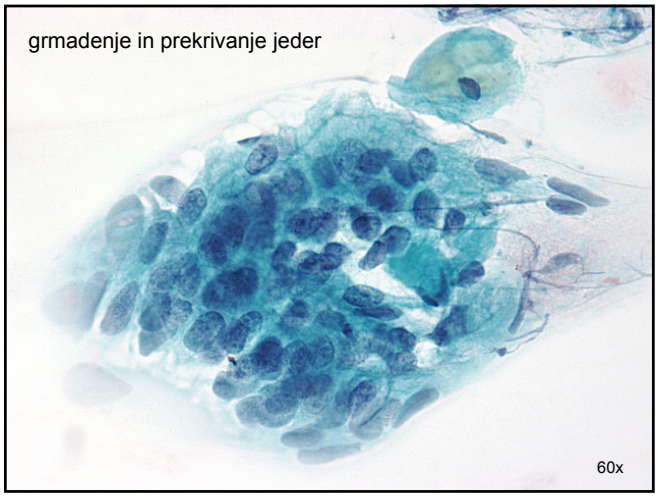
- Morfologija celic spominja na AIS ali celo na invazivni adenokarcinom, vendar niso izpolnjeni vsi diagnostični kriteriji ali pa je spremenjenih celic premalo, da bi lahko postavili diagnozo AIS ali invazivnega adenokarcinoma.

Kriteriji za diagnozo

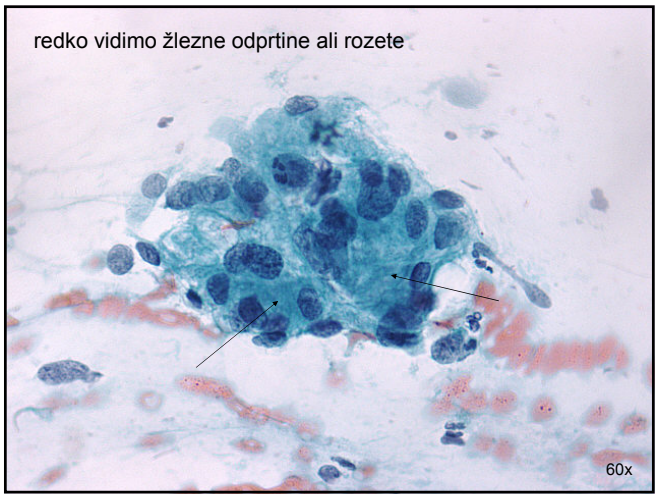
- atipične žlezne celice ležijo v krpah ali tračkih
- jedra so nagrmadena druga čez drugo in se prekrivajo
- v redkih celičnih skupinah vidimo žlezne odprtine, rozete in perjenje
- jedrno citoplazmatsko razmerje je povečano v korist jedra
- celične meje so običajno zabrisane
- količina citoplazme je zmanjšana
- jedra so povečana, hiperkromna, kromatin je fino zrnat, nukleoli niso vidni ali zelo majhni
- redko vidimo jedra v mitozi


krpe in skupki atipičnih žleznih celic
20x

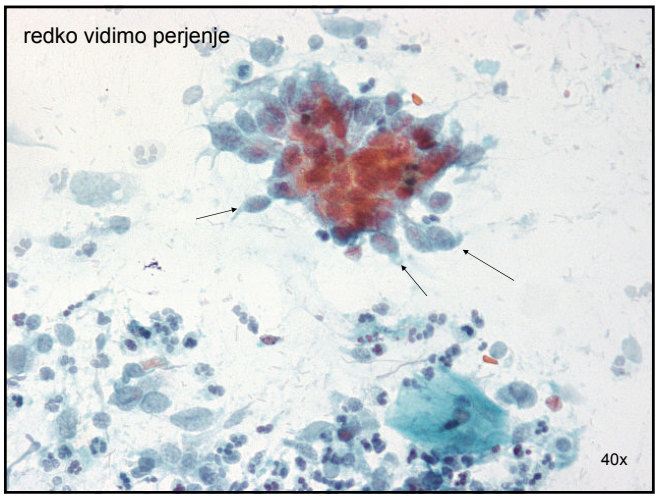

trački
40x


grmadenje in prekrivanje jeder
60x

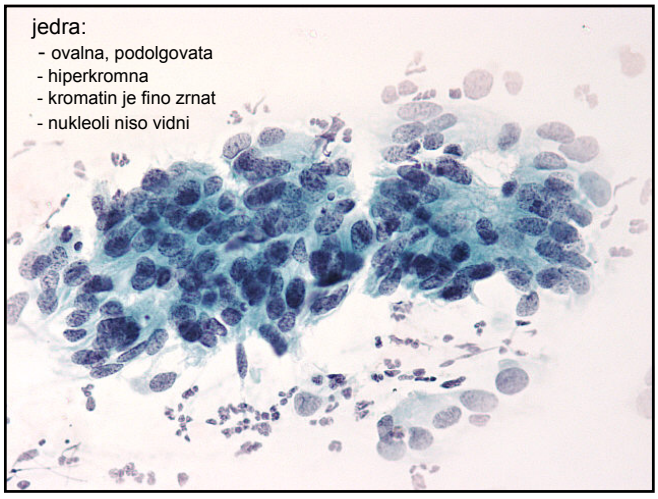
redko vidimo žlezne odprtine ali rozete



redko vidimo perjenje



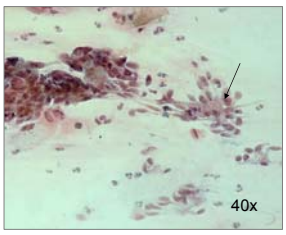
jedra:
- ovalna, podolgovata
- hiperkromna
- kromatin je fino zrnat
- nukleoli niso vidni



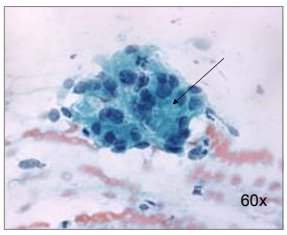
Diferencialna diagnoza

- AIS
- PIL visoke stopnje
- invazivni adenokarcinom
- atipične žlezne celice, neopredeljene
- atipične žlezne celice, ne-neoplastične
  - tubarna metaplazija
- normalne žlezne celice
  - odvzem BMV s krtačko
  - celice spodnjega uterinega segmenta
  - celice iz neovagine

Žlezne odprtine



4 leta po citološki diagnozi (atipične žlezne celice, najverjetneje neoplastične) je bolnica zdrava, brez znakov bolezni ali dokazane neoplazme žleznih celic



AIS

Katere histološke spremembe se skrivajo za citološko diagnozo atipične žlezne celice, verjetno neoplastične?

