



Case report

Giant hepatic angiomyolipoma presenting with severe anemia: A surgical case report and review of literature

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ABSTRACT

Background: Angiomyolipoma (AML) is a solid benign neoplasm with mesenchymal features. The clinical signs and symptoms of hepatic angiomyolipoma are nonspecific, and treatment strategy is variable.

Presentation: A 35-years-old male patient has admitted to the hospital with symptoms of severe anemia. Abdominal multi-slice computed tomography (MSCT) and Gadoteric acid (GA)-enhanced magnetic resonance imaging (MRI) revealed a heterogeneous 23 × 17 cm-in-sized tumor with heterogeneous enhancement and increased angiogenesis. Percutaneous hepatic biopsy was proceeded and in immunohistochemistry, tumor cells responded positively to the HMB-45, SMA, and Glutamine stains, the CD-34 stain was positive for blood vessels as well as Ki-67 sporadically positive, but the Heppar1, S-100, CK stains reacted negative. The final pathologic result was consistent with the primary hepatic angiomyolipoma. The final surgical management was extended right hepatectomy with ligation of the right hepatic artery (RHA) and vein (RHV), as well as the middle hepatic vein (MHV), one month after portal embolization as well as to enlarge the remnant liver volume.

Discussion: A hepatic angiomyolipoma (HAML) primary origin is relatively rare, the clinical manifestations are variable and non-specific. Histological examination and immunohistochemistry staining are considered as the gold standard for HAML diagnosis. HAML are commonly expressed benign behaviors, but HAML cases with malignant behaviors were reported in a cumulative incidence. Radical surgery must be still the most effective and major treatment approach.

Conclusion: The present case being the first case with initial syndrome of severe anemia accounted in the English literature. Giant angiomyolipoma is composed of blood vessels and could lead to extensive internal tumoral hemorrhage. We here present a report of this case with had primary hepatic angiomyolipoma with clinical picture of severe anemia.

1. Introduction

Angiomyolipoma (AML) is a solid neoplasm with mesenchymal features within group of perivascular epithelioid cell tumors, or **PEComa** [1]. AML included typical components: blood vessels, smooth-muscle and adipose cells [2]. Angiomyolipoma was found mainly in the kidney, and Primary Hepatic Angiomyolipoma (HAML) was rare original site, with about 600 cases were reported in English literature up to 2017 [2]. The specific etiology and pathogenesis of AML, and HAML

particularly, remain unknown [3,4]. But there are several risk factors and related disorders that have been associated with its development, including tuberous sclerosis complex (TSC), which was associated with more than 50% of the AML in the kidney and 5%–15% of HAML [3]. AML, and HAML particularly, are mainly benign, although some malignant cases were reported, with some invasive characteristics of liver parenchyma and the vessels as well as distant metastasis [5]. The clinical signs and symptoms of HAML are nonspecific, with the main symptoms are abdominal discomfort or palpation of an abdominal mass [4,6]. Anemia was rarely reported in HAML cases, but due to composed of

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Abbreviations

AE	Arterial embolization
AFP	Alpha-fetoprotein
AFP-L3	An isoform of Alpha-fetoprotein
AML	Angiomyolipoma
CT	Computed tomography
EGD	Esophagogastroduodenoscopy
GI	Gastrointestinal
HBM45	Human Melanoma Black 45
LT	Liver transplantation
PEComa	perivascular epithelioid cell tumors
PIVKA-II	Prothrombin induced by vitamin K absence-II
RFA	Radiofrequency ablation
SMA	Smooth muscle actin
TSC	tuberous sclerosis complex

blood vessels, so that, in case of tumor with giant size, symptoms related to severe anemia could be initially presented and became the main complaint led the patient admitted to the hospital.

So that, we herein present a report of this case presented initially with severe anemia secondary to internal tumoral hemorrhage is consistent with the presence a giant hepatic angiomyolipoma. All our work has been reported in line with the SCARE criteria and guidelines [7].

