

[CASE REPORT]

Long-term Follow-up of a Patient with Portal Hypertension and Hepatic Failure Due to Hepatic Hydatid Disease

Yuki Takenaka, Tomomi Kogiso, Yuri Ogasawara, Miki Koroku, Sho Yatsuji, Makiko Taniai, Shinichi Nakamura and Katsutoshi Tokushige

Abstract:

We observed liver failure with a presumed etiology of echinococcosis in an 89-year-old woman. Our patient had been born and then resided on Rebun Island until she was 12 years old. At 46 years old, she had been referred to our hospital due to right abdominal pain. Ultrasound had revealed multilocular cysts in the right lobe of the liver. At 84 years old, the hepatic cyst occupied nearly the entire liver with ring-shaped calcification along the cyst wall. The patient was diagnosed with decompensated cirrhosis and hepatic hydatid disease based on typical imaging and the long-term natural clinical course.

Key words: echinococcosis, hepatic hydatid disease, liver failure, portal hypertension

(Intern Med 60: 1855-1861, 2021)

(DOI: 10.2169/internalmedicine.6397-20)

Introduction

Hepatic hydatid disease is a pathogenic, zoonotic, and parasitic infection (1, 2). Cystic hydatid disease usually affects the liver (i.e. in 50-70% of patients) and obstructs the bile ducts, leading to portal hypertension and Budd-Chiari syndrome (3). There are several species in the genus *Echinococcus*, and *E. multilocularis*, which causes alveolar echinococcosis (AE), and *E. granulosus*, which causes cystic echinococcosis, are important human pathogens.

The first epidemic of *Echinococcus* infection in Japan (4) occurred on Rebun Island, to which the pathogen had been transferred by foxes. Humans are infected through the ingestion of eggs excreted by the definitive hosts. The National Epidemiological Surveillance of Infectious Diseases system conducted surveillance of echinococcosis in humans in Japan (5). From April 1999 to December 2018, 425 cases were identified, and 400 of these (94%) were AE. More than 95% of these cases were from Hokkaido, the northern part of Japan, a domestic endemic area (382 cases). Most affected patients were asymptomatic during the early stage and were diagnosed incidentally (6). However, infection results in destructive tissue growth, invasion of adjacent organs, and metastasis to distant organs.

We herein report a patient with AE who exhibited portal hypertension and hepatic failure over more than 40 years of follow-up. This investigation was conducted in accordance with the principles of the Declaration of Helsinki and the ethical principles of the Tokyo Women's Medical University Hospital (Tokyo, Japan).

Case Report

Our patient was an 89-year-old woman with liver failure. She had a history of papillary thyroid cancer and colorectal cancer at 65 and 85 years old, respectively. She had been born and resided on Rebun Island in the northern section of Hokkaido, Japan, until 12 years old. At 46 years old, she experienced right abdominal pain and received a diagnosis of hepatomegaly in another hospital; she had then been referred to our hospital. On ultrasound, multilocular cysts were observed in the right liver lobe. A laparoscopic examination of the liver showed redness and a slight depression (Fig. 1a). Multiple cloudy cysts of various sizes were identified on the surface of the right lobe of the liver (Fig. 1b-d). A liver biopsy specimen from the left lobe showed local congestion (blue arrows) and nuclear vacuolation on Hematoxylin and Eosin staining (orange arrow, Fig. 2a). Portal vein fibrosis was observed on silver-stained tissues (Fig. 2b).

