[CASE REPORT]

Giant hepatic hemangioma causing prolonged fever and indicated for resection

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Abstract:

Hepatic hemangiomas are benign liver tumors, and most of them progress asymptotically. We report a case of hepatic hemangioma considered the cause of fever. A 53-year-old woman had a fever of 40°C for about 3 months without infection. Hepatic hemangiomas with internal bleeding of 10 cm in size on liver S8/7 and S3/2 were observed. These were resected laparoscopically for diagnostic treatment. She was afebrile after the operation. The pathological diagnosis was hematoma inside cavernous hemangioma. It should be noted that a bleeding hepatic hemangioma may cause fever of unknown origin and be indicated for resection.

Key words: giant hepatic cavernous hemangioma, fever of unknown origin (FUO), hepatectomy

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Introduction

Hepatic hemangiomas are common benign liver tumors, and most of them progress asymptotically (1, 2). These tumors are present in 0.4-20% of the general population (2). They are blood-filled cavities within the liver parenchyma lined by endothelial cells supplied by a branch of hepatic artery (3, 4). Hepatic hemangiomas are predominantly observed in females (5). They are diagnosed at all ages and the mean age of presentation is 30 to 50 years (2). The pathological development of hemangioma is suspected to relate to congenital factors, abnormal vasculogenesis, and hormonal factors (estrogen) (6). The definition of giant hemangioma in some studies is a size >4 cm but >5 cm or even >10 cm in others (2, 3, 7). The major complications of giant hemangioma are abdominal pain, nausea, vomiting, jaundice, and spontaneous or traumatic rupture (5). Fever of unknown origin (FUO) is not a typical symptom of hemangioma.

FUO is defined as fever $\geq 101^{\circ}\text{F}$ (38.3°C) for ≥ 3 weeks (8). Antibiotic treatment is often tried, and other common causes including infection, neoplastic/malignant, rheumatic/inflammatory, and miscellaneous disorders should be excluded. Schumacker *et al.* (9) in 1942 described he-

patic hemangioma presenting as FUO, and 1 of 66 surgically treated liver hemangioma patients had fever.

We report a case of hepatic hemangioma considered the cause of a prolonged fever. This study was conducted in accordance with the principles of the Declaration of Helsinki and the ethical guidelines of Tokyo Women's Medical University Hospital (Tokyo, Japan).

Case Report

A 53-year-old woman had a fever of 40°C (104°F) during an outpatient visit to our hospital due to follow-up for Sjögren syndrome. She was not on medication or hormonal therapy, and had no history of pill use. A 3 cm hemangioma in S5/8 of the liver was discovered 16 years prior, however, it was not followed up. The blood examination at visit to our hospital with fever showed total protein, 8.3 g/dL; albumin, 3.3 g/dL; total bilirubin, 0.9 mg/dL; aspartate aminotransferase (AST), 27 U/L; alanine aminotransferase (ALT), 20 U/L; alkaline phosphatase (ALP), 245 U/L; gamma-glutamyl transferase (GGT), 78 U/L; platelet count, $34.1 \times 10^4/\mu\text{L}$; and prothrombin time, 100%. Thus, liver functions were almost normal. Inflammatory markers including white blood cells (WBCs) 6,900/ μL and C reactive protein

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Figure 1. Abdominal CT findings. a) Plain CT, b), c) late phase of enhanced CT. Plain CT of the abdomen showed slightly high intensity inside the mass (a, circle). Hepatic masses of 10 cm in size in liver S8/7 (b) and S3/2 (c) with prolonged enhancement suggesting hepatic hemangiomas (arrows). Imaging examination revealed no other abnormalities. CT: computed tomography

Figure 2. Abdominal MRI and gadolinium scintigraphy findings. T1 weighted-enhanced images of the right lobe after a) 15 s and b) 180 s, and of the left lobe after c) 15 s and d) 180 s. T2 weighted-enhanced image of the left lobe. Masses in S8/7 (a, b) and S3/2 (c, d) were low intensity in T1 weighted-enhanced MRI, and revealed peripheral nodular enhancement after gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid administration. It consisted of a fine honeycomb-like septum inside hemangioma in S8/7. Hepatic bleeding was suspected inside the mass in S3/2 on a T2 weighted-enhanced image (e, arrow). Gadolinium scintigraphy showed slightly positive in the right lobe (f, arrow). MRI: magnetic resonance imaging

