Gastroenterology and Hepatology From Bed to Bench.
2023 **RIGLD**, Research Institute for Gastroenterology and Liver Diseases

CASE REPORT

Isolated focal intrahepatic extramedullary hematopoiesis mimicking hepatocellular carcinoma in a cirrhotic patient with secondary hemochromatosis from thalassemia

Tatsanai Sattayaraksa[1], Cheep Charoenlap[2], Keerati Akarapatima[3], Attapon Rattanasupar[3], Arunchai Chang[3]

[1] *Department of Internal Medicine, Hatyai Hospital, Songkhla, Thailand*
[2] *Department of Anatomical pathology, Hatyai Hospital, Songkhla, Thailand*
[3] *Division of Gastroenterology, Department of Internal Medicine, Hatyai Hospital, Songkhla, Thailand*

ABSTRACT

Extramedullary hematopoiesis is a common complication of ineffective erythropoiesis and bone marrow replacement disorders. Because of its nonspecific presentation and radiological appearance, diagnosing focal intrahepatic extramedullary hematopoiesis is challenging and often misdiagnosed as a hepatic tumor. Herein, we describe the case of a 48-year-old male with thalassemia and AE Bart's disease with secondary hemochromatosis and cirrhosis who developed focal intrahepatic extramedullary hematopoiesis mimicking hepatocellular carcinoma. After hepatic resection, extramedullary hematopoiesis was not observed at any site, including in the remaining liver, at the 4-year follow-up.

Keywords: Extramedullary hematopoiesis, Thalassemia, Hemochromatosis, Hepatocellular carcinoma.

(Please cite as: **Sattayaraksa T, Charoenlap C, Akarapatima K, Rattanasupar A, Chang A. Isolated focal intrahepatic extramedullary hematopoiesis mimicking hepatocellular carcinoma in cirrhotic patient with secondary hemochromatosis from thalassemia. Gastroenterol Hepatol Bed Bench 2023;16(1):527-531. https://doi.org/10.22037/ghfbb.v16i1.2696).**

Introduction

Extramedullary hematopoiesis (EMH) is a common complication of ineffective erythropoiesis and bone marrow replacement disorders (1). Because of the lack of specific symptoms or unique radiological findings, diagnosing focal intrahepatic EMH is challenging and often misdiagnosed as a hepatic tumor (2). Herein, we report a rare case of isolated focal intrahepatic EMH in a cirrhotic patient with secondary hemochromatosis from thalassemia. We also reviewed the literature for focal intrahepatic extramedullary hematopoiesis cases and their radiological patterns.

Case report

A 48-year-old male presented with abdominal discomfort for 3 months and no other specific organ symptoms except jaundice. He denied having a fever or experiencing other gastrointestinal symptoms. He reported a history of jaundice since childhood but had never had a workup. He had a history of symptomatic gallstone for which he had undergone an open cholecystectomy 15 years ago. He had not previously received any blood transfusion and denied having any underlying disease. He was a nonsmoker and did not consume alcohol. Physical examination revealed thalassemic facies, moderately pale conjunctiva, and mildly icteric sclera. Abdominal examination revealed hepatomegaly (9 cm below the right costal margin) and splenomegaly (14 cm below the left costal margin); otherwise, it was unremarkable, with no ascites.

Laboratory blood tests indicated a low hemoglobin level (6.4 g/L), low mean corpuscular volume (59.8 fL), slightly elevated total bilirubin level (4.3 mg/dL),

Received: 18 November 2022 *Accepted*: 21 December 2022
Reprint or Correspondence: **Arunchai Chang,** *Division of Gastroenterology, Department of Internal Medicine, Hatyai Hospital, Songkhla 90110, Thailand.*
E-mail: busmdcu58@gmail.com
ORCID ID: 0000-0002-0158-2685

normal direct bilirubin level (0.8 mg/dL), and normal aminotransferase levels. Ultrasonography of the hepatobiliary system revealed parenchymatous liver disease with a 2.8×2.0-cm isoechoic lesion with a peripheral halo in the left hepatic lobe and marked splenomegaly. Thus, multiphase abdominal computed tomography was performed, demonstrating a borderline prominent caudate lobe of the liver, possibly indicating liver cirrhosis. A 2.2×3.0×2.8-cm well-defined hypodense lesion was observed with an arterial enhancement and a faint wash-out in the delayed phase at segment IVa of the left hepatic lobe (Figure 1). Severe splenomegaly and diffuse coarse trabeculation of the bony structures were observed. Serologic tests were negative for hepatitis B and C infection, and the alpha-fetoprotein level was 4.66 IU/mL. An iron workup indicated a serum ferritin level of 1, 057 mg/dL and transferrin saturation of 86%. Hemoglobin typing results revealed AE CS Bart's (Hb A, 86.6%; Hb E, 11.9%; Hb CS, 1.2%; Hb Bart's, 0.3%).