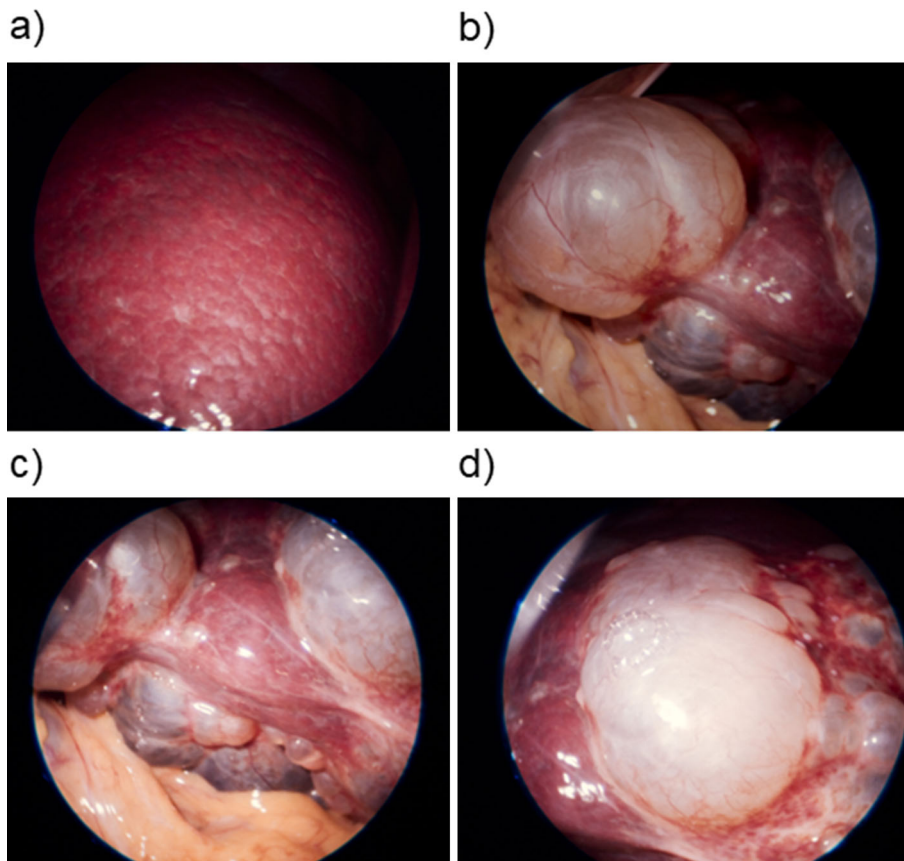


Figure 1. A laparoscopic analysis of the liver. a: Left liver lobe, b-d: Right liver lobe. A laparoscopic analysis revealed redness and slight depression in the left liver lobe when the patient was 46 years old. In the right hepatic lobe, multiple cloudy cysts of various sizes were located on the surface of the liver (b-d).

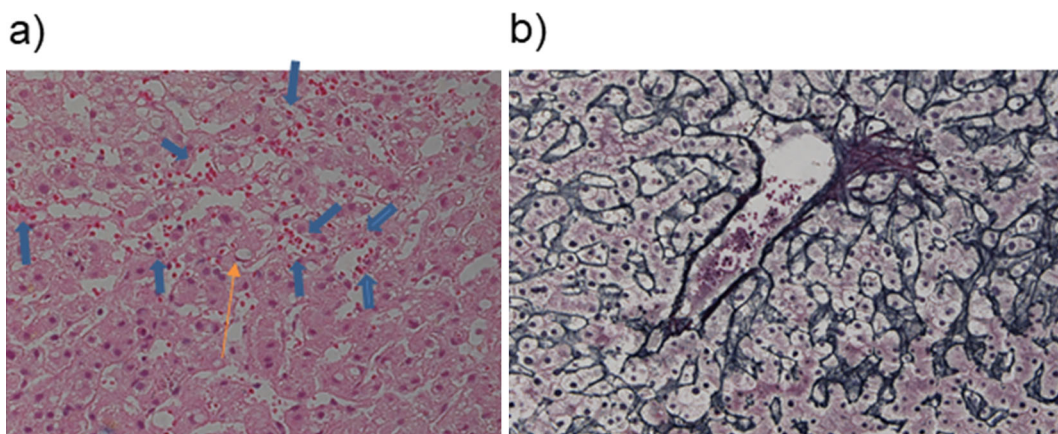


Figure 2. Microscopic findings in the liver biopsy specimen. Liver biopsy specimen taken from the left lobe showed local congestion (blue arrows) and portal vein fibrosis, lipid droplets, and nuclear vacuolation (orange arrow). a: Hematoxylin and Eosin staining, b: Silver impregnation staining results.

Multiple cysts were also observed on the kidney, suggestive of multiple hepatic renal cysts. At that time, the etiologies of the cysts were unclear. The patient was then lost follow-up.

At 80 years old, multiple cysts <10 cm in size were observed in the right lobe of the liver on ultrasound (Fig. 3a).

