CHARLES UNIVERSITY

FACULTY OF MEDICINE IN PILSEN

SELF-REPORT TO THE DISSERTATION

CLINICOPATHOLOGICAL AND MOLECULAR BIOLOGIC CHARACTERISTICS OF SELECTED CUTANEOUS EPITHELIAL AND NONEPITHELIAL TUMORS

MD. LIUBOV KASTNEROVA

PILSEN 2019

STUDY PROGRAM – PATHOLOGY

Doctoral thesis was drafted in full-time of the doctoral study program D4PA5145 PATHOLOGY at Charles University, Faculty of Medicine in Pilsen, Pilsen, Czech Republic.

CANDIDATE:	**MD. LIUBOV KASTNEROVA** DEPARTMENT OF PATHOLOGY, CHARLES UNIVERSITY, FACULTY OF MEDICINE IN PILSEN, PILSEN, CZECH REPUBLIC; BIOPTICAL LABORATORY, S.R.O
CHAIR OF SUBJECT AREA BOARD:	**prof. MD. ALENA SKALOVA, CSc.** DEPARTMENT OF PATHOLOGY, CHARLES UNIVERSITY, FACULTY OF MEDICINE IN PILSEN, PILSEN, CZECH REPUBLIC
SUPERVISOR:	**prof. MD. DMITRY KAZAKOV, CSc.** DEPARTMENT OF PATHOLOGY, CHARLES UNIVERSITY, FACULTY OF MEDICINE IN PILSEN, PILSEN, CZECH REPUBLIC
OPPONENTS:	**doc. MD. JOSEF FEIT, CSc.** LABORATORY MDGK PLUS, BRNO, CZECH REPUBLIC INSTITUTE OF PATHOLOGY, UNIVERSITY OF OSTRAVA, FACULTY OF MEDICINE, OSTRAVA, CZECH REPUBLIC **RNDR. RADEK ŠÍMA, Ph.D.** INSTITUTE OF PARASITOLOGY, BIOLOGY, CENTRE OF THE CZECH ACADEMY OF SCIENCES, ČESKÉ BUDĚJOVICE, CZECH REPUBLIC

The paper was sent out: _____

The dissertation defense of the doctoral thesis in the study program D4PA5145 PATOLOGY, in front of defense committee, is held on the _____ at _____ in the lecture hall of the Bioptical Laboratory s.r.o. in Rejskova street 10 in Pilsen.

It is possible to get acquainted with the dissertation at the dean's office of the Faculty of Medicine of Charles University in Pilsen, Husova 3, 30100 Pilsen.

CONTENT

INTRODUCTION

Skin tumors encompass a broad group of entities, with which a pathologist deals every day in his/her practice. Due to the complexity of the skin, the number of neoplasms that occur in this organ is likely the largest one compared to that seen in any other anatomic site, which portent potential diagnostic difficulties. The new WHO classification of skin tumors included listing a total of 250 entities divided into 6 chapters: 1) keratinocytic/epidermal tumors, 2) melanocytic tumors, 3) appendageal tumors, 4) tumors of hematopoietic and lymphoid origin, 5) soft tissue tumors and 6) inherited tumor syndromes associated with skin malignancies. (1) The classification of cutaneous neoplasms are based on their primary site of origin.

Some cutaneous neoplasms are commonly seen in routine practice and therefore easily recognized based on the typical histological features, whereas for the diagnosis of complex and rare tumors the clinical data, immunohistochemistry and molecular-genetic studies are often necessary.

Immunohistochemistry (IHC) is an important adjunct tool for the diagnosis of difficult neoplastic skin lesions, tumor staging, and, in some instances, for the identification of genetic variants of therapeutic significance. In addition to the many established and long-used IHC markers, due to rapid progress in our understanding of the genetic and epigenetic mechanisms of tumorigenesis, numerous new IHC markers have recently become available for application in the field of diagnostic dermatopathology. In some diagnostically difficult tumors, IHC can be decisive for the correct diagnosis, but in other neoplasms, the role of IHC is limited. IHC becomes a particularly powerful tool in the differential diagnosis of cutaneous lesions from the following categories: melanoma, epidermal tumors, cutaneous metastasis, soft tissue neoplasms, and hematologic malignancies.