2. Case presentation

A 35-years-old male patient has admitted to the hospital with symptoms of severe anemia (fatigue, weakness and dizziness). The patient had a medical history of accidental discovery of a liver tumor 2 months ago in another hospital, but there was no clear diagnosis and no treatment. The results of ultrasound showed that the right liver had a giant fluid-like tumor measuring 23×17 cm, with much increased angiogenesis. In the abdominal multi-slice computed tomography (MSCT) and Gadoxetic acid (GA)-enhanced magnetic resonance imaging (MRI), the tumor had heterogeneous density, including fluid and fat density (25 Hounsfield-HU) with natural hyperattenuating part, and after injection, the mass was strongly enhanced with heterogeneous enhancement, increased angiogenesis, and had dilated vascular branches in a cystic structure (Fig. 1). Hematological investigations showed severe anemia with a red blood cell count of 1.3 T/l (normal value from 3.76 to 5.9 T/l), as well as the AFP/AFP-L3/PIVKA-II levels were in normal range, respectively (Table 1). The Esophagogastroduodenoscopy (EGD) showed an ulcer of the duodenal bulb measuring 0.8 cm, but there were no signs of bleeding from the ulcer. An inter-department consultation of Gastroenterology - Radiology - Surgery - Pathology - Hematology was held to discuss and agree on diagnostic biopsy intervention. The patient had a percutaneous hepatic biopsy of the liver tumor at the Department of Gastroenterology. The histopathological result was tumor cells with large nuclear intermingle with adipose cells, and in immunohistochemistry, tumor cells responded positively to the HMB-45, SMA, and Glutamine stains, the CD-34 stain was positive for blood vessels as well as Ki-67 sporadically positive, but the Heppar1, S-100, CK stains reacted negative (Fig. 2). The final