Mild splenomegaly (major axis \times minor axis: 10 \times 5 cm) was shown, but the accumulation of ascites was absent (Fig. 3b, c). The biochemical tests revealed a serum albumin level of 4.4 g/dL, aspartate aminotransferase level of 38 U/L, alanine aminotransferase level of 22 U/L, and platelet

count of $10.7 \times 10^4/\mu\text{L}$, suggesting early-stage liver cirrhosis. At 84 years old, the patient was admitted to another hospital due to the appearance of ascites. Hepatitis echinococcosis

was suspected based on her life history and clinical findings. Abdominal computed tomography (CT) showed multiple cysts in the right liver lobe with a septum and a ring-shaped calcification along the cyst wall. A serum examination of the liver cyst had been considered but ultimately was not performed because we had missed the window for curative treatment, and there was a possibility that the cysts had progressed.

At 88 years old, the patient returned to our department because of esophageal varices (F1 form, red color sign was negative) (Fig. 4a). Diffuse antral vascular ectasia (DAVE) was also revealed, suggesting portal hypertension (Fig. 4b). At 89 years old (6 months prior to the most recent admission), multilocular cysts were observed in the patient's right liver lobe on ultrasound (Fig. 5a, b). She was unable to be examined by enhanced CT due to renal dysfunction. A hepatic cyst occupied the majority of the liver with ring-shaped calcification along the cyst wall, a typical imaging finding in patients with AE; the right branch of the portal vein was occluded (Fig. 5c). Only a portion of the left segment remained. The renal cysts also contained ring-shaped calcifications (Fig. 5d, upper arrow); the lesion may have spread to the abdominal wall and retroperitoneum (Fig. 5d, lower arrows). Furthermore, the liver cysts showed septa (Fig. 5e). The parasitic mass in the liver (P), involvement of neighboring organs (N) and metastasis (M) classification (7, 8) by the World Health Organization-Infomal Working Group on Echinococcosis was P4N1M1, Stage IV (Supplementary material). Subsequently, the patient was admitted to our hospital due to physical movement difficulty, appetite loss, and abdominal distention.

Blood tests on admission showed serum albumin 2.4 g/dL, total bilirubin 2.2 mg/dL, aspartate aminotransferase 49 U/L, alanine aminotransferase 22 U/L, gamma-glutamyltransferase 40 U/L, prothrombin time 57.1% (Table), and Child-Turcotte-Pugh score 12 points. She was diagnosed with grade C decompensated cirrhosis. Pleural effu-

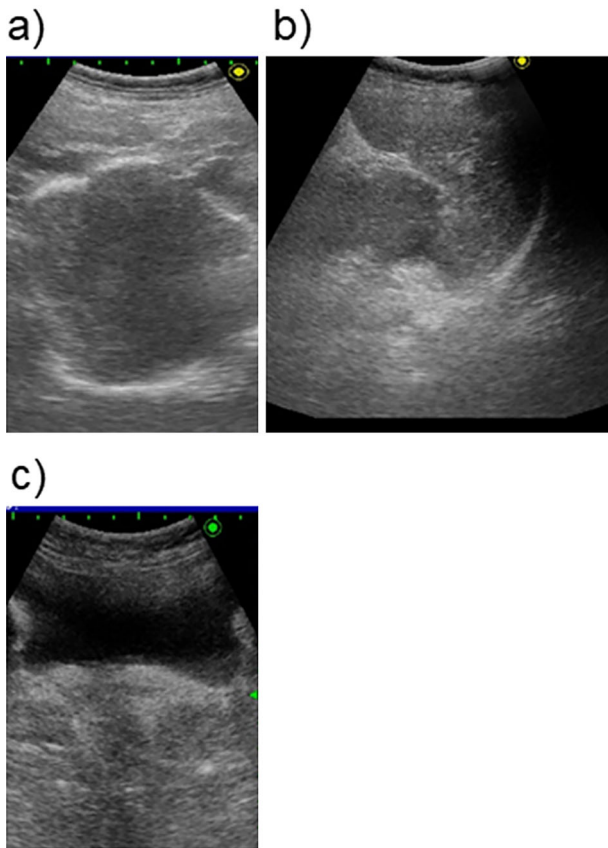


Figure 3. Abdominal ultrasound findings at nine years prior to admission. Abdominal ultrasound findings of the abdomen when the patient was 80 years old showed multiple (<10cm diameter) hepatic cysts in the right liver lobe (a). Mild splenomegaly (major axis×minor axis: 10×5 cm) was shown, however, the accumulation of ascites was absent (b, spleen, and c, pelvic space around the bladder). CT: computed tomography