Lately, various molecular techniques have also been integrated into the routine diagnostic process and currently play an important role in diagnostic dermatopathology, which is highlighted in the new WHO classification of skin tumors. (1) Molecular biologic assay such as comparative hybridization (CGH), fluorescence in situ hybridization (FISH), and next-generation sequencing (NGS) can aid in the differential diagnosis between malignant and benign melanocytic neoplasms and identify prognostic parameters in certain cases. Several significant and/or common gene mutations or gene fusions provided the basis for the classification of melanocytic neoplasms, along with the epidemiological, clinical, and pathological characteristics. Some genetics events are correlated with clinical behavior. In

particular, homozygous deletion 9p21 and *TERT* promoter *(TERT-p)* mutations have been described as potential features suggesting an aggressive course of spitzoid lesions. (2), (3) Recently, mutually exclusive activating kinases fusions, involving *ALK, NTRK1, NTRK2, NTRK3, RET, MET, ROS1*, and *BRAF* have been found in a subset of spitzoid lesions. (4) Some of these genetic alterations have been correlated with specific morphological features.

In the dissertation thesis, the author underscores the application of IHC, and various molecular genetic techniques in cutaneous neoplasms, identification of new gene fusions and possible genotype-phenotype correlations. We used in our papers the broad spectrum of available molecular tests and cytogenetic analysis, including CGH, FISH, polymerase chain reaction (PCR)-based techniques, and NGS mutation analysis.

Due to the high numbers and complexity of cutaneous tumors, the author focuses on the clinicopathological and molecular biologic characteristics of selected cutaneous epithelial and nonepithelial tumors. The results have been published in a total of 20 articles in which the author of the dissertation listed as the first author and as a coauthor in 8 and 12 papers, respectively. All 20 articles have been published in American journals with impact factor. The dissertation is elaborated in the form of a summary/comments of the annotated publications. All publications are accompanied by a copy of the reprints (14 works) or by the submitted and accepted manuscripts with proof of acceptance (3 work) or epub ahead of print (3).

The first and the most substantial part of the doctoral thesis is focused on cutaneous epithelial tumors, including various adnexal neoplasms, such as lesions with apocrine and eccrine differentiation, follicular tumors, sebaceous neoplasms and lesions of anogenital mammary-like glands (AGMLG).

The second part covers selected nonepithelial cutaneous tumors, such as melanocytic tumors, lymphoproliferative disorders, and mesenchymal tumors.

SUMMARY

The doctoral thesis MD. Liubov Kastnerova (previous name Kyrpychova) is focused on the histomorphological and molecular biologic features of selected cutaneous epithelial and nonepithelial tumors and is structured as a commentary to the 20 articles published during four years, representing the completed scientific projects in the Ph.D. course. In eight papers, the author of the thesis is the first author, whereas she coauthored in the remaining 12 papers. The thesis is composed of the commented files of authors own publications and it is divided into cutaneous epithelial and nonepithelial tumors.

The first section, «Cutaneous epithelial tumors», includes 14 articles that are subdivided into two parts: adnexal tumors (9 articles) and lesions of anogenital mammary-like glands (5 articles).

Of the nine articles on adnexal tumors, there are 5 articles focused on various benign and malignant adnexal lesions with apocrine or eccrine differentiation. Novel findings in this part include the identification of hitherto unreported alterations of the *MYBL1* gene in adenoid cystic carcinoma of the skin and lack of deletion of the 1p36 locus in this neoplasm; the lack of a correlation between cellular composition and the presence *CRTC1-MAML2* fusions in hidradenoma, the absence of *CRTC3-MAML2* fusions in this tumor, and new histopathological features and novel *NFIX-PKN1* translocation in primary cutaneous secretory carcinoma. Also, we performed a complex study including the HPV analysis and *HRAS* and *BRAF V600* mutations in syringocystadenoma papilliferum located in the anogenital area, which has never been a subject of such investigation in this location.

