Příběh bizarní dysplázie čípku dělohy (aneb jak se „dělá“ věda)

Ondič O., Kinkorová-Luňáčková I.

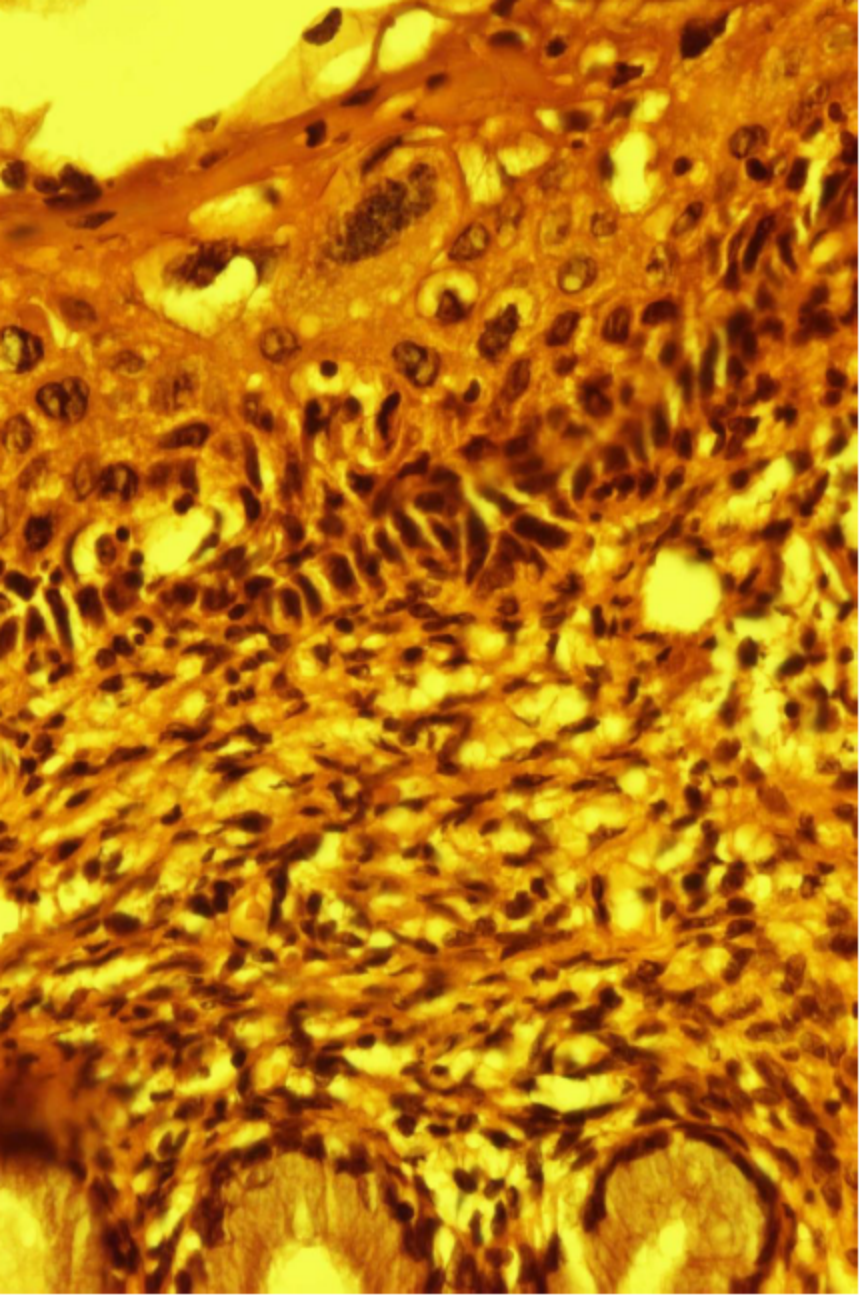
XXII. Cytologický den, Brno, 29.10.2014

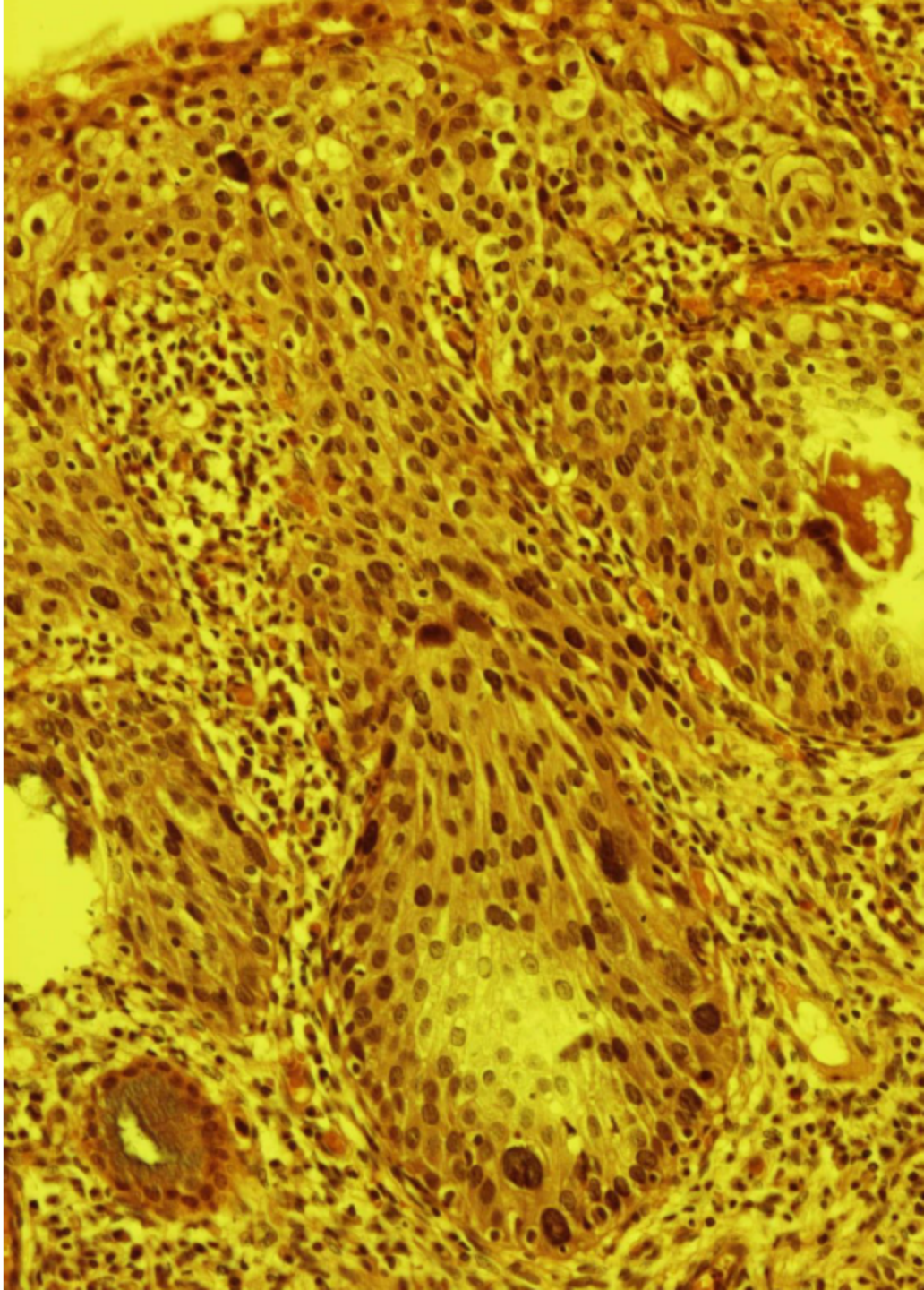
Mnohojaderné buňky v gynekologické cytologii