1. AIS
2. CIN 2 ali CIN3
3. invazivni adenokarcinom
4. ne-neoplastične spremembe na žleznih celicah
   - polip
   - cervicitis
   - tubarna metaplazija

Poreklo atipičnih žleznih celic

- kadar govorimo o atipičnih žleznih celicah moramo vedno opredeliti poreklo žleznih celic
  - endocervikalne
  - endometrijske
  - metastatske
  - neopredeljene
    - kadar porekla celic ni možno opredeliti

Klasifikacija atipičnih žleznih celic glede na poreklo

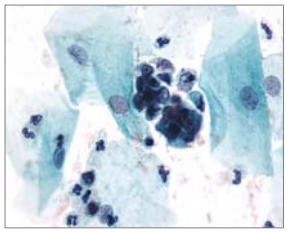
atipične žlezne celice

1. atipične žlezne celice, neopredeljene
2. atipične žlezne celice, verjetno neoplastične

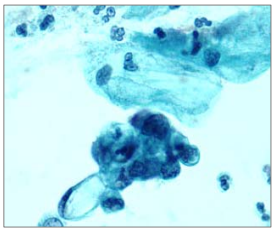
- atipije endometrijskih celic ne klasificiramo, ker je reproducibilnost slaba

Atipične endometrijske celice

- ležijo v majhnih skupinah, ponavadi 5-10 celic v skupini
- jedra so v primerjavi z normalnimi endometrijskimi celicami rahlo povečana
- blaga hiperkromazija jeder
- drobni nukleoli so lahko vidni
- citoplazma je pičla, lahko vakuolizirana
- celične meje so zabrisane



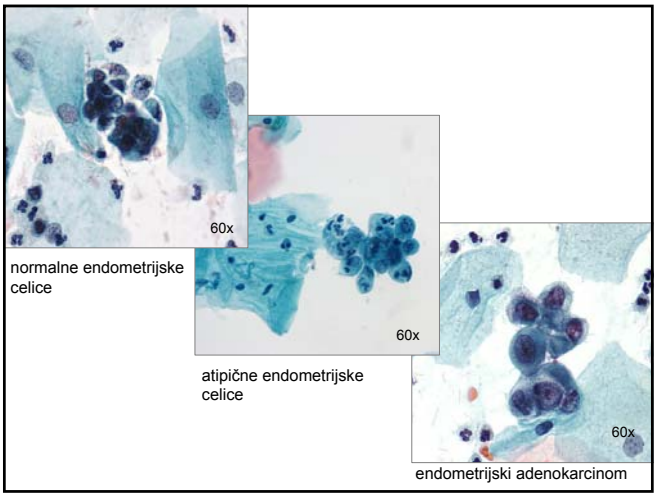
normalne endometrijske celice



atipične endometrijske celice

Diferencialna diagnoza

1. normalne endometrijske celice
2. endometrijski adenokarcinom



normalne endometrijske celice

atipične endometrijske celice

endometrijski adenokarcinom

ŽLEZNE CELICE

BETHESDA:
Endocervikalni adenokarcinom in situ

Veronika Kloboves Prevodnik
Onkološki inštitut Ljubljana

Definicija

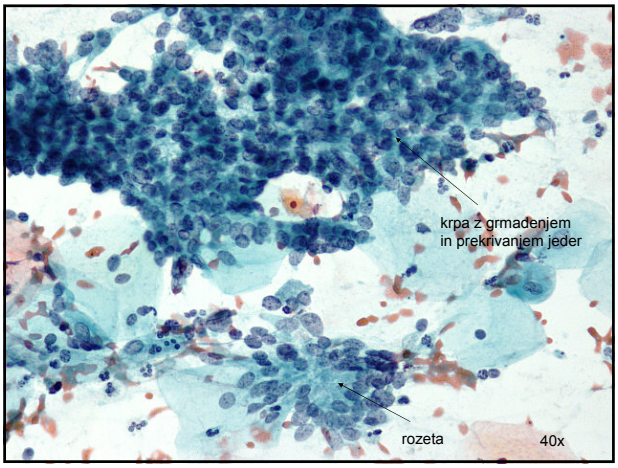
- neoplazma endocervikalnih celic, ki je omejena le na endocervikalne žleze
- invazije preko bazalne membrane ni

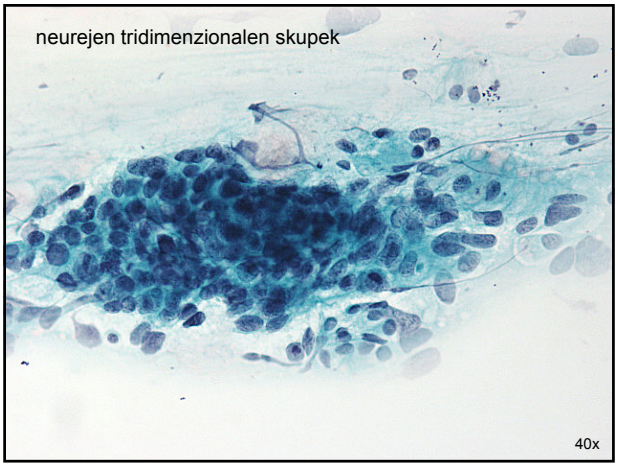
Značilnosti in situ in invazivnega adenokarcinoma

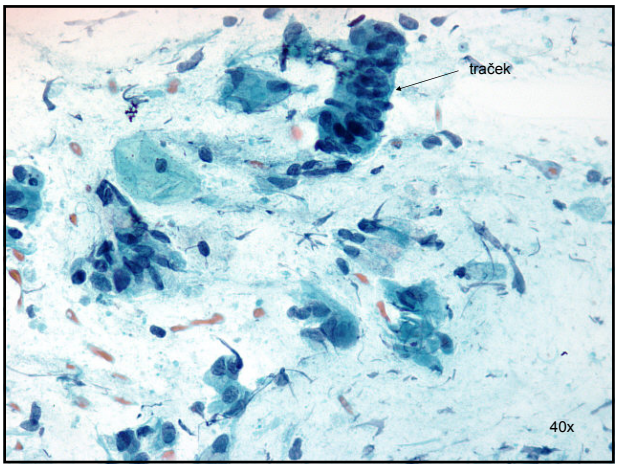
Značilnosti	In situ adenokarcinom	Invazivni adenokarcinom
Celični znaki malignosti	DA	DA
Invazija preko bazalne membrane	NE	DA
Metastaziranje	NE	DA
Ozdravitev	popolna	odvisna od stadija tumorja

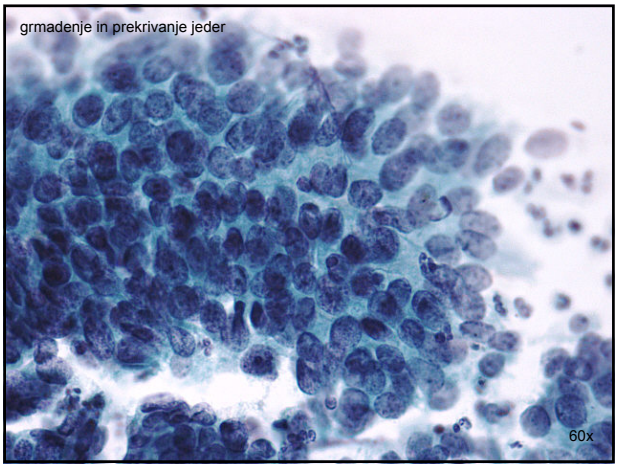
Kriteriji za diagnozo endocervikalnega adenokarcinoma in situ (AIS)

