Comparative Evaluation of Blood Vessels in Serous Tumors of the Ovaries by Color Doppler Mapping and Morphometry

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Morphometric study of blood vessels in serous tumors of the ovaries was carried out. Vascularization of benign, borderline, and malignant tumors is different, which agrees with the data of color Doppler mapping. Pronounced morphological changes in vascular wall (degenerative changes, sclerosis, and hyalinosis) were detected mainly in borderline and malignant tumors.

Key Words: *color Doppler mapping; serous tumors of ovaries; morphometry; vascularization*

Angiogenesis in tumors plays a key role in tumor progress [2]. Doppler mapping (CDM) allows visual and quantitative blood flow evaluation in tumors and their early diagnosis [5,7]. Ovarian tumors, specifically malignant, with just 40% 5-year survival, are particularly interesting in this respect [1]. According to published reports, the maximum systolic blood flow velocity (V_{max}) measured by CDM is higher, while intratumor blood flow resistance is lower in malignant tumors than in benign ones [3, 4]. However these parameters do not always help precisely identify the type of the tumor. On the other hand, the vascular network of benign, borderline, and malignant serous tumors of the ovaries is little studied, there are virtually no morphometric data on tumor vessels, and the mechanisms determining the differences in intratumor blood flow are unclear.

We investigated the morphology and functions of blood vessels in benign, borderline, and malignant serous tumors of the ovaries and compared the morphometric values with CDM data.

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MATERIALS AND METHODS

Thirty-three patients aged 27-48 years with serous tumors of the ovaries were examined with an Acuson 128/XP 10 ultrasonic device before surgery. The tumors were: 10 papillary cystadenomas, 11 borderline papillary cystadenomas, and 12 papillary cystadenocarcinomas. Vascularization zones, their location, and intensity of blood supply were evaluated by CDM. Resistance index V_{max} and blood flow pulsation index were measured by spectral analysis. Operation material was fixed in 10% formalin and after histological treatment embedded in paraffin. Sections (5-7-μ) were stained with hematoxylin and eosin, by Mallory and Van Gieson combined methods; in addition, semithin sections stained with methylene blue—azur 2—main fuchsin were examined. The reference material was ovarian tissue from 15 patients aged 25-48 years without ovarian diseases, obtained at autopsy. Qualitative and quantitative parameters of the vessels (volume density (VDV)/mm^2, vascular wall area and thickness, area of vascular lumen, Kernogan index, and Kernogan modified area index) were evaluated by morphometry with image analysis using Leica Qwin software. Arteries, veins, and capillaries were measured in different compartments of the tumors.

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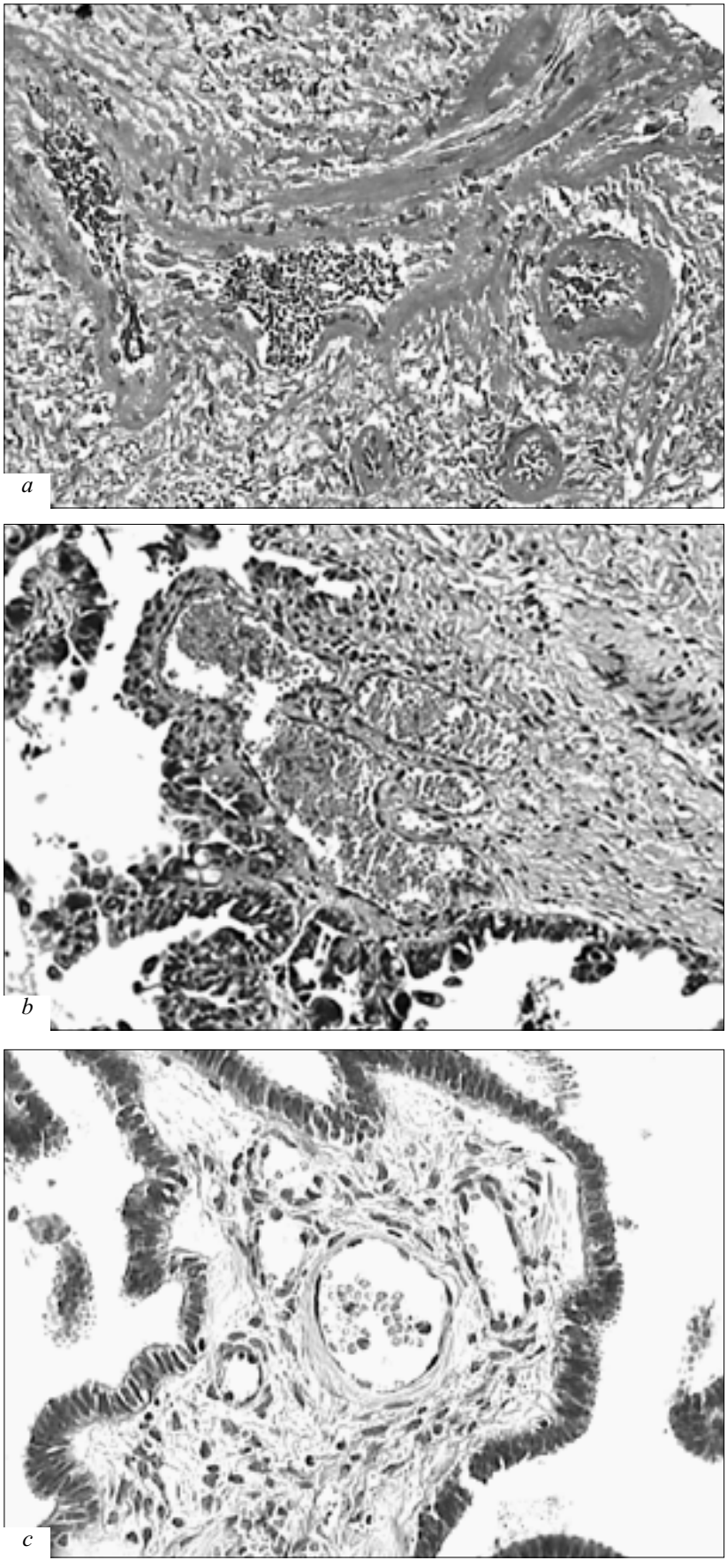