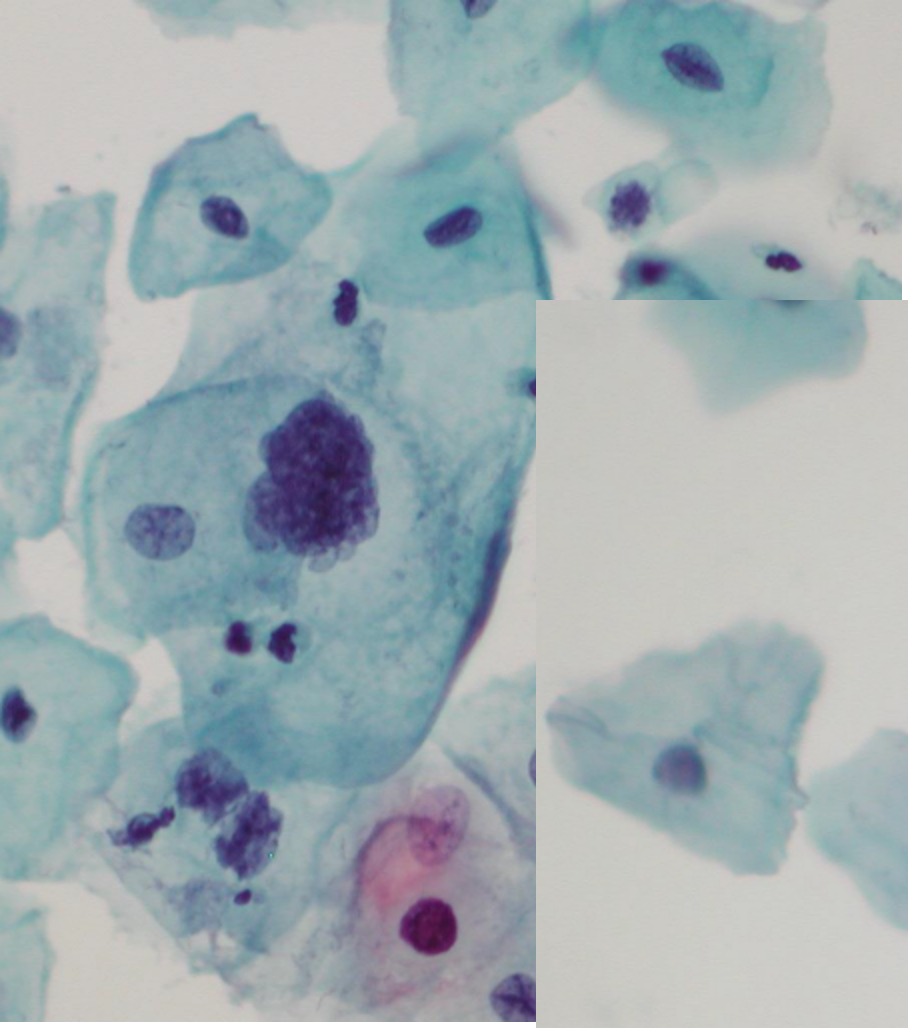
O.Ondič
Bioptická laboratoř s.r.o., Plzeň