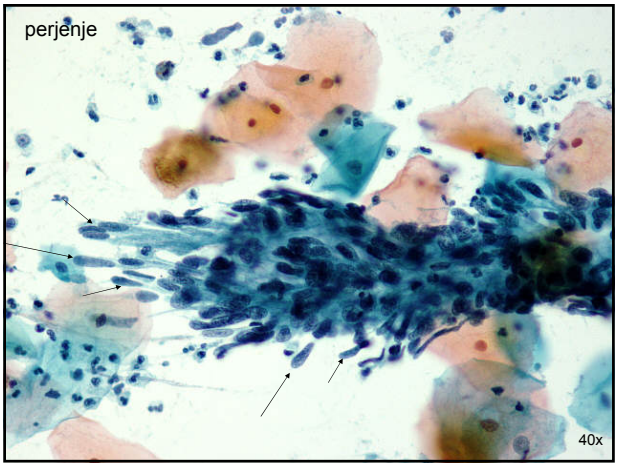
1. urejanje celic
   - krpe, neurejeni tridimenzionalni skupki, trački, rozete
   - posamezne atipične žlezne celice redko najdemo
   - izguba sataste strukture
   - grmadenje in prekrivanje jeder
   - palisadenje jeder, perjenje, žlezne odprtine

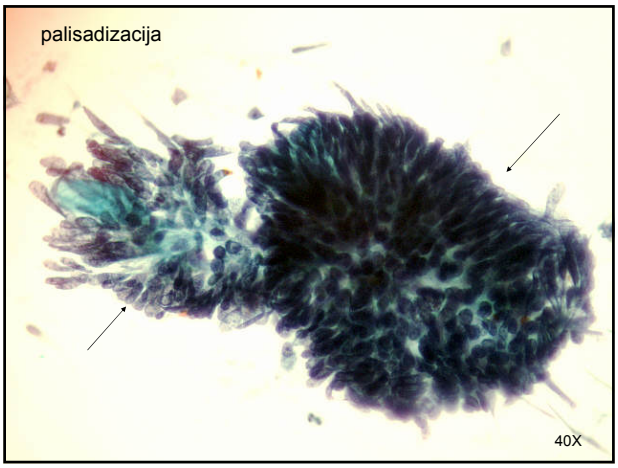


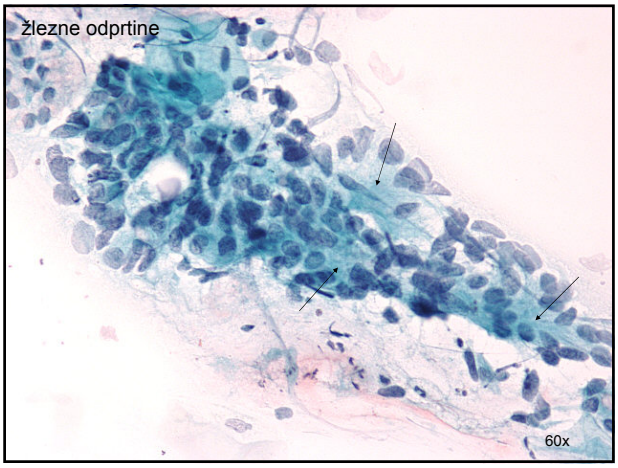



traček
40x


grmadenje in prekrivanje jeder
60x

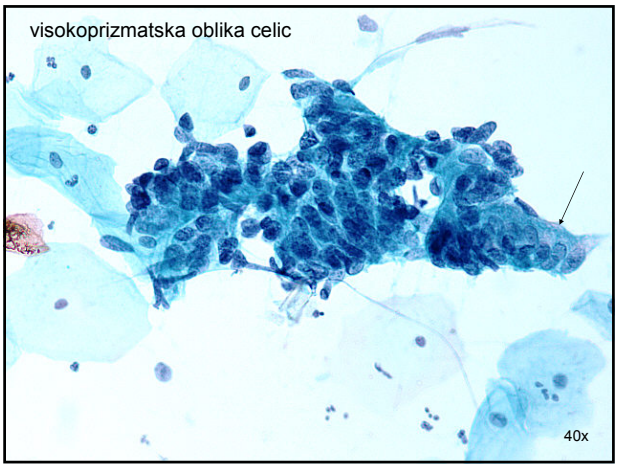

perjenje
40x

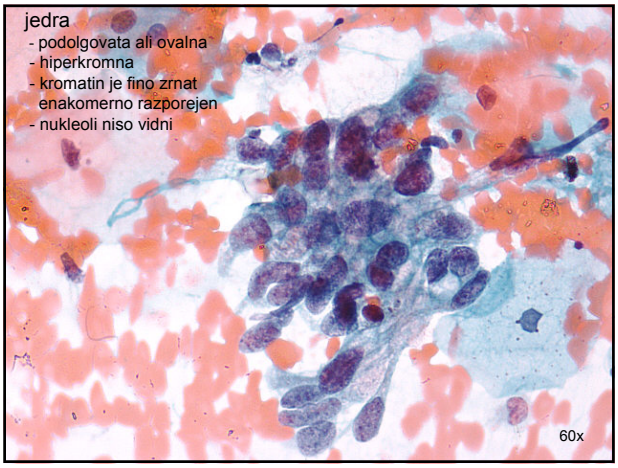


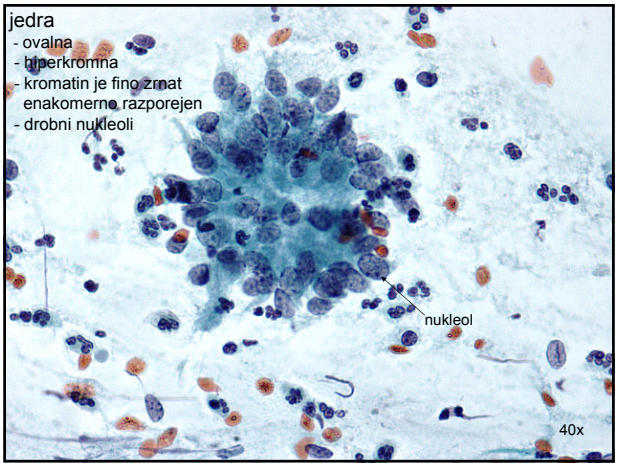


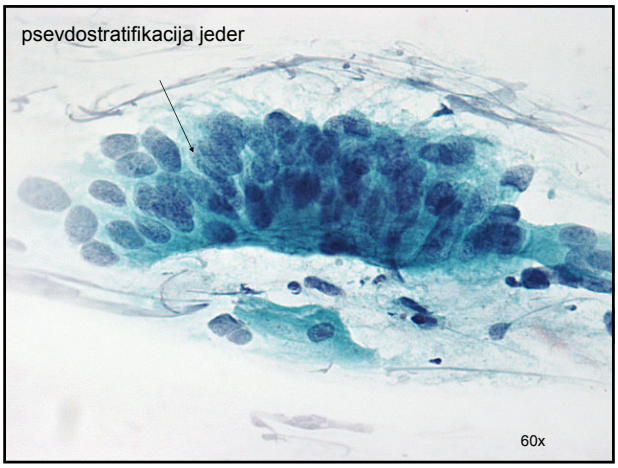
2. celične značilnosti

- oblika celic
  - posamezne celice izrazito visokoprizmatske
- jedra
  - povečana
  - različno velika
  - ovalna ali podolgovata
  - psevdostratifikacija
  - hiperkromna
- kromatin
  - fino zrnat
  - enakomerno razporejen
- nukleoli
  - običajno majhni ali neopazni


visokoprizmatska oblika celic
40x

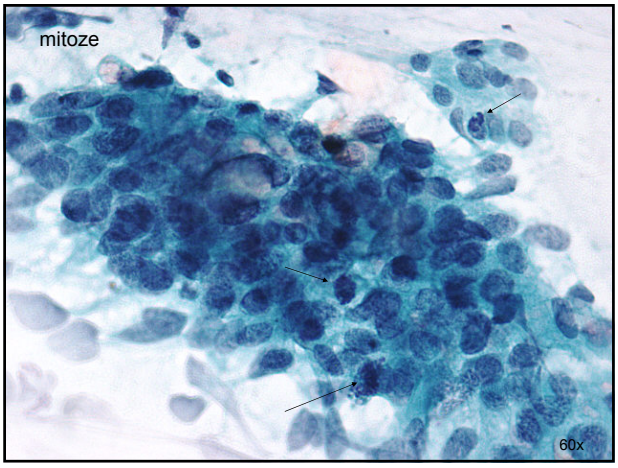

jedra
- podolgovata ali ovalna
- hiperkromna
- kromatin je fino zrnat enakomerno razporejen
- nukleoli niso vidni
60x