One of two articles on follicular tumors is a clinicopathological, immunohistochemical, and molecular biological study of 22 cases of basal cell carcinoma with matrical differentiation. The novel findings included the description of an atypical matrical component in 2 cases and the mutation spectrum in these rare variants. The second article is based on IHC study of BAP1 expression in trichoblastomas, both solitary sporadic and multiple ones occurring in the setting of multiple familial trichoepithelioma (MFT)/Brooke-Spiegler syndrome (BSS).

Two articles are focused on sebaceous neoplasms. One is the largest series of sebaceous lesions with so-called organoid patterns, namely the rippled, labyrinthine/sinusoidal, carcinoid-like and petaloid patterns. We confirmed the previously suggested proposition that all these patterns represent a variation of a single morphological spectrum. We established no association

with Muir–Torre syndrome and detected no missmatched repair (MMR) deficiency in most cases, the new data. The second study on periocular sebaceous carcinoma reports new features that may be used as a differential diagnostic clue, namely cells with squared-off nuclei and so-called “appliqué” pattern (peritumoral subnecrosis of peripherally located neoplastic cells).

The subsection on the lesions of anogenital mammary-like glands includes five articles, which add new data regarding their normal histology, provide the detailed immunohistochemical profile of AGMLG, and demonstrate molecular changes in lesions arising from AGMLG comparing these to breast homologs. The novel data also includes the depth of adnexal involvement by neoplastic cells in extramammary Paget disease (EMPD) a large series, which provides practical treatment implications.

The second part, «Cutaneous nonepithelial tumors», includes five articles which are divided between 3 subcategories: lymphoproliferative disorders, mesenchymal tumors, and melanocytic tumors.

One of the three articles in the subgroup of lymphoproliferative disorders represents the largest series of cutaneous Hodgkin disease in which we provide the first description of so-called mummified cells in this condition in the skin. These cells are known in lymph node disease but have been overlooked in skin biopsies judging from the previously published articles. Their presence can serve as a clue to the diagnosis. Included were also two case reports. The first on an extraordinary clinicopathological course of a recently described variant of lymphomatoid papulosis, type E. The second article is an extraordinary case report of cutaneous primary effusion lymphoma (PEL) with an unusual intravascular presentation, combined with Kaposi sarcoma (KS) involving the skin, lung and gastrointestinal tract harboring a *FAM175A* germline mutation.

In the subsection of melanocytic tumors, there are two articles. In the first paper, the author presents a detailed pathological study on spitzoid lesions with *ROS1* fusion and novel fusions of this gene. The study also includes the extensive genetic investigation of other genes, with some novel data. The second article is an extraordinary case report which describes a case of a polypoid atypical Spitz tumor a with a prominent fibrosclerotic stromal component, harboring a *CLIP2-BRAF* fusion, which has hitherto been not reported in melanocytic lesions.

As a representative entity of mesenchymal tumors, the authors describe a series of epithelioid fibrous histiocytomas in which new histopathological features and novel *ALK* gene fusions were found.

ABSTRAKT

Disertační práce MD. Liubov Kastnerové (dříve Kyrpychova) se zaměřuje na histomorfologické a molekulárně biologické vlastnosti vybraných kožních epiteliálních a neepiteliálních nádorů. Je strukturována jako komentář k 20 článkům publikovaným v průběhu čtyř let, které představují dokončené vědecké projekty v Ph.D. studiu. V osmi článcích je autorka první autor, ve zbývajících 12 pracích je spoluautorem. Doktorská dizertační práce je prezentovaná ve formě komentovaného souhrnu vlastních publikací a je rozdělena na kožní epiteliální a neepiteliální nádory.

První část, "Kožní epiteliální tumory", obsahuje 14 článků, které jsou členěny do dvou částí: adnexální tumory (9 článků) a léze z anogenitálních „mammary-like“ žlázek (AGMLG) (5 článků).