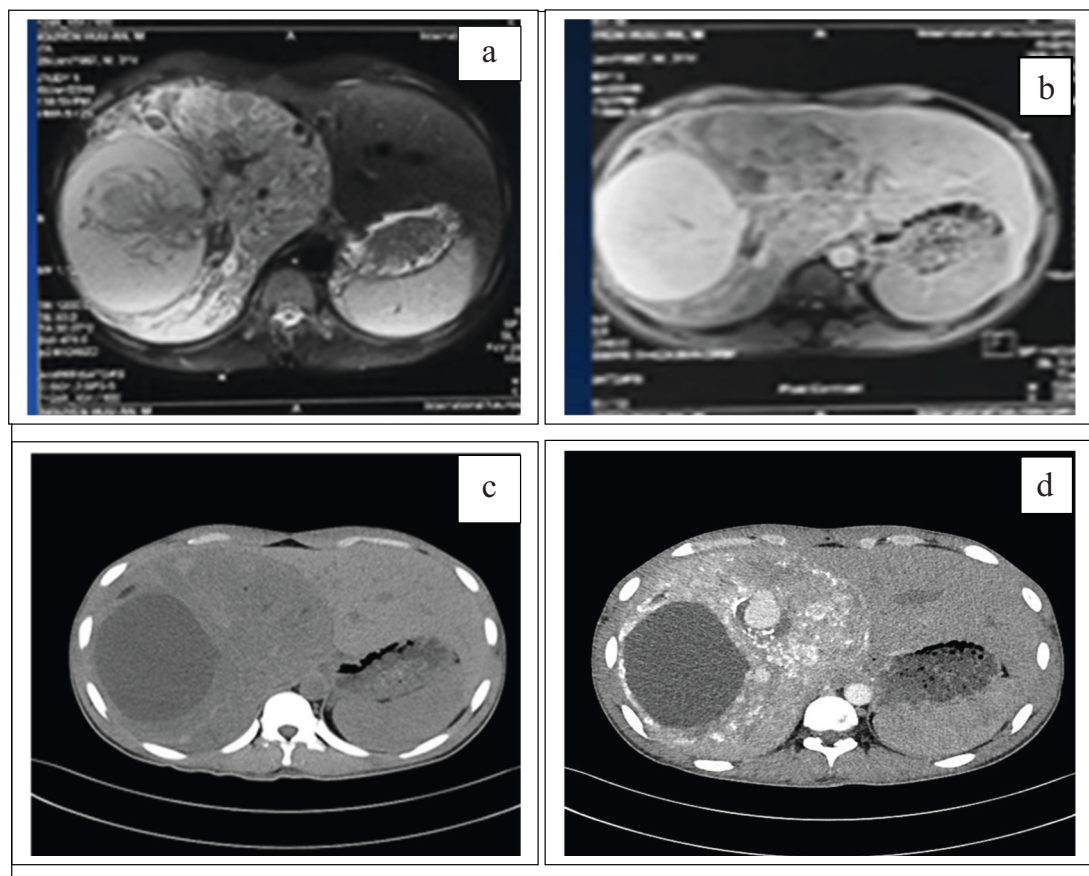


Fig. 1. (a) (b) GA-MRI showed a giant well-defined tumor, hypointense on T1-weighted and hyperintense on T2-weighted images and inhomogeneous enhanced in Contrast-enhanced MRI that occupy the entire right liver. (c) (d) The MSCT showed a giant tumor in the entire right liver with heterogeneous density with natural hyperattenuating part, and strongly heterogeneous enhancement after injection, increased angiogenesis, and had dilated vascular branches in a cystic structure.

Table 1

Laboratory data on admission.

	Value	Reference range
Peripheral blood		
Red blood cells	1.39	$4.5\text{--}5.9 \times 10^{12}/\text{L}$
Hemoglobin	26	135–175 g/L
Plateletes	209	$150\text{--}400 \times 10^9/\text{L}$
Serum		
Creatinin	46	72–127 $\mu\text{mol}/\text{L}$
Blood urea nitrogen	3.8	3.2–7.4 mmol/L
Total bilirubin	18.2	$\leq 17 \text{ Umol}/\text{L}$
AST	713	$\leq 37 \text{ U}/\text{L}$
ALT	645	$\leq 41 \text{ U}/\text{L}$
HBsAg	Negative	
Anti-HCV	Negative	
Anti-HIV	Negative	
AFP	0.8	$< 20 \text{ ng}/\text{mL}$
AFP-L3	< 5	$< 5\%$
PIVKA-II	20	$< 40 \text{ AU}/\text{L}$

Abbreviations: AST, aspartate aminotransferase; ALT, alanine transaminases; AFP, Alpha-fetoprotein; AFP-L3, An isoform of Alpha-fetoprotein; PIVKA-II, Prothrombin induced by vitamin K absence-II; HBsAg, Hepatitis B surface antigen; HCV, Hepatitis C virus.

pathologic result was consistent with the primary hepatic

angiomyolipoma. Because the tumor is too large that occupy the entire right liver, so the plan of intervention to portal embolization as well as to enlarge the remnant liver volume before surgical removal of the liver tumor was indicated. The patient had undergone selective embolization of the right gastric artery (RGA) and right hepatic artery (RHA) with lipiodol and absolute alcohol at the Department of Radiology (Fig. 3).

One month after the hepatic vascular embolization, the doctors have carefully calculated the volume of the liver along with the cooperation to plan blood products for serve the surgery. Giant liver tumor resection was planned. Intraoperatively, the whole right liver was a giant tumor of $25 \times 20 \times 15 \text{ cm}$ in size, spreading to Subsegment IV-b according to Couinaud's classification [8], the tumor's posterior surface is firmly attached to the inferior vena cava (IVC), right adrenal gland (RAG), diaphragm, many vessels proliferate into the tumor from the RAG. The final surgical management was extended right hepatectomy with ligation of the right hepatic artery (RHA) and vein (RHV), as well as the middle hepatic vein (MHV). The patient had undergone an 8-h surgery to remove a 5-kg liver tumor with dimensions of $25 \times 20 \times 15 \text{ cm}$ (Fig. 3). After surgery, the patient recovered quickly, after 8 days, the patient was discharged in a clinical condition with no fever, no abdominal pain.

