Clinical Significances of Measuredvalue of Microvessel Density and Lymphatic Vessel Density in Pancreatic Carcinoma Tissue

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ABSTRACT Objective: To investigate the changes of the microvessel density(MVD) and Lymphatic vessel density(LVD) and their relationship with the clinical pathology parameer and their interaction. Methods: The MVD and LVD were detected by using CD34 and monoclonal antibody D2-40 in 41 patients with pancreatic ductal adenocarcinoma was detected by using immunohistochemical method SABC. The expression of MVD and LVD in the cancer, paraneoplastic and normal pancreatic tissue were analyzed. The relationship with the clinical pathology parameter like as the pathological stage, tumor differentiation and lymph node metastasis, and the correlation between the MVD of cancer tissues and LVD of paraneoplastic were analyzed. Result: The mean MVD value in paired cancer and normal pancreatic tissue were 46.585± 16.935, 11.100± 4.036 respectively. There was statistically significant difference between the two groups (P=0.000＜0.01). The mean MVD value in paired cancer and normal pancreatic tissue were 46.585± 16.935, 11.100± 4.036 respectively. There was statistically significant difference between the two groups (P=0.000＜0.01). The average LVD of cancer, paraneoplastic and normal pancreatic tissue were 11.244± 4.800, 15.829± 7.470 and 13.512± 5.139 respectively in 41 cases, and there was significant differerce between the paraneoplastic and cancer tissue (P=0.000＜0.01) and contrary between paraneoplastic and normal pancreatic tissue (P=0.060＞0.05). There was relationship between the MVD values of tissues and the LVD values of paraneoplastic tissues (P=0.025＜0.05). Conclusion: The MVD values and LVD values of pancreatic ductal adenocarcinoma were associated with the tumor differentiation, pathological stage and lymph node metastasis. The MVD values of pancreatic cancer tissues were correlated with the LVD values of paraneoplastic tissues.

Key words: Pancreatic carcinoma; MVD; LVD; CD34; D2-40

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Introduction

As a highly malignant intraperitoneal tumor, the pancreatic tumor is associated with high ratio of recurrence and distant metastasis . The generation and metastasis of tumor relies on the tumor angiogenesis, which refers to a behavior in the existing vasoganglion that the cancer cells induce the formation of micro-vessels. Micro-vessel density (MVD) is now an important indicator of detecting the activity of tumor angiogenesis. However, there are differences between the detection of MVD of pancreatic tumor tissue and the clini copathological parameters. the endothelial cells in the micro-vessels of pancreatic tumor and normal pancreatic tissue were marked by immunohistochemical method and the specificity of CD34 monoclonal antibody. Researches showed that the pancreatic cancer cells mainly spread and metastasis through lymphatic system, so it was of great significance to study the generation and mechanism of the lymphatic vessels in the pancreatic tumor tissue [1-3]. As a recently founded specificity label of the endothelial cells of lymphatic vessels, D2-40 can specifically label the lymphatic vessels without labeling the blood vessel. D2-40 specificity was applied to label the endothelial cells of lymphatic vessels in the pancreatic tumor tissue, and the lymphatic vessel density (LVD) in the pancreatic tumor, the tumor paraneoplastic areas and normal pancreatic tissue . The relationship between D2-40 specificity and the clinical pathological features of tumor and the relationship between the tumor vessel density and LVD in the tumors' growing and developing process was analyzed.

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1 Material and method

1.1 Sample collection

The samples were collected from the wax stone samples from the people who accepted excision in Department of Hepatobililiary Surgery,The Affiliated Hospital of Medical college Qingdao University during 2003 and 2007, and they were proved to suffer from pancreatic duct tumor through postoperative pathology. The samples numbered 41, including 24 males and 17 females, or 36 carcinoma of head of pancreas and 5 carcinoma of body and tail of pancreas, ranging from 32 to 78(56± 10). Their pathology all presented duct adenoma, in which 10 samples high differentiated, 17 samples moderately differentiated, 3 samples moderately-low differentiated and 11 samples low differentiated. According to the UICC classification, class Ⅰ and class Ⅱ took 23 and class Ⅲ and class Ⅳ took 18.