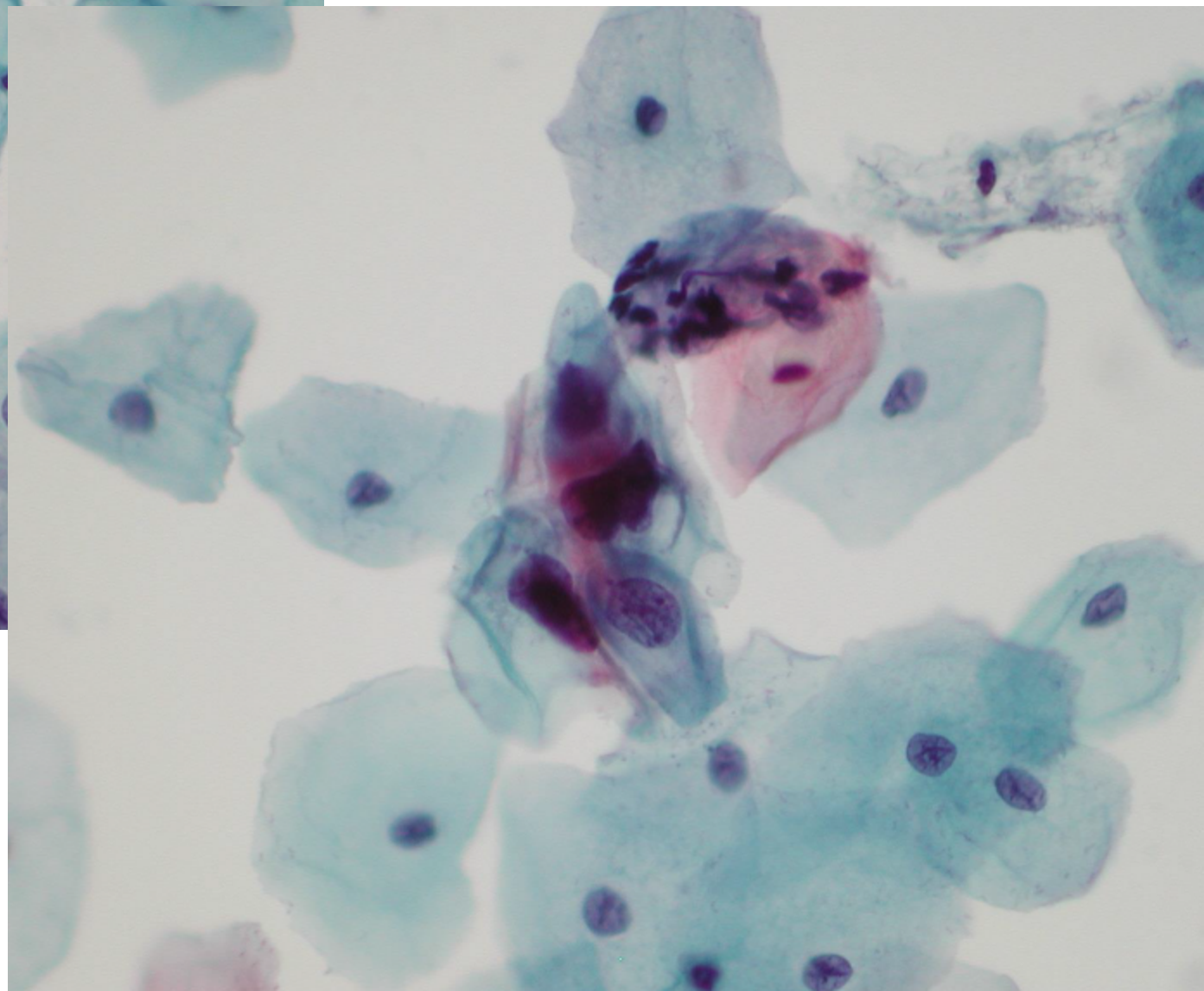

AVANTI
Hotel

- **Neobvyklý typ dysplázie dlaždicového epitelu krčka maternice**









Diskuse s Dr. Kičinovou (Košice)

Záver

- Mnohojadrové bunky LSIL možu predstavovať korelát zvláštnej HSIL lézie.

Je čas publikovat –poster,USCAP 2015

Bizzare Cell Dysplasia of the Cervix

Jana Kaspirkova [1, 2], Ondrej Ondic [1, 2], Radoslav Ferko [1,2], Michal Michal [1,2]
Biopticka laborator s.r.o. [1] / Sikl's dpt. of Pathology, Charles University [2], Pilsen, Czech Republic

Abstract

Background: A proportion of cervical squamous intraepithelial lesions encountered in surgical pathology practice contain high grade dysplastic epithelium HSIL (CIN III) with enlarged cells containing bizarre nuclei - so called **bizarre cell dysplasia (BCD)** that are outside of the current classification criteria. To elucidate the nature of these lesions we studied 19 cervical cone biopsy cases containing BCD.
Design: BCD cells were **defined as 1)** Presence of large cells comparable in size to superficial cells of squamous epithelium in normal ectocervix. **2)** Presence of cells with abnormal, large pleomorphic nuclei with bizarre shapes resulting from massive nuclear enlargement or fusion of several dysplastic nuclei within a single cell. This results in **3)** very high N/C ratio. **4)** Bizarre cells scattered throughout the whole thickness of dysplastic squamous epithelium. Multi-target PCR and ISH HPV detection was performed on all cases in routine examinations within a year with special anti-cross-contamination precautions.
Results: BCD lesions arise within the conventional high grade or ‚bland' type squamous dysplasia HSIL (CIN III). Epithelium with BCD is prone to exhibiting biological features of endocervical crypt glandular extension. Surprisingly, all BCD-lesions were HPV type 16 related. This finding is statistically significant ($p< 0.01$) in comparison to HPV type distribution in SCC in general Czech population as well as in comparison to control group of 50 consecutive CIN III lesions in cone biopsies examined in our laboratory. One case was identified at the stage of invasive carcinoma.
Conclusion: Cytologically BCD displays characteristic morphologic changes which are recognizable, but poses a significant risk of misdiagnoses as LSIL due to the enlargement of dysplastic cells and multinucleation. This pitfall is of clinical importance since histological verification of the lesion might be delayed. BCD represents an unrecognized and potentially clinically significant subgroup of cervical intraepithelial lesions. Based on the unique histological, cytological and biological features of BCD together with its exclusive association with HPV 16 infection, we believe that BCD presents a specific variant of HSIL (CIN III).

Background

Most of the cervical squamous intraepithelial lesions are readily classified according to the existing histologic criteria. A small number of cases are problematic (mostly because of metaplastic phenotype) (1, 2). Still other types of lesions present multi-nucleation and bizzare nuclei (fig.1). Bizzare cell dysplasia (BCD) has never been concisely described before. It was partly described in the setting of low grade dysplasia by Park in 2007 (3).

Objective

We aimed to better characterize BCD lesions, elucidate their nature, and investigate the association with HPV infection and possible non-HVP DNA virus coinfection which is known to cause multinucleation in various histopathologically defined lesions, namely 6 human herpes viruses and human polyomaviruses BK, and JC.