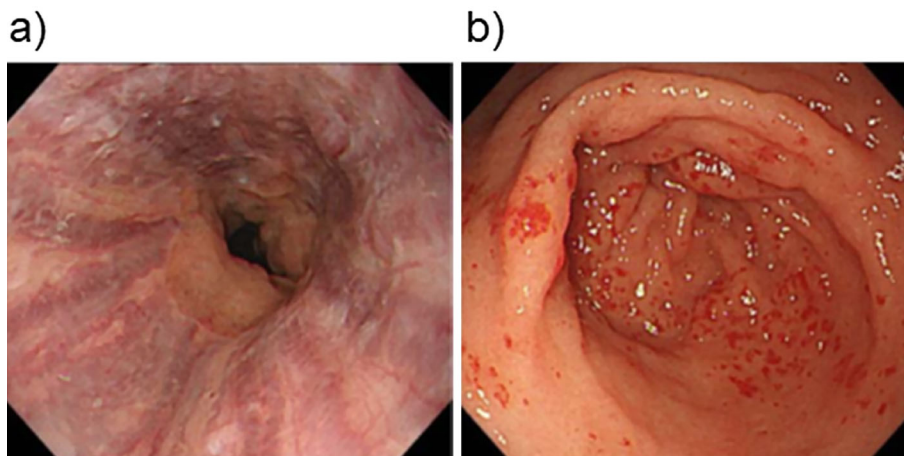


Figure 4. Upper endoscopic appearance of esophageal varices and diffuse antral vascular ectasia (DAVE). Upper endoscopic appearance of esophageal varices (F1 form, red color sign was negative) at 88 years old (a). DAVE was also observed, suggesting portal hypertension (b).

