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Progress of Microvascular Invasion in Hepatic Alveolar Echinococcosis

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Abstract: ***Alveolar echinococcosis (AE) is a kind of zoonotic parasitic disease caused by multi-atrial echinococcus tapeworm infection in humans or animals. Multi-atrial echinococcus larvae are often parasitized in the liver, and the treatment is based on surgical resection, supplemented by drug treatment. Hepatic alveolar echinococcosis(HAE) larvae foci are chronic infiltrative growth, no special symptoms in the early stage, most of the patients are already in the late stage at the onset of the disease, mostly accompanied by tissue invasion around the foci and metastasis to distant organs, at this time, most of the patients do not have the indications for radical surgery, recent studies have shown that HAE larvae foci around the microvascular infiltration may be an important basis for its infiltration and proliferation of metastasis. In this paper, we synthesize the latest research progresses at home and abroad, and give an in-depth description of the pathological mechanism, imaging and serological characteristics of microvascular invasion in HAE is foci, aiming to promote the development of diagnosis and treatment of microvascular invasion in HAE.***

Keywords: Hepatic alveolar echinococcosis, Microvascular invasion, Vascular endothelial growth factor**.**

1. Introduction

Echinococcosis is a kind of human-veterinary parasitic disease that is prevalent in the world and widely spread all over the world, the western plateau and pastoral areas of China are the high prevalence areas of echinococcosis, which poses a great threat to the lives and properties of the people in the pastoral areas, Echinococcosis is mainly classified into two kinds of diseases, and the clinical situation is mostly common in the form of fine-grained echinococcosis [1-3]. Echinococcosis is common in the liver. HAE larvae show expansive growth, and the harm to the human body is dominated by the foci's pressure on the surrounding tissues. Late stages of unintervened foci may result in rupture of the encapsulated sacs, causing diffuse implantation in the abdominal cavity and peritonitis, which can be life-threatening in severe cases. HAE foci show chronic infiltrative growth and penetrate deep into the liver parenchyma, because of its similar growth pattern with hepatocellular carcinoma, so it has the name of “worm cancer” [4]. Surgical treatment is considered to be an effective measure for the eradication of HAE, but due to the limited medical conditions in pastoral areas, and also because of the strong hidden nature of the foci, the majority of the patients have been accompanied by serious intrahepatic and biliary tract invasion at the time of diagnosis. This greatly increases the difficulty of radical surgery. Benzimidazole antiparasitic drugs with albendazole as the representative drug are commonly used therapeutic drugs for echinococcosis, but with the long-term use of this drug, but it is difficult to achieve the goal of eradication, long-term medication has a serious impact on liver function, and the majority of patients have appeared to be resistant to the phenomenon. Recent studies have shown that neovascularization around HAE foci may be an important basis for their growth and proliferation, and research into their pathogenesis and the development of new therapeutic modalities targeting the pathological basis involved will provide help and new ideas for the diagnosis and treatment of HAE [5-7].

2. Lesion Characteristics and Clinical Manifestations of HAE

Among many malignant tumors, microvascular invasion is often used as a reference index for malignant tumor invasion and metastasis, and tumor growth is closely related to tumor vascularization and blood supply, and the index of tumor vascularization is often expressed as microvessel density (MVD) [8]. The biological characteristics of HAE are similar to those of liver malignancies, and the liver is the main host organ of AE. The lesion of HAE consists of numerous small vesicles with a diameter of about 0.1-1.0 cm, and the gross view is usually a single giant type, a yellowish or white vesicular mass with a hard texture and poorly demarcated from the surrounding tissues [9].

The clinical manifestations of HAE depend on the location, type and stage of development of the parasite. The disease is characterized by chronic infiltrative growth, with no obvious symptoms in the early stage, and when symptoms are obvious, the disease is often in the middle or late stage. At the time of consultation, a large abdominal mass may be palpable, and obstructive jaundice may occur when the lesion increases in size and encroaches on the hepatic bile ducts. If the liquefied cavity is secondary to infection, abscess can be formed; when the portal vein is seriously invaded, it can cause narrowing or even occlusion of the lumen of the main trunk and/or branches of the portal vein, forming spongy degeneration of the portal vein, and resulting in portal vein thrombosis combined with portal hypertension. HAE is extremely dangerous, and radical resection is necessary to cure the disease, and it requires sufficient understanding of its growth and migration patterns to determine the safe scope of surgical resection. Unlike hepatocellular carcinoma, which is rich in blood flow in the center of the lesion, the blood supply of HAE lesions is concentrated in the periphery of the lesion, while the center of the lesion is “lack of blood supply” [10]. Chen et al. [11] found that the vascularization of HAE lesions mainly existed in the edges of the lesion through the pathological observation of HAE lesions in mice. Studying the characteristics of HAE

microvascular invasion and clarifying its growth and degree of infiltration can help to deepen the understanding of the development of HAE lesions and indirectly assess the activity of HAE lesions, thus further guiding the treatment.