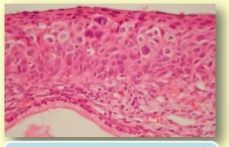


Fig. 1 Bizzare Cell Dysplasia is characterized by the presence of large dysplastic cells with dysmorphic nuclei of bizzare shapes including the confluence of multiple nuclei. (HE 400x)

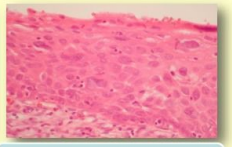


Fig. 2A Variant of BCD; the bizarre nuclei at the background of „bland type / deceiving " dysplasia. (HE 400x)

Materials & Methods

We have identified 19 cases of BCD featuring bizzare nuclei within squamous dysplastic epithelium. It comprises of 5 incidentally identified routine cervical cone biopsy cases since 2011 and 14 prospectively identified cases during the period of September 2013 and August 2014 in the setting of cone biopsies harboring HSIL (CINIII) examined at University hospital Pathology dept. and private laboratory. In each case demographic data and PAP smear history was obtained. Representative PPFE block was provided for molecular genetic studies.
PCR analyses were performed on all cases in routine examinations within a year with special anti-cross-contamination precautions. The HPV DNA detection was performed using **3 different** in house PCR methods with primers **GP5+/6+, CPSGB**, and **type specific primers for HPV16, 18, 31, 33, 35, 45** (4- 7). In case of possible multi-type HPV infection, commercial system RHA kit HPV **SPF10** was used. In order to reveal site specific infection pattern, in situ hybridization of HPV DNA was done by commercial kit INFORM HPV III Family 16 Probe on Ventana medical system. DNA detection of herpes viruses **HSV1, HSV2, VZV (Varicella zoster), EBV, CMV, and HHV6, and polyomaviruses BK, JC** was performed using Real Time PCR with specific primers and hydrolyses probes (8).

Summary

BCD represents a specific type of squamous intraepithelial dysplasia of the cervix. Incidence of BCD is about 11% (19/169) of cone biopsies with HSIL (CIN III). It was associated with classic HSIL (CIN III) (17/19 cases) or with "bland" type of dysplasia earlier described by Kitahara and Park (2/19 cases).

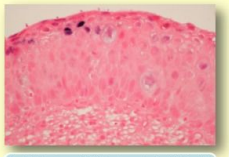


Fig. 2B Topology of HPV in the variant of BCD - the bizarre nuclei are present at the background of „bland type / deceiving " dysplasia. (ISH HPV 16, 400x)

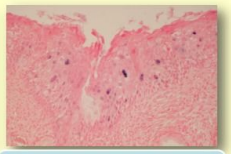


Fig. 3 ISH method reveals topology of HPV in dysplastic epithelium. Bizzare cells display weak/dotted integrated type of signals mostly when they reside in the lower part of the dysplastic epithelium. Strong nuclear signals of the episomal type is present in the upper portion of the dysplastic epithelium. (ISH HPV 16, 100x)

Histologically bizzare nuclei could be present throughout the thickness of the dysplastic squamous epithelium (Fig. 2A, B).

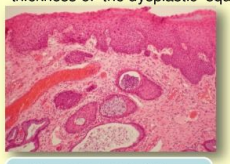


Fig. 4A -Bizzare Cell Dysplasia HSIL (CIN III) may present glandular extension. Scattered bizzare nuclei can be found in the superficial dysplastic epithelium as well as in the endocervical crypts. (HE 100x)

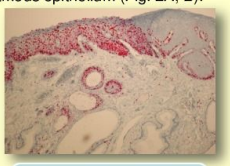


Fig. 4B - Diffuse positive nuclear expression of MIB1 antigen throughout the thickness of BD dysplastic epithelium including endocervical crypt compartment. (MIB1, 100x)

The number of HPV copies varies. It might be lower when bizzare cells are located in the lower third of the epithelium, higher doses were usually found in cells present in the upper 2/3 of the dysplastic epithelium. It was demonstrated by the ISH method (Fig. 2B, 3).

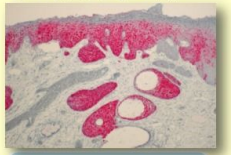


Fig. 4C - Diffuse positive nuclear and cytoplasmic expression of p16 antigen in 2/3 of the thickness of BCD dysplastic epithelium including endocervical crypt compartment. (p16, 100x)

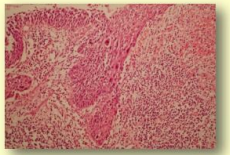
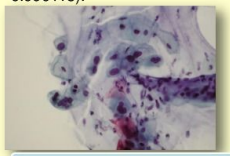


Fig. 5 The bizzare nuclei of BCD may be the part of invasive squamous cell carcinoma of the cervix. (HE 200x)

Case	Histol. type	Age	HPV type	Herpes v.	Polyoma v.	Recent cytology
1	Bland	28	16	neg.	neg	NA
2	C+AIS	46	16	neg.	neg	ASC-H
3	C	25	16	neg	neg	HSIL
4	C	31	16	neg	neg	HSIL
5	C	26	16	neg	neg	HSIL
6	C - gland.e	47	16	neg	neg	NA
7	C (Ca)	39	16	neg.	neg.	HSIL
8	C +AIS	31	16, 45	neg.	neg.	LSIL
9	C	29	16	neg.	neg.	HSIL
10	C	39	16	neg.	neg.	HSIL
11	C	29	16	neg.	neg.	NA
12	C	28	16	neg.	neg.	NA
13	Bland	45	16	neg.	neg.	HSIL
14	C	39	16	neg.	neg.	HSIL
15	C - gland.e	37	16	neg.	neg.	ASC-H
16	C	24	16	neg.	neg.	HSIL
17	C	40	16	neg.	neg.	HSIL
18	C	38	16	neg.	neg.	HSIL
19	C	26	16	neg.	neg.	NA

Tab.1 C - HSIL (CIN3) classic type, AIS - Adenocarcinoma in situ, Bland - HSIL (CIN3) "bland" type, C - gland.e - HSIL (CIN3) classic type with glandular extension, Ca – invasive carcinoma, neg. - negative, NA – not available

This type of dysplasia was also identified in dysplastic epithelium extending into the endocervical crypts (Fig. 4) and also in the infiltrative portion of cervical squamous cell carcinoma (Fig. 5). We did not notice the association with other non-HPV DNA viruses (Table 1). BCD is strongly associated with HPV 16 (Fig. 6). This finding is statistically significant (Fisher exact test) in comparison to HPV type distribution in SCC in general Czech population ($p = 0.011196$) as well as in comparison to control group of 50 consecutive CIN III lesions in cone biopsies examined in our laboratory ($p = 0.000118$).



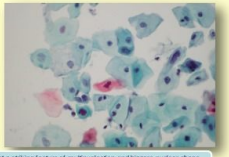


Fig. 6A,B Cytology samples (LBC) show many LSIL cells. Some present a striking feature of multinucleation and bizzare nuclear shape formation, which is a sign of bizzare cell dysplasia (HSIL). Labelling this case as LSIL would be an understatement. (PAP, 400x)

Discussion

In this study we have designated a distinctive cervical squamous intraepithelial lesion as BCD. It is a histologically identifiable entity in about 11 % of cone biopsies with HSIL (CIN III). It could be **the source of diagnostic difficulties** in punch biopsies of the cervix and PAP smears. It may be **diagnosed as LSIL** (9). This would cause an unnecessary delay in the proper management of the patient. The issue of the "bland type dysplasia" was discussed in the past by Park (3) and Kitahara (2). They commented on "low-grade squamous intraepithelial lesions of the cervix with marked cytological atypia", and "deceiving dysplasia" respectively.