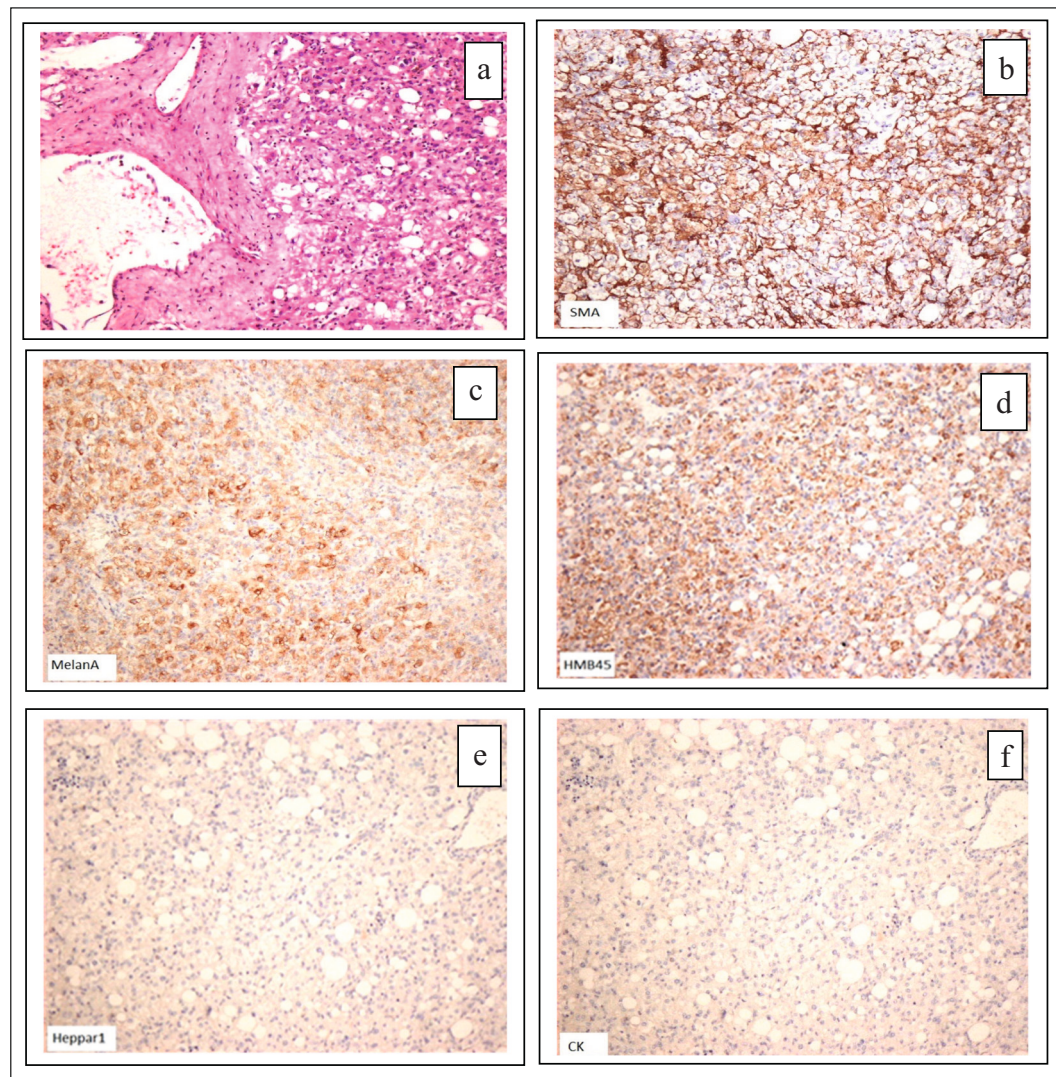


Fig. 2. (a) The HE staining result showed mature fat, blood vessels, and epithelioid-spindle cells. Immunohistochemical staining, with positivity for SMA (b), MelanA (c) and HMB 45 (d), but negativity for Heppar-1 (e) and CK (f).