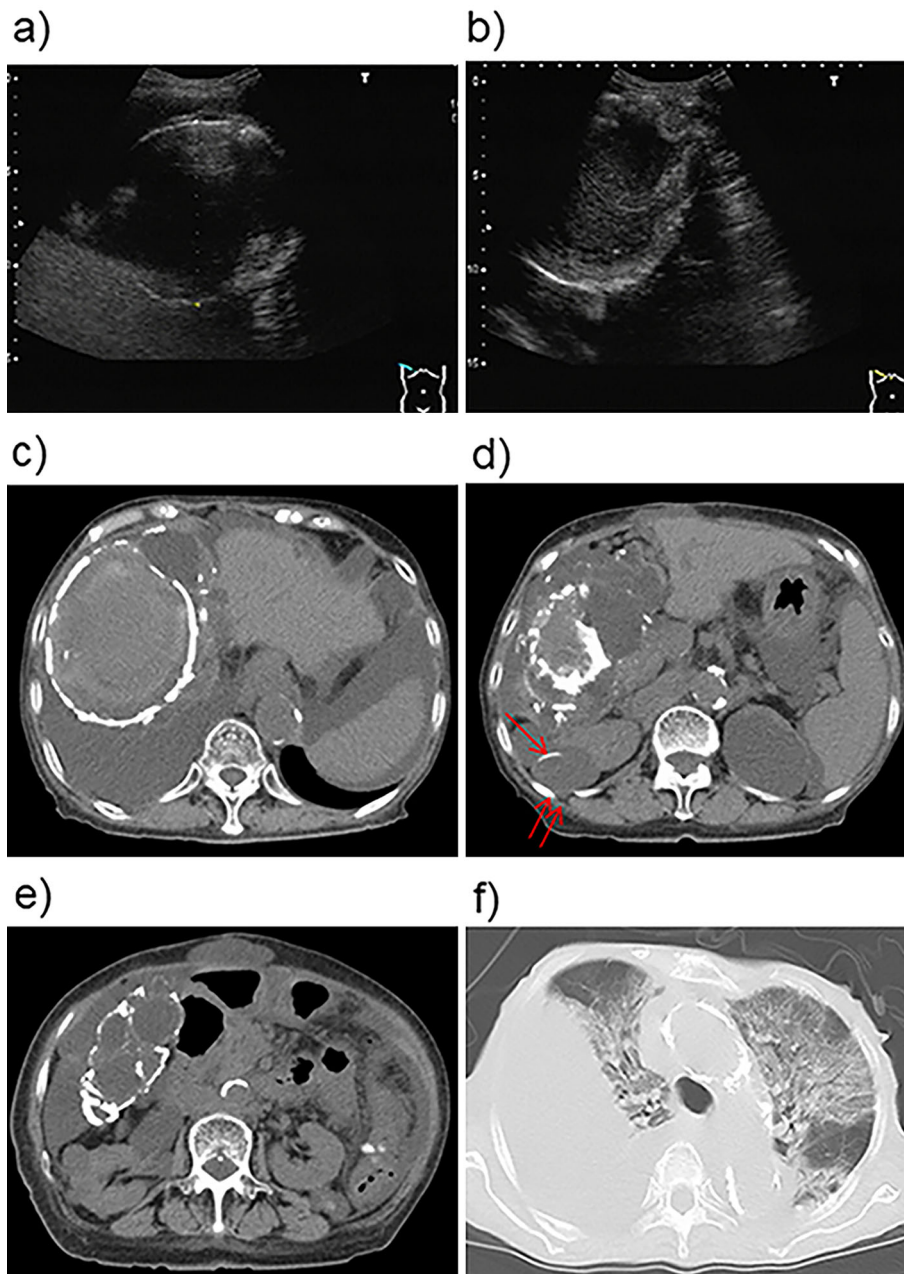


Figure 5. Abdominal ultrasound and computed tomography findings. a, b: Abdominal ultrasound, c-e: plain CT of the abdomen at six months prior to admission, f: plain chest CT on admission. On ultrasound, multilocular cysts were observed in the right liver lobe (a, b). The patient could not be examined by enhanced CT due to renal dysfunction. Plain abdominal CT showed a hepatic cyst occupying the majority of the liver with ring-shaped calcification along the cyst wall (c). The right branch of the portal vein was occluded, and only a portion of the left segment remained. Renal cysts also contained ring-shaped calcifications (d, upper arrow); the lesion may have spread to the abdominal wall and retroperitoneum (lower arrows). The liver cysts had septa (e). Plural effusion with congestion of the lungs and ascites was evident on admission (f). CT: computed tomography

sion with congestion of the lungs and ascites was evident (Fig. 5f) and was not ameliorated with diuretic treatment. The patient showed progression of hepatic encephalopathy, bleeding from DAVE of the stomach, and pulmonary edema; her respiratory condition gradually deteriorated. She eventually died of sepsis due to concurrent urinary tract infection.

Our patient's condition could not be confirmed by serological testing, such as for *Echinococcus* species-specific se-

rum antibodies (by high-sensitivity serological tests) or the *E. multilocularis* nucleic acid sequence. However, she was diagnosed with hepatic echinococcosis based on her life history and imaging findings typical of the disease. This report describes the natural history of hepatic echinococcosis over a period of 40 years.

Table. Laboratory Parameters on Admission to Our Hospital at 89 Years Old.

Hematology		Coagulation	
WBC	10,160 / μ L	PT-INR	1.37
RBC	3.05 $\times 10^6$ / μ L	PT%	57.1 %
Hb	9.7 g/dL	APTT	37.9 sec
Ht	29.4 %	APTT control	27.7 sec
PLT	9.8 $\times 10^4$ / μ L		
Biochemistry		Hepatitis virus	
TP	5.6 g/dL	HBs antigen	(-)<0.02 IU/mL
ALB	2.4 g/dL	HBs antibody	(-)<1.0 IU/mL
T-BIL	2.2 mg/dL	HBc antibody	(-) S/CO
AST	49 U/L	HCV antibody	(-) COI
ALT	22 U/L		
ALP	362 U/L		
γ -GTP	40 U/L		
LDH	373 U/L		
ChE	69 U/L		
BUN	52.3 mg/dL		
Cr	1.49 mg/dL		
eGFR	25.6 mL/min/1.73 m ²		
Na	134 mEq/L		
K	5.0 mEq/L		
Cl	100 mEq/L		
Uric acid	11.1 mg/dL		
FBS	137 mg/dL		
Hb _{A1c} (NGSP)	4.4 %		
NH ₃	89 μ g/dL		
TC	147 mg/dL		
TG	44 mg/dL		
CRP	6.81 mg/dL		