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104th USCAP Annual Meeting, March 21-27, 2015, Boston, MA, USA

2015 Karlovy Vary

15.10.2015

XXIII Cytologický den Karlovy Vary

O. Ondič, J. Kašpírková, R. Ferko

OPLATÍ SA REPORTOVAŤ BIZARDNÉ BUNKY V GYNEKOLOGICKEJ CYTOLÓGII? AK ÁNO, TAK AKO?

Cyto-bioptická korelácia

Por.číslo	Číslo případu v reg.	Cytologický nález	Histologická diagnóza
1	36	HSIL	CIN III
2	43	HSIL	CIN I-II
3	44	HSIL	CIN II - III
4	51	ASC-H	punch CIN I zvláštny typ
5	56	HSIL	CIN III
6	59	ASC-H	CIN I, HPV+ 16,18,45
7	60	ASC-H	CIN III
8	61	HSIL	CIN III
9	62	ASC-H	CIN III

Článek - JOGR, 2017

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Bizarre cell dysplasia of the cervix

Ondrej Ondič[1,2], Radoslav Ferko[1,2], Jana Kašpírková[1,2], Marián Švajdler Jr[1,2], Boris Rýchly[4,5], Peter Talarčík[4,5], Jiří Bouda[3] and Michal Michal[2]

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Cytopathology

Significance of bizarre cells in cervical screening LBC: a prospective study of 15 cases.

Journal:	*Cytopathology*
Manuscript ID	CYT-2017-0020.R3
Manuscript type:	Original article
Date Submitted by the Author:	n/a
Complete List of Authors:	Ondic, Ondrej; Charles University and Charles University Hospital Pilsen, Pathology; Biopticka laborator s.r.o., Pathology Ferko, Radoslav; Charles University and Charles University Hospital Pilsen, Pathology; Biopticka laborator s.r.o., Pathology Kičinová, Jana; Medicyt, s.r.o., Pathology Bouda, Jiří; Charles University and Charles University Hospital Pilsen, Gynaecology and Obstetrics Kinkorová-Luňáčková, Iva; Biopticka laborator s.r.o., Pathology Kupcová, Ludmila; Biopticka laborator s.r.o., Pathology Zůchová, Miloslava; Biopticka laborator s.r.o., Pathology Chytra, Jan; Charles University and Charles University Hospital Pilsen, Gynaecology and Obstetrics Waloschek, Tomáš; Biopticka laborator s.r.o., Pathology Tůmová Bartošková, Monika; Charles University and Charles University Hospital Pilsen, Pathology; Biopticka laborator s.r.o., Pathology Alaghehbandan, Reza; University of British Columbia, Pathology Kašpírková, Jana; Charles University and Charles University Hospital Pilsen, Pathology; Biopticka laborator s.r.o., Genetics
Key Words:	cervix, LBC, HSIL, ASC-H, HPV, multinucleation

Table 1. Correlation of the results of LBC, HPV testing and histology in 15 patients.

Case No.	Original LBC	HPV testing	Follow-up	Diagnosis	Bizarre cells
1	HSIL	HC2+	cone biopsy	HSIL	
2	HSIL	HC2+	cone biopsy	HSIL	
3	HSIL	mRNA +	cone biopsy	HSIL	
4	ASC-H	mRNA +	cone biopsy	LSIL	
5	ASC-H	mRNA +	LBC	LSIL	
6	ASC-H	mRNA +	cone biopsy	HSIL	+
7	HSIL	HC2+	cone biopsy	HSIL	+
8	ASC-H	HC2+	LBC	LSIL	
9	ASC-H, LSIL	HC2+	HYE+AE	LSIL	
10	ASC-H, LSIL	HC2+,16,18,45	cone biopsy	LSIL	
11	LSIL	HC2+,16,18,45	cone biopsy	HSIL	
12	HSIL	mRNA +	cone biopsy	HSIL	
13	ASC-H	mRNA +	cone biopsy	HSIL	+
14	ASC-H,LSIL	mRNA+,16,18,45	cone biopsy	HSIL	+
15	ASC-H, LSIL	NA	cone biopsy	HSIL	+

„Historky z natáčení“

1. pokus

- **26.Nov., 2015 Virchows Archives**
- Recenzenti vznesli k rukovipu závažné připomínky. Práci nelze považovat za akceptovatelnou k publikováni ve VA.
- **Pripomínky:** nejasná definice, necituje zásadní publikace pro definici HSIL (Studie LAST) .

2. pokus

- **Leden , 2016, International Journal of Gynecologic Pathology**
- Bohužel, na základě hodonocení recenzentú a priorit časopisu nebudeme schopni Váš článek příjmout k publikováni.
-
- **Připomínky:**
- - Vzhledem k variabilite názorů patologů, je někdy těžké odlišit LSIL od HSIL. BCD má nejasné odlišení od LSIL.
- -konkrétni úpravy definice a textu, upřesnění metodiky IHC a genetiky. Kvalita fotografií.

3. pokus

29-Mar-2016

Dear Dr. Ondic:

Manuscript ID JOGR-2016-0212 entitled "Bizzare Cell Dysplasia of the Cervix"

Thank you for submitting your manuscript to The Journal of Obstetrics and Gynaecology Research.

Your manuscript has been reviewed by experts in the field, and although they found merit in your study, they have raised a number of serious concerns. However, I invite you to respond to the comments of the reviewers and associate editors, and revise your paper accordingly.

Dr. Kiyoko Kato
Editor in Chief, The Journal of Obstetrics and Gynaecology Research

Editorial Office email address:
jog@wiley.com

Připomínky recenzentů (A)

- Vše co autoři ukazují je HSIL a nová jednotka není potřebná.
- Cytologická diagnosticka není vůbec rozvedena.
- Nedostatečná definice "klasické" a "blandní" BCD.
- Chyby gramatické.