1.2 The operation process of immunohistochemistry

Paraffin wax was sliced and de-waxed and gradient alcohol being hydrated; The slices were incubated in the condition of 3%

H_2O_2 at room temperature for 20 minutes; The antigen retrieval was conducted with microwave;the normal blocking serum of goat is diluted with 0.02M PBS1:10; the PBS liquid is removed, and the first antibody (which were preliminarily experimented and be diluted by 1: 100) is added to every slice, and then they are incubated with room temperature for 20 minutes and washed with PBS for three times, each time lasting for 2 minutes; the PBS liquid is removed, and the second antibody is added to every slice, and then they are incubated with room temperature for 20 minutes, and washed with PBS for three time, each time lasting for 2 minutes; 1ml 0.02MPBS is added into SABC10μl, the liquid is blended and then added to the slices, the slices are incubated for 20 minutes, and then washed with PBS liquid for three times, each time lasting for 5 minutes, the slices are puffed into PBS liquid; DAB solution developed color; the samples are dyed again with hematoxylin; the slices are dehydrated and dried with gradient alcohol, (make them transparent with xylene), and sealed with neutral vegetable gum.

1.3 The establishment of immunohistochemistry contrast

Positive control: the positive control is conducted with known positive slices of pancreas tumor and the positive results are acquired.

Negative control: conduct negative control with known positive slices of pancreas tumor by replacing first antibody incubation with PBS liquid and get negative results.

1.4 Result decision

Reference the methods reported by Maeda et al [4] and Weidner et al [5] to conduct MVD count: first, the slices are wholly observed with low-power lens (× 100) to locate the peak of micro-vessel density in the cancer; second,5 micro-vessels with top number in sight are counted under high-power lens (× 200) and their average number is calculated. The micro-vessel can be the endothelial cells or endothelial cell plexus presenting brownish yellow or chocolate brown, whose branches can also be considered as a micro-vessel as long as their structures were not connected. The thick-walled vessels and vessels whose caliber surpassed 50 μm, however, were excluded. Specifically, the LVD count: first,the most concentrated area of D2-40 positive staining vessels is identified under 40 times light microscope; second, three sights are chosen under 200 times light microscope and count the positive staining lymphatic vessels are counted to get the average, and then the LVD value of every organization is acquired.

1.5 Statistical

$\bar{x} \pm s$ was applied to describe measurement data; The constituent ratio was applied to describe categorical data; the Wilcoxon examination of pair-wise correlated samples is applied to compare the two teams; t examination is applied to conduct inter-team control; Spearman and Kendall analysis of correlated grade are applied to interrelate relationship; the statistical significance is acquired when $P<0.05$. The above analysis were all conducted with SPSS13.0 software.

2 Results

2.1 The relationship of the MVD value between paired tumor tissues of pancreatic tumor and normal pancreatic tissues

The MVD values of 41 paired tumor tissues were 46.585± 16.935, which was significantly higher than that of normal tissues, 11.100± 4.036. The differences between the two teams were statistically significant ($P=0.000<0.01$, Table 1).

Table 1 The MVD value of pancreas tumor tissues and normal tissues

	n	MVD	Z	P
Normal pancreas tissues	41	11.100± 4.036	-5.580	0.000
Pancreatic carcinoma tissues	41	46.585± 16.935		

2.2 The relationship of the MVD value of pancreatic tumor tissues and the level of clinical grade, pathological stage and lymphatic metastasis

Among the 41 pancreatic tumor tissues, the MVD value of the high and moderately differentiated tumor tissues was 39.07± 11.82, obviously lower than that of the low differentiated team, 61.07 ± 16.12; there were obvious difference between the two teams ($P=0.000<0.01$). The MVD value of class Ⅰ and class Ⅱ tumor tissues was 41.57± 15.64, lower than that of class Ⅲ and class Ⅳ, 53.00± 16.75; The difference was statistically significant ($P=0.030<0.05$). The MVD value of un-metastasized tumor tissues was 41.96± 15.40, and it was lower than that of the metastasized tumor tissues, 53.81± 17.15; The difference between the two teams was statistically significant ($P=0.027<0.05$).