Z devíti článků týkajících se adnexálních nádorů je jich 5 zaměřeno na různé benigní a maligní adnexální léze s apokrinní nebo ekrinní diferenciací. Nové poznatky v této části zahrnují identifikaci dosud nepopsaných změn genu *MYBL1* v adenoidně cystickém karcinomu kůže a absenci delece lokusu 1p36 v tomto nádoru. Dále prokazujeme chybění korelace mezi buněčným složením a přítomností fúzí *CRTC1-MAML2* v hidradenomu, absenci fúzí *CRTC3-MAML2* v tomto nádoru, a nové histopatologické znaky a translokace *NFIX-PKN1* v primárním kožním sekrečním karcinomu. Také jsme provedli první komplexní studii zahrnující analýzu HPV a prokázali jsme role *HRAS* a *BRAF V600* mutace v syringocystadenoma papilliferum nacházející se v anogenitální oblasti, která nikdy nebyla předmětem tohoto zkoumání v této lokalitě.

Jedním ze dvou článků o folikulárních nádorech je klinicko-patologická, imunohistochemická (IHC) a molekulárně biologická studie 22 případů bazocelulárního karcinomu s matrikální diferenciací. Nové poznatky zahrnovaly popis atypické matrikalní složky ve 2 případech a mutačního spektra v těchto vzácných variantách. Druhý článek je založen na IHC studii exprese *BAP1* v trichoblastomech a to jak solitárních, tak vícečetných, vyskytujících se v rámci mnohočetného familiárního trichoepiteliomu (MFT) / Brooke-Spieglerova syndromu (BSS).

Dva články jsou zaměřeny na sebaceozní nádory. Jedním z nich je největší série sebaceozních lézí s takzvanými organoidními rysy, jmenovitě s vlnitými, labyrintovými / sinusovými, karcinoidními a petaloidními vzory. Potvrdili jsme dříve navrhovanou hypotézu,

že všechny tyto vzory představují variantu jednoho morfologického spektra. Nezjistili jsme žádnou souvislost se syndromem Muir – Torre a ve většině případů, s novými údaji, jsme nezjistili žádnou missmatched repair deficiency (MMR). Druhá studie o periokulárním sebaceozním karcinomu nachází nové rysy, které mohou být použity jako diferenciálně diagnostické vodítko, a to buňky s kvadratickým jádrem a tzv. „aplikaque“ pattern (peritumorální subnekróza periferně lokalizovaných neoplastických buněk).

Podsekce o lézích anogenitálních prsních žláz obsahuje pět článků, které přidávají nová data týkající se jejich normální histologie, poskytují podrobný IHC profil AGMLG a demonstrují molekulární změny v lézích vyplývajících z AGMLG ve srovnání s homology prsu. Nová data také zahrnují hloubku adnexálního postižení nádorovými buňkami při extramamární Pagetově chorobě (EMPD), což je velká série, která poskytuje praktické poznatky pro léčbu.

Druhá část, "Kožní neepiteliální nádory", zahrnuje pět článků, které jsou rozděleny do 3 podkategorií: lymfoproliferativní onemocnění, mesenchymální tumory a melanocytární tumory.

Jeden ze tří článků v podskupině lymfoproliferativních poruch představuje největší sérii kožních Hodgkinových nemocí, ve kterých poskytujeme prvopopis tzv. mummifikovaných buněk vyskytujících se v kůži u pacientů s tímto onemocněním. Z dříve publikovaných článků vyplývá, že tyto buňky jsou známy u onemocnění lymfatických uzlin, ale bývaly přehlédnuty v kožních biopsiích. Jejich přítomnost může sloužit jako vodítko k diagnóze. Zahrnuty byly také dvě kazuistiky. První z nich je mimořádný klinicko-patologický případ nedávno popsané varianty lymfomatoidní papulosy typu E. Druhým článkem je mimořádná kazuistika primárního kožního efuzního lymfomu (PEL) s neobvyklou intravaskulární prezentací v kombinaci s Kaposiho sarkomem (KS) postihujícím kůži, plíce a gastrointestinální trakt. V lézi jsme prokázali zárodečnou mutaci *FAM175A*.