Připomínky recenzentů (B)

- Ohledně BCD s autori scela souhlasím.
- **Navrhuji:**
- Upřesnit argumentaci.
- Upřesnit terminologii a používat pouze HSIL/LSIL. Zdokumentovat BCD 4 případy po 5 fotografiích (HE, p16, MIB-1, HPV-ISH).
- Podrobně analyzovat výsledky HPV ISH.
- Doplnit podrobně klinické detaily u případu s pozitivtou HHV 6.
- Nevztahovat se k cytologii.

Zástupce šéfredaktora

- Autoři navrhují novou jednotku BCD. Myslíme, že tato jednotka by mohla být akceptována mezi patology a tak je článek vhodný k publikaci. Avšak protože navrhováni nové jednotky by mělo být opatrné a styl článku tomu nevyhovuje, prosím upravte ho podle připomínek recenzentů.

Článek - JOGR, 2017

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Key Words:	cervix, LBC, HSIL, ASC-H, HPV, multinucleation

Akceptační dopis

- 2.5.2017
- Dear Dr Ondic,

  Thank you for sending your paper to Cytopathology. It has been read by an Editor and two independent referees, whose comments are attached for your information.

  As it stands, the manuscript is almost suitable for publication, and if you can make the minor revisions suggested by the referees, we would be pleased to look at a revised version of your paper.

Připomínky rev 1

- Gramatika.
- Malá sestava.
- Změnit filozofii článku na popis nové histologické jednotky s jejím cytologickým korelátem.

Připomínky rev 2

- Upřesnit definici.
- Ukázat fotkou rozdíl oproti LSIL buňce.
- Upřesnit vztah BCD k diagnóze HSIL u každéh případu.

Připomínky splněny

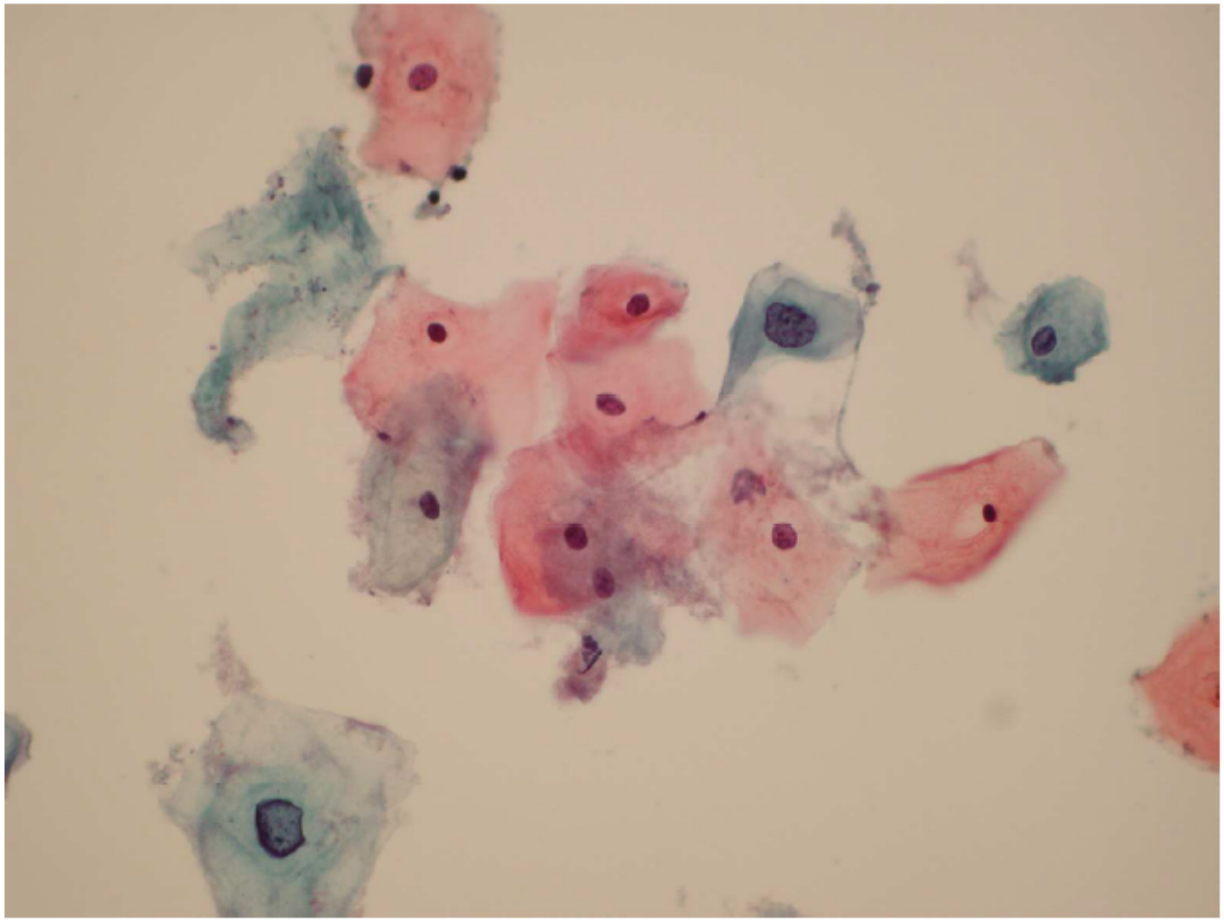


Figure 2. Typical low–grade squamous intraepithelial lesion (LSIL) cells in Liquid–based cytology (LBC) sample (Papanicolaou, 400x).