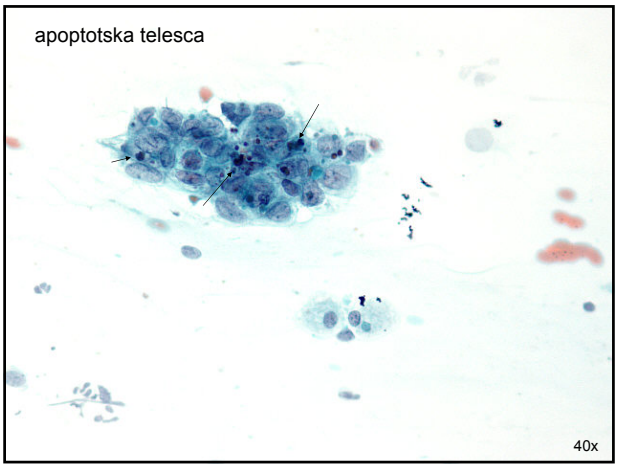

jedra
- ovalna
- hiperkromna
- kromatin je fino zrnat enakomerno razporejen
- drobni nukleoli
nukleol
40x

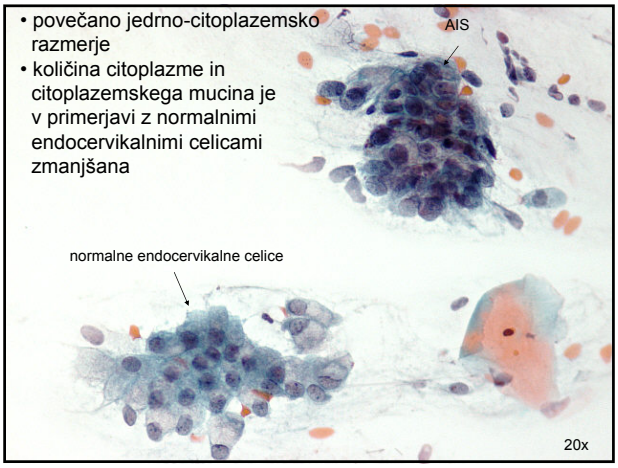


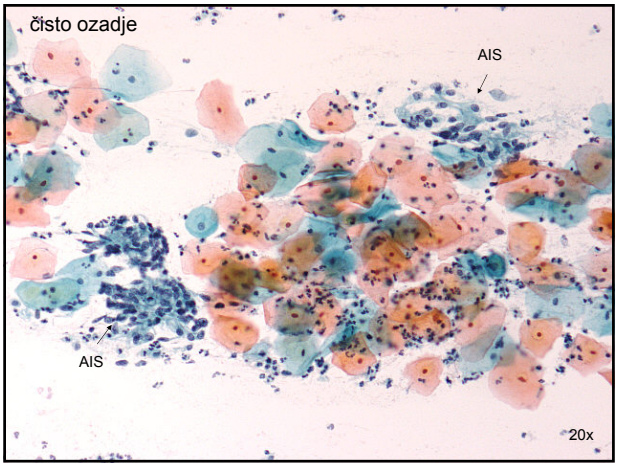
3. druge značilnosti

- mitoze
  - pogoste
- apoptotska telesca
  - pogosta
- povečano jedrno-citoplazemsko razmerje
- citoplazma
  - količina citoplazme in citoplazemskega mucina je zmanjšana
- ozadje
  - tipično čisto
  - ni tumorske diateze
  - ni vnetja
- ploščate celice značilne za PIL visoke stopnje
  - koeksistenca AIS in PIL visoke stopnje

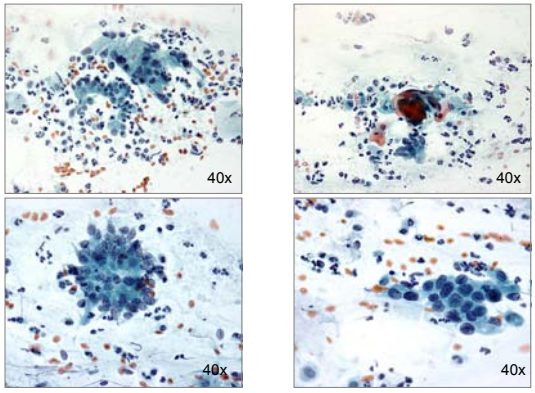



apoptotska telesca
40x


• povečano jedrno-citoplazemsko razmerje
• količina citoplazme in citoplazemskega mucina je v primerjavi z normalnimi endocervikalnimi celicami zmanjšana
AIS
normalne endocervikalne celice
20x


čisto ozadje
AIS
AIS
20x

koeksistenca AIS in PIL visoke stopnje



AIS PIL visoke stopnje

Diferencialna diagnoza

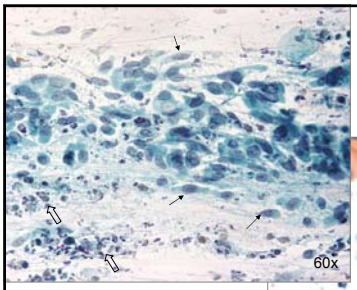
1. **atipične žlezne celice, verjetno neoplastične**
2. **invazivni adenokarcinom**
3. **PIL visoke stopnje**
4. atipične žlezne celice, neopredeljene
5. atipične žlezne celice, ne-neoplastične
   - tubarna metaplazija
6. normalne žlezne celice
   - odvzem BMV s krtačko
   - celice spodnjega uterinega segmenta
   - celice iz neovagine

1. Atipične žlezne celice, verjetno neoplastične / AIS

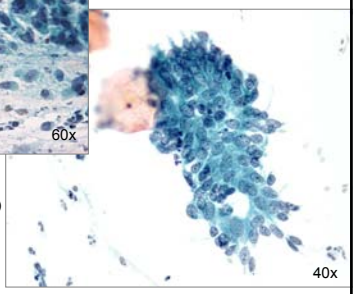
- podobne morfološke značilnosti
  - za diagnozo atipične žlezne celice, verjetno neoplastične se odločimo kadar morfologija celic spominja na AIS, vendar niso izpolnjeni vsi diagnostični kriteriji ali pa je spremenjenih celic premalo, da bi lahko postavili diagnozo AIS