3. Detection of Microvascular Invasion in HAE

3.1 Radiographic Examination

3.1.1 Color Doppler ultrasound contrast technology

Ultrasonography is cheap and convenient, and is widely used in the imaging diagnosis of most liver diseases. It is also widely used in the diagnosis of HAE, which is strongly echogenic in ultrasonography, with a very irregular shape, unclear boundary with the surrounding liver tissues, uneven internal echoes, a small amount of calcification, and obvious sound attenuation and acoustic shadows in the rear. In recent years, color Doppler energy mapping and ultrasonography have greatly improved the clinical value of ultrasonography. The morphological evaluation of ultrasonography is significantly better than that of normal ultrasound, which can provide a better basis for determining the scope of surgery and evaluating the efficacy of drugs [12]. HAE lesions have the characteristic of “lack of blood supply”, and their blood flow maps have the characteristic feature that there is no blood flow signal inside the lesion, which is manifested as a black hole sign of a contrast-filled defect, while the periphery of the lesion is surrounded by the black hole sign [13]. “Chen Lu et al. [14] evaluated the activity of HAE infiltrating and proliferating zones by ultrasonography, which helped clinicians to make a preliminary judgment of the activity of the lesion through simple, non-invasive and effective imaging, and to evaluate the activity of early and mid-term HAE patients. Evaluate the therapeutic effect of HAE patients after early and mid-stage surgery, and evaluate the effect of drug therapy in patients with advanced HAE.

3.1.2 CT

CT is widely used as a preoperative diagnostic and resectability assessment tool for the diagnosis of HAE due to its high sensitivity. multislice spiral CT (MSCT) multiphase enhancement scanning of the hepatic region [15]. MSCT can comprehensively show the characteristic images of HAE and the severity of vascular invasion. Liu Li et al. [16] studied 117 patients with HAE, and the results showed a high degree of consistency between the manifestations of vascular involvement on MSCT and those seen intraoperatively. CT angiography (CTA) can accurately show the adjacency of important intrahepatic vessels to the lesion, and through a three-dimensional perspective to more thoroughly and intuitively show the relationship between the lesion and the important blood vessels and bile ducts in three-dimensional view. The imaging manifestations of vascular involvement under CTA are arterial phase The arterial phase shows that the hepatic artery and its main branches are compressed and pushed, the angle of intersection between the branches increases, and the lesion compresses the blood vessels, which appears similar to the “hand holding the ball” sign; the portal venous phase shows that the main trunk or the main branches of the portal vein are narrowed or interrupted because of being encircled by the lesion, and the distribution of the portal vein vessels in the area where the lesion is located in the advanced portal venous phase is obviously reduced, and it even appears as a vascular-free zone; In the advanced portal vein stage, the distribution of portal vein vessels in the area where the lesion is located is significantly reduced or even shows an avascular zone; when the lesion encroaches on the main trunk of the hepatic vein or the second hepatic portal, the branches of the hepatic vein are poorly visualized or locally narrowed, and the intrahepatic segment of the inferior vena cava shows a “bird's beak”-like stenosis: There was a high level of perfusion at the edge of the HAE lesion, suggesting that there was a vascular distribution in the edge region of the HAE lesion [17-18].

3.1.3 MRI

MRI is the main imaging method for the evaluation of HAE because of its noninvasive nature, high soft tissue resolution, and lack of ionizing radiation to the body [19]. MRI of hepatic blastomycosis is characterized by a wide variety of lesions, sometimes without clear features. The lesions are mainly characterized by infiltrative growth with irregular margins, and on T1WI, most of the lesions are characterized by low-signal areas with slightly uneven signal intensity, irregular morphology, and unclear borders. It has been reported in the literature that the marginal zone of liver follicles is a low-signal mixed signal zone with a width of about 5 mm on DWI [20], and Azizi et al. [21] found that there is a correlation between the small vesicles in the HAE lesions and their metabolic activity on MRI. MRI can accurately visualize the marginal and peripheral bands of HAE lesions (a characteristic sign of HAE), and can be used as the first choice of preoperative imaging. Since MRI does not require consideration of radiation dose, it can be used to follow up patients with HAE and provide a reference for clinical evaluation of the efficacy of treatment and termination of therapy [22].

