



## REVIEW

From Professor Sevdalin Slavov Nachev, DMSc

Laboratory of Clinical Pathology of University Multiprofile Hospital for Active Treatment " St. Ivan Rilski " - Sofia

on the Dissertation for acquisition of educational and scientific degree of '**doctor**'

Professional field: **Medicine; " Pathoanatomy and cytopathology "** – 03.01.03 doctoral program

**Author:** Dr. Mariya Stoyanova Koleva-Ivanova

**Form of doctoral studies:** - *free doctoral studies*

**Department of General and Clinical Pathology**

**Topic: " Eosinophilic metaplasia in prostatic epithelium: main characteristics, morphology, morphogenesis "**

**Supervisor:** *Assoc. Prof. d-r Dorian Ivanchev Dikov, PhD – Department of General and Clinical Pathology – Medical University of Plovdiv*

### **1. General presentation of the procedure and the doctoral student**

The presented set of paper material and / electronic form **is/is not** in accordance with Art. 115 ( 1 ) of the Procedure for Acquisition of educational and scientific degree (ESD) "Doctor" in MU - Plovdiv; Regulations of MU-Plovdiv from 06.11.2014 and includes the following documents:

- Application to the Rector of MU-Plovdiv for disclosure procedure for defense of the dissertation
- CV in European format with the signature of the doctoral student
- notarized copy of the diploma for Higher Education
- orders to enroll in doctoral studies , interruption of studies and expulsion with the right to defense
- orders to conduct the examination from the individual plan and a corresponding protocol for passing an exam or doctoral minimum of speciality
- protocol from the Department Board for preliminary discussion of the Dissertation and decisions about disclosure of procedure and for the composition of the scientific jury
- dissertation
- abstract
- list of scientific publications on the topic of the dissertation
- copies of scientific publications
- list of participations in scientific forums

The doctoral student has attached 3 / three / publications.

Notes and comments on documents - none

## 2. **Brief biographical data about the doctoral student**

**D-r Mariya Koleva-Ivanova** graduated English Language School in Bourgas in 2002y. and the Medical University - Faculty of Medicine in Plovdiv – 2009y. She works as an assistant at the Department of General and Clinical Pathology - Plovdiv. She received a speciality in general and clinical pathology in 2017y.

## 3. **Relevance of the topic and expediency on the set aim and tasks**

The relevance of the investigated problem in the dissertation in scientific and scientific-applied term is related to the fact that **benign prostatic hyperplasia, prostate cancer** and related chronic inflammation and adaptive processes are the most common pathology in men after lung cancer in our country. Therefore, they are also associated with the mortality of this population. In some countries, this pathology is even in the first place. This determines the main tasks for investigation in this dissertation. These are: study of the morphology of **eosinophilic metaplasia / EM /** in two populations: Bulgarian and French; the relation with another pathology of prostate gland and thus to derive a differential diagnostic algorithm. Thus, as a final result to clarify the **pathogenesis** and **general pathological significance** of EM.

## 4. **Knowledge of the problem**

A guarantee that the doctoral student knows the state of the problem and can creatively evaluate the literature data material is the fact that her supervisor has been working in the same field for many years. Thus, a continuity and further development of the achievements of a proven specialist such as Assoc. Prof. D. Dikov is obtained.

## 5. **Research methods**

The chosen research methods: classical histological techniques / incl. semi-quantitative /, histochemical, immunohistochemical methods and statistical hypotheses, and methods with applied software, allows to achieve the aim and obtain an adequate response to the tasks in the dissertation.

## 6. **Characteristics and evaluation of the dissertation**

The dissertation is written on a total of 165 pages and contains 28 tables, 6 figures and 75 microscopic pictures.

It is presented in 9 sections: Introduction; Aim and task ; Material and methods; Results; Discussion; Conclusions; Illiation; Contributions; Scientific publications related to the dissertation.



The literature review includes: 1. Detailed examination of metaplasia as a morphological phenomenon; 2. Definition and types, frequency, localization, pathogenesis and morphogenesis of the prostate metaplasia with a detailed discussion of morphological feature of eosinophilic metaplasia / EM / from the facts known so far. Similar changes in other organs are presented – mammary gland, epididymis, endometrium. All this is illustrated with relevant photo documentation, which I find to be an excellent idea. An electronogram also presents the granules in a secretory cell, but there is no comparative one that shows the electron microscopic characteristic of the granules in EM. A detailed insight into the problem allows the author to highlight a few important things with which to build a hypothesis for additional scientific research. Below I will try to determine the most characteristic of them and the results obtained.

1. The observed by the author granules in EM are with large and small sizes, which corresponds to a different stage of their formation. They contain glycogen (PAS.D) + and proteins, and are located apically. They evolve into a residual pigment and are phagocytosed, incl. from surrounding macrophages. They must be distinguished from artefact eosinophilia.