2. Invazivni adenokarcinom / AIS

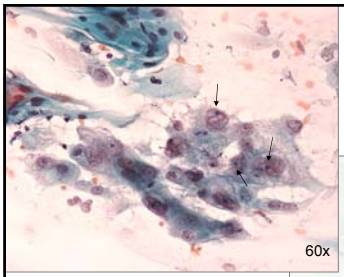
morfološke značilnosti	**invazivni adenokarcinom**	**AIS**
ozadje	tumorska diateza	čisto
neoplastične celice	zelo številčne	običajno niso zelo številčne
celična ureditev - posamezne celice - trački, rozete - krpe - tridimenzionalni skupki	 zelo številčne lahko prisotni prisotne lahko prisotni	 izjemoma prisotne običajno prisotni prisotne običajno prisotni
jedra - oblika - jedrna membrana - kromatin - nukleoli	 pleomorfna iregularna bolj grobo znat, neenakomeren, pogosto makronukleoli	 unimorfna (ovalna ali podolgovata) nepomembno iregularna fino zrnat, enakomeren prisotni, komaj vidni
citoplazma	običajno drobno vakuolizirana	rahla/vakuolizirana



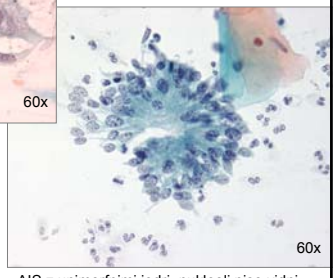
invazivni adenokarcinom s posamezno ležečimi neoplastičnimi celicami (→) in tumorsko diatezo(⟹)



AIS, ni posameznih neoplastičnih celic, ozadje je čisto



invazivni adenokarcinom s pleomorfnimi jedri in prominentnimi nukleoli

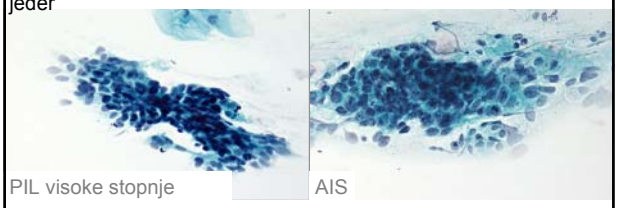


AIS z unimorfnimi jedri, nukleoli niso vidni

3. PIL visoke stopnje /AIS

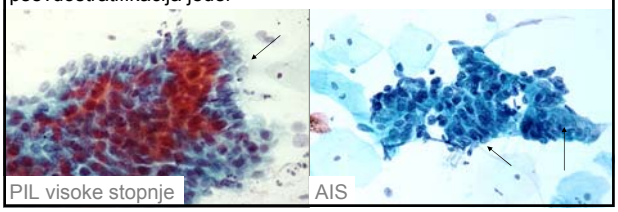
morfološke značilnosti	PIL visoke stopnje	AIS
perjenje, rozete, žlezne odprtine, trački	niso prisotni	prisotni
psevdostratifikacija jeder	izjemoma prisotna (CIN3 v žlezah)	prisotna
vrtinčenje	lahko prisotno	ni prisotno
posamezne diskariotične celice	običajno prisotne	niso prisotne
jedra		
- oblika	ovalna, zašiljena	ovalna ali podolgovata
- hiperkromazija	zmerna do huda	blaga
- jedrna membrana	iregularna, nazobčana, zareze	nepomembno iregularna
- nukleoli	običajno niso prisotni	prisotni; neopazni
citoplazma	gosta/rahla	rahla/vakuolizirana

neurejeni skupki hiperkromnih celic z grmadenjem in prekrivanjem jeder



PIL visoke stopnje AIS

psevdostratifikacija jeder

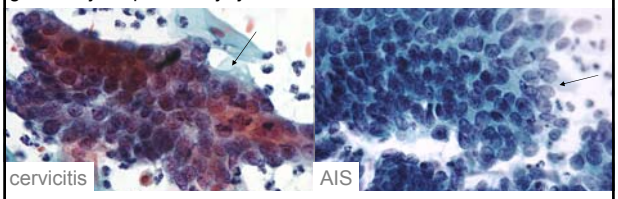


PIL visoke stopnje AIS

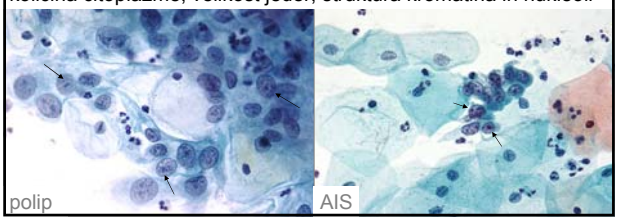
4. Atipične žlezne celice, neopredeljene /AIS

- atipične žlezne celice, neopredeljene
  - v krpah in tračkih
  - grmadenje in prekrivanje jeder
- odsotnost rozet, žleznih odprtin, psevdostratifikacije jeder, perjenja in jedrne značilnosti so ključne za pravilno diagnozo

grmadenje in prekrivanje jeder



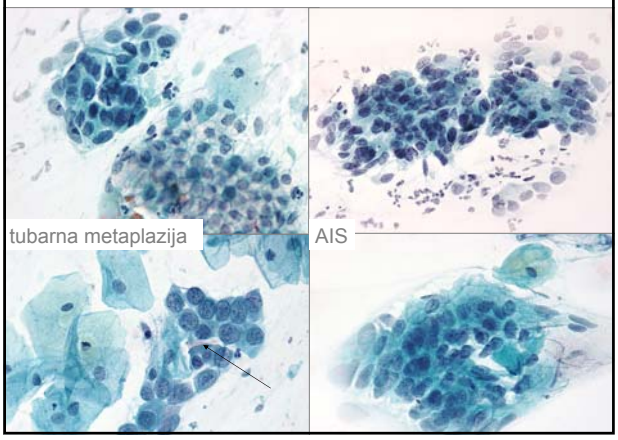
količina citoplazme, velikost jeder, struktura kromatina in nukleoli



5. Atipične žlezne celice ne-neplastične / AIS

- tubarna metaplazija
  - •neurejeni skupki visokoprizmatskih celic
  - •prekrivanje jeder
  - •anizonukleoza
  - •hiperkromazija
- ključne za pravilno diagnozo so cilije in terminalne plošče

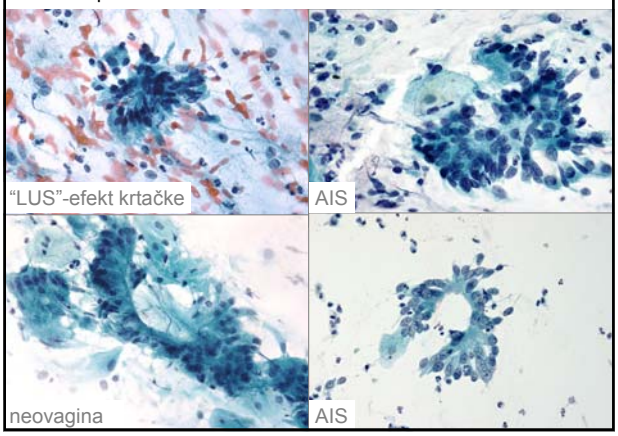
prekrivanje jeder, anizonukleoza, hiperkromazija, cilije (→)



