

Hepatic angiosarcoma: three case reports and review of the literature in Thailand

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We report the clinical, laboratory and pathologic features of 3 hepatic angiosarcomas in 3 female patients treated in the past 13 years at Chulalongkorn University Hospital. The first case was seen in 1983, a 2 month old baby girl who presented with progressive abdominal distension and hepatomegaly. She died 6 days after admission. Autopsy showed angiosarcoma involving the liver, spleen, lymph nodes, bone marrow and adrenals. The second patient was seen in 1987, a 53 year old female who presented with acutely progressive liver failure and hepatomegaly. She died 10 days after admission. Her autopsy showed angiosarcoma involving the liver, parapancreatic lymph nodes and bone marrow. The third case was diagnosed by liver biopsy in a 28 year old female. She presented with abdominal discomfort with abnormal findings in a computerized tomography of the liver. She was lost to follow up. The clinical course, hematologic and histopathologic findings were diagnostic of hepatic angiosarcoma. Immunohistochemistry and electron microscopy also confirmed the pathologic diagnosis.

Key words: Angiosarcoma, Liver.

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Angiosarcoma ในตับเป็นมะเร็งปฐมภูมิของตับที่พบน้อย และยังไม่เคยมีรายในประเทศไทย
ผู้ป่วยทั้ง 3 รายมาหาแพทย์ด้วยอาการปวดแน่นในท้องและตับโต ผู้ป่วย 2 รายแรกถึงแก่กรรมใน
ระยะเวลาอันสั้น ด้วยอาการตับวาย ผลการตรวจพบเซลล์มะเร็งในตับทั่วไปและกระจายไปที่ไขกระดูก
ต่อมน้ำเหลือง ม้าม ต่อมหมวกไต ผู้ป่วยรายที่ 3 วินิจฉัยจากการตรวจชิ้นเนื้อตับ และไม่สามารถ
ติดตามผลภายหลังการวินิจฉัยได้ การวินิจฉัยทางพยาธิวิทยาต้องอาศัยการตรวจพิเศษทางอิมมูโน
ฮิสโตเคมีและการตรวจทางกล้องจุลทรรศน์อิเล็กตรอน

Hepatic angiosarcoma, a rare malignant neoplasm is the most common sarcoma arising in the liver.⁽¹⁾ Over 200 cases are diagnosed annually worldwide.^(1,2) To our knowledge, angiosarcoma of the liver has never previously been reported in Thailand. We, therefore report 3 cases of hepatic angiosarcoma treated at Chulalongkorn Hospital in the past 13 years.

Case Reports

Case 1

This 2 month old baby girl was noticed to have abdominal distension when she was 2 weeks old. She was admitted to a local hospital where x-rays of the abdomen revealed ileus of the bowel. Two weeks later she was readmitted because of a progressively enlarged abdomen associated with fever and vomiting. The liver was palpable 5 cm. below the right costal margin. She was then referred to Chulalongkorn Hospital.

Physical examination revealed an active child with a body temperature of 38°C, a pulse rate of 160/min, and a respiratory rate of 88/min. There were icteric sclerae and pale conjunctiva. A marked abdominal distension with evidence of ascites was noted. The liver was 10 cm. below the right costal margin and the spleen was 3 cm. Pitting edema of the lower extremities was present.

Laboratory investigations were as follows: hemoglobin 6.8 g/dl, white blood cell count 17,450/mm³ with 41 % neutrophils, 7 % band, 46 % lymphocytes, 3 % large lymphocytes, 2 % atypical lymphocytes and 1 % monocytes. Nucleated red

blood cell was 4/100 WBCS, reticulocytes 1.6 %, platelets 10,400/mm³. A blood coagulogram showed a prothrombin time of 24.6 seconds (control 15 seconds) and PTT 53.6 seconds (control 46.4 sec). A liver function test showed total bilirubin 8.3 mg/dl, direct bilirubin 4.45 mg/dl, alkaline phosphatase 38 I.U., SGOT 130 I.U., SGPT 63 I.U. Urinalysis showed sp.gr 1.035, albumin -1+, sugar-negative. Blood chemistry showed BUN 5 mg/dl, Cr 0.3 mg/dl, cholesterol 308 mg/dl, albumin 3.2 mg/dl, globulin 1.6 mg/dl.

Serum HBsAg was negative. Alpha-feto-protein was negative. Ascitic fluid was straw colored with numerous unidentified cells, 50 WBCS and 278 RBCS. X-rays of the abdomen showed an enlarged liver. Fresh whole blood, frozen plasma and vitamin K were given. Her condition rapidly deteriorated and she expired on the sixth hospital day.

Autopsy Findings

A 180g noncirrhotic liver was diffusely enlarged and contained multiple ill-defined hemorrhagic areas (Fig. 1). Microscopically, the tumor was composed of malignant vasoformative endothelial cells with ill-defined borders (Fig 2.) Hepatocytes were compressed by tumor cells and sinusoids were diffusely infiltrated by the malignant cells (Fig 3). Immunohistochemistry was also positive for factor VIII-related antigen.

The autopsy diagnosis was angiosarcoma involving the liver, spleen abdominal lymph nodes, bone marrow and adrenals.

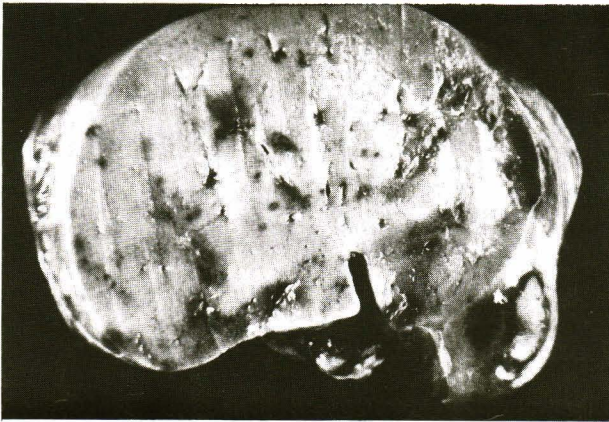


Figure 1. (case 1). Showing a solid tumor with multiple hemorrhagic areas in a 2 months old child.