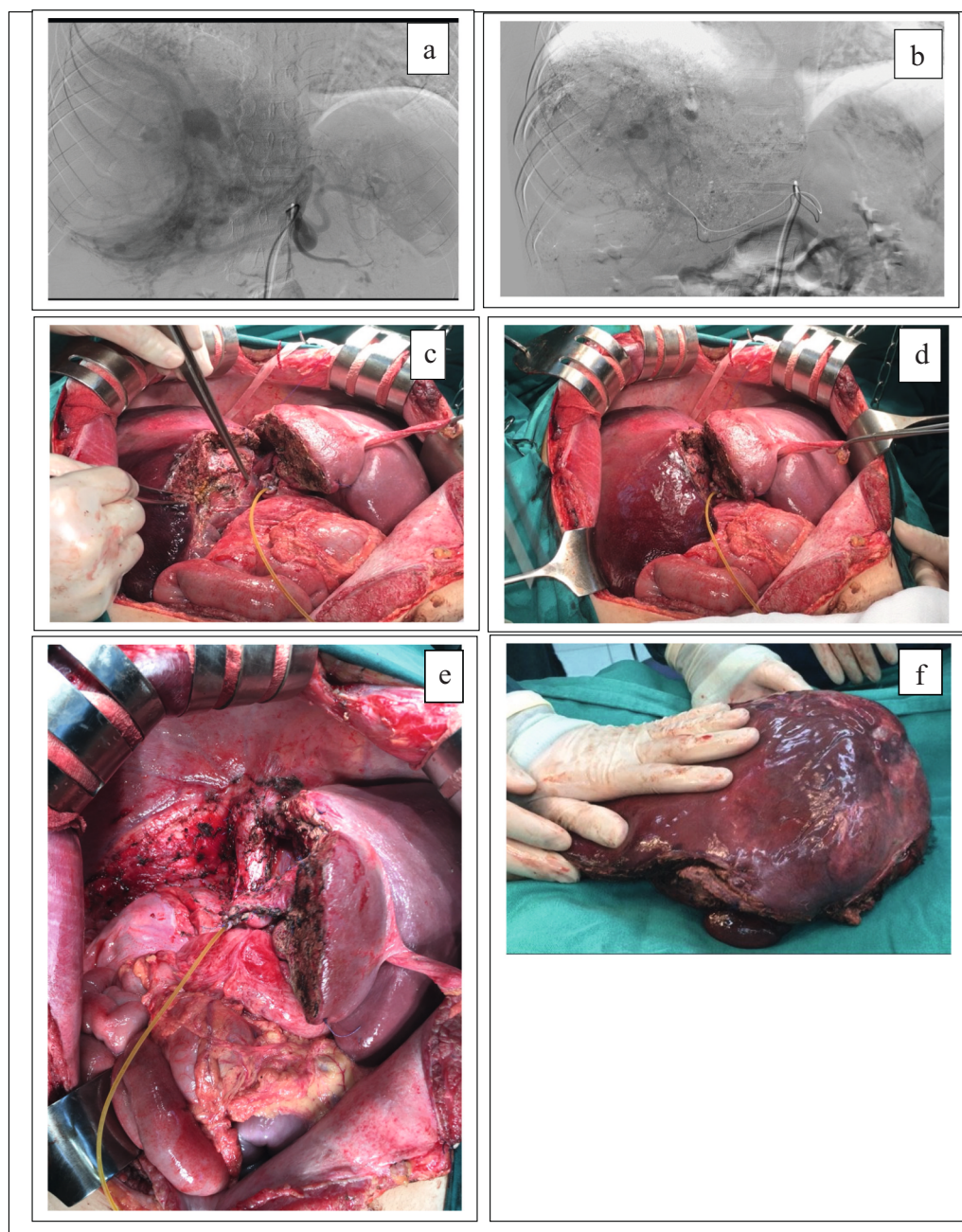


Fig. 3. (a) The right liver has a vascular tumor, which is supplied with blood from the right hepatic artery and right gastric artery. (b) Selective embolization of the right gastric artery and the hepatic artery with 15 ml of Lipiodol and absolute alcohol suspension. (c) (d) the tumor's posterior surface is firmly attached to the inferior vena cava (IVC), right adrenal gland (RAG), diaphragm, many vessels proliferate into the tumor from the RAG. (e) (f) extended right hepatectomy with ligation of the right hepatic artery and vein, as well as the middle hepatic vein (MHV) was proceeded and a 5-kg tumor with dimensions of $25 \times 20 \times 15$ cm was removed.

3. Discussion

Angiomyolipoma develops mostly in the kidney, which had an occasional association with tuberous sclerosis complex (TSC) [9,10]. A hepatic angiomyolipoma primary origin is relatively rare, with about 600 cases have been reported in the English literature, and about 5 to 15% HAML cases had associated with TSC [2,3]. In aspect of patient characteristics, HAML typically occurred in a non-cirrhotic liver, with dominance in middle-aged women [1]. In location, 60% of HAML cases locate in the right liver, which median size ranges from 2 cm to 12.7 cm and 84% cases are solitary liver tumor [2,9,11]. The clinical manifestations of hepatic angiomyolipoma are variable and non-specific. Several studies showed that 42% to 72% of HAML cases were asymptomatic [2,6,9]. In symptomatic cases, abdominal pain or discomfort is the most common manifestation, and other symptoms include abdominal bloating, weight loss and rarely palpation of abdominal mass [6].

Though majority of the cases reported with a mild or moderate clinical presentation so far, ours was discovered with initial syndrome of severe anemia secondary to internal tumoral hemorrhage is consistent with the presence a giant hepatic angiomyolipoma, with the present case being the first accounted in the English literature.