WBC: white blood cell, RBC: red blood cell, Hb: hemoglobin, Ht: hematocrit, PLT: platelet, TP: total protein, ALB: albumin, T-BIL: total bilirubin, AST: aspartate aminotransferase, ALT: alanine aminotransferase, ALP: alkaline phosphatase, γ -GTP: gamma-glutamyltransferase, LDH: lactate dehydrogenase, ChE: cholinesterase, BUN: blood urea nitrogen, Cr: creatinine, Na: sodium, K: potassium, Cl: chloride, FBS: fasting blood sugar, NGSP: national glycohemoglobin standardization program. NH₃: ammonia, TC: total cholesterol, TG: triglyceride, CRP: C-reactive protein, PT-INR: international normalized ratio of prothrombin time, PT: prothrombin time, APTT: activated partial thromboplastin time, HBs antigen: hepatitis B surface antigen, HBc antibody: hepatitis B core antibody, HCV: hepatitis C virus

Discussion

We herein report a patient with hepatic hydatid disease complicated by portal hypertension and hepatic failure, along with esophageal varix and refractory ascites during long-term follow-up. Although the disease could not be confirmed with serological tests, based on typical clinical findings and the patient's life history, we concluded that our patient had AE. The disease progressed slowly over several decades. This case provides valuable information regarding the long-term natural course of AE without treatment.

Among patients with polycystic echinococcosis, approximately 98% develop primary lesions in the liver (9, 10). Typical images of AE have been reported as a juxtaposition

of hyper- and hypoechogenic areas in a pseudo-tumor with irregular and scattered calcification, as well as a pseudocystic appearance with central necrosis (8, 11). Calcified lesions have been presumed to represent either dead or small-sized developing parasites. Microcysts engrafted in the liver form a solid cactus-like mass due to exogenous sprouting; as the mass grows, it is accompanied by hepatomegaly, abdominal pain, jaundice, and liver dysfunction. The disease is often characterized by an asymptomatic incubation period of 5-15 years with the slow development of a primary tumor-like lesion. If the disease progresses further, it causes obstructive jaundice, central lesion necrosis, and lesion infection. In our patient, the cysts had formed on the surface of the right liver lobe 40 years prior to the most recent admission. These had invaded the liver and caused calcification, presumably an in-

dication of gradual parasite death. The liver damage progressed to cirrhosis, and symptoms of decompensation appeared at 84 years old, more than 70 years after the had infection started.

Metastases predominantly occur in the lungs in approximately 10% of patients. Kern et al. reported 13 (2%) isolated extra-hepatic locations involving the spleen, peritoneum, lung, vertebra, brain, kidneys, and heart (12). Our patient exhibited renal lesions and presumptive spread to the abdominal wall and retroperitoneum.

Portal hypertension has been reported as a severe complication of AE in a few patients (13, 14). Notably, caval and hepatic vein obstruction may contribute to the development of fibrosis in patients with AE. In a previous study, the pathological findings of AE indicated that the cyst has an irregular, fragmented, thin and laminated wall (15). The center is often necrotic and fibrotic. A granulomatous reaction may occur in the parenchymal membranes, characterized by mixed inflammatory infiltration consisting of lymphocytes, plasma cells, and numerous eosinophils outside of the cyst wall (16). In our case, we were unable to obtain a sample from the cyst. A liver biopsy specimen from the left lobe revealed local congestion with nuclear vacuolation and portal vein fibrosis. These findings were not specific to AE. A histopathological examination revealed that the periparasitic granuloma enhanced the nonspecific immune response. In a previous study, collagen and other fibrosis-inducing extracellular matrix protein deposits were identified (17). Therefore, the immunological response may induce fibrosis in patients with AE. Recent studies have indicated that microribonucleic acid and transforming growth factor-beta signaling are associated with the development of fibrosis caused by *Echinococcus* spp. This signaling is known to activate hepatic stellate cells, thereby causing liver fibrosis (18). In our patient, local congestion and portal vein fibrosis were observed 40 years prior to decompensation. Therefore, both mechanical obstruction of the hepatic vein and the concomitant immune response may facilitate fibrosis in patients with AE.