V subsekci melanocytárních nádorů jsou představeny dva články. V první práci autorka předkládá podrobnou patologickou studii o spitzoidních lézích s fúzí *ROS1* a nových fúzích tohoto genu. Studie také zahrnuje rozsáhlé genetické vyšetření jiných genů, s některými novými daty. Druhý článek je mimořádnou kazuistikou, která popisuje případ polypoidního atypického Spitzova nádoru s prominentní fibrosklerotickou stromální složkou, která obsahuje fúzi *CLIP2-BRAF*, která nebyla dosud publikována u melanocytárních lézí.

Jako reprezentativní entitu mezenchymálních nádorů autoři popisují série epitelioidních fibrózních histiocytomů, ve kterých byly nalezeny nové histopatologické znaky a nové fúze genu *ALK*.

FOCUS AND OBJECTIVES

The aim of the dissertation was to study selected epithelial and nonepithelial cutaneous tumors. We focused on the morphological characteristics and molecular biologic features of various tumors of the skin, including adnexal neoplasms, lymphoproliferative disorders, mesenchymal lesions and melanocytic tumors.

Our main objective was to find the correlation between the histological features and detection of mutations or fusions in various benign and malignant cutaneous neoplasms, to describe unusual microscopic features, the novel gene fusions and new histological clues in the studied types of the neoplasms.

MATERIAL AND METHODS

The included cases with available paraffin blocks were retrieved from the institutional, consultation, and personal archives. The hematoxylin and eosin stained slides were reviewed together with the clinical information to confirm the diagnosis. All selected cases were always examined by at least two pathologists, cases suitable for a further study were selected based on the morphology, immunohistochemistry, and the appropriate clinical context. In most cases, follow-up information was obtained from the attending clinicians or referring pathologists.

For the immunohistochemical studies, there were more than 500 antibodies available in the Bioptical Laboratory and the Sikl Department of Pathology, Charles University. The following methods were used for the genetic analysis: polymerase chain reaction (PCR), reverse transcription PCR, fluorescence in situ hybridization (FISH), comparative hybridization (CGH), next-generation sequencing (NGS) using the FusionPlex Solid Tumor,

Sarcoma and Lymphoma kits (ArcherDX), Variant Plex Solid Tumor (ArcherDX) and TruSight Solid tumor 170 panel (Illumina, San Diego, CA), targeting a large number of genes (various mutation type and fusions). For NGS analyses, variant annotations were performed according to databases and in-silicon prediction software, including somatic database COSMIC, My Cancer Genome, and TCGA and predictive software SIFT, PolyPhen2, MutTaster, and CADD, depending on a particular project.

RESULTS

The four-year study resulted in 20 papers published or accepted to publication in various American pathology and dermatopathology journals with impact factor.

The dissertation thesis is presented in the form of the comments to the author's publications. In most publications, we reported detailed histopathological, immunohistochemical characteristics of selected cutaneous tumors, both relatively common and rare. In some studies, we detected novel genes fusions and described new morphological features of cutaneous neoplasms, which can be used as a clue to the specific diagnosis.

CONCLUSIONS

Ph.D. thesis concludes postgraduate studies in the field of pathology performed by MD. Liubov Kastnerova (previous name Kyrpychova). During the Ph.D. course, the required goals and tasks were fulfilled. With the aid of co-authors, we have documented the clinicopathological and molecular biologic characteristics of various cutaneous epithelial and nonepithelial tumors.

The outcome of the four-year study is 20 articles, in 8 of which the author of the dissertation is the first author and 12 articles in which she is a co-author. The results of all papers presented in the doctoral thesis were published in American journals with impact factor and were presented at national and international meetings.