Fig. 1. Ovarian serous papillary cystadenoma (*a*, *c*) and cystadenocarcinoma. Staining with methylene blue—azur 2—main fuchsine (*a*), hematoxylin and eosin (*b*, *c*), ×320. *a*) dilatation of arterial lumens, sometimes with aneurysmal protrusions, with signs of sclerosis and hyalinosis; *b*) sharply dilated thin-wall venule-like vessels with pronounced plethora; *c*) intermediate type. The papilla contains numerous capillaries and venules.

The results were statistically processed and analysis of correlations carried out using Microsoft Origin 6.1 software.

RESULTS

In 84% patients with serous papillary cystadenomas CDM revealed inactive multiple vessels at the tumor periphery and avascular papillary processes. V_{max} was above 0.16±0.01 cm/sec ($p \leq 0.05$ *vs.* malignant tumors). Serous cystadenomas were characterized by medium- and highly resistant blood flow: pulsation index 1.08±0.04, resistance index 0.57±0.05, $p \leq 0.05$ *vs.* malignant tumors. Histological analysis showed that all the studied compartments of benign serous tumors were poorly vascularized. Solitary capillaries were seen in some papillae. The wall and peripheral part of cystadenoma contained medium-sized veins and arteries, often dilated, plethoric, with thickened internal elastic membrane and degenerative changes in the wall (Fig. 1, *a*). Morphometry showed that VDV in all compartments of benign serous tumors was significantly lower than in borderline and malignant tumors (2.2 and 1.8 times, respectively) (Fig. 2).

By contrast, in malignant serous tumors the blood flow was active and the vessels were numerous, located both at the periphery and in the central parts of the tumor, including the papillary growth. Quantitative analysis of peripheral vascular resistance in patients with serous papillary cystadenocarcinomas showed a significant (2.1 times) increase of blood flow velocity in comparison with benign tumors. Dopplermapping of malignant serous tumors revealed decreased peripheral vascular resistance and predominance of venous locuses. High vascularization of all compartments of these tumors was seen. Central parts of malignant tumors contained numerous capillary-like vessels forming ramified networks (Fig. 1, *b*). Venule-like vessels resembling postcapillary venules were often seen. Slit-like vessels with irregularly-shaped lumen and thinned walls, resembling sinusoid capillaries, were often seen. Larger vessels, more often venous type, were seen at the periphery of malignant serous tumors; arterial type vessels were extremely rare. Their walls were loose, edematous, with hardly discernible smooth-muscle elements. According to morphometry, the thickness of arterial walls in intact ovarian tissue was 92.3±6.1 μ in the medulla, 69.90±9.64 μ in the cortex, and 64.27±5.61 μ in the portal vessels. These values were significantly lower in malignant tumors (Table 1), wall thinning being due to poorly developed muscle layer.