152x114mm (300 x 300 DPI)

Bizarní buňky 1

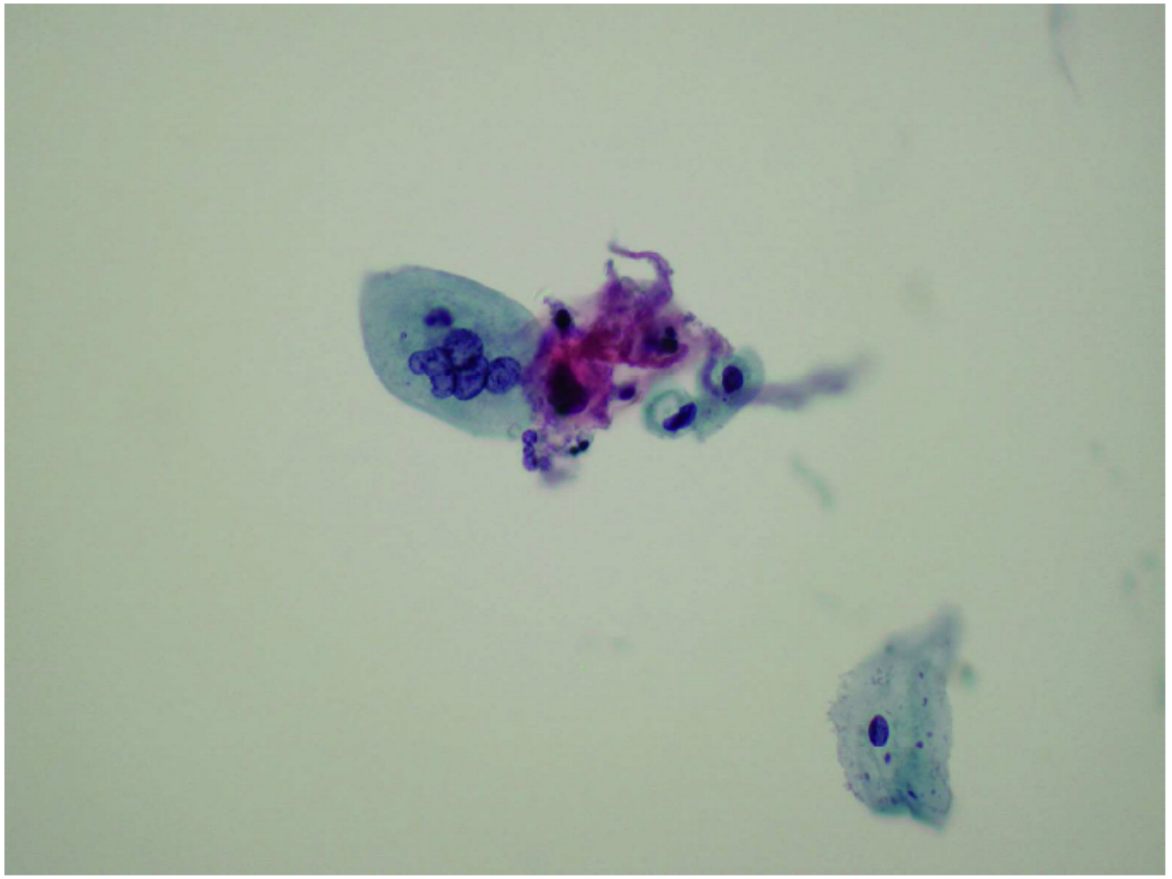


Figure 1. (a–d) Multinucleated cells of squamous origin and superficial level size – designated bizarre cells – were present in all 15 Liquid–based cytology (LBC) samples (Papanicolaou, (a) 400x, (b) 200x, (c) 200x, (d) 400x).

152x114mm (300 x 300 DPI)