REFERENCES

1. Elder DM, D; Scolyer, RA; Willemze, R. *WHO classification of skin tumours.* Lyon: IARC; 2018.
2. Gerami P, Scolyer RA, Xu X, et al. Risk assessment for atypical spitzoid melanocytic neoplasms using FISH to identify chromosomal copy number aberrations. *Am J Surg Pathol.* 2013;37:676-684.
3. Lee S, Barnhill RL, Dummer R, et al. TERT Promoter Mutations Are Predictive of Aggressive Clinical Behavior in Patients with Spitzoid Melanocytic Neoplasms. *Sci Rep.* 2015;5:11200.
4. Wiesner T, He J, Yelensky R, et al. Kinase fusions are frequent in Spitz tumours and spitzoid melanomas. *Nat Commun.* 2014;5:3116.

LIST OF OWN PUBLICATIONS

During my doctoral studies, I published 20 papers (8x first author, 12x co-author). All publications are related to the topic of the dissertation and listed in chronological order.

1. **Kyrpychova L**, Kacerovska D, Vanecek T, Grossmann P, Michal M, Kerl K, Kazakov DV. **Cutaneous hidradenoma: a study of 21 neoplasms revealing neither correlation between the cellular composition and CRTC1-MAML2 fusions nor presence of CRTC3-MAML2 fusions**. *Ann Diagn Pathol*. 2016 Aug;23:8-13, IF 1,633.

2. Konstantinova AM, Shelekhova KV, Stewart CJ, Spagnolo DV, Kutzner H, Kacerovska D, Plaza JA, Suster S, Bouda J, Pavlovsky M, **Kyrpychova L**, Michal M, Guenova E, Kazakov DV. **Depth and Patterns of Adnexal Involvement in Primary Extramammary (Anogenital) Paget Disease: A Study of 178 Lesions From 146 Patients**. *Am J Dermatopathol*. 2016 Nov;38(11):802-808, IF 1,426.

3. Konstantinova AM, Vanecek T, Martinek P, **Kyrpychova L**, Spagnolo DV, Stewart CJR, Portelli F, Michal M, Kazakov DV. **Molecular alterations in lesions of anogenital mammary-like glands and their mammary counterparts including hidradenoma papilliferum, intraductal papilloma, fibroadenoma and phyllodes tumor**. *Ann Diagn Pathol*. 2017 Jun;28:12-18, IF 1,633.

4. Broekaert SM, Flux K, **Kyrpychova L**, Kacerovska D, Ivan D, Schön MP, Ströbel P, Michal M, Denisjuk N, Kerl K, Kazakov DV. **Squared-Off Nuclei and "Appliqué" Pattern as a Histopathological Clue to Periocular Sebaceous Carcinoma: A Clinicopathological Study of 50 Neoplasms From 46 Patients**. *Am J Dermatopathol*. 2017 Apr;39(4):275-278, IF 1,426.

5. **Kyrpychova L**, Carr RA, Martinek P, Vanecek T, Perret R, Chottová-Dvořáková M, Zamecnik M, Hadravsky L, Michal M, Kazakov DV. **Basal Cell Carcinoma With Matrical Differentiation: Clinicopathologic, Immunohistochemical, and Molecular Biological Study of 22 Cases**. *Am J Surg Pathol*. 2017 Jun;41(6):738-749, IF 5,878.

6. Konstantinova AM, Spagnolo DV, Stewart CJR, Kacerovska D, Shelekhova KV, Plaza JA, Suster S, Bouda J, **Kyrpychova L**, Michal M, Belousova IE, Kerl K, Kazakov DV. **Spectrum of Changes in Anogenital Mammary-like Glands in Primary Extramammary (Anogenital) Paget Disease and Their Possible Role in the Pathogenesis of the Disease.** *Am J Surg Pathol*. 2017 Aug;41(8):1053-1058, IF 5,878.

7. Konstantinova AM, Stewart CJ, **Kyrpychova L**, Belousova IE, Michal M, Kazakov DV. **An Immunohistochemical Study of Anogenital Mammary-Like Glands**. *Am J Dermatopathol*. 2017 Aug;39(8):599-605, IF 1,426.