Initially, he was diagnosed with AE Bart's disease with secondary hemochromatosis and compensated cirrhosis with a hepatic mass. Further investigation, including an MRI liver and A percutaneous ultrasound-

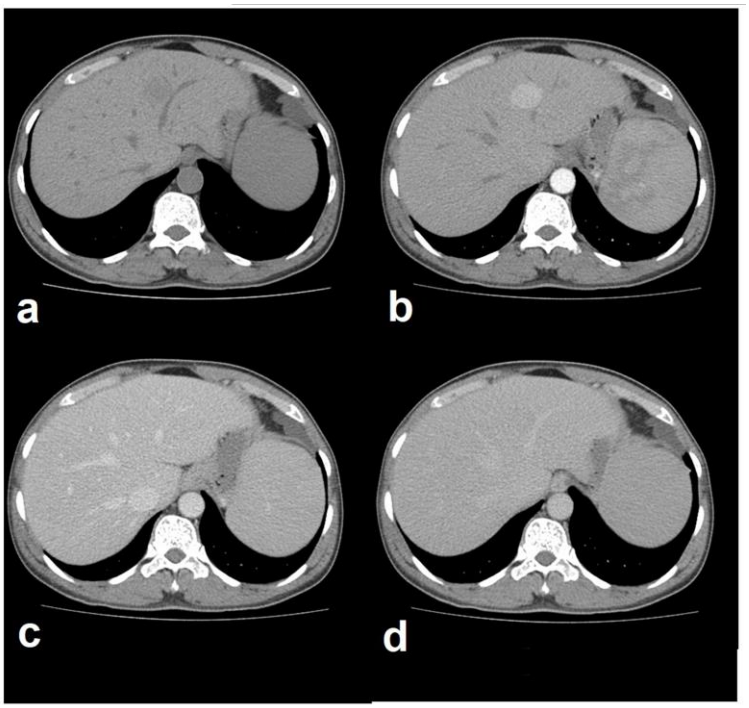

Figure 1. Computed tomography scans showing a 2.2×3.0×2.8-cm well-defined hypodense lesion with arterial enhancing lesion and faint wash-out in the delayed phase at segment IVa of the left hepatic lobe. Plain (a), arterial phase (b), portovenous phase (c), and delayed phase (d).

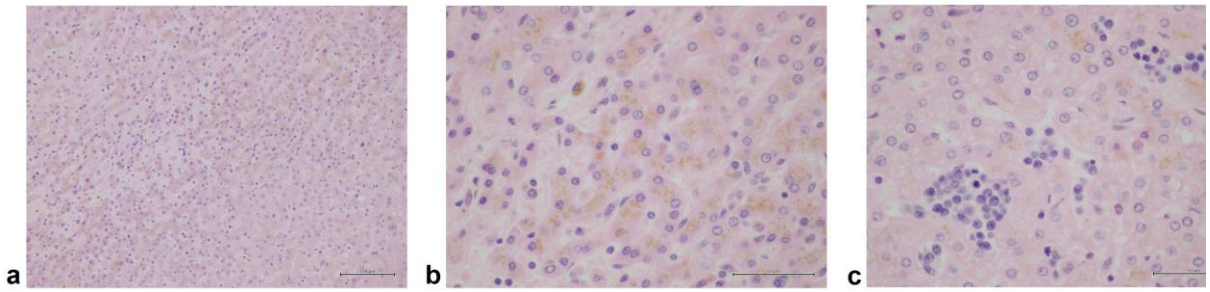

Figure 2. Pathological examination of the hepatic lesion. (a) Revealed brownish pigment in hepatocytes (hematoxylin and eosin staining, bar = 100 μm). At higher power, the granular brown pigment was present within hepatocytes, and Kupffer cells (b), and hematopoietic tissue proliferated in the sinusoids, comprising erythroid and myeloid precursors (c) (bar = 50 μm).

guided liver biopsy, was offered for the diagnosis of hepatic nodule; however, after discussion with the doctors in a multidisciplinary team of the institute, the patient refused liver biopsy and decided to undergo hepatectomy due to concerns of possible hepatocellular carcinoma (HCC). Microscopic examination revealed a brownish pigment in the hepatocytes and Kupffer cells. Hematopoietic tissue proliferated in the sinusoids, comprising erythroid and myeloid precursors compatible with features of hepatic extramedullary hematopoiesis without any evidence of a hepatic tumor (Figure 2). Finally, a definite diagnosis of extramedullary hematopoiesis of the liver in association with alpha-thalassemia was made, and computed tomography was performed regularly for follow-up. Extramedullary hematopoiesis was not observed at any site, including in the remaining liver, at the 4-year follow-up.