Figure 3. Clinical course of the patient. The patient received several antibiotics and antipyretics and her fever declined to $<38^{\circ}\text{C}$, but the symptoms recurred after treatment discontinuation (a). The fever continued for about 3 months. Both hemangiomas were resected laparoscopically. On day 4 after the operation, the fever decreased to 36°C , and was absent thereafter (b). The patient was discharged 7 days after the operation and was afebrile for 2 months. WBC: white blood cell, CRP: C-reactive protein, Hb: hemoglobin, CMZ: cefmetazole sodium, TAZ/PIPC: tazobactam/piperacillin, CFPM: cefepime dihydrochloride hydrate, CTRX+MNZ: ceftriaxone+metronidazole, MEPM: meropenem hydrate

(CRP) 29.24 mg/dL were increased. Des- γ carboxyprothrombin (DCP) was slightly elevated (72 mAU/mL), other tumor markers were not elevated. Plain computed tomography (CT) of the abdomen showed slightly high intensity inside the mass (Fig. 1a, circle). Abdominal contrast CT revealed hepatic masses 10 cm in size on liver S8/7 (Fig. 1b, arrow) and S3/2 (Fig. 1c, arrow) with pro-

longed enhancement suggesting hepatic hemangiomas. Imaging examination revealed no other abnormalities. Masses in S8/7 (Fig. 2a, b) and S3/2 (Fig. 2c, d) were seen as low-intensity masses by T1 weighted-enhanced magnetic resonance imaging (MRI) and revealed peripheral nodular enhancement after gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid (Gd-EOB-DTPA) administration. It con-

Figure 4. Laparoscopic findings of the liver a) left and b) right lobe. Laparoscopic findings of the liver showed hemangioma on the surface of the left lobe (a, S8/7) and (b, S3/2). Hepatic resection of both hemangiomas was performed. The figures on the right show the liver after hepatectomy (a, b).

sists of fine honeycomb-like septum inside of hemangioma in S8/7. Hepatic bleeding was suspected inside the mass in S3/2 on a T2 weighted-enhanced image after Gad-EOB-DTPA enhancement (Fig. 2e). Gadolinium scintigraphy showed slightly positive in the right lobe (Fig. 2f). All cultures were negative and no infections were found in blood, urine, or cerebrospinal fluid. There was no progression of dry mouth, dry eye, or salivary gland swelling and no exacerbation of Sjögren syndrome was evident. Fever was reduced to $<38^{\circ}\text{C}$ (100.4°F) by administration of antibacterial and antipyretics, and serum levels of CRP gradually decreased (Fig. 3a). However, the symptoms recurred after treatment discontinuation. The fever continued for about 3 months. Because hepatic hemangiomas and their bleeding were considered the cause of fever, these were resected laparoscopically for diagnostic treatment. Laparoscopic findings of the liver showed hemangiomas on the surface of the right (S8/7) (Fig. 4a) and left (S3/2) lobes (Fig. 4b). The cross-sections showed bleeding inside the S3/2 mass (Fig. 5b), but not in S8/7 mass (Fig. 5a). The pathological diagnosis was cavernous hemangiomas (Fig. 5c, d, black arrows), and there were no malignant findings, but hematoma was observed inside the S3/2 hemangioma (Fig. 5d, red arrows). Immunohistochemically, positive staining for IL-1 β and IL-6 was detected in sinusoidal endothelial cells in S8 hemangioma (Fig. 5e, g), whereas those were in sinusoidal endothelial cells and inflammatory infiltrates in S3 hemangioma (Fig. 5f, h). On day 4 after the operation, the fever decreased to 36°C (96.8°F), and no fever was observed thereafter (Fig. 3b). CRP levels also declined after the op-

eration. The patient was discharged 7 days after the operation and was afebrile for 2 months.

