Morphometric features of blood vessels in adenomas and carcinomas of the parathyroid gland

10.52739/bio-up.1.2021.8-13

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ABSTRACT

In this article discussed the problem of neoangiogenesis in neoplastic processes of the parathyroid gland. Applying morphometric methods for the assessment of sectional tissue samples of patients with adenoma and carcinoma of the parathyroid gland, we obtained the results of quantitative and qualitative vascular growth during neoangiogenesis. At present, there are not many studies that assess vascular factor in parathyroid cancer. This study may be useful in research cancer treatment, as it highlights the pathological aspects of the formation of new blood vessels, which is similar in all malignant processes.

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Keywords: neoangiogenesis; parathyroid gland adenoma; parathyroid gland carcinoma; parathyroid gland blood vessels; cancer morphology.

INTRODUCTION

Tumor growth has many stimulating factors, except oncogenes, tumor suppressor genes and environmental stimuli it requires an optimal internal environment. Researches [1] demonstrated that tumors implanted into isolated perfused organs failed to develop, but in contrast, the same tumors implanted within 6 mm of blood vessels induced angiogenesis, grew, and metastasized, therefore proposing that solid tumors are dependent on angiogenesis for growth further than a few millimeters in size. There are now several experimental [2] and clinical data [3] showing that growth of solid tumors is angiogenesis-dependent.

Parathyroid tissue has the ability to spontaneously induce angiogenesis in vitro [4] and in vivo models [5]. Autotransplantation of parathyroid tissue after thyroidectomy maintains calcium homeostasis [6] because the transplanted parathyroid tissue spontaneously revascularizes [7]. There is a previous study analyzing vascularity in parathyroid proliferative lesions [8], which showed that the endothelial component of hyperplastic PTG was increased in glands from six patients with primary hyperparathyroidism associated with Multiple endocrine neoplasia, type 1 (MEN 1) syndrome compared with those from six patients with secondary hyperparathyroidism associated with chronic renal failure.

Parathyroid tumors (adenomas and carcinomas) are composed of epithelial tissue that is avascular (has no blood supply) [9], making the microenvironment of these tumors hypoxic, therefore stimulating angiogenesis. In normal blood vessel physiology, angiogenesis is a highly regulated process, as seen in wound healing, menstrual cycles, or granulation tissue formation. The effectiveness of blood circulation in the human body is due to the division of its blood vessels into veins, venules, capillaries, arterioles, and arteries in comparison to tumor vasculature that is less-differentiated [10] as a result of the abundance

of pro-angiogenic factors such as VEGF in the tumor microenvironment [9,11], which therefore impedes the maturation and differentiation of these new blood vessels hence the disorderly look and inefficient supply of blood causing the formation of areas with intermittent hypoxia. Tumor blood vessels have breached endothelial junctions lead to an increase in permeability and interstitial fluid pressure, thereby serving as an obstacle to cancer therapy due to an inability to efficiently distribute the drug [9].

Therefore, neoangiogenesis plays a critical role in the formation and course of cancer. The purpose of our work is to analyze all the morphological features of pathological new vessels and to find a statistical paradigm in their development [12].

MATERIALS AND METHODS

For research the sectional material of parathyroid tissue from archives was taken. We used tissue samples from 19 patients and divide them in 2 groups: group 1-patients with parathyroid gland adenoma (n=10), group 2-patients with parathyroid gland carcinoma (n=9). For histological examinations, samples of biopsy materials approximately 10 mm thick were fixed overnight in 10% buffered formalin at room temperature. Fixed tissues were embedded in paraffin. From paraffin blocks, 5 µm thick sections were made using a microtome. The sections were stained with hematoxylin and eosin. Histological specimens were examined using a Leica BX 51 microscope, a Leica MC 190 digital camera, and the Leica LAS software at magnifications of 100×–200×. Morphometric investigations included the assessment of the number of vessels in the histological slides and measurement the thickness of the vessels, using the Image J software. Statistical analysis was performed using SPSS IBM Statistics v. 24.0. Study groups were compared according the values of mean ± standard deviation, median, number of positive indicator in group, statistical difference were calculated with non-parametric tests such as Mann-Whitney criterion (for two independent samples).

RESULTS

Table 1 shows the distribution of morphometric parameters among the study groups.

Parameter	Group		p-value
	parathyroid gland adenoma (n=10)	parathyroid gland carcinoma (n=9)	
Number of vessels			
Mean±SD	30,20±13,26	18,67± 9,58	= 0,32
Median	27,50	20,00	
Wall thickness, µm			
Mean±SD	8,46±3,19	12,89± 4,27	<0,001
Median	7,35	13,00	

Analyzing the data obtained during morphometry, the results show the process of neoangiogenesis in patients with parathyroid gland adenoma and carcinoma and the difference between the pathological indicators in both cases.

Comparing the obtained numbers in the two groups, we observe a larger number of total vessels in patients with parathyroid gland adenoma. However, when measuring the thickness of the vessels, the group of parathyroid gland carcinoma samples shows larger numbers.