2.3 The relationship of the LVD value between paired tumor tissues of pancreatic cancer, the adjacent tissues and the normal pancreatic tissues

Among the 41 pancreatic tumor tissues, the LVD value of the adjacent tissues was 15.829± 7.470, which was higher than that of pancreatic tumor tissues(13.512± 5.139)and normal pancreatic tissues (11.244± 4.800); The difference between the LVD values of adjacent tissues and normal pancreatic tissues was statistically insignificant ($P=0.060>0.05$) while there was obvious difference between the LVD values of the adjacent tissues and pancreatic tumor tissues ($P=0.000<0.01$).

2.4 The relationship of the LVD value of adjacent tissues

and the level of clinical grade, pathological stage and lymphatic metastasis

Among the 41 pancreatic tumor tissues, the LVD value of the high and moderately differentiated tumor tissues was 13.19± 4.25, obviously lower than that of the low differentiated team (20.93± 9.64); The difference was statistically significant (P=0.011＜0.05). The LVD value of class Ⅰ and class Ⅱ tumor tissues was 13.45± 4.65, which was lower than that of class Ⅲ and class Ⅳ (19.00± 9.18); The difference between the two team was statistically significant (P=0.026＜0.05). The LVD value of un-metastasized tumor tissues was 12.04± 2.52, which was lower than that of the metastasized tumor tissues (21.75± 8.79); There was obvious difference between the two teams (P=0.001＜0.01, Table 2).

Table 2 The relationship of the MVD value of the pancreatic tumor tissues, the LVD value of adjacent tissues, and the level of clinical grade, pathological stage and lymphatic metastasis

		n	The MVD value of tumor tissues	t	P	The LVD value of adjacent tissues	t	P
The level of clinical grade	High and moderate differentiation	27	39.07± 11.82			13.19± 4.25		
	Low differentiation	14	61.07± 16.12	-4.98	0.000	20.93± 9.64	-2.86	0.011
The TNM classification	Class Ⅰ and class Ⅱ	23	41.57± 15.64			13.45± 4.65		
	Class Ⅲ and class Ⅳ	18	53.00± 16.75	-2.25	0.030	19.00± 9.18	-2.38	0.026
Lymphaden	Un-metastasized	25	41.96± 15.40			12.04± 2.52		
	Metastasized	16	53.81± 17.15	-2.30	0.027	21.75± 8.79	-4.31	0.001

2.5 The relationship between the MVD value of pancreatic tumor tissues and the LVD value of adjacent tissues

The LVD value of the 41 adjacent tissues and the MVD value of tumor tissues had correlation (P=0.025). Take 41 as the threshold value of the high/low level of the MVD value of the tumor tissues, and then in the team of high MVD value, the MVD value and the LVD value were of obvious correlation (P=0.001,Table 3).

Table 3 The relationship between the LVD value of adjacent tissues and the MVD value of pancreatic tumor tissues

	The LVD value of adjacent tissues	The LVD value of the team of high MVD value
The MVD value of the tumor tissues	τ=0.252 P=0.025	
The MVD value of the team of high MVD value		τ=0.608 P=0.001

3 Discussion

3.1 The relationship between the MVD values of the pancreatic tumor tissues and the clinical pathological features

Most scholars hold that the MVD value of the tumor is tightly related to the size, class of the cancer, the lymphatic metastasis and the survival rate, etc. The new-born micro-vessels were the first station for the invasion and metastasis of the cancer. On one hand, the basement membrane of the new-born micro-vessels was incomplete and of high permeability, so they can easily be passed through by cancer cells [24]. On the other hand, in the generation process of the micro-vessels, several ground substance digestive enzymes such as Ⅳ type collagenase and plasminogen, etc, which will destroy the barrier made by ground substance and promote the metastasis of the cancer cells, will be produced by the endothelial cells. Besides, the formation of tumor metastasis was clonal and the cancer cells with high promoting ability of vessel generation would form metastasis focus more easily. The growth, invasion and metastasis of the malignancy were influenced by many factors, among which the angiogenesis reaction induced by cancers is extremely important. In the case of lacking vessel and nutrition, the tumor can not quickly reproduce [26]. The MVD can be regarded as