8. Konstantinova AM, **Kyrpychova L**, Belousova IE, Spagnolo DV, Kacerovska D, Michal M, Kerl K, Kazakov DV. **Anogenital Mammary-Like Glands: A Study of Their Normal Histology With Emphasis on Glandular Depth, Presence of Columnar Epithelial Cells, and Distribution of Elastic Fibers**. *Am J Dermatopathol*. 2017 Sep;39(9):663-667, IF 1,426.

9. **Kyrpychova L**, Kacerovska D, Michal M, Kazakov DV. **Sporadic Trichoblastomas and Those Occurring in the Setting of Multiple Familial Trichoepithelioma/Brooke-Spiegler Syndrome Show No *BAP1* Loss**. *Am J Dermatopathol*. 2017 Oct;39(10):793-794, IF 1,426.

10. Wiedemeyer K, **Kyrpychova L**, Tanas O, Spagnolo DV, Kutzner H, Rütten A, Fernandez-Figueras MT, Denisjuk N, Suster S, Pavlovsky M, Petersson F, Michal M, Lee J, Kerl K, Kazakov DV. **Sebaceous Neoplasms With Rippled, labyrinthine/Sinusoidal, Petaloid, and Carcinoid-Like Patterns: A Study of 57 Cases Validating Their Occurrence as a Morphological Spectrum and Showing No Significant Association With Muir–Torre Syndrome or DNA Mismatch Repair Protein Deficiency**. *Am J Dermatopathol*. 2018 Jul;40(7):479-485, IF 1,426.

11. **Kyrpychova L**, Vanecek T, Grossmann P, Martinek P, Steiner P, Hadravsky L, Belousova IE, Shelekhova KV, Svajdler M, Dubinsky P, Michal M, Kazakov DV. **Small Subset of Adenoid Cystic Carcinoma of the Skin Is Associated With Alterations of the *MYBL1* Gene Similar to Their Extracutaneous Counterparts**. *Am J Dermatopathol*. 2018 Oct;40(10):721-726, IF 1,426.

12. Kazakov DV, **Kyrpychova L**, Martinek P, Grossmann P, Steiner P, Vanecek T, Pavlovsky M, Bencik V, Michal M, Michal M. ***ALK* gene fusions in epithelioid fibrous histiocytoma: a study of 14 cases, with new histopathological findings**. *Am J Dermatopathol*. 2018 Nov;40(11):805-814, IF 1,426.

13. Belousova IE, **Kyrpychova L**, Samtsov AV, Kazakov DV. **A Case of Lymphomatoid Papulosis Type E With an Unusual Exacerbated Clinical Course**. *Am J Dermatopathol*. 2018 Feb;40(2):145-147, IF 1,426.

14. Konstantinova AM, **Kyrpychova L**, Nemcova J, Sedivcova M, Bisceglia M, Kutzner H, Zamecnik M, Sehnalkova E, Pavlovsky M, Zateckova K, Shvernik S, Spurkova Z, Michal M, Kerl K, Kazakov DV. **Syringocystadenoma Papilliferum of the**

Anogenital Area and Buttocks: A Report of 16 Cases, Including Human Papillomavirus Analysis and *HRAS* and *BRAF V600* Mutation Studies. *Am J Dermatopathol*., 2019 April; 41(4):281-285, IF 1,426.

15. **Kyrpychova L**, Šteiner P, Michal M, Kazakov DV**. Lack of Deletion of 1p36 in 8 Cases of Primary Adenoid Cystic Carcinoma of the Skin**. *Am J Dermatopathol*. 2019 Jan 11. [Epub ahead of print], IF 1,426.

16. **Kastnerova L**, Luzar B, Goto K, Grishakov V, Gatalica Z, Kamarachev J, Martinek P, Hájková V, Grossmann P, Imai H, Fukui H, Michal M, Kazakov DV. **Secretory carcinoma of the skin: report of 6 cases, including a case with a novel *NFIX-PKN1* translocation.** *Am J Surg Pathol*. 2019 Aug;43(8):1092-1098, IF 5,878.

