

REVIEW

from Prof. Radina Stefanova Ivanova-Boyanova, PhD, DSc
Department of Endocrinology, Faculty of Medicine, Medical University-Sofia

Of dissertation for awarding the educational and scientific degree "Doctor"

Professional direction: 7.1 « Medicine»

Doctoral program: «Pathology and cytopathology»

Author: Dr. Maria Stoyanova Koleva-Ivanova

Form of doctoral studies: individual course

Department: "General and clinical pathology", Faculty of Medicine, Medical University
-Plovdiv

Topic: „Eosinophilic metaplasia of the prostatic epithelium: general characteristics,
morphology, morphogenesis ”

Supervisor: Assoc. Prof. Dorian Ivanchev Dikov, MD, Ph.D

Brief biographical data

Dr. Maria Koleva-Ivanova completed her medical education in the Faculty of Medicine at Medical University of Plovdiv in 2009. Since 2010 r. and until now she has worked as Assistant Professor at the Department "General and clinical pathology" in the Faculty of Medicine, Medical University of Plovdiv and as pathologist at University Hospital "St. George" of Plovdiv. In the period 2011-2015 she was a post graduate student in general and clinical pathology, MU-Plovdiv and since 2017 she has acquired specialty in general and clinical pathology. She has learned fluently English and German. Dr. Koleva participated in 5 Bulgarian and international postgraduate courses, including various areas of clinical pathology and also pedagogical problems in medical education. She is a member of Bulgarian Society of Pathology.

The proposed for review by me of dissertation on topic „ Eosinophilic metaplasia of the prostatic epithelium: general characteristics, morphology, morphogenesis ” with author Dr. Maria Koleva is topical. The benign prostatic hyperplasia and prostatic carcinoma are ones of the most common diseases of urogenital system in male. Numerous factors including androgens, estrogens, growth factors and

neurotransmitters take part in their pathogenesis but the exact mechanisms related to the increased size of the prostate or its malignant transformation remain unclear.

During the last years, much evidence has been accumulated for the essential role of chronic inflammation and adaptive processes such as atrophy and hyperplasia in the etiology and pathogenesis of benign and malignant proliferative diseases of the prostate. Eosinophilic metaplasia is characterized by the presence of large eosinophilic intracytoplasmic granules in the benign prostatic epithelium. Knowledge of the features of eosinophilic metaplasia in benign prostatic hyperplasia is essential for diagnostic pathological practice because large eosinophilic granules can be found also in malignant prostate epithelium as a sign of neuroendocrine differentiation.

The term prostatic eosinophilic metaplasia (EM) was recently introduced by Cheng L. et al. (2008). The results of their studies prove that EM is found microscopically only in the benign prostatic epithelium and differs significantly from neuroendocrine granules in the cases of prostatic carcinoma with neuroendocrine differentiation. In recent years, prostatic EM has been the subject of intensive study by a number of researchers.

In this direction is the dissertation work of Dr. Maria Koleva-Ivanova. The presented dissertation meets the requirements for structure and volume of the Faculty of Medicine, MU-Plovdiv. It is written on 165 pages, designed in the following sections: Introduction (1 page), Literature review (38 pages), Aim and purposes (1 page), Material and methods (10 pages), Results (59 pages), Discussion (39 pages), Conclusions (1 page), Contributions (7 pages), References (12 pages) and Publications related to the dissertation (1 page).

The literature review is devoted to the metaplasia, the types of prostatic metaplasia, including eosinophilic metaplasia, and synthesizes the state of scientific knowledge at the moment. Dr. Koleva focuses in detail on the data accumulated in the literature on the light microscopic, immunohistochemical and electron microscopic characteristics of EM of the benign prostatic epithelium, as well as EM in other organs (breast, endometrium, epididymis). At the end of the literature review, the most important solved and unresolved questions about the nature and characteristics of prostate eosinophilic metaplasia are summarized. The bibliography contains 156 literature sources, of which only 10 - in Bulgarian. The literature citations are up-to-date as over 50% of them are from the last 10 years.