one of the standards of measuring angiogenesis[7]. In the pancreatic tissues, the micro-vessels were not distributed evenly and the densely vessel areas mainly concentrate on the adjacent areas of the tumor focus. The oxygen tension of the areas adjacent tumor focus was low, the expression of the angiogenesis factors like VEGF was strengthened and the angiogenesis is active [8,9]. The pancreatic tumor tissues with high MVD value would easily suffer from distant metastasis like lymphatic metastasis and liver, etc. By using tyrosine kinase inhibitors like PTK787 and PKI166, Baker et al blocked the signal transduction of the acceptors of BEGF and EGF and further inhibited the angiogenesis, which realized obviously reducing the growth speed and metastasis of the pancreatic tumor of bandicoots [10]. Thus the formation of angiogenesis is closely related to the generation and metastasis of cancer is further proved. According to the study of Stipa the VEGF expression in the pancreatic tumor tissues is closely related to their MVD value and both indexes are independent evaluating elements of pancreatic tumor prognosis [11]. However, some scholars found that in most pancreatic tumor tissues, the MVD values were obviously high; the MVD values of the team with lymphatic metastasis were significantly higher than the team without lymphatic metastasis [12,13]; According to the TNM classification, the team of Ⅲ+Ⅳ is obviously higher than the team of Ⅰ+Ⅱ by MVD value, and the MVD value of highly and moderately differentiated pancreatic tumor tissues than the lowly differentiated tissues, which proved that the level of angiogenesis was tightly related to the lymphatic metastasis of pancreatic tumor and clinical stages, which was same to part of the study results of Ikeda et al. These researches showed that MVD was closely related to the growth, metastasis and prognosis of the pancreatic cancer, reflected the necessary connection between the level of the formation of tumor MVD and the tumor invasiveness, and acted as one important index of measuring the tumor biological behavior. The pancreatic MVD plays an important role in the process of pancreatic tumor process, so the suggestion of inhibiting the angiogenesis will probably become a new target of curing pancreatic tumor or an index of supervising and evaluating the healing effect.

3.2 The relationship between the LVD value of pancreatic tumor tissues and the clinical pathological features of cancer:

As the micro-vessels of tumor and adjacent areas, the lymph micro-vessels were tightly related to the growth, infiltration and metastasis of tumor and the findings like D2-40, the specificity label of the endothelial cells of lymphatic micro-vessels, provide new tools of studying the lymphatic generation. D2-40 can strictly distinguish the vessel and lymphatic endodermis and accurately evaluate the vasculature of cancer, so it has become one of the focuses of studying tumor and achieved great advancement. The lymphatic generation is restrained by the micro environmental elements like the hydrostatic pressure and the mechanical pressure of hyperplasia and spread of cancer cells, and thus it is distributed unevenly in the cancer [15]. Currently, some studies proved that intratumor all lymphatic micro-vessels were non-functional lymphatic vessels and will not cause tumor metastasis while the adjacent tumor area exist functional lymphatic micro-vessels that were enough to cause tumor metastasis. The lymphatic metastasis in the tumors were directly related to the lymphatic micro-vessels density of the adjacent tumor areas and the overgrown pericancerous lymphatic vessels will easily cause the lymphatic metastasis, and these lymphatic vessels will become the new target of curing cancer[16,17]. The studies of the clone T-241 in the transfected VEGF-C mouse fiber and melanoma clone B16-F10 in the orthotopic implantation model of nude mice, the pericancerous lymphatic vessel density and the lymphatic metastasis rate were obviously higher than the control teams, but the radiography of lymphatic micro-vessels suggested that in the tumor there were insufficient function lymph vessels while the pericancerous areas exist hyperplasia lymph vessels. Many other studies showed that in the tumor tissues of many malignancies of human being like melanoma[18], stomach cancer[19], breast cancer [20], rectum cancer [21], bladder cancer [22], there were lymphatic micro-vessels lymph angiogenesis or lymphoid lost and that the pericancerous lymphatic micro-vessels increased and they were related to the lymphatic metastasis. In recent years there were also reports on the relationship between pancreatic tumor LVD and its growth speed. According to a study aiming at explaining the clinical pathological significance of lymphatic vessel density and distribution of pancreatic tumor by Jin G, the LVD in the pancreatic tumor is obviously lower than the LVD in the pericancerous areas and the areas without tumor and the distribution of lymphatic vessels and pericancerous lymph hyperplasia promote the malignant infiltration of pancreatic tumor and the lymphatic metastasis [23]. Laura Rubbia B apply anti-LYVE-I, anti-VEGFR-C and anti-Podoplanin immunohistochemical technology to mark the lymphatic micro-vessels and evaluate the lymphatic system of the pancreas endocrine tumors of human beings and its biological behaviors [24]. The results showed there were lymph angiogenesis in the pancreas endocrine tumors, no matter innocent or malignant tumors, and the LVD was related to the size of innocent tumors and the liver metastasis of malignant tumors. This study showed that there were lymphatic vessels distributing in the ductal adenocarcinoma of pancreas tumors, the tumor paraneoplastic areas and normal pancreatic tissues, in which the LVD value of tumor paraneoplastic areas was the highest and was significantly different from the LVD values in the tumor tissues and normal pancreatic tissues. Besides, the LVD value of tumor paraneoplastic areas is obviously related to the clinical pathological features like differentiation level of pancreatic tumors, the pathological stage and metastasis or not; it also suggests that the pancreatic tumors induce