Discussion

Extramedullary hematopoiesis (EMH) is hematopoiesis outside the bone marrow that can occur in physiological or pathological states. Physiological EMH occurs in the liver, spleen, and yolk sac during fetal development prior to bone marrow formation (1). In contrast, pathological EMH occurs in adult life and is defined as a compensatory response to longstanding anemia for increased red blood cell production in organs outside the bone marrow (3). Pathological EMH results from ineffective erythropoiesis (thalassemia, hereditary spherocytosis, and sickle cell anemia) or bone marrow replacement disorders (myeloproliferative disorders, leukemia, and lymphoma). Moreover, it has also been reported in patients with solid organ malignancies such as breast cancer, lung cancer, and colon cancer (2). The pathogenesis of EMH postulates that circulating hematopoietic stem cells may be trapped via endothelial cell-expressed ligands, with consequent organs and tissues (4).

Our patient had AE Bart's disease, which results from the interaction of alpha-thalassemia and heterozygous Hb E (5). It is non-transfusion-dependent thalassemia (NTDT), defined by various clinical spectrums of the thalassemia phenotype, requiring only occasional blood transfusion (6). Clinical complications often seen in NTDT are rarely seen in transfusion-dependent thalassemia (TDT), including extramedullary hematopoiesis (EMH), gallstones, and pulmonary hypertension. The incidence of EMH in NTDT is approximately 20%, compared to less than 1% in TDT (7).

Common anatomical sites of EMH include the spleen and liver. Furthermore, it can be found in the paravertebral region, lymph nodes, kidney, adrenal gland, lung, pleura, breast, ovary, thymus, skin, gastrointestinal tract, and central nervous system (8). EMH in the liver commonly presents as a diffuse infiltration (9). Rarely, hepatic involvement can manifest as a focal mass representing solitary or multiple lesions, called focal intrahepatic EMH, which can mimic hepatic neoplasms.

To our knowledge, 30 focal intrahepatic extramedullary hematopoiesis cases have been reported in the past 35 years, the first of which occurred in 1986 (10). Almost all cases had an underlying hematologic disorder, but only five had thalassemia, as depicted in Table 1. Radiologic demonstration of focal intrahepatic masses of EMH has no specific characteristics (11). It often appears as a variable echogenic mass on ultrasonography; meanwhile, on CT scans, it is observed as a well-defined, heterogeneous mass with a variable contrast enhancement pattern. It may be present with a central necrosis component (9, 12-15).

However, focal intrahepatic extramedullary hematopoiesis is a general diagnostic challenge because there are no specific symptoms or radiological appearances. HCC is a well-known complication of cirrhosis; moreover, HCC has also been an emerging morbidity of thalassemia, with an annual incidence rate of approximately 2%, and is also a known cause of mortality in thalassemia (16, 17). HCC in patients with thalassemia can be caused by hepatitis B and hepatitis C infections from a blood transfusion, especially before effective blood donor screening and universal HBV vaccination. Another important risk factor for HCC development is hemochromatosis.

Hemochromatosis is a systemic iron overload disorder that disturbs iron hemostasis, resulting in abnormal iron deposition in the organs. The liver, pancreas, joints, heart, skin, testes, and pituitary gland are all commonly involved in organ damage. Iron overload in NTDT patients can be caused by blood transfusions and ineffective erythropoiesis, which gives rise to hepcidin suppression, leading to increased

intestinal iron absorption and increased release of recycled iron from the reticuloendothelial system (18).

In hepatic involvement, iron accumulation leads to hepatocyte necrosis and fibrosis, which progress to cirrhosis and, consequently, HCC. A study by Jean et al. showed that cirrhotic changes could be observed as early as 7 years in some people with thalassemia (19). Additionally, a cohort study from Greece showed that 33% of patients with NTDT who had hepatic hemochromatosis developed cirrhosis and HCC without a history of viral hepatitis infections (20).