Abdominal ultrasound is initial and simple examination for diagnosing hepatic masses, which is well circumscribed and homogenous because contains many fatty components with rapid enhancement in the arterial phase of ultrasound contrast and distinguish from hemangiomas with a posterior echogenic image [12]. Endoscopic ultrasound guided fine-needle aspiration (EUS-FNA) was rarely used in selective case for diagnosing, due to component of blood vessels could led to internal tumoral hemorrhage or rupture [13]. In computed tomography (CT), the tumor was hypodense due to adipose component, hypervascular in richly vascularized HAML with wash-out in the portal and late portal phase, or persistent portal and late-phase enhancement in HAML with

few or no vessels [14]. In magnetic resonance imaging, especially Gadoxetic acid (GA)-enhanced magnetic resonance imaging (MRI), the typical HAML was high intensity on T1W and T2W sequences [12], and hypo-signal in the hepatobiliary phase after injection of hepatocyte specific agents such as gadoxetic acid [11].

Due to the challenge in diagnosis of hepatic angiomyolipoma with non-specific clinical characteristics and imaging features, so that histological examination and immunohistochemistry staining are considered as the gold standard for HAML diagnosis [15]. In our case, severe anemia was occurred before the patient's admission due to the giant size of the tumor and not related to percutaneous biopsy. And due to the unparticular imaging characteristics as well as the normal AFP level and no medical history of hepatitis, we think percutaneous hepatic biopsy of the liver tumor was necessary. In histological analysis, AML was classified in PEComa, which is defined as “mesenchymal tumors containing distinctive perivascular epithelioid cells” according to the World Health Organization (WHO) classification, and contained adipose tissue, smooth muscle and blood vessels [16]. HAML can be classified into four subtypes depend on the tissue components and type of dominant tissue [17]:

- Hybrid or mixed AML: the most common group, which contain similar proportions of each tissue components.
- Myomatous AML: smooth muscle cells are the dominant tissue component.
- Lipomatous AML: adipose tissue is the dominant tissue component.
- Vessels, or epithelioid AML: vessels with dystrophic walls are the dominant tissue component.