Discussion

We experienced a case of giant hepatic hemangioma with fever due to spontaneous bleeding inside the hemangioma forming a hepatoma. Laparoscopic hepatic resection was performed as a diagnostic treatment, and the patient was completely cured. For hepatic hemangiomas, a maximum diameter of ≥ 10 cm, intra-tumoral hemorrhage, and tumor rupture, as well as hematomas causing fever, are indicated for surgical resection.

Hepatic hemangiomas are sevenfold more frequent in females than males (5). Associations with pregnancy and sex hormones are suspected (6, 10). Glinkova *et al.* (6) reported that age at first menstrual period is inversely associated, and age at menopause is positively correlated, with the number of hemangiomas. In addition, in a previous study, hemangiomas grew by 0.5-6.0 cm over 2-17 years in 12/94 cases (12.7%), and 5 cases received hormone therapy whereas tumor tissues were negative for estrogen receptors and progesterone receptors (10). In our case, the patient had no history of hormonal therapy and was menopausal, suggesting that estrogen was not linked to the hemangioma. In the cases with hepatic hemangioma which caused a prolonged fever, the seven females and 4 males were reported (Table 2). Although, we did not know why the proportion of male increased, suspected to be a cause other than hormones.

Hepatic hemangioma is generally asymptomatic. Sympto-

Figure 5. Pathological findings of the liver. a), b) Macroscopic and c), d) microscopic findings of the liver; Hematoxylin and Eosin staining. e), f) IL-1 β and g), h) IL-6 staining. Cross-sections of the masses in S8/7 (a) and S3/2 (b) revealed areas of hematoma in a S3/2 hemangioma (b, d, red arrow). Both were confirmed pathologically to be cavernous hemangiomas (c, d, black arrows). Immunohistochemically, positive staining for IL-1 β and IL-6 was detected in sinusoidal endothelial cells (black arrow) in S8 hemangioma (e, g), whereas those were in sinusoidal endothelial cells (black arrow) and inflammatory infiltrates (blue arrow) in S3 hemangioma (f, h). IL: interleukin

matic (size increase, pain, and Kasabach-Merritt syndrome) hepatic hemangiomas are indicated for surgical treatment due to exposure of platelets to subendothelial collagen (11-13). In a nationwide survey in Japan, surgical resec-

tion was indicated in patients with >5 cm hemangiomas when a malignant tumor could not be ruled out (14). In our case, because we applied several antibiotics and antipyretics, the effect was transient. We attempted to use gallium scin-

Table 1. Laboratory Parameters upon Admission to Our Hospital.

Hematology		Tumor markers		Cerebrospinal fluid test	
WBC	6,900 / μ L	AFP	2 U/mL	Cell counts	1 / μ L
Neut	89.7 %	CEA	1.1 ng/mL	Specific gravity	1.005
Lymph	5.8 %	DCP	72 mAU/mL		
Mono	4.5 %				
Eos	0.0 %	Serology			
Baso	0.0 %	IgG	2,029 mg/dL		
RBC	3.85 $\times 10^6$ / μ L	IgM	46 mg/dL		
Hb	11.1 g/dL	IgA	416 mg/dL		
Ht	36.6 %	ANA	160		
PLT	34.1 $\times 10^4$ / μ L	RF	9 U/mL		
		DNA antibody	11 IU/mL		
Biochemistry		SS-A antibody	3620 U/mL		
TP	8.3 g/dL	SS-B antibody	333 U/mL		
ALB	3.3 g/dL	Scl-70 antibody	<1.0 U/mL		
T-BIL	0.9 mg/dL	SM antibody	4.3 U/mL		
AST	27 U/L	MPO-ANCA	<1.0 U/mL		
ALT	20 U/L	PR3-ANCA	1.1 U/mL		
ALP	245 U/L				
GGT	78 U/L	Hepatitis virus			
LDH	173 U/L	HBs antigen	(-)<0.02 IU/mL		
BUN	11.4 mg/dL	HBs antibody	(-)<1.0 IU/mL		
Cr	0.75 mg/dL	HBc antibody	(-) S/CO		
Na	136 mEq/L	HCV antibody	(-) COI		
K	3.4 mEq/L	CMV-IgM	0.18 (-)		
Cl	97 mEq/L	CMV-IgG	2.4 (+)		
Uric acid	3.5 mg/dL	EBV-VCA-IgM	<40 (-)		
Ferritin	516 ng/dL	EBV-VCA-IgG	40(-)		
NH ₃	132 μ g/dL	EBV-EBNA	40		
CRP	29.24 mg/dL	VZV-IgM	0.33 (-)		
		VZV-IgG	12.2 (+)		
Coagulation		HSV-IgM	<4 (-)		
PT-INR	1.21	HSV-IgG	3.2 (+)		
PT%	69.4 %	T-SPOT	(-)		
PT control	11.3 sec	β -D galcan	22.3 pg/mL		
PT	13.6 sec	Cryptococcus antigen	(-)		
APTT control	27.8 sec	Aspergillus antigen	(-)		
APTT	30.2 sec				
FDP	9.7 μ g/mL	Urine			
D-dimer	3.4 μ g/mL	WBC	(-)		
fibrinogen	766 mg/dL				