Iron is hypothesized to play a critical role in carcinogenesis induced by hemochromatosis as it is a potent inducer of free radical formation, leading to oxidative stress and resulting in DNA damage and malignant formation (21). The 5-year cumulative incidence of HCC resulting from cirrhosis due to hereditary hemochromatosis is 17–30% (22); however, the incidence of secondary hemochromatosis remains uncertain. Furthermore, there are few reports of HCC in non-cirrhotic patients with secondary hemochromatosis (23-26). The classical imaging appearance of HCC is a hypodense lesion on non-contrast CT, which is enhanced during the arterial phase compared to the liver background, demonstrating a rapid wash-out of contrast in the portal venous phase (27). This can result in a homogenous increase in the density of the liver parenchyma in hepatic hemochromatosis.

In this context, we suggest that HCC should always be included in the differential diagnosis of hepatic masses in thalassemia patients with secondary hemochromatosis with or without cirrhosis. In our case, the patient exhibited no clinical evidence of liver disease; nonetheless, CT showed a hypodense lesion with arterial enhancement and a faint wash-out in a cirrhotic background during the delayed phase, which was compatible with the HCC pattern. Besides liver biopsy, MRI should be considered the next step of investigation because it may be the best diagnostic option. However, the knowledge of MRI features of

Table 1. Case of thalassemia patients with focal intrahepatic EMH.

Author and Year	Age/Sex	Thalassemia type	Hepatic lesion	Ultrasound	CT	MRI	Hepatomegaly	Other EMH site	Diagnostic procedure
Bradley MJ 1990 [12]	31/F	βThalassemia	Solitary	Heterogenous hypoechoic	- Heterogenous hypodense on unenhanced - Patchy enhancement	N/A	Yes	-	Trucut biopsy
Kumar A 1995 [9]	38/M	βThalassemia	Solitary	-	- Hyper/isodense on unenhanced - Central necrosis	- T1&T2 Hypointense - Central necrosis	No	Thoracic paraspinal	MRI
Wong Y 1999 [13]	51/F	βThalassemia	Solitary	Heterogenous hypoechoic	- Heterogenous hypodense on unenhanced - Hyperdense in arterial and portovenous phase Stellate hypodense in lesion	- T1 Hyperintense to liver, Isointense to muscle - T2 Heterogenous - T1 Hypointense and T2 Hyperintense in stellate lesion with delayed enhancement	No	-	Fine needle aspiration
Priola AM 2012 [14]	36/F	αThalassemia	Multiple	hypoechoic	-	-	No	-	^{52}Fe-scintigraphy
Shakeri R 2013 [15]	15/F	βThalassemia	Solitary	hypoechoic	- Hypodense on unenhanced - Homogenous enhancement - Central necrosis	-	Yes	-	Fine needle aspiration

intrahepatic EMH is still sparse, and no specific feature could help differentiate this condition from HCC. In this case, the patient underwent hepatectomy according to his preference and received a definite diagnosis. This underscores the importance of histopathological analysis as necessary for a definite diagnosis when facing a case at risk for a malignant hepatic lesion.

Conclusion

In summary, focal intrahepatic EMH is a rare condition that needs to be distinguished from HCC, particularly in cirrhosis and hemochromatosis. We suggest that focal intrahepatic EMH should be considered when hepatic mass is identified in a patient with various hematologic disorders, including thalassemia.

Conflict of interests

Authors have no conflicts of interest or financial ties to disclose.

References

1. Kim CH. Homeostatic and pathogenic extramedullary hematopoiesis. J Blood Med 2010;1:13–19.

2. Bao Y, Liu Z, Guo M, Li B, Sun X, Wang L. Extramedullary hematopoiesis secondary to malignant solid tumors: a case report and literature review. Cancer Manag Res 2018;10:1461–1470.

3. Yang X, Chen D, Long H, Zhu B. The mechanisms of pathological extramedullary hematopoiesis in diseases. Cell Mol Life Sci 2020;77:2723–2738.

4. Yamamoto K, Miwa Y, Abe-Suzuki S, Abe S, Kirimura S, Onishi I, et al. Extramedullary hematopoiesis: Elucidating the function of the hematopoietic stem cell niche (Review). Mol Med Rep 2016;13:587–591.

5. Thonglairuam V, Winichagoon P, Fucharoen S, Wasi P. The molecular basis of AE-Bart's disease. Hemoglobin 1989;13:117–124.