In terms of treatment for hepatic hydatid disease, surgery remains the primary approach for the treatment of hepatic AE; radical resection combined with oral albendazole/mebendazole administration is a common method of treating AE (19). However, most patients experience a delayed diagnosis, and liver transplantation has been necessary to cure some patients (20, 21). In our patient, the liver cysts had already spread, and curative treatment could not be performed at the initial suspicion of echinococcosis; only the ascites could be treated. While the patient did not receive any AE drugs or surgery, she was able to survive until 89 years old.

During a long-term follow-up study, Matsudaira et al. described a patient who underwent surgical treatment of AE, which progressed slowly following 29 years of infection with *E. multilocularis* (22). Wilson et al. evaluated 33 Alaskan Eskimo patients and found that the disease progressed to a fatal outcome in 70% of untreated patients (23). According to a report by the World Health Organization, if AE

remains untreated, 70% of affected patient will die within 5 years, while 94% will die within 10 years (24). The mortality in patients with progressive disease (including clinical manifestations) is presumed to be 50-75%. Piarroux et al. reported the clinical features among 387 patients in France; the mortality decreased in the first 2 years and remained nearly absent during 5 years of follow-up (25). Extrahepatic metastasis was not identified as an independent prognostic factor for AE-specific mortality, whereas aging was negatively associated with AE-specific mortality, and drug treatment was correlated with an improved survival (25). Therefore, appropriate treatment should be performed at the initial diagnosis. Our patient survived for many years without treatment. Parasite larvae grow inside of the cysts and may die spontaneously during various stages of disease development.

In recent studies including patients in Japan, mass-screening programs have been shown to improve the survival of patients with AE (26). Bresson-Hadni et al. reported that the survival at 5 years improved from 67% to 88% in a 20-year study (11). However, the present patient had moved away from the endemic area and might not have received notification of such mass-screening programs.

In conclusion, we encountered a patient with a rare manifestation of portal hypertension and hepatic failure due to hepatic hydatid disease and available long-term follow-up data. The cysts matured slowly and caused cirrhosis over a period of 40 years. This was a rare case of a long-term survival without radical treatment.

Informed consent was obtained for publication of this case report.

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

Acknowledgement

We thank Dr. Shunichi Kikuchi of the Kikuchi Clinic and Dr. Mikio Yanase of the National Center for Global Health and Medicine for providing information on the patient.

References

- Moro P, Schantz PM. Echinococcosis: a review. *Int J Infect Dis* **13**: 125-133, 2009.
- Nunnari G, Pinzone MR, Gruttadauria S, et al. Hepatic echinococcosis: clinical and therapeutic aspects. *World J Gastroenterol* **18**: 1448-1458, 2012.
- Dumortier J, Valette PJ. Transjugular intrahepatic portosystemic shunt for alveolar echinococcosis of the liver and Budd-Chiari syndrome. *Clin Res Hepatol Gastroenterol* **42**: e61-e62, 2018.
- Deplazes P, Rinaldi L, Alvarez Rojas CA. Global distribution of alveolar and cystic echinococcosis. *Adv Parasitol* **95**: 315-493, 2017.
- Infectious Agents Surveillance Report [Internet]. 2019 Available from: <https://www.niid.go.jp/niid/images/idsc/iasr/40/469e.pdf>
- Mihmanli M, Idiz UO, Kaya C, et al. Current status of diagnosis and treatment of hepatic echinococcosis. *World J Hepatol* **8**: 1169-1181, 2016.
- Eckert J, Gemmell MA, Meslin FX, Pawłowski ZS. WHO/OIE manual on echinococcosis in humans and animals: a public health