Recently, another subtype of HAML, which is named inflammatory HAML, has been reported, with over 50% of tumor area was inflammatory infiltration [18]. However, due to 15% of HAML cases were mimicking, immunohistochemistry staining is mandatory [9]. Typical HAML was positive reaction for stains of both melanocytic markers (Human Melanoma Black 45 or HMB45 and Melan-A) and smooth muscle markers (Smooth Muscle Actin – SMA and/or Desmin) [19,20]. HMB-45 stain is the most specific, with 91,5% positive HAML cases [4,21]. After HMB-45, Melan-A and a-SMA stains were the second common stains [22]. In our case, the strong positivity of HMB-45, SMA, Glutamine, CD-34 stains as well as negativity of Hepar-1, S-100, CK satins, and the morphology of the lesions allowed us to make the diagnosis of angiomyolipoma.

HAML are commonly expressed benign behaviors, but HAML cases with malignant behaviors were reported in a cumulative incidence of 4,1% [2]. There are no clear criteria to detect a case with aggressive behavior, but some characteristics such as tumor size over 10 cm, evidence of coagulative necrosis, cytological atypia and epithelioid subtype were believed “favor” risk factors [1,2,23]. In a systematic review, the mortality rate of HAML was 0,8% [2]. The best treatment option for hepatic angiomyolipoma remains controversial and need to be manage by a multidisciplinary team including radiologists, pathologists, surgeries and hepatologists. With asymptomatic HAML cases and no risk factors, monitoring with regular radiological could be applied. Radical surgery must be still the most effective and major treatment approach for all symptomatic or big-sized HAML, with over 75% of all cases [2,9]. The post-resection recurrence rate is 2,4% in all cases, but 10% in epithelioid subtype [2,24]. In unresectable case of HAML with excessive size or bilobar hepatic masses, liver transplantation (LT) could be considered the last resort treatment [25,26]. Otherwise, the alternative therapeutic options (arterial embolization – AE, radiofrequency ablation – RFA) could be choices in selective cases (AE for hemorrhagic cases and RFA with relatively small (<5 cm) tumors) [1,27]. In the present case, we performed extended right hepatectomy to radical resection, and a 5 kg liver tumor with dimensions of 25 × 20 × 15 cm was completely removed. Due to extra size of this tumor, regular radiological monitoring was recommended, and after 3-year follow-up, no signs of local

recurrence or distant metastasis were found.

4. Conclusion

To the best of our knowledge, the present patient is the first case report presented initially with severe anemia secondary to internal tumoral hemorrhage and consistent with the presence a giant hepatic angiomyolipoma in English literature. Imaging diagnoses are non-specific, with histology and immunohistochemistry analysis are gold standards. Our report emphasizes the difficulty of diagnosis and management for this rare type of hepatic neoplasms.

Ethical approval

Ethics approval of this study was given by the Research Ethics Committees of Bach Mai Hospital. Authors have agreed to submit it in its current form for consideration for publication in the Journal.

Consent for publication

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Guarantor

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Availability of data and materials

All data generated or analyzed during this study are included in this published article.

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CRediT authorship contribution statement

CLN conceived and edited the manuscript; HHN performed the operation; THL wrote the manuscript; NTN analyzed the data and followed up the patient; VKL provided imaging diagnosis and interventions as well as illustrated figures to the article; TKV and the other authors discussed the results together and contributed to the final manuscript. All authors read and approved the final manuscript.

Declaration of competing interest

The authors declare that there is no conflict of interest regarding the publication of this article.

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