Based on morphological and pathophysiological data on the development of these pathological conditions, it can be assumed that a significant number of vessels in adenomas are associated with hypoxia, which occurs in the tissue of the parathyroid gland during epithelial hyperplasia. Hypoxia is a major trigger in the physiological and pathological vascularization of tissues [13]. In contrast to adenoma in carcinoma, the process of hypoxia is not so pronounced, as there is metaplasia of the epithelium and the release of oncogenic vascular growth factors, which can explain the abnormal structure of vessels with increased thickness and impaired morphological structure.

Figure 1. Number of vessels in both groups

Figure 1 shows distribution and ranks of the number of vessels in samples of tissue with parathyroid gland adenoma and parathyroid gland carcinoma

Figure 2. Wall thickness in both groups

Figure 2 shows distribution and ranks of the vessels wall thickness in samples of tissue with parathyroid gland adenoma and parathyroid gland carcinoma.

DISCUSSION

In this study we proved the difference in the morphological component of neoangiogenesis between benign and malignant formations of the parathyroid gland. Based on previous studies, it can be argued that our results are indicative of the role of hypoxia and oncogenic growth factors in the formation of new blood vessels.

According to studies [9], there are several mechanisms of neoangiogenesis they include many biochemical trigger factors, biologically active substances (vascular endothelial growth factor (VEGF), hypoxia-inducible factor 1 (HIF1)) and receptors on endothelial cells (VEGF receptor-1, VEGF receptor-2, VEGF receptor-3). In our study, we cannot draw parallels with all the mechanisms, but we will clearly see the relationship of these mechanisms to the formation of new vessels in parathyroid adenoma and parathyroid carcinoma.

Analyzing the research conducted by our colleagues on the nature and mechanisms of neoangiogenesis [14], we can come to the only conclusion that the latter is not possible without the hormone, both in physiological and pathological formation of new vessels. The answer we wanted to find in this scientific work is why under the action of the same hormone there is such a significant difference in the morphological structure and number of vessels in pathologies that have a fairly similar pathophysiology of development.

If we talk in more detail about adenoma, there are a large number of studies proving the role of hypoxia as a driving factor in neoangiogenesis in pituitary adenoma [15, 16, 17]. The pituitary gland, like the parathyroid gland, is part of the endocrine system, as well as a fine -developed physiological blood supply system. Hypoxia, which occurs during epithelial hyperplasia, is caused by a rapid increase in the number of cells that need more oxygen and nutrients, respectively, more vessels [18]. In this case, the process of neoangiogenesis is closer to physiological, because hypoxia is the main trigger factor in the process of vascularization of all tissues. The lack of oxygen stimulates the expression of hypoxia-inducible factor 1 (HIF1), a transcription factor of the basic helix—loop—helix family, which in turn increases the

VEGF expression by the interaction of HIF1 with HIF1-responsive elements within the VEGF promoter.[19]

In view of these data and the data obtained during our study, we can conclude that since the process of neoangiogenesis in adenoma is quite close to physiological — morphometry data we received are quite logical: increased number of vessels but normal wall thickness — vascular architectonic is not disturbed.

With regard to parathyroid cancer, the process of neoangiogenesis is somewhat more complicated, because in the case of cancerous degeneration of the gland, the cells are not controlled by the body and the classical DNA code and made their own microenvironment. Cancer cells can produce growth factors that stimulate neoangiogenesis regardless of the concentration of oxygen in the tissues. Specific transforming events also result in induction of VEGF gene expression. Oncogenic mutations or amplification of ras genes leads to VEGF up-regulation. [20,21]

Research on vascular mimicry of tumors should also be considered. Aggressively growing tumor cells can form vessel like structures through a process denoted as "vascular mimicry". These structures, which are formed without contribution of endothelial cells, represents an alternate channel for tumor cells to source sufficient blood supply and nutrients. Vascular mimicry has been

observed in many tumor types including head and neck cancer. [22]

The phenomenon of vascular mimicry alone and together with other mechanisms of pathological neoangiogenesis is the most logical explanation of the morphological picture in researched cases, in our opinion. These phenomena may explain the abnormal structure of the vessels analyzed in our study. However, in order to establish a clear connection, a deeper immuno-histochemical revision of these vessels is required.

CONCLUSION

Modern vascular targeting strategies are based on the suppression of key angiogenic signaling pathways, which are known to promote tumor angiogenesis. Although several antiangiogenic drugs have been approved, intrinsic and acquired resistances to therapy decrease their effectiveness.

The purpose of our study was to illuminate the morphological aspects of neoangiogenesis on the example of patients with adenoma and parathyroid carcinoma.

An in-depth understanding of the structure of tumor vessels and the mechanisms involved in neoangiogenesis is necessary to overcome the problems that make it impossible to successfully control and treat the cancer process.

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Manuscript was received on 28 October; accepted for publication on 22 December.

CITE AS: BOGDAN YA. SERBIN ET AL. MORPHOMETRIC FEATURES OF BLOOD VESSELS IN ADENOMAS AND CARCINOMAS OF THE PARATHYROID GLAND.

BIOMEDICAL UPDATE, ISSUE 1, 2021