17. **Kastnerova L**, Belousova I.E, Hadravsky L, Kerl H, Cerroni L, Kerl K, Boudova L, Jindra P, Cerna K, Michal M, Kazakov D.V **Mummified cells are a common finding in cutaneous Hodgkin lymphoma and can be used as a diagnostic clue**. *Am J Dermatopathol*., 2019 May. [Epub ahead of print], IF 1,426.

18. **Kastnerova L**, Belousova IE, Michal M, Ptakova N, Michal M, Kazakov DV. **Kaposi sarcoma associated extracavitary primary effusion lymphoma with unusual intravascular presentation in a patient with a *FAM175A* germline mutation: a case report including next-generation sequencing.** *Am J Dermatopathol*., 2019 June; [Accepted], IF 1,426.

19. Donati M, **Kastnerova** L, Martinek M, Grossman P, Sticová E, Hadravský L, Torday T, Kyclova J, Michal M, Kazakov DV. **Spitz tumors with *ROS1* fusions: a clinicopathological study of 6 cases, including FISH for chromosomal copy number alterations and mutation analysis using next generation sequencing**. *Am J Dermatopathol*., 2019 [Accepted], IF 1,426.

20. Donati M, **Kastnerova L**, Ptakova N, Michal M, Kazakov DV. **Polypoid atypical Spitz tumor with a fibrosclerotic stroma, *CLIP2-BRAF* fusion and homozygous loss of 9p21**. *Am J Dermatopathol*., 2019 [Accepted], IF 1,426.

SUMMARY OF LECTURE ACTIVITIES

1) **106th Annual Meeting of the United States & Canadian Academy of Pathology, 4.-10.3.2017 Henry B. Gonzalez Convention Center, San Antonio, TX, USA**

   Poster: Basal cell carcinoma with matrical differentiation: clinicopathological, immunohistochemical and molecular biological study of 22 cases.

   Poster: Spectrum of changes in anogenital mammary-like glands (AGMLG) in primary extramammary Paget disease (EMPD).

   Poster: Genetic alterations in lesions of anogenital mammary–like glands and their mammary counterparts.

2) **57. Student scientific conference LF UK in Pilsen, 17.5.2017**

   Lecture: Cutaneous hidradenoma: a study of 21 neoplasms revealing neither correlation between the cellular composition and *CRTC1-MAML2* fusions nor presence of *CRTC3-MAML2* fusions.

3) **107th Annual Meeting of the United States & Canadian Academy of Pathology, March 17 – 23, 2018 in Vancouver, BC, Canada**

   Poster: Sebaceous neoplasms with rippled, labyrinthine/sinusoidal, petaloid and carcinoid-like patterns: a study of 56 cases validating their occurrence as a morphological spectrum and showing no significant association with Muir-Torre Syndrome or DNA Mismatch Repair Protein Deficiency.

   Poster: A subset of adenoid cystic carcinoma of the skin is associated with alterations of the *MYBL1* gene similar to their extracutaneous counterparts.

   Poster: Novel *ALK* gene fusions in spitzoid melanocytic lesions: a clinicopathological study of 16 cases, including FISH analysis for chromosomal copy number changes and *TERT* promoter mutations.

   Poster: *ALK* gene fusions in epithelioid fibrous histiocytoma: a study of 14 cases, with new histopathological findings.

4) **58. Student scientific conference LF UK in Pilsen, 30.5.2018**

   Lecture: Basal cell carcinoma with matrical differentiation: clinicopathological, immunohistochemical and molecular biological study of 22 cases.

5) **108th Annual Meeting of the United States & Canadian Academy of Pathology, March 16 – 21, 2019 at National Harbor, Maryland, USA.**

   Poster: Syringocystadenoma papilliferum of the buttock, vulva and perianal areas harbor mostly *BRAF V600* mutations and are associated in some cases with high-risk HPV.

6) **59. Student scientific conference LF UK in Pilsen, 21.5.2019**

   Lecture: A subset of adenoid cystic carcinoma of the skin is associated with alterations of the *MYBL1* gene similar to their extracutaneous counterparts.