Bizarní buňky 2

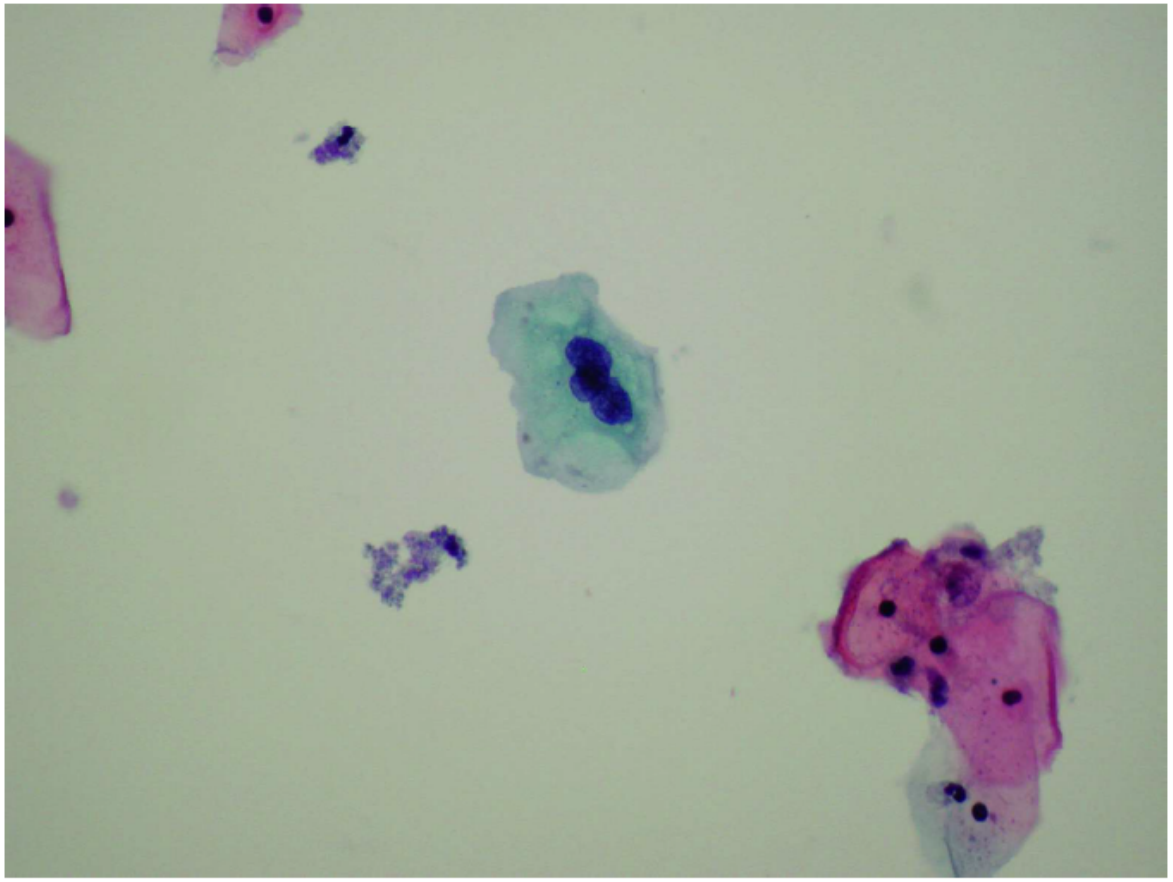
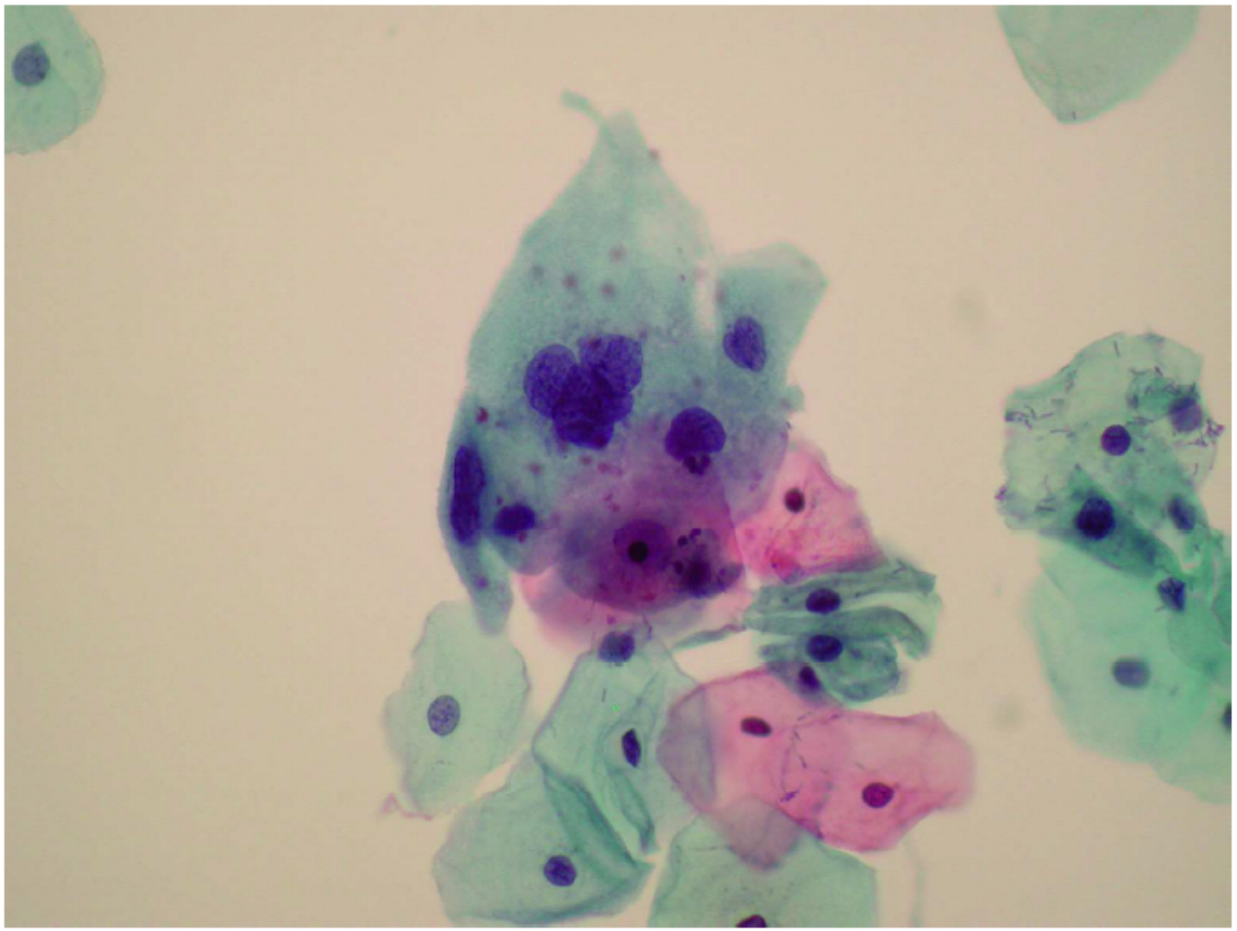


Figure 1. (a–d) Multinucleated cells of squamous origin and superficial level size – designated bizarre cells – were present in all 15 Liquid–based cytology (LBC) samples (Papanicolaou, (a) 400x, (b) 200x, (c) 200x, (d) 400x).

152x114mm (300 x 300 DPI)

Bizarní buňky 3



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152x114mm (300 x 300 DPI)

2. Kolo - připomínky

- Zlepšit srozumitelnost.
- Srovnejte incidenci histologických nálezů HSIL po cytologické diagnoze LSIL a po bizarní dysplazii.
- Gramatika.

2. Kolo - splněno

Moreover, our laboratory frequency of cytology cases with follow–up histologic data increased from 10% for LSIL to 22% for ASC–H and 32% for HSIL. This shows a

cases, of which 376 included histologic follow–up data. End–point HSIL diagnosis was rendered in 48% of cases. At the same time, there were 598 LBC ASC–H cases,

3. Kolo – připomínky.

- Není důvod ustanovovat novou cytologickou kategorii.
- Srovnat % nálezů ASC-H z Vašeho pracoviště s následnou histologikcou diagnozou HSIL oproti cytologickým nálezům s bizarními buňkami.

3.Kolo - splněno

was rendered in 48% of cases. At the same time, there were 598 LBC ASC–H cases, of which 133 included histologic follow–up data. End–point HSIL diagnosis was rendered in 71% of cases. Similarly, in the current study, the finding of bizarre cells

rendered in 71% of cases. Similarly, in the current study, the finding of bizarre cells was associated with histologic end–point HSIL diagnosis in 77% (10/13) of cases.

Článek, Cytopathology *(in press)*

21.9.2017

Dear Dr Ondic

Thank you for submitting this paper to Cytopathology.

Thank you for submitting an edited version of your paper which I am pleased to say has now been accepted for publication.

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Yours sincerely,

Dr Louise M Smart
Associate Editor
Cytopathology

Conclusions

The presence of bizarre cells in LBC specimens is associated with squamous dysplasia in cone biopsies, particularly with HSIL in 77% of the cases. Further, the presence of bizarre cells in LBC specimens is associated with bizarre cell dysplasia in 50% of cone biopsies harbouring HSIL. We believe that it may be more appropriate to diagnose LBC samples containing bizarre cells as ASC–H with a secondary diagnosis of LSIL in routine practise as opposed to only LSIL. BCD, as a specific subtype of HSIL, could potentially serve, in a proper setting, as an explanation for discordant cases of cytologic LSIL and histologic HSIL end–point in cone biopsies.

Děkuji za pozornost