the generation of lymph angiogenesis and promotes the tumor realize metastasis through lymphatic channels.

3.3 The relationship between the LVD value and MVD value of the pancreatic tumor tissues

Along with the continuous occurrence of a series of specificity label of lymph vessels, the lymph angiogenesis and tumor metastasis and the prognosis become the new studying focuses after tumor angiogenesis [25,26]. However, it is rarely reported abroad and home to apply the labels to inspect the lymph micro-vessel density in the tumor tissues, analyze the relationship between LVD and MVD and the roles they are playing in the processes of the growth and transfer of the pancreatic tumor tissues. This study shows that in the pancreatic tumor growth and transfer, the micro-vessels and lymph micro-vessels all play important roles and they both relate to each other, presenting that there are obvious relation between the MVD value of the high MVD leveled pericancerous tumor tissues and the LVD value of the pericancerous tumor tissues, which will greatly guide the judgment prognosis and curing process.

4 Conclusion

(1) The LVD values are related to the clinical pathological features like the level of clinical grade, pathological stage and the metastasis, etc.

(2) The MVD values are related to the clinical pathological features like the level of clinical grade, pathological stage and the metastasis, etc.

(3) There is relativity between LVD values and MVD values.

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测定胰腺癌组织微血管密度及淋巴管密度的临床意义

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摘要 目的:研究胰腺癌组织中微血管密度(Microvessel density ,MVD)和淋巴管密度(Lymphatic vessel density ,LVD)的变化、与胰腺癌临床病理的联系。方法:采用免疫组织化学 SABC 法应用 CD34 及 D2-40 分别检测 41 例胰腺导管腺癌患者配对癌组织内、癌旁及正常胰腺组织中 MVD 及 LVD 的表达情况,分析其与肿瘤分化程度、分期和淋巴转移间的相关性;以及癌组织 MVD 与癌旁组织 LVD 表达之间的关系。结果:在 41 例胰腺癌组织配对癌组织及正常胰腺组织平均 MVD 值分别为 46.585± 16.935,11.100± 4.036,两组之间差别有统计学意义(P=0.000<0.01)。配对癌组织内、癌旁及正常胰腺组织中平均 LVD 值分别为 11.244± 4.800,15.829± 7.470 和 13.512± 5.139;其中癌旁组织与正常胰腺组织 LVD 值差别无统计学意义(P=0.060>0.05),癌旁组织与胰腺癌组织的 LVD 值有显著性差异 (P=0.000<0.01)。癌组织内 MVD 值与癌旁组织 LVD值之间有相关性 (P=0.025< 0.05)。结论:胰腺导管腺癌组织中 MVD 及 LVD 与肿瘤分化程度、病理分期及淋巴转移存在关联。胰腺癌组织内 MVD 值与癌旁组织 LVD 之间存在相关性。

关键词 胰腺癌;微血管密度;淋巴管密度;CD34;D2-40

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