3.2 Relationship between Angiogenic Factors and Microvascular Invasion

Vascular endothelial growth factor A (VEGFA) is a dimeric glycoprotein belonging to the VEGF family, which includes VEGFB, VEGFC, VEGFD, and placental growth factor (PIGF). VEGFA is the most potent inducer of the vascular permeability mechanism in the VEGF family. VEGFA enhances microvascular permeability and induces angiogenesis by upregulating the expression of urokinase-type plasminogen activator (uPA), tissue plasminogen activator (tPA), and plasminogen activator inhibitor 1 (PAI-1) [23]. Nowadays, with the deepening of HAE genomics research, many scientists have found that the lesion and its peripheral infiltration area have abundant microvessel density, and experiments have proved that the signaling pathways of HIF-1α, VEGFA, and VEGFR may be involved in the formation of microvessels and the occurrence and development of HAE [24], Zhang et al. [25] found that by measuring MVD and vascular endothelial growth factor in the tissues of gerbil hepatic vesicles with echinococcosis, the infected dentate vesicles were more permeable and could induce angiogenesis. Zhang et al. measured MVD and vascular endothelial growth factor (VEGF) in gerbil hepatic vesicular echinococcosis tissues and found that MVD and VEGF were highly expressed in gerbil tissues infected with

vesicular echinococcosis and were higher than those in surrounding liver tissues, and that the expression levels of MVD and VEGF in liver tissues around the lesions increased with the extension of the time of onset of the disease. Animal models showed neoangiogenesis in the hepatic vesicular echinococcosis lesions and surrounding liver tissue, which may be related to VEGF and other related signaling factors.

CD34 (cluster of differentiation 34) antigen is a highly glycosylated transmembrane glycoprotein that is selectively expressed on the surface of human hematopoietic stem cells, progenitor cells and vascular endothelial cells and disappears gradually as the cells mature, and it is a marker of vascular endothelial progenitor cells, which is used to mark neovascularization in tumor tissues [26]. It is a marker of vascular endothelial progenitor cells, which is used to mark neovascularization in tumor tissues. Studies have shown that small vessels in healthy extrahepatic tissues are different from hepatic sinusoids in terms of their ultrastructure and specific functions, and that CD34 can be expressed on endothelial cells of small blood vessels in other organs, but is not detected in endothelial cells of healthy hepatic sinusoids, but it is highly expressed in tissues of hepatocellular carcinoma accompanied by neovascularization, which suggests that it plays an important role in hepatic vascular neogenesis. In addition, CD34 has the dual roles of hematopoiesis and endothelial cell metastasis. Li et al. [27] showed that there was no CD34 expression in healthy liver tissue, indicating no angiogenesis; there was also no CD34 expression in liver tissue around Echinococcus multilocularis 20 d after infection, and then, with the prolongation of the post-infection period, the vasculogenesis of the lesion increased. This suggests that one of the mechanisms of infiltrative growth of Echinococcus multilocularis may be angiogenesis.

4. Impact of Microvascular Invasion on HAE Treatment

The infiltrative growth characteristic of HAE determines that surgical resection is the first choice of curative treatment, and the common surgical modalities include radical hepatectomy, palliative surgery, local ablation therapy, liver transplantation, isolated hepatectomy and autologous liver transplantation. Radical hepatic lesion resection is the first choice of treatment for hepatic alveolar encapsulated worms, and the principle of radical liver lesion resection is in accordance with the principles of “tumor-free surgery” and “precise liver surgery”. The principle of radical hepatectomy is to completely remove the encapsulated worm foci in accordance with “tumor-free surgery” and “principle of precise liver surgery”, while the scope of surgical resection should be in accordance with the infiltration depth of peripheral hepatic blood vessels, and a large number of pathological researches have shown that 1cm of the foci edge is the “infiltration zone” in which the HAE is actively proliferating. “In order to achieve radical resection, the resection scope should reach the normal liver tissue of the edge of the lesion greater than 1cm, in order to eliminate the “infiltration zone” of the lesion with active proliferation [28].

Drug therapy, as an adjuvant therapy for HAE, is often used as a treatment for patients with advanced multi-organ encapsulated worms after surgical resection to prevent recurrence and those who have lost the chance of radical resection and liver transplantation. Albendazole is currently recognized as an effective anti-encapsulation drug of choice, but the adverse effects of the drug is heavy, with the long-term use of the drug, some patients have developed drug resistance problems, vasopressors have been used in a variety of malignant tumors, some scholars applied vasopressors to HAE model mice, Dang Zhisheng et al. [29] established a HAE mouse model through animal experiments, in the use of sorafenib (tyrosine kinase inhibitor) After treatment, the cells of the internal hair layer of the lesion capsule were shed and completely inactivated, and showed better therapeutic effect than that of the albendazole treatment group.