- problem of global concern. Eckert J, et al., Eds. France World Organisation for Animal Health, Paris, 2001.
8. Brunetti E, Kern P, Vuitton DA. Writing panel for the WHO-IWGE. Expert consensus for the diagnosis and treatment of cystic and alveolar echinococcosis in humans. *Acta Trop* **114**: 1-16, 2010.
 9. National institute of infectious disease 2001 [Internet]. Available from: <https://www.niid.go.jp/niid/en/iasr-vol33-e/865-iasr/8695-469te.html>
 10. WHO. Fact sheet, Media Centre. Updated March 2020 Echinococcosis [Internet]. Available from: <https://www.who.int/news-room/fact-sheets/detail/echinococcosis>
 11. Bresson-Hadni S, Vuitton DA, Bartholomot B, et al. A twenty-year history of alveolar echinococcosis: analysis of a series of 117 patients from eastern France. *Eur J Gastroenterol Hepatol* **12**: 327-336, 2000.
 12. Kern P, Wen H, Sato N, et al. WHO classification of alveolar echinococcosis: principles and application. *Parasitol Int* **55** (Suppl): S283-S287, 2006.
 13. Emre A, Arioğul O, Alper A, Okten A, Uras A, Yalçın S. Hydatid cysts of liver and portal hypertension. *HPB Surg* **2**: 129-133, 1990.
 14. Karadas S, Cumhuri DA, Bilge G, Mehmet B, Mustafa K. A case of Budd-Chiari syndrome associated with alveolar echinococcosis. *J Pak Med Assoc* **64**: 465-467, 2014.
 15. Reinehr M, Micheloud C, Grimm F, et al. Pathology of echinococcosis: a morphologic and immunohistochemical study on 138 specimens with focus on the differential diagnosis between cystic and alveolar echinococcosis. *Am J Surg Pathol* **44**: 43-54, 2020.
 16. Kanel G KJ. Atlas of Liver Pathology. 3rd Edition. Saunders, 2010: 180-183.
 17. Yamasaki H, Nakayama K, Nakao M, Sako Y, Itho A. Significance of molecular diagnosis using histopathological specimens in cestode zoonoses. *Trop Med Health* **35**: 307-321, 2007.
 18. Tsuchida T, Friedman SL. Mechanisms of hepatic stellate cell activation. *Nat Rev Gastroenterol Hepatol* **14**: 397-411, 2017.
 19. Bakhtiar NM, Akbarzadeh A, Casulli A, et al. Therapeutic efficacy of nanocompounds in the treatment of cystic and alveolar echinococcoses: challenges and future prospects. *Parasitol Res* **118**: 2455-2466, 2019.
 20. Sakçak I, Eriş C, Ölmez A, Kayaalp C, Yılmaz S. Replacement of the vena cava with aortic graft for living donor liver transplantation in Budd-Chiari syndrome associated with hydatid cyst surgery: a case report. *Transplant Proc* **44**: 1757-1758, 2012.
 21. Yang C, Yang HJ, Deng SP, Zhang Y. Current status of ex-vivo liver resection and autologous liver transplantation for end-stage hepatic alveolar echinococcosis. *Ann Palliat Med* **9**: 2271-2278, 2020.
 22. Matsusaira S, Ishizaki Y, Yoshimoto J. A case of hepatic alveolar echinococcosis treated radically by hepatectomy 29 years after infection by echinococcus multilocularis. *Journal of Japan Surgical Association* **79**: 2145-2149, 2018.
 23. Wilson JF, Rausch RL. Alveolar hydatid disease. A review of clinical features of 33 indigenous cases of echinococcus multilocularis infection in Alaskan Eskimos. *Am J Trop Med Hyg* **29**: 1340-1355, 1980.
 24. Guidelines for treatment of cystic and alveolar echinococcosis in humans. WHO Informal Working Group on Echinococcosis. *Bull World Health Organ* **74**: 231-242, 1996.
 25. Piarroux M, Piarroux R, Giorgi R, et al. Clinical features and evolution of alveolar echinococcosis in France from 1982 to 2007: results of a survey in 387 patients. *J Hepatol* **55**: 1025-1033, 2011.
 26. Suzuki K, Uchino J, Sato N, Takahashi H. Development and efficacy of mass screening of alveolar echinococcosis. In: *Alveolar Echinococcosis Strategy for Eradication of Alveolar Echinococcosis of the Liver*. Uchino J, Sato N, Eds. Fuji Shoin, Sapporo, 1996: 212-217.

The Internal Medicine is an Open Access journal distributed under the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License. To view the details of this license, please visit (<https://creativecommons.org/licenses/by-nc-nd/4.0/>).