WBC: white blood cell, RBC: red blood cell, Hb: hemoglobin, Lymph: lymphocyte, Mono: monocyte, Eos: eosinophil granulocyte, Baso: basophil leucocyte, Ht: hematocrit, PLT: platelet, TP: total protein, ALB: albumin, T-BIL: total bilirubin, AST: aspartate aminotransferase, ALT: alanine aminotransferase, ALP: alkaline phosphatase, GGT: gamma-glutamyl transferase, LDH: lactate dehydrogenase, BUN: blood urea nitrogen, Cr: creatinine, Na: sodium, K: potassium, Cl: chloride, NH₃: ammonia, CRP: C-reactive protein, PT-INR: international normalized ratio of prothrombin time, PT: prothrombin time, APTT: activated partial thromboplastin time, FDP: fibrin degradation product, AFP: α -fetoprotein, CEA: carcinoembryonic antigen, DCP: des-gamma-carboxy prothrombin, IgG: immunoglobulin G, IgM: immunoglobulin M, IgA: immunoglobulin A, ANA: antinuclear antigen, RF: rheumatic factor, DNA antibody: anti-native DNA antibody, SS-A antibody: anti-Sjögren syndrome-A antibody, SS-B antibody: anti-Sjögren syndrome-B antibody, Scl-70 antibody: anti-scleroderma antibody, SM antibody: anti-SM antibody, MPO-ANCA: myeloperoxidase antineutrophil cytoplasmic antibody, PR3-ANCA: proteinase3 antineutrophil cytoplasmic antibody, HBs antigen: hepatitis B surface antigen, HBc antibody: hepatitis B core antibody, HCV: hepatitis C virus, CMV: cytomegalovirus, EBV-VCA: Epstein-Barr virus-viral capsid antigen antibody, EBV-EBNA: EB virus nuclear antigen, VZV: Varicella and herpes zoster vaccines, HSV: herpes simplex virus

tigraphy to identify the cause of fever, and it was slightly positive for the right mass.

Hepatic hemangioma is a very rare cause of FUO. Al-

though collagen diseases can cause FUO, there was no evidence of deterioration of Sjögren syndrome in this case.

Therefore, we suspected hemangioma as a source of fever.

Table 2. Cases of Hepatic Hemangioma Causing FUO.