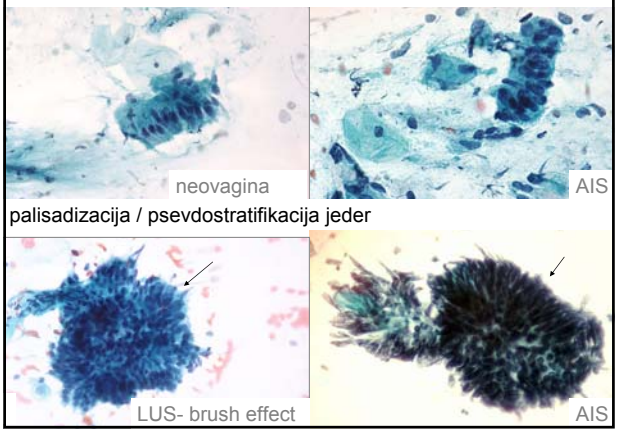
6. Normalne žlezne celice / AIS

- normalne žlezne celice
  - lahko v krpah, tračkih, rozetah,
  - žlezne odprtine
  - psevdostratifikacija jeder
- jedrne značilnosti so odločilne za pravilno diagnozo

žlezne odprtine / tvorba žlez



trački



ŽLEZNE CELICE

BETHESDA: Adenokarcinom

Vivijana Snoj
SB Izola

ADENOKARCINOM

- ENDOCERVIKALNI
- ENDOMETRIJSKI
- ZASEVKI

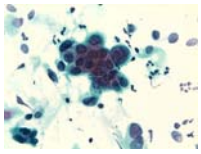
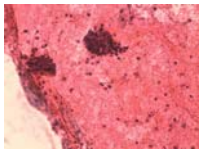
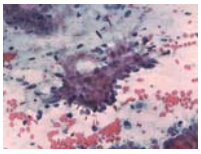
ENDOCERVIKALNI CA

- WHO RAZDELITEV

1. Mucinozni adenokarcinom (endocervikalni, intestinalni, pečatnično celični, z minimalno deviacijo, viloglandularni)
2. Endometrioidni adenokarcinom
3. Svetlo celični adenokarcinom
4. Serozni adenokarcinom
5. Mezonefrični adenokracinom

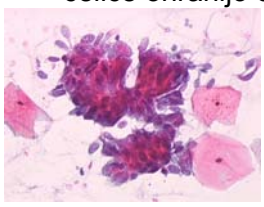
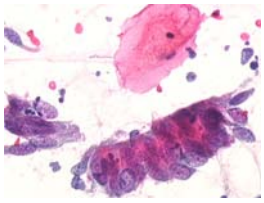
CITOLOGIJA EC ADENOKARCINOMA

- celični tip
- diferenciacija

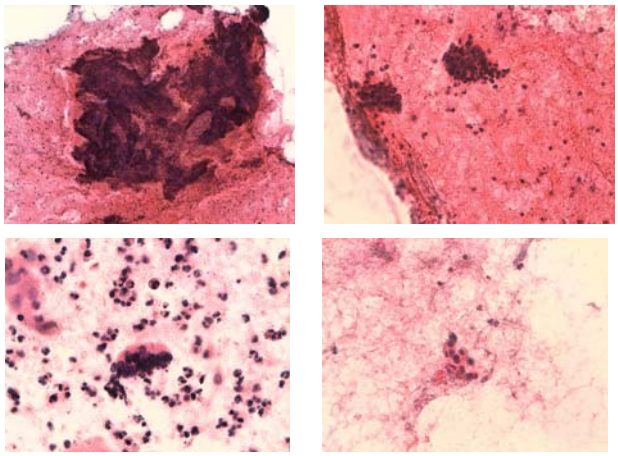
DOBRO DIFERENCIRAN EC ADENOKARCINOM

- lahko so razporejene v obliki perjanice
- celice ohranijo cilindrično obliko

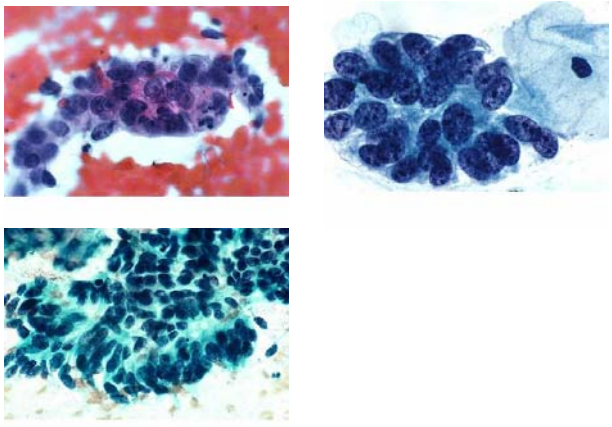
SLABŠE DIFERENCIRAN EC ADENOKARCINOM

- dvo ali tridimenzionalne strukture
- sincicijske skupine ali posamezne celice
- žlezne odprtine, psevdostratifikacija



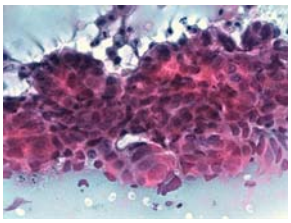
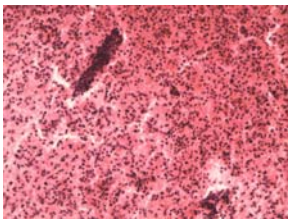
CELICE EC ADENOKARCINOMA

- bleda do eozinofilna citoplazma, včasih vakuolizirana
- jedra velika, lahko pleomorfna, se prekrivajo
- kromatin grobozrnat
- prisotna so jedrca
- lahko najdemo mitoze



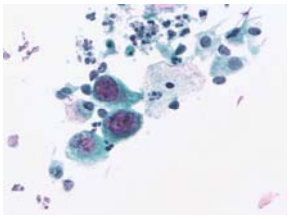
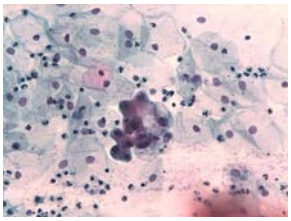
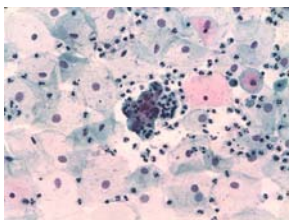
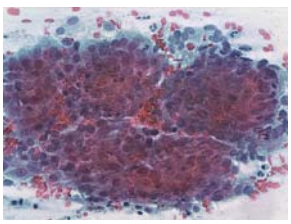
TUMORSKA DIATEZA

- drobno zrničast beljakovinski eksudat
- stara kri

ENDOMETRIJSKI CA

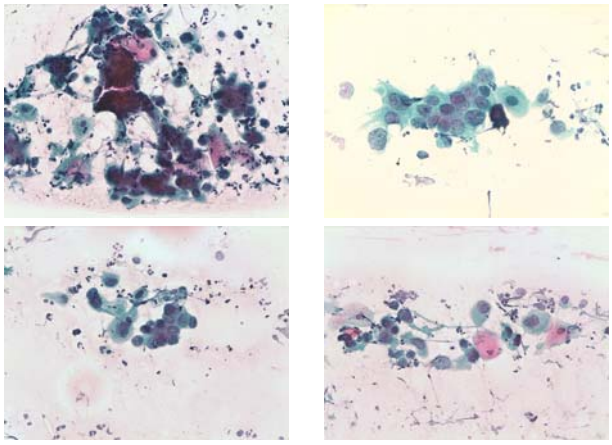
- posamezne in skupine tumorskih celic
- citoplazma pičla, bazofilna, vakuolizirana
- jedra hiperkromna
- jedrca
- tumorska diateza – vodenkasto ozadje

ZASEVKI

Genitalni trakt:

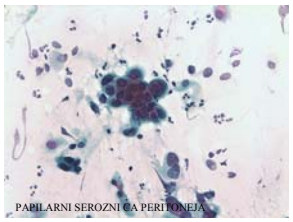
- endometrij
- jajcevod
- jajčnik – kompleksne papile, visok jedrni gradus

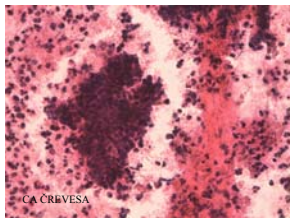


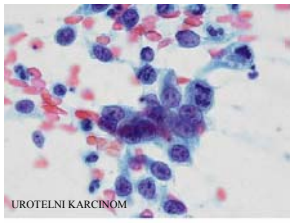
ZASEVKI

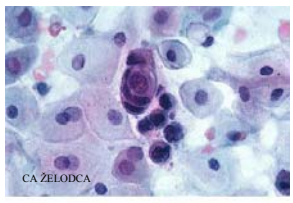
Drugi:

- dojka – običajno lobularni CA
- pljuča – slabo diferencirani
- ledvica – podobna svetloceličnemu CA
- GIT – želodec – pečatnice; črevo – direktno vraščanje, nekroza, kribriformni vzorec


PAPILARNI SEROZNI CA PERITONEJA

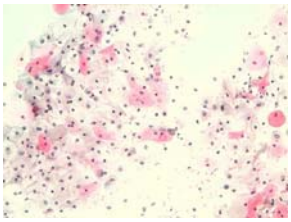

CA ČREVESA

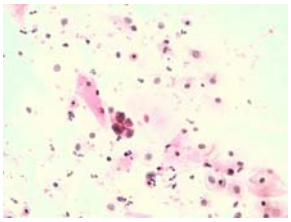

UROTELNI KARCINOM

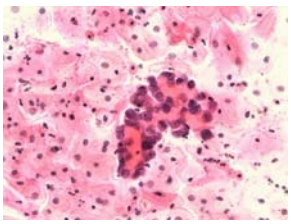

CA ŽELODCA

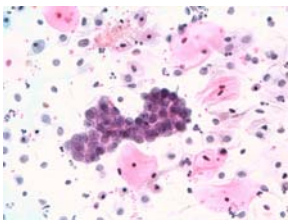
EKSTRAUTERINI TUMORJI V BMV

- tumor ne vrašča v maternico
- tumorske celice pridejo v maternico po jajcevodih
- število tumorskih celic je majhno
- ozadje je čisto
- če se urejajo v papilarne strukture, pomislimo na jajčnik!









OKRAJŠAVE

- EC – endocervikalni
- EM – endometrijski
- CA – karcinom

BETHESDA
Izpolnjevanje citološkega izvida BMV

Ana Pogačnik
Onkološki inštitut Ljubljana

Splošna navodila

- V splošnih navodilih ni sprememb

Obdelava BMV v laboratoriju

- Sprejem BMV
- Barvanje
- Pokrivanje
- Shranjevanje preparatov in izvidov

Ocenjevanje BMV

- Kakovost brisa ocenimo kot:
  a. uporaben
  b. neuporaben

Bris uporaben

- Razmaz je tanek, celice se ne prekrivajo, celice imajo ohranjeno morfologijo
- Če v brisu ni elementov transformacijske cone, BMV uporaben, vendar označimo na napotnici
- Na napotnici navedemo tudi druge značilnosti kakovosti BMV (n.pr.: epitelijske celice so delno prekrite s krvjo, vnetnicami, delno slabše fiksirane)
- Pri atrofičnih BMV lahko BMV označimo kot uporaben tudi pri manjšem številu celic kot to zahtevamo pri ženskah z normalnim hormonskim statusom

Bris neuporaben

- Če razmaz vsebuje premajhno število celic ali pa so celice mehanično poškodovane
- Če je BMV v celoti slabo fiksiran
- Če je nepregleden zaradi levkocitov, krvi, spermijev, bakterij (več kot 75% celic ploščatega epitelija prekritih)
- Če je prekomerno izražena citoliza (več kot 75% celic izraža citolizo)

Ocenjevanje sprememb

- NEGATIVEN BRIS
- PATOLOŠKI BRIS

Ocenjevanje sprememb

NEGATIVEN BRIS

- Normalen bris:
  - normalne ploščate celice
  - normalne metaplastične
  - normalne žlezne celice (endocervikalne, endometrijske)
  - atrofija
- Ne-neoplastične spremembe

Ocenjevanje sprememb

NEGATIVEN BRIS

- Ne-neoplastične spremembe:
  - vnetje
  - regeneracija
  - hiper/parakeratoza
  - mehanski vpliv maternične vložka (IUD)
  - žlezne celice po histerektomiji
  - vpliv terapije
  - prisotnost endometrijskih celic po 40. letu
  - tubarna metaplazija
  - folikularni cervicitis
  - drugo

Ocenjevanje sprememb

BRIS PATOLOŠKI: patološke spremembe

- Ploščate celice
- Žlezne celice
- Druge celice

Ocenjevanje sprememb

BRIS PATOLOŠKI

- Ploščate celice
  - atipične ploščate celice, neopredeljene
  - atipične ploščate celice, ne moremo izključiti PIL visoke stopnje
  - ploščatocelična intraepitelijska lezija (PIL) nizke stopnje (blago-diskariotične ploščate celice)
  - ploščatocelična intraepitelijska lezija (PIL) visoke stopnje (zmerno in hudo-diskariotične ploščate celice)
  - ploščatocelični karcinom

Ocenjevanje sprememb

BRIS PATOLOŠKI

- Žlezne celice
  - atipične žlezne celice, neopredeljene
  - atipične žlezne celice, verjetno neoplastične
  - endocervikalni adenokarcinom in situ
  - adenokarcinom

Poreklo žleznih celic:
- endocervikalne
- endometrijske
- metastatske
- neopredeljene

Ocenjevanje sprememb

BRIS PATOLOŠKI

- Druge celice
  - sumljive celice, neopredeljene
  - druge maligne celice

Priporočila

- Kontrola oziroma postopek kot je zapisano v smernicah za ginekologe
- Izjemoma predlog citopatologa:
  - bris ponoviti najkasneje v roku 3 mesecev (bris neuporaben)
  - bris ponoviti po zdravljenju
  - bris ponoviti po estrogenskem testu
  - drugo

Delovna skupina

Ana Pogačnik
Alenka Repše Fokter
Margareta Strojan Fležar
Vivijana Snoj

Opis sprememb na žleznih celicah – nova klasifikacija po Bethesdi

Ana Pogačnik, Margareta Strojan Fležar, Alenka Repše Fokter, Vivijana Snoj

V prispevku so opisane spremembe na žleznih celicah, kot jih bomo uporabljali po novi klasifikaciji.

NEGATIVEN BRIS

Ne-neoplastične spremembe

V napotnici smo pri ne-neoplastičnih spremembah dodali tubarno metaplazijo, in endometrijske žlezne celice po 40. letu.

Tubarna metaplazija

V brisu najdemo cilidrične endocervikalne celice v majhnih skupinah ali nagrmadene druga čez drugo. Jedra so okroglo-ovalnih oblik, često povečana, pleomorfna in pogosto tudi hiperkomna, vendar pa je kromatin enakomerno razporejen, jedrca večinoma niso vidna. Razmerje med velikostjo jeder in citoplazme je nekoliko porušeno v korist jeder. Citoplazma je lahko drobno vakuolizirana. Prisotnost cilij na terminalni plošči je značilnost tubarne metaplazije, vendar pa morajo biti prisotne na več celicah v skupini, posamezne celice s cilijami niso dovolj za diagnozo tubarna metaplazija.