2. Additional immunohistochemical examinations with MUC 1, 2, 5AC, 6; Lamps 1,2 allow the author to confirm "the double" character of granules - exocrine and lysosomal, not Paneth cell, endocrine. Both the large granules (apically located) and the small ones (mostly perinuclear-aberrant) are of different stages of secretion and distribution.

On the one hand, the author explains the secreted mucins from the cells with compensatory mobilization as a modulator of concomitant inflammation. On the other hand - with attempt of cells to maintain tissue lumenization. Dr. Koleva believes that MUC 1 which is present in 100% of the cells with EM can be accepted as a **phenotypic marker of this type of cell metaplasia**.

3. Positive granules with lysosomal markers Lamps, Lamp 1, 2 allow the author to define them as a different from the normal secretory granules, ie. as modified.

These characteristics of the granules MUC 1 / + / Lamp 1,2 / + / author suggests to be used as summarised **diagnostic and DD algorithm allowing EM to be distinguished from Paneth cell-like prostate changes / PCLC / in prostate cancer / PCa /**

4. In the studied 120 cases of EM and other manifestations such as basal cell hyperplasia (BCH), benign prostatic hypertrophy / BPH / and prostate carcinoma / PCa /, the author points out some quantitative indicators. Thus, we understand that EM is 100% combined with histological prostatitis / HP / and in 70.5% it is chronic histological prostatitis with a low degree of manifestation. In 83.3% EM is combined with acute histological prostatitis. This proves the **adaptive nature of EM**.

5. Based on the selection of the patients - without radiotherapy, hormonal therapy and previous surgical intervention - the author accepts as **a major pathogenic factor in EM the persistent active chronic inflammation.**

From a **general pathological point of view, EM is indirect (phenotypic) metaplasia.**

### **7. Contributions and significance of the dissertation for the science and practice.**

The contributions of the present dissertation are presented by the author in sections / tasks /, a little wasteful. For example: on task 1. and 2. the theoretical contribution can be summarized and from 3 tasks to be presented in a single; on task 3 the theoretical contributions from tasks 1. and 2. can combine, because it is the same - the size of eosinophilic granules and that they are found in a benign epithelium. Points 3 and 4 are also related to the topography / location / of EM and can be summarized.

I must especially emphasize the scientific-applied methodological contributions of the dissertation. The used staining methods both classical and modern allow the author:

1. To differ EM from artifactual events in cells;
2. To make conclusions about the nature of the granules - exocrine and lysosomal;
3. To create an algorithm for diagnosis and differential diagnosis of the studied phenomenon / EM /;
4. To make an assumption for the pathogenesis of EM, namely that chronic prostatitis is associated with this metaplasia. Just as prostate cancer is associated with it!

**5. The constant relationship between BCH and EM is an indicator that these cellular phenomena have something in common with stem cells and this can completely change the "classification" of eosinophilic metaplasia as indirect metaplasia!**

All of the above is a prospect for studying new aspects of the presence of EM in prostate epithelial cells, namely for studying chronic prostatitis in the light of autoimmune processes, prostate cancer and others. All hypotheses on which the author has focused in the conclusion of his work.

### **8. Evaluation of the publications on the dissertation**

3 / three / publications of the author are presented. Two of them are in a foreign journals and one - in Bulgarian. All three articles are in English.

### **9. Abstract**

It is formed very well, as required, and reflects the full picture in the dissertation.



Here I would like to emphasize that the photographs of the studied process are brilliantly made and give the work the necessary persuasiveness!

#### 10 . Critical remarks and recommendations

I made critical remarks and recommendations in the text above. Here I will only mention that there is unnecessary, in my opinion, extravagance in discussing the phenomenon that are relevant but not in the focus of the work / PM, UM, MM /. In addition, the accumulation of abbreviations in places makes the text illegible. The use of IHC, etc. such also distort the otherwise good impression of the text. I recommend other Bulgarian morphological journals to be cited in future publications.

#### CONCLUSION

The dissertation *includes scientific, scientific-applied and applied results which represents an original contributions to science* and **meet all** the requirements of the Lowon the Development of Academic Staff in the Republic of Bulgaria (LDASRB) The presented materials and dissertation results **fully comply** with the specific requirements of MU - Plovdiv.

The dissertation shows that the doctoral student Dr. Mariya Stoyanova Koleva - Ivanova **has** in-depth theoretical knowledge and professional skills in the scientific specialty of pathoanatomy and cytopathology by **demonstrating** qualities and skills for independent research.

Due to the above, I confidently give my positive assessment of the study presented by the above review of the dissertation, abstract, results and contributions, and I proposed *to theesteemed scientific jury to awardthe educational and scientific degree 'Doctor'* to d-r Mariya Stoyanova Koleva Ivanova- in doctoral program of general and clinical pathology

Reviewer:  .....

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( Prof. Sevdalin Natchev DMSc . )