Author	Published year	Age	Sex	Symptoms	Duration of fever	Tumor size	Cause of fever	Complications	Treatment	Outcome
Fenster <i>et al.</i> ¹⁵	1978	43	F	Malaise, myalgias, progressive weakness, shaking chills and fever with profuse night sweats.	8 Mo	Entire right lobe	Internal Hemorrhage	-	Right hepatic lobectomy/prednisone	Cured
Hopkins <i>et al.</i> ¹⁷	1990	46	F	Right upper quadrant abdominal pain, fever, chills, night sweats, anorexia, cough	1 Mo	18×14 cm	Thrombosis	-	Right hepatic lobectomy	Cured
Pateron <i>et al.</i> ²¹	1991	47	M	Fatigue, weight loss, anorexia, and fluctuating fever	4 Mo	Giant, right lobe	Thrombosis and necrosis	-	Right hepatectomy	Cured
		44	M	Epigastric pain, weight loss of 8 kg, and night sweats.	5 Mo	Giant, left lobe	Thrombosis and necrosis	-	Left hepatectomy	Cured
Khalid <i>et al.</i> ²²	2013	50	M	Lump in the epigastric region, fever, weight loss and progressive weakness	11 Mo	Left lobe of the liver	-	ALD	Surgical resection of the mass	Cured
Hao ¹⁸	2017	52	F	Fever	1 Mo	15 cm	Internal hemorrhage	-	Interventional therapy and resection	Cured
Pandit <i>et al.</i> ²³	2018	49	F	Fever	3 Mo	15×11 cm	Necrosis	-	Laparoscopic-assisted left lateral segmentectomy	Cured
Liu <i>et al.</i> ¹⁹	2018	33	M	Fever	2 Mo	20 cm	Necrosis	-	Right trisectionectomy	Cured
Desai <i>et al.</i> ⁴	2020	38	F	Fever	1 Mo	Right lobe of the liver	Hemorrhage and thrombus	-	Right hepatectomy	Cured
Wang <i>et al.</i> ²⁴	2020	59	F	Fever, night sweat, chills, weight loss	6 Mo	9×6.6×10 cm	Infected necrosis and internal hemorrhage	-	Hepatic resection	Cured
Our case		53	F	Fever	3 Mo	10 cm	Internal hemorrhage and hematoma	Sjögren syndrome	Hepatic resection	Cured

ALD: alcoholic liver disease, F: female, FUO: fever of unknown origin, M: male, Mo: months

Fenster *et al.* (15) described a 43-year-old female with a huge hepatic hemangioma presenting with fever for 8 months and treated with prednisone. However, fever was not resolved, and right hepatic lobectomy was required. By contrast, Lee *et al.* (16) reported a 37-year-old female with a 50 mm hemangioma and fever. Fever improved over 28 days with observation. Most cases resolved after <1 month by resection (4, 16-20), whereas some experienced >3 months of fever (15, 21-24) (Table 2). The possibility of hepatic hemangioma with necrosis or bleeding may have caused fever. Among 11 cases, intrahepatic hemorrhage, necrosis, and thrombus were observed in 5 cases (45.5%), 5 cases (45.5%), and 4 cases (36.4%), respectively. Stimulated hepatic macrophages (Kupffer cells) release cytokines, which play a role in host defense against antigens. The release of immune mediators by sinusoidal lining cells such as Kupffer cells lining the hemangioma may induce fever. Moreover, these cells release IL-1 and IL-6 may contribute to the hepatic inflammatory response in animal models (25). Although, we did not measure those markers in our case, im-

munohistochemically, positive staining for IL-1 β and IL-6 was detected in sinusoidal endothelial cells and inflammatory infiltrates and those might be associated with a prolonged fever. The patient's anemia gradually developed and intra-hemorrhage was suspected in the left mass. CT and MRI findings and gallium scintigraphy were inconsistent; therefore, we decided to resect both hemangiomas surgically for diagnostic treatment. Active small bleeding forming hematoma (S3/2) may result in continuous fever for >3 months.

In conclusion, it should be noted that giant, bleeding hepatic hemangiomas can cause prolonged fever and are indicated for surgical resection. Because hematoma or necrosis can cause FUO, detecting the lesion is important for deciding whether to perform resection.

The authors state that they have no Conflict of Interest (COI).

Human and animal rights

All procedures were performed in accordance with the ethical

standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Informed consent

Informed consent was obtained from the patient for the publication of this case study.

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