Endometrijske žlezne celice po 40. letu

V BMV lahko normalno vidimo odluščene endometrijske celice v proliferativni fazi menstruacijskega. cikla. Nasprotno pa predstavljajo endometrijske celice najdene v BMV žensk po 40 letu starosti izven proliferativne faze znanilce endometrijskega karcinoma. Spontano odluščene celice običajno vidimo v obliki kroglic, zelo redko posamezno. Jedra so majhna, okrogla, velikosti jeder intermediarnih celic. Jedrni kromatin je slabo pregleden, jedrca niso poudarjena. Citoplazma je pičla, bazofilna,

včasih drobno vakuolizirana. Včasih lahko vidimo v prvem delu menstruacijskega cikla skupine z dvojno strukturo, kjer na površini ležijo žlezne celic v sredini pa je slabo pregledna stroma (eksodus).

Drugo

V to rubriko običajno uvrstimo nespecifične reaktivne spremembe bodisi na ploščatem ali na žleznem epiteliju. Celice ležijo v skupinah, imajo povečana jedra, vidni so nukleoli. Citoplazma je obilna, vidne so jasne meje med celicami. Po citoplazmi ločimo ali so spremenjene ploščate ali žlezne celice.

PATOLOŠKE SPREMEMBE

Pri patoloških spremembah smo atipične žlezne celice razdelili na atipične neopredeljene in atipične, verjetno neoplastične, kar ima za posledico različno obravnavanje žensk, zato je pomembno da te kategorije dobro poznamo.

Patološke spremembe žleznih celic

- atipične žlezne celice, neopredeljene;
- atipične žlezne celice, verjetno neoplastične;
- endocervikalni adenokarcinom in situ (AIS);
- adenokarcinom.

POREKLO ŽLEZNIH CELIC:

- endocervikalne;
- endometrijske;
- metastatske;
- neopredeljene.

Endocervikalne žlezne celice

Atipične žlezne celice, *neopredeljene*

Celična in jedrna atipija sta bolj izraženi kot pri reaktivnih spremembah, vendar celice nimajo značilnosti AIS. Celice ležijo v skupinah in trakovih, prekrivanje jeder je neizrazito, bolj izjema kot pravilo. Jedra so povečana do 3x v primerjavi z jedri endocervikalnih celic, vidni sta blaga anizonukleoza in hiperkromazija, zelo redko so

prisotne mitoze. Razmerje med velikostjo jeder in citoplazme je povečano v korist jedra. Meje med celicami so ohranjene.

Atipične žlezne celice, verjetno neoplastične

Morfologija celic spominja na AIS, vendar niso izpolnjeni vsi morfološki kriteriji, ali pa je spremenjenih celic malo. Atipične žlezne celice ležijo v razmazu v skupinah in trakovih, jedra so nagrmadena druga čez drugo, redko v razmazu vidimo vzorce rozete in perjanice (gola jedra oziroma jedra z ohranjeno minimalno citoplazme, ki uhajajo s površine skupin kolumnarnih žleznih celic, pri tem pa ohranjajo polarnost – (*angl*. feathering). Celice so povečane s povečanimi in podolgovatimi jedri, kromatin je granuliran. Redko vidimo jedra v mitozi. Meje med celicami so zabrisane.

Endocervikalni adenokarcinom in situ

Celice ležijo v neurejenih skupinah, tračkih, rozetah, ni več urejanja celic v obliki satovja. Prekrivanje jeder je izrazito. Značilna je palisadizacija jeder in značilno uhajanje posameznih golih jeder ali jeder obdanih z minimalno količino citoplazme iz skupin, ki spominjajo na perjanico. Jedra so povečana, ovalna in podaljšana, variirajo po velikosti in obliki. Kromatin je grobo, vendar je enakomerno zrnat, lahko so vidna drobna jedrca. Prisotne so mitoze in apoptotične celice. Razmerje med velikostjo jeder in citoplazme je povečano v korist jedra. Citoplazma je pičla, posamezne celice so izrazito visokoprizmatske. Ozadje je čisto, brez tumorske diateze in vnetja.

Adenokarcinom (žlezni karcinom)

Celična morfologija je odvisna od diferenciacije tumorja. Pri dobro diferenciranem žleznem karcinomu lahko celice ohranijo cilindrično obliko, so zelo podobne normalnim celicam, ležijo v krpah in so lahko razporejene v tudi obliki perjanice. Pri slabše diferenciranih žleznih karcinomih pa celice tvorijo dvo in tridimenzionalne strukture, sincicijske skupine, ali pa ležijo posamezno. Vidne so žlezne odprtine, psevdostratifikacija. Jedra se prekrivajo, so povečana, tudi pleomorfna, hiperkromna z neenakomerno razporejenim grobim kromatinom, jedrna membrana je nepravilna. Prisotna so velika jedrca. V ozadju je lahko vidna tumorska diateza. Lahko vidimo tudi atipične celice ploščatega epitelija, v kolikor je prisotna tudi ploščatocelična lezija ali pa če ima adenokarcinom ploščatocelično diferenciacijo.

Endometrijske celice

Atipične endometrijske celice

Atipične endometrijske celice ležijo v majhnih skupinah, ponavadi 5 do 10 celic v skupini in imajo jedra v primerjavi z normalnimi endometrijskimi celicami rahlo povečana. Vidni so lahko majhni nukleoli. Citoplazma je običajno slabo omejena in je pičla in je lahko vakuolizirana. Pri endometrijskih celicah ne ločujemo atipične neopredeljene in atipične verjetno neoplastične, ker je reproducibilnost zelo slaba.

Endometrijski adenokarcinom

Značilnost endometrijskega karcinoma je, da celice ležijo v brisu posamezno ali pa v stisnjenih skupinah. Velikost jeder je odvisna od diferenciacije tumorja. Pri dobro diferenciranih tumorjih so jedra malo povečana od ne-neoplastičnih jeder in se povečujejo z naraščanjem gradusa tumorja. Pri visokem gradusu je prisotna anizonukleoza in izguba polarnosti jeder. Vidna je hiperkromazija jeder, nepravilna razporeditev kromatina in tudi razredčine in zgostitve v kromatinu. Tudi nukleoli so majhni pri dobro diferenciranih tumorjih in večji pri slabo diferenciranih. Citoplazma je pičla, bazofilna, pogosto vakuolizirana; v citoplazmi lahko vidimo tudi fagocitirane neutrofilce. V ozadju je vidna tumorska diateza kot drobno granulirano vodeno ozadje.

Metastatske maligne celice

V BMV lahko najdemo tudi metastatske celice znanega ali neznanega izvora. Metastatske maligne žlezne celice ležijo večinoma v skupinah, ločenih od ostalih celic, in delujejo kot tujek v razmazu, ker v razmazu ni atipičnih žleznih celic, ki bi predstavljale prehod normalnega žleznega epitelija preko atipičnega v maligne celice. Najpogosteje metastazirajo v vrat maternice karcinom dojke, karcinom jajčnikov, karcinom materničnega telesa in drugi, vendar redkeje. Pravilna ocena malignih celic je enostavnejša, če je na napotnici napisana osnovna bolezen preiskovanke; če to ni mogoče, na izvidu označimo metastatske maligne celice.