5. Summary and Outlook

Angiogenesis is an indispensable index for evaluating the survivability of HAE patients. If a non-invasive, simple and effective method can be found to determine the angiogenesis next to the lesion and clarify the infiltration range of the disease, and if an accurate localization can be made for the invasion site of the lesion, determine the site of the affected vessels, clarify the surgical procedure, and reduce the blood supply of the lesion and infiltration zones before the operation, it will help to make an assessment of the scope of the surgical resection and the postoperative recurrence, and improve the Surgical cure rate and provide more effective treatment for patients. Relatively few studies have focused on the state of vascular invasion, and even fewer studies have been conducted on the physiologic features of vascular invasion. In addition, researchers have a limited understanding of the characteristics of vascular invasion, and the potential significance of using them to guide clinical treatment has yet to be explored. Now relevant studies have shown that the internal blood supply of HAE lesions is lacking and peripheral blood supply is available, and there are venophilic vascular features in HAE, and there is also a certain connection with the hepatic arteries, so the relationship between neovascularization of HAE and hepatic vasculature still needs to be further researched. The effect of postoperative drug therapy on inhibiting the related angiogenesis is still more doubtful and needs to be solved.

References

[1] Jensenius M, Mørch K, Yaqub S, Halvorsen DS, Reims HM, Björk IG, Røsok BI, Oltmanns G, Helbak K, Øines Ø, Lier T. Alveolar echinococcosis [J]. Tidsskr Nor Laegeforen, 2024, 144(10).

[2] Zhao SY, Zhu HH, Wang XQ, A JD, Lu XL, Tian QS, Pan HS, Liu LX, Wu SL, Han XM, Guo YM. Present situation and progress of comprehensive treatments for hepatic alveolar echinococcosis [J]. Zhongguo Xue Xi Chong Bing Fang Zhi Za Zhi, 2019, 31(6): 676-678.

[3] Deplazes P, Rinaldi L, Alvarez Rojas CA, Torgerson PR, Harandi MF, Romig T, Antolova D, Schurer JM, Lahmar S, Cringoli G, Magambo J, Thompson RC, Jenkins EJ. Global Distribution of Alveolar and Cystic Echinococcosis [J]. Adv Parasitol, 2017, 95:315-493.

[4] Mihmanli M, Idiz UO, Kaya C, Demir U, Bostanci O, Omeroglu S, Bozkurt E. Current status of diagnosis and treatment of hepatic echinococcosis [J]. World J Hepatol. 2016, 8(28):1169-1181.

[5] Hemphill A, Stadelmann B, Rufener R, Spiliotis M, Boubaker G, Müller J, Müller N, Gorgas D, Gottstein B. Treatment of echinococcosis: albendazole and mebendazole--what else? [J]. Parasite, 2014, 21:70.
[6] Xu X, Qian X, Gao C, Pang Y, Zhou H, Zhu L, Wang Z, Pang M, Wu D, Yu W, Kong F, Shi D, Guo Y, Su X, Hu W, Yan J, Feng X, Fan H. Advances in the pharmacological treatment of hepatic alveolar echinococcosis: From laboratory to clinic [J]. Front Microbiol, 2022, 13:953846.
[7] Wang Z, Jiang T, Aji T, Wen H. Massive sympathetic nerve infiltration in advanced hepatic alveolar echinococcosis: a case report and review of the literature [J]. BMC Infect Dis, 2022, 22(1):489.
[8] Svagzdys S, Lesauskaite V, Pavalkis D, Nedzelskiene I, Pranys D, Tamelis A. Microvessel density as new prognostic marker after radiotherapy in rectal cancer [J]. BMC Cancer, 2009, 9:95.
[9] YIN Qiuping, ZHANG Yuying, MA Qinfeng, et al. A study on the correlation between ARFI examination of the marginal zone and pathologic histology of different types of hepatic vesicular encapsulated lesions [J]. Journal of Medical Imaging, 2023, 33(01):52-55.
[10] Liu Y, Hou B, Chen R, Jin H, Zhong X, Ye W, Liang C. Biliary collateral veins and associated biliary abnormalities of portal hypertensive biliopathy in patients with cavernous transformation of portal vein [J]. Clin Imaging, 2015, 39(5):841-844.
[11] CHEN Qian, ZHANG Huai, SU Qiangming, et al. Experimental study of recombinant human vascular endothelial inhibitor inhibiting perivascular angiogenesis in gerbil liver vesicular echinococcus [J]. Chinese Journal of Pathobiology, 2017, 12(04): 321-324+327.
[12] Song T. Gray-scale ultrasonography on the infiltration and proliferation zone of hepatic vesicular echinococcosis [D]. Xinjiang Medical University, 2012.
[13] WANG Ying, Lv Yongquan. Application of color Doppler energy mapping in the differential diagnosis of hepatic vesicular echinococcosis and hepatocellular carcinoma [J]. Chinese Journal of Ultrasonography, 2002, (01):25-27.
[14] Chen L. Consistency study of ultrasonography in evaluating the activity of infiltrating and proliferating zones of rat liver follicular schistosomiasis [D]. Xinjiang Medical University, China, 2019.
[15] YAN Youxia, TIAN Qingshan, WANG Shunjuan, et al. Application value of positron emission-computed tomography in resectability and resection range of hepatic vesicular echinococcosis [J]. Chinese Journal of Liver Diseases (Electronic Edition), 2020, 12(04):78-82.
[16] LIU Li, DING Shirong, PU Peng, et al. Diagnostic value of multislice spiral CT for hepatic vesicular echinococcosis involving the vascular system [J]. Chinese Journal of CT and MRI, 2016, 14(10):74-76.
[17] LIU Wenya, LOU Jianru, XING Yan, et al. Multislice spiral CT imaging features of vesicular echinococcosis of the liver [J]. Chinese Journal of Radiology, 2005, (08):860-863.
[18] JIANG Yi, WANG Jing, XIAO Hu, et al. Dual source CT energy imaging to assess the blood supply distribution of hepatic blastomycosis: quantitative iodine concentration and histopathologic correlation study [J]. Journal of Xinjiang Medical University, 2015, 38(10):1207-1212.
[19] ZHANG Hongqian, BAO Haihua, LI Weixia, et al. Preoperative evaluation of hepatic blastomycosis by magnetic resonance multimodal imaging [J]. Journal of Plateau Medicine, 2020, 30(03):10-15.
[20] Ren Bo. Contrasting analysis of imaging features and histopathology of the marginal zone of hepatic vesicular bulbous larvae based on MR diffusion imaging [D]. Xinjiang Medical University, 2011.
[21] Azizi A, Blagosklonov O, Lounis A, Berthet L, Vuitton DA, Bresson-Hadni S, Delabrousse E. Alveolar echinococcosis: correlation between hepatic MRI findings and FDG-PET/CT metabolic activity [J]. Abdom Imaging, 2015, 40(1):56-63.
[22] Nikendei C, Greinacher A, Berkunova A, Junghanss T, Stojkovic M. Psychological burden and resilience factors in patients with Alveolar Echinococcosis - A cross-sectional study [J]. PLoS Negl Trop Dis, 2019, 13(1):e0007082.
[23] Melincovici CS, Boşca AB, Şuşman S, Mărginean M, Mihu C, Istrate M, Moldovan IM, Roman AL, Mihu CM. Vascular endothelial growth factor (VEGF) - key factor in normal and pathological angiogenesis [J]. Rom J Morphol Embryol, 2018, 59(2):455-467.
[24] JIANG Huijiao, GUI Xianwei, GUO Lijiao, et al. Expression and role of VEGFA/VEGFR2 in angiogenesis of hepatic multilocular echinococcus granulosus tissue in mice [J]. Chinese Journal of Parasitology and Parasitic Diseases, 2020, 38(06): 673-681.
[25] ZHANG Shijie, WU Hexing, LI Qi, et al. Expression and significance of microvessel density and vascular endothelial growth factor in gerbil hepatic blastococcal larvae tissues [J]. Chinese Basic and Clinical Journal of General Surgery, 2015, 22(02):134-138.
[26] Fina L, Molgaard HV, Robertson D, Bradley NJ, Monaghan P, Delia D, Sutherland DR, Baker MA, Greaves MF. Expression of the CD34 gene in vascular endothelial cells [J]. Blood, 1990, 75(12):2417-26. PMID: 1693532.
[27] Li-Tong,Zhang Shi-Jie. Role of neovascularization in the infiltrative growth of hepatic vesicular coccidia [J]. Chinese Journal of Animal and Human Diseases. 2014, 30(10):1071-1074.
[28] Guidelines for treatment of cystic and alveolar echinococcosis in humans. WHO Informal Working Group on Echinococcosis [J]. Bull World Health Organ. 1996, 74(3):231-42. PMID: 8789923; PMCID: PMC2486920.
[29] XU Shuo, DANG Zhisheng, ZHANG Haobing, et al. Research progress of drug therapy for echinococcosis [J]. Chinese Journal of Parasitology and Parasitic Diseases, 2018, 36(03):297-302.