

## Peer Review File

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### Review Comments

**The authors described a case report of spontaneous subacute intratumoral hemorrhage of hepatic hemangioma treated with TAE.**

#### Major points:

**1. What do you think about the necessity of the 2nd TACE? And the kind of embolus material should be described.**

**Reply 1:** Thank you very much for your careful review and meaningful question. First of all, for the first treatment of this patient, the "Multidisciplinary expert consultations on the diagnosis and treatment of medical ethics (2019 Edition)" published by the "Professional Committee of Hepatic Hemangioma, Chinese Branch of International Hepatobiliary Pancreatic Association" [1] recommended that patients with hepatic hemangiomas with severe complications that may have fatal consequences, such as spontaneous or traumatic rupture and Kasabach-Merritt syndrome, are the absolute indications for the treatment of hemangiomas. The diagnosis of spontaneous intratumoral hemorrhage in this patient was clear, and the associated symptoms of fever and anemia were the indications for treatment. We had a multi-disciplinary treatment (MDT) discussion. Considering that the patient refused surgical resection, transcatheter arterial embolization (TAE) has been used clinically for more than 40 years. Because of its advantages of small trauma, little pain, good repeatability and high efficiency, TAE has become one of the main treatment methods for hepatic hemangioma [2-3]. Finally, we performed the first TAE for this patient.

At the follow-up after 3 months, the tumor body of hepatic hemangioma was 13.4cm x 11.6cm reduced to 8.7cm x 5.6cm. As for whether the patient should be treated again and the choice of treatment method, we conducted MDT discussion and solicited the patient's opinions, and finally implemented the second TAE treatment for them, mainly based on the following reasons:

1) At present, the tumor size is still relatively large (8.7cm x 5.6cm). Although the size of the lesion does not seem to be the standard for hepatic hemangiomas to receive intervention, a large retrospective study pointed out that giant hemangiomas ( $\geq 4$ cm) are more likely to have symptoms and higher risk of rupture and bleeding [4]. Considering that the patient has a history of spontaneous intratumoral hemorrhage of hepatic hemangiomas, it is necessary to re-treat the patient. 2) TAE treatment has less trauma and faster recovery. In recent years, a large number of literatures have also reported that interventional therapy is considered as the first choice for the treatment of multiple or giant hepatic hemangiomas [5-6]. In addition, the patient had no special discomfort and obvious complications after the first TAE treatment, and recovered rapidly. Therefore, the patient also hopes to receive TAE treatment again. 3) Embolization was not complete during the first TAE because the tumor was large (13.4 cm x 11.6cm) before the first TAE, considering that too much embolization would lead to liver failure, only part of the blood supply vessels of the tumor were embolized. The remaining vessels can be further embolized during the second TAE. 4) There is little experience in the treatment of intratumoral hemorrhage in hepatic hemangioma. From 1993 to 2021, only 9 cases of intratumoral hemorrhage were reported. Therefore, the experience that can be used for reference is still limited as to which treatment method is better. 5) After the implementation of the second TAE, we asked the patients to follow up regularly. If fever, abdominal pain and other symptoms occur again or hemangioma increases again during the follow-up, she needed to be hospitalized again. After nearly 4 years of follow-up, the hemangioma of the patient has been relatively stable (5.7cm x 5.4cm), and there were no related symptoms, so she was not treated again and were in the process of regular follow-up.

**1. And the kind of embolus material should be described.**

**Reply 1:** We are much appreciated for your advice. Your suggestion will improve our manuscript. We have modified the original manuscript and added the embolic materials used in the operation in the revised manuscript with track (see Page 5, line 15-18).

**Changes in the text :** *we considered another TAE in order to further reduce the size of the lesion and relieve patient's anxiety. During the second TAE, 6 ml of pingyangmycin-lipiodol emulsion and gelatin sponge particles were injected into the feeding artery branch of the hepatic hemangioma until the tumor staining basically disappeared.*

[Reference]

【1】 Professional Committee of Hepatic Hemangioma, Chinese Branch of International Hepatobiliary Pancreatic Association. Multidisciplinary expert consensus on the diagnosis and treatment of hepatic hemangioma (2019 edition). Chinese Journal of Digestive Surgery 2019;18(8):705-710. doi: 10.3760/cma.j.issn.1673-9752.2019.08.001.

【2】 Liu X, Yang Z, Tan H, et al. Long-term result of transcatheter arterial embolization for liver hemangioma. Medicine (Baltimore). 2017;96(49):e9029. doi: 10.1097/MD.00000000000009029.

【3】 Sun JH, Nie CH, Zhang YL, et al. Transcatheter Arterial Embolization Alone for Giant Hepatic Hemangioma. PLoS One. 2015;10(8):e0135158. doi: 10.1371/journal.pone.0135158.

【4】 Mocchegiani F, Vincenzi P, Coletta M, et al. Prevalence and clinical outcome of hepatic haemangioma with specific reference to the risk of rupture: A large retrospective cross-sectional study. Dig Liver Dis. 2016;48(3):309-14. doi: 10.1016/j.dld.2015.09.016.

【5】 Dong W, Qiu B, Xu H, et al. Invasive management of symptomatic hepatic hemangioma. Eur J Gastroenterol Hepatol. 2019;31(9):1079-1084. doi: 10.1097/MEG.0000000000001413.

【6】 Li Y, Jia Y, Li S, et al. Transarterial Chemoembolization of Giant Liver Haemangioma: A Multi-center Study with 836 Cases. Cell Biochem Biophys. 2015;73(2):469-472. doi: 10.1007/s12013-015-0680-y.

**2. While the author described “pingyangmycin-lipiodol emulsion” at line 3, in page 5, the authors described “coil embolization” at line 21, in page 6. Which is correct?**

**Reply 2:** Thank you very much for your patient reviewing of our manuscript. At line 3, in page 5, "Pingyangmycin lipiodol emulsion" is the embolic material used by the 54-year-old female patient to receive TACE treatment reported in this paper, which is "Pingyangmycin lipiodol emulsion"; "Coil embolization" at line 21, in page 6 is a

description of the treatment process of another patient who was also misdiagnosed as "liver abscess" reported in reference [9] in the discussion section of this article. It may be that our statement is not clear enough, which may easily lead to confusion among readers. Therefore, the original text at page 6 has been modified. We have modified our text (see Page 6, line 25, and Page 7, line 1-3) in the revised manuscript with track.

**Changes in the text :** *Among the previously reported nine cases, three patients developed fever, of which one reported by Hao et al. (9) was also misdiagnosed as liver abscess. After giving antibiotics and blood transfusion to this patient, her fever and anemia did not improve.*

**Minor points:**

**1. The expression “but” is recommended to revise “and” at line 24, in Page 3, because hepatic hemangioma is a benign tumor.**

**Reply 1:** We are much appreciated for your advice. We have modified our text as advised (see Page 3, line 25) in the revised manuscript with track.

**Changes in the text:** *...and she received no medical treatment.*

**2. Although capital letters were used in the Figure 1 and E~H in figure legends of Figure 1, a, b, c, and d were described as small letters. Please correct these.**

**Reply 2:** We are very sorry for the writing mistakes. We have modified our text as advised (see Page 19, line 4-8) in the revised manuscript with track

**3. Table 1. is too complicated. For example, “image manifestations” are recommended to divide into each imaging modality.**

**Reply 3:** We are much appreciated for your advice. Your suggestion will improve our manuscript. We have modified Table 1 as advised (see Page 16-17) in the revised manuscript with track.