6. Musallam KM, Rivella S, Vichinsky E, Rachmilewitz EA. Non-transfusion-dependent thalassemias. Haematologica 2013;98:833–844.

7. Taher A, Isma'eel H, Cappellini MD. Thalassemia intermedia: revisited. Blood Cells Mol Dis 2006;37:12–20.

8. Tamiolakis D, Venizelos J, Prassopoulos P, Simopoulos S, Bolioti S, Tsiapali M, et al. Intrahepatic extramedullary hematopoietic tumor mimicking metastatic carcinoma from a colonic primary. Onkologie 2004;27:65–67.

9. Kumar A, Aggarwal S, de Tilly LN. Case of the season. Thalassemia major with extramedullary hematopoiesis in the liver. Semin Roentgenol 1995;30:99–101.

10. Kopecky KK, Moriarty AT, Antony AC, Baker MK. Extramedullary hematopoiesis in acute lymphocytic leukemia masquerading as hepatic, renal, and splenic microabscesses. AJR Am J Roentgenol 1986;147:846–847.

11. Navarro M, Crespo C, Pérez L, Martínez C, Galant J, González I. Massive intrahepatic extramedullary hematopoiesis in myelofibrosis. Abdom Imaging 2000;25:184–186.

12. Bradley MJ, Metreweli C. Ultrasound appearances of extramedullary haematopoiesis in the liver and spleen. Br J Radiol 1990;63:816–818.

13. Wong Y, Chen F, Tai KS, Yip LK, Tsang KW, Chan FL, et al. Imaging features of focal intrahepatic extramedullary haematopoiesis. Br J Radiol 1999;72:906–910.

14. Priola AM, Gned D, Boccuzzi F, Priola SM. Unusual focal intrahepatic extramedullary haematopoiesis in alpha-thalassaemia. Liver Int 2012;32:771.

15. Shakeri R, Rahmati A, Zamani F. Solitary huge intrahepatic mass (extramedullary hematopoiesis). Arch Iran Med 2013;16:315–316.

16. Mancuso A. Hepatocellular carcinoma in thalassemia: a critical review. World J Hepatol 2010;2:171–174.

17. Mancuso A, Sciarrino E, Renda MC, Maggio A. A prospective study of hepatocellular carcinoma incidence in thalassemia. Hemoglobin 2006;30:119–124.

18. Musallam KM, Cappellini MD, Wood JC, Motta I, Graziadei G, Tamim H, et al. Elevated liver iron concentration is a marker of increased morbidity in patients with β thalassemia intermedia. Haematologica 2011;96:1605–1612.

19. Jean G, Terzoli S, Mauri R, Borghetti L, Di Palma A, Piga A, et al. Cirrhosis associated with multiple transfusions in thalassaemia. Arch Dis Child 1984;59:67-70.

20. Fragatou S, Tsourveloudis I, Manesis G. Incidence of hepatocellular carcinoma in a thalassemia unit. Hemoglobin 2010;34:221–226.

21. Lefkowitch JH. Hepatobiliary pathology. Curr Opin Gastroenterol 2006;22:198–208.

22. Tsochatzis EA, Bosch J, Burroughs AK. Liver cirrhosis Lancet. 2014;383:1749–1761.

23. De Tomás J, Louredo A, Turégano F, Alonso A, Martín-Merino MR. Hepatocellular carcinoma in a non-cirrhotic coal miner with secondary haemochromatosis. Eur J Gastroenterol Hepatol 1997;9:633–634.

24. Chung H, Kudo M, Kawasaki T, Kitano M, Minami Y, Suetomi Y ,et al. Hepatocellular carcinoma associated with secondary haemochromatosis in non-cirrhotic liver: a case report. Hepatol Res 2003;26:254–258.

25. Ikoma N, Shinozaki H, Kozuki A, Ibuki S, Sugano K,Mukai M, et al. A case report of hepatocellular carcinoma in a non-cirrhotic patient with liver iron overload associated with myelodysplastic syndrome. World J Oncol 2013;4:248–251.

26. Yamauchi R, Takata K, Shinagawa Y, Tanaka T, Fukuda H, Fukuda S,et al. Hepatocellular carcinoma arising in a non-cirrhotic liver with secondary hemochromatosis. Intern Med 2019;58:661–665.

27. Clark T, Maximin S, Meier J, Pokharel S, Bhargava P. Hepatocellular carcinoma: review of epidemiology, screening, imaging diagnosis, response assessment, and treatment. Curr Probl Diagn Radiol 2015;44:479–486.