TABLE 1. Arteriolar Section Area and Wall Thickness in Benign, Borderline, and Malignant Serous Tumors of the Ovaries (*M*±*m*)

Tumor	Lumen area, mm²	Wall thickness, μ
Benign		
papillae	—	—
wall	795.1±50.8	39.56±11.30
Borderline		
papillae	1619.4±296.5	40.28±1.86
wall	4593.4±38.6	25.49±1.50
Malignant		
papillae	2032.6±627.2	45.1±10.4
wall	6264.5±105.4	38.4±5.6

Note. All differences between the groups are significant ($p<0.01$).

According to CDM, blood flow in borderline serous tumors did not differ from that in malignant tumors, and only histological analysis of resected material showed the borderline type of the tumor. However both histological and morphometric examination showed some specific features of blood vessels in these tumors. The papillae of borderline serous tumors were better vascularized than the wall. We saw there capillary-like vessels resembling postcapillary venules and slit-like vessels similar to those seen in malignant tumors (Fig. 1, *c*). VDV was significantly higher in borderline tumors than in benign ones and negligibly higher than in malignant tumors (Fig. 2). The walls of borderline tumors were poorly vascularized, similarly to that in benign tumors. The vessels were solitary and medium-sized. No smooth-muscle fibers were detected in arterial walls, the internal elastic membrane was thickened, and hyalinosis of the wall was seen.

Analysis of V_{max} and VDV values in all groups of tumors showed a positive correlation between these parameters in all tumors (Fig. 2). High blood flow velocity in borderline and malignant serous tumors is most likely to be due to the great number of vessels forming a network and anastomoses, while in benign tumors the vessels are usually solitary and form neither a network nor anastomoses. However it is noteworthy that in borderline tumors neither V_{max} nor VDV can serve as the differential diagnostic signs, as both the parameters are close to those in malignant tumors.

We tried to elucidate which morphometric parameter is responsible for vascular resistance (largely determined by the arteries. Blood flow resistance is inversely proportionate to square vessel lumen area [6]: $R=8\eta l/\pi r^4$, where η is blood viscosity, *l* and *r are* length and radius of the vessel. Hence, blood flow resistance is lower in vessels

with a wider lumen. According to morphometric data, the total lumen area of arterial vessels is different in the studied tumor types (Table 1). These values are higher in borderline and malignant tumors compared to benign ones, and we therefore hypothesized that vessel resistance in borderline and malignant tumors is lower than in benign tumors. Spectral dopplerometry showed similar picture: resistance index in malignant and borderline tumors (0.36±0.14 and 0.39±0.04, respectively) was lower than in benign tumors (0.56±0.07, $p \leq 0.05$).

Hence, borderline and malignant serous tumors of the ovaries are characterized by more intensive blood supply than benign tumors. Degenerative changes (sclerosis, hyalinosis) and the absence or decreased number of smooth-muscle elements in the arterial wall were observed in all tumors. In addition, we detected a direct correlation between V_{max} and VDV in all studied groups of tumors. Borderline serous cystadenomas occupy an intermediate position by their proliferative activity and vascular status. It is important that the vascular lumen is larger in malignant and borderline tumors than in benign ones, which can be responsible for low blood flow resistance in malignant and borderline tumors.

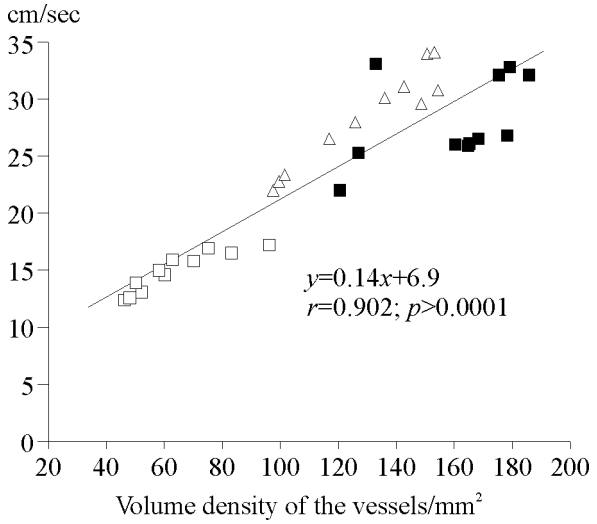

Fig. 2. Correlation between volume density of blood vessels and maximum systolic blood flow velocity (ordinate). Light squares: benign; dark squares: borderline; triangles: malignant serous tumors of the ovaries.

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