The aim of the dissertation is clearly formulated, namely to investigate quantitatively and qualitatively prostatic eosinophilic metaplasia in transurethral resection of the prostate (TURP) materials in order to clarify its pathogenesis and general pathological significance. There are 6 purposes that fully meet the aim.

To perform the set purposes, a retrospective histological examination of TURP materials from 123 patients with surgery for benign prostatic hyperplasia (61 Bulgarian and 62 French patients) was done. In all cases, a semi-quantitative assessment of the distribution of EM and morphometric determination of the size of the eosinophilic granules was performed. The expression of the immunohistochemical markers PSA, MUC1, MUC2, MUC5, MUC6, AHT (alpha-1-antichymotrypsin), lysosome-associated membrane proteins Lamp1 and Lamp2, synaptophysin, chromogranin and p63 was assessed in 34 cases with EM. The methods used for statistical analysis, as well as the morphological methods of research are adequate to the set aim and purposes, and all the necessary conditions for their implementation were observed.

It was obtained original results, illustrated with 27 tables, 6 figures and 48 microscopic photographs. A detailed comparative analysis of the frequency and clinical and morphological features of EM in the two groups of patients (Bulgarian and French) was performed. It was found that in almost half of the studied TURP materials (46%) there was EM. There was no statistically significant difference in terms of frequency, age and clinical symptoms in comparison the both groups groups of patients with and without EM. Precise histological and histochemical examination of eosinophilic cytoplasmic granules with respect to their size, intracellular and topographic tissue localization was performed. Based on the results of immunohistochemical studies, it is concluded that MUC1 is a reliable marker for tissue diagnosis of EM, and the simultaneous expression of exocrine (PSA and MUC1) and lysosomal (AHT and Lamps) markers in eosinophilic granules is evidence of mixed exocrine and lysosomal nature. The evaluation of concomitant presence of EM with other pathological processes in the TURP materials shows that there is a close relationship between EM on the one hand and chronic prostatitis, basal cell hyperplasia, urothelial or squamous cell metaplasia on the other hand. All obtained results are well interpreted and compared with those of other authors. It is summarized that from a general pathological point of view, the prostatic EM is an

indirect epithelial metaplasia, the pathogenesis of which is closely related to chronic inflammation.

The 7 conclusions made by Dr. Koleva fully correspond to the obtained results. The indicated contributions of the dissertation work (with total number of 31) are of scientific-theoretical or scientific-applied nature; they correspond to the "Results" and can be summarized and abbreviated. Based on the obtained results, Dr. Koleva proposes a generalized algorithm of histological, histochemical and immunohistochemical criteria for diagnosis of EM in benign prostatic epithelium.

The dissertation abstract of Dr. Koleva meets the requirements according to the Rules for the terms and conditions for obtaining scientific degrees of MU-Plovdiv and reflects the main elements of the research and the results in the dissertation.

In connection with the dissertation, the PhD student Dr. Koleva has 3 publications, all three in specialized scientific journals, referenced in the world databases Web of science and Scopus (1 - Acta morphologica et anthropologica и 2 - Indian J Pathol Microbiol). In addition, the journal "Indian J Pathol Microbiol" has an impact factor. Dr. Koleva is the first author of one and second – of the remaining two publications, which is proof of its leading role in the research.

In summary, the dissertation of Dr. Maria Koleva is fully completed, with clear aim and tasks, original results and conclusions about the morphological characteristics and morphogenesis of eosinophilic metaplasia in benign prostatic epithelium. It meets the requirements of the Law for the development of the academic staff in our country, the Rules for its implementation and the terms and conditions for obtaining scientific degrees of Medical University of Plovdiv. Therefore, I recommend to the honoured members of the Scientific Jury for conducting the defense to give a positive vote of Dr. Maria Stoyanova Koleva-Ivanova for the award of the educational and scientific degree "Doctor" in the scientific specialty "Pathology and Cytopathology".

Reviewer:



12.11.2020

(Prof. R. Ivanova-Boyanova, PhD, DSci)