Interventional treatments for hepatic hemangioma: A state-of-the-art review

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ARTICLE INFO

Keywords:
Hepatic hemangioma
Interventional treatment
Pathological properties
Type of blood supply

ABSTRACT

Hepatic hemangiomas (HHs) are the most common benign tumors of the liver. These tumors are mainly asymptomatic and do not require treatment. Nevertheless, there are some special cases that require therapeutic intervention, and surgery and intervention are currently the primary treatment modalities. Despite significant advances in the development of minimally invasive techniques and their popularization, interventional treatment of HH is still the preferred choice. In the present review, we discuss the pathological properties, type of blood supply, and treatment indications for HH and assess the status and progress of the existing interventional treatments.

1. Epidemiology and pathological properties of hepatic hemangiomas (HHs)

HHs are the most common idiopathic benign liver tumors, typically detected incidentally during a health check or examination of nonspecific abdominal pain. Previous studies reported a prevalence in the range of 0.4–7.3% for HHs. Moccagianii et al. 10 concluded that the morbidity of HH was 2.5% based on the review of data from more than 83,000 patients with HH who underwent computed tomography (CT) and/or magnetic resonance imaging (MRI) of the abdomen. HH can develop in a broad range of age groups, but 60–80% of patients with HH are 30–50 years old; women were found to be more susceptible to HH than men, with a female-to-male ratio of 1.2–6.1. The etiology of HH has not been fully explored, but it could be related to vascular malformation caused by excessive development or abnormal differentiation of blood vessels during embryonic development. Previous studies have suggested that sex hormones may contribute to vascular endothelial cells’ proliferation, migration, and formation of capillary-like structures. For instance, pregnancy and oral contraceptives can increase the levels of estrogen and progesterone in the body, leading to the growth of hemangiomas. This may possibly explain the high incidence of HH in women. Winkfield et al. demonstrated that tumors grew during pregnancy and found that estrogen levels partly regulate tumor growth. Glinkova et al. pointed out that HH could be influenced by both endogenous and exogenous sex hormones, although significant enlargement could occur only in a minority of patients. No study has yet confirmed the presence of estrogen receptors in hemangiomas, and tumor growth has been demonstrated in patients undergoing estrogen-free treatment and postmenopausal women.

As early as 1997, Yakes reported that hemangiomas are venous malformations caused by developmental disorders of the undifferentiated capillary network at the embryonic stage. He based his conclusion on the new classification of hemangiomas and vascular malformations by Mulliken et al. and studies on various types of vascular malformations caused by vascular embryogenesis, evolution, and development disorders at various stages. In 2004, Ouyang et al. further pointed out that hemangioma is a mass of venous malformations formed during the embryonic stage when multiple small branches of the yolk sac vein evolve into a larger lumen (5–30 μm), presenting irregular, thin luminal walls encircled by a single layer of endothelial cells that covered the sinusoidal capillaries (namely sinusoidal gaps or blood sinusoids). In brief, hemangioma is the result of a disorder in the embryonic development of the blood sinusoids connecting the hepatic artery, portal vein, and hepatic vein. When observed microscopically, the HH tumor is composed of multiple thin- and thick-walled abnormal blood sinuses of varying sizes. The luminal wall is lined with a single layer of endothelial cells, and no abnormal proliferation of endothelial cells is observed. No normal hepatocytes, Kupffer cells, or vascular or bile duct components are detected inside the tumor, while dysmorphic tumor cells or peritumoral fibrous capsules are noted. The above-mentioned histopathological findings also fully support the theory that “HH originates from an embryonic developmental disorder of the hepatic blood sinusoids” and is a vascular malformation as opposed to a tumor. As for hyaline changes, thrombosis, necrosis, liquefaction, fibrosis, calcification, and rarely, intratumoral hemorrhage can be observed in some giant HH tumors; these are secondary or concurrent pathological changes in HH, even though a fibrous tissue may eventually replace an HH tumor.

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https://doi.org/10.1016/j.jimed.2021.12.009
Received 3 November 2021; Received in revised form 23 December 2021; Accepted 29 December 2021

2096-3602/© 2022 Shanghai Journal of Interventional Radiology Press. Publishing services by Elsevier B.V. on behalf of KeAi Communications Co. Ltd.
The rate of premature portal vein thrombosis in arterial phase images in HH patients using iodine contrast for hepatic arterial evaluation by digital subtraction angiography (DSA) was 73%. On the other hand, the rate of tran- sient hepatic parenchymal enhancement (THPE) on arterial phase images was 23.5–29.7% in patients with HH (up to 89% in high-flow HH), which was higher than the rate (19%) of THPE on arterial phase images captured by dynamic contrast-enhanced MRI (up to 41% in high-flow HH). This finding not only disproves the previous misconception that "only malignant tumors of the liver are associated with hepatic artery-portal vein shunts" but also provides important evidence for the classification of HH as a vascular malformation.

2. Clinical symptoms

HHs are mainly asymptomatic and require no treatment; although, follow-up is essential. However, multiple large HHs can present with symptoms such as abdominal pain, nausea, vomiting, and loss of appetite, indicating the necessity of treatment. The spontaneous or traumatic rupture of HHs is rare and typically results in acute abdominal pain and hemorrhagic shock; however, once rupture occurs, the mortality rate becomes considerably high (36–39%). Compared with spontaneous or traumatic rupture of HH, the incidence of intratumoral hemorrhage is even lower, associated with atypical clinical symptoms, and only 9 cases have been reported worldwide. Kasabach-Merritt syndrome, also known as hemangioma thrombocytopenia syndrome, is an infre- quent hemangioma-related complication, characterized by excessive blood cell depletion, leading to platelet drop, coagulation dysfunction, and hemorrhagic purpura that seriously threatens patients’ lives and requires immediate treatment. The de- finition of giant hepatic hemangioma is still not unified; Chinese scholars mainly defined a giant hemangioma as a hemangioma with a diameter of ≥10 cm, while non-Chinese scholars have typically classified a large hemangioma as one with a diameter of >4 cm.

The accuracy of ultrasound, CT, and MRI examinations for diagnosing HHs was reported to be as high as 61%, 77%, and 92%, respectively. However, a more careful diagnosis may be required in case of a history of hepatitis B virus infection or cirrhosis. Additionally, atypical hemangio- ma should be differentiated from blood-rich hepatocellular carcinoma and liver metastases.

3. Indications for the treatment of HH

HH treatment should strictly follow the treatment indications and observe the principle of delivering the most significant therapeutic effect with the least trauma to patients. The treatment indications are as follows:

1. The appearance of associated clinical symptoms or serious complica- tions, such as abdominal pain, abdominal distension, dyspepsia, ruptured bleeding, and Kasabach-Merritt syndrome.
2. Progressive enlargement of hepatic hemangioma. The current view is that an annual growth rate >2 cm in diameter represents rapid growth. If the initially detected tumor is already large, there may be a risk of complications with various symptoms, and the treatment is recommended as appropriate.
3. HH cannot be definitively diagnosed, and it is generally difficult to di- agnose hemangioma by combining one or more imaging modalities. However, atypical tumors may present in some imaging modalities, especially in patients with viral hepatitis, cirrhosis, liver cancer, or other malignancies that may be treated effectively.
4. Severe anxiety and other psychiatric symptoms caused by hepatic hemangioma, including in patients with HH receiving treatment, as well as patients requiring treatment because of anxiety or other adverse psychological conditions due to fear of tumor growth, malignant transformation, or rupture. However, psychological factors could be an indication for the treatment of HH has not yet been comprehensively clarified. The main reason is that the assessment of psychological factors is complex, and some concerns may be resolved by a simple explanation, while serious ones may lead to malignant consequences. It has been shown that only some patients who were treated for psychological factors had psycho- logical symptoms that could be resolved postoperatively, and some pa- tients experienced a relapse of anxiety symptoms after postoperative remission that may put patients at significant surgical risk. Thus, psychological anxiety is generally not advocated as an indication for surgical treatment of HH. In necessary cases, the assessment of psycho- logical factors must be very cautious and rigorous. We strongly advise patients to consult a psychiatrist before making a comprehensive judg- ment. Discretionary treatment is recommended for patients with anxiety, with a clear causal relationship and more severe symptoms.

4. Interventional treatment of HHs

Surgical and interventional therapies for HHs have the highest dominance; however, both have advantages and disadvantages. Although surgery is considered the most appropriate option for some HHs, treating multiple and/or massive HHs remains a major clinical challenge. Due to recent advances in minimally invasive interventional techniques, surgery is no longer the preferred treatment for multiple or extensive lesions. Interventional treatment, including transarterial embolization, ablation, percutaneous sclerotherapy, and percutaneous argon-helium cryotherapy, has gradually developed as an alternative approach to surgical resection for treating hepatic tumors. Transcatheter arterial embolization, which was proposed by Yamada in 1977, has been applied clinically for more than 40 years. With the improvement in interventional devices and the application of super-selective techniques, transcatheter arterial embolization has become the main treatment method for HH because of its advantages of being minimally invasive, less painful, reproducible, and highly efficient.

The rationale is that the combination of a chemotherapy drug and lipiodol superimposes the inhibitory effect on the proliferation of the vascular endothelial cells by the chemotherapy drug with the selective characteristics of lipiodol in the blood vessels, so that the chemotherapy drug forms highly concentrated aggregates and is slowly released in HH, thereby facilitating its inhibitory effect and achieving the destruction of hepatic sinusoidal lumen, causing fibrosis and gradual tumor shrinkage.

However, we noticed that some patients with HH have different interventional outcomes and complications in clinical practice. This may be related to the type of blood supply to hemangiomas. Therefore, phy- sicians should pay more attention to the type of blood supply to hem- angiommas than the tumor size when developing treatment plans. The current criteria defined by Ouyang et al. and Zeng et al. are as follows:

1. Rich blood supply: mild-to-moderate thickening of the arteries, associated with abnormal blood sinusoids in the arterial phase and dilatation of the majority of sinusoidal blood-filled spaces in the parenchymal phase; moderate blood supply: mild thickening of the arteries, abnormal blood sinusoids in the arterial phase, and dilatation of some sinusoidal blood-filled spaces in the parenchymal phase; and lack of blood supply: no thickening of the arteries, few abnormalities in blood-filled...
sinuses can be observed in the arterial phase, as well as paranasal sinus tumors in the parenchymal phase; (4) portal vein: no abnormal blood-filled sinuses can be found in the arterial and parenchymal phases, and direct or indirect portal venograms show abnormal blood-filled sinuses.

The type of blood supply of HH has the following influences on interventional treatment and prognosis: (1) The effects of the type of blood supply on the treatment efficacy. Jia et al.\(^{39}\) reported that the rates of effectiveness (18.8%, 8.7% and 0, respectively) and safety (35.2%, 21.2% and 0, respectively) of the rich blood supply of HH were significantly higher than those of the other two types (moderate and lack of blood supply) within 3 months after surgery, while the inefficacy (46.1%, 76.2%, 100%, respectively) rate was marked lower than that of the other two types, indicating that the short-term efficacy of hepatic artery embolization of HH (for rich blood supply) is optimal. In contrast, a poor prognosis of HH is associated with a deficient blood supply, and the dosage of drugs used to treat HH is significantly less than that of the other two types; thus, the clinical efficacy is significantly lower than that of the other two types. (2) The influence of the type of blood supply on complications, such as a noticeable reduction in liver function, liver abscess, and biliary tract injury, is also greatly correlated with the type of blood supply (the incidence of severe complications in these three types was 5.4%, 5.7%, and 18.9%, respectively), mainly due to the use of chemotherapy drugs and accidental embolization of the blood supply to the biliary ductal system. Chemotherapy drugs such as anticancer drugs destroy vascular endothelial cells and inhibit cell regeneration causing fibrosis in tissues, resulting in degeneration of corneal endothelial cells and necrosis, followed by thrombus formation, leading to vascular occlusion.\(^{37,42}\) Anatomically, the blood supply of the bile ducts originates from the hepatic artery; blood is transmitted to the bile duct via branches of the hepatic artery, forming a peribiliary vascular plexus with the bile duct as the axis, converging from the output venous branches into the accompanying portal vein or directly into the hepatic sinusoids. Because the blood supply of the intrahepatic bile duct is relatively homogeneous, receiving only the nutritional blood supply from the hepatic artery may lead to ectopic embolization.\(^{43}\) Lipiodol mixed with chemotherapy drugs has long been used in the interventional treatment of HH, as HHs are rich in blood supply and have a more pronounced “siphoning” effect on lipiodol.\(^{42,44}\) However, the “siphoning” effect of poor blood supply is insignificant because blood vessels are not notably thickened, and the blood supply is weak. Therefore, even if the microcatheter in super-selective angiography is used to reach the tumor’s arterial supply, lipiodol mixed with chemotherapy drugs may partly cause ectopic embolization of the vessels. As mentioned above, the efficacy and complications of hepatic hemangioma after interventional surgery vary according to the type of hemangioma, but there is no research report on whether the endpoint of intraoperative embolization is related to the type of blood supply. The endpoints of embolization reported in the literature were based on the apparent slowdown of intravascular blood flow or the stagnation of intravascular contrast medium after embolization. Whether different blood supply types of HHs should adopt the same standard for the endpoint of embolization and whether it will have an impact on the prognosis still needs further research.

Ablation treatment of hepatic hemangioma has been used throughout the 21st century. It is a promising treatment approach for symptomatic giant hepatic hemangioma when surgery is not feasible or is declined by the patient. The main ablation techniques are radiofrequency ablation and microwave ablation.\(^{35}\) Radiofrequency ablation involves placing a radiofrequency needle electrode into the focus of the hemangioma, converting the ions of the surrounding tissue into heat through radiofrequency current, locally generating high temperature, and carbonizing and necrotizing the surrounding tumor tissue. Zou et al.\(^{46}\) retrospectively analyzed 121 patients with subcapsular HHs treated with radiofrequency ablation and showed that ablation was successful in all patients; 95.2% of the hemangiomas were completely ablated with a complication rate of 21.5%. Complications included bleeding at the electrode entry site, rupture and bleeding of hemangioma, abscess formation, and puncture injuries of adjacent organs, such as gastrointestinal perforation, hemoysis, and bile duct damage. Microwave ablation uses a tiny catheter built into the ablation electrode for the water cycle to decrease the temperature of the electrode tips and prevent local coagulation and necrosis. It has the advantages of high thermal efficiency, strong ability to coagulate blood vessels, short treatment time, and good heat conduction. Xiao et al.\(^{47}\) reported that after microwave ablation of 191 lesions in 120 cases, the total remission rate was 96.3% (184/191), and the average diameter of hemangioma decreased by 67.8% (50.2% ~ 85.4%). The curative effect is significant when multiple hemangiomas in the liver cannot be treated entirely by surgery. For example, in cases where the blood supply of hepatic hemangioma is rich, when combined with transarterial embolization, it can reduce the blood flow in the treatment focus area, reduce the heat loss, and shorten the ablation time.\(^{46}\) Radiofrequency therapy’s timely effectiveness, minimal invasiveness, and safety have been clinically recognized; however, further research is required to establish its long-term efficacy.

Percutaneous sclerotherapy involves percutaneous puncture of the lesion and injection of drugs under the guidance of imaging equipment. Pingyangmycin, anhydrous alcohol, and sodium morrhuate are commonly used. A previous study\(^{39}\) reported that percutaneous sclerotherapy combined with arterial embolization could positively affect ischemic hemangiomas. Percutaneous argon-helium cryotherapy employs freezing technology to generate a percutaneous puncture; the formation of ice crystals in cells and necrosis can lead to degeneration of proteins in cells and cell membranes, blood stasis, and local ischemia. Argon-helium knife cryotherapy for the treatment of hemangioma has been reported,\(^{50}\) but it is rarely used in clinical practice because its long-term effect is not satisfactory.

5. Conclusions

As a benign lesion with slow growth, no malignant tendency, and an extremely low incidence of serious complications, HH generally does not require treatment. However, provided it meets the treatment indications, physicians should pay further attention to the relationship between the type of blood supply of an HH tumor and its prognosis when choosing an interventional treatment. Numerous studies have reported that the arterial supply of HH entirely originates from the hepatic artery, and it is not related to the portal vein.\(^{37,51,52}\) This is the theoretical basis for hepatic arterial embolization for the treatment of HH. However, Yu et al.\(^{53}\) reported that the portal vein exclusively supplies hemangiomas; thus, conventional hepatic arterial embolization is undoubtedly inappropriate. Furthermore, Jia et al.\(^{38}\) demonstrated that the type of blood supply affects the therapeutic efficacy and postoperative complications. Therefore, if the type of blood supply can be identified by preoperative imaging, it can be targeted during clinical consultations. In case of poor blood supply, due to the poor efficacy of conventional interventions and the higher occurrence of complications than with the other two types, while appropriately lowering patients’ expectations preoperatively, we can alternatively choose other modalities, such as conventional hepatic arterial embolization. Alternatively, the iodine-oil-deficient area can be punctured, followed by injection of an emulsion of lipiodol and chemotherapy drug mixed with polyglactin. In addition, radiofrequency ablation can also be utilized in combination therapy to improve therapeutic efficacy.

However, no broadly accepted criteria for the classification of blood supply exist, and the categorization is based mainly on DSA. Further non-invasive imaging tests may assist clinicians in classifying the blood supply of HH to increase therapeutic efficacy.

Declaration of competing interest

The authors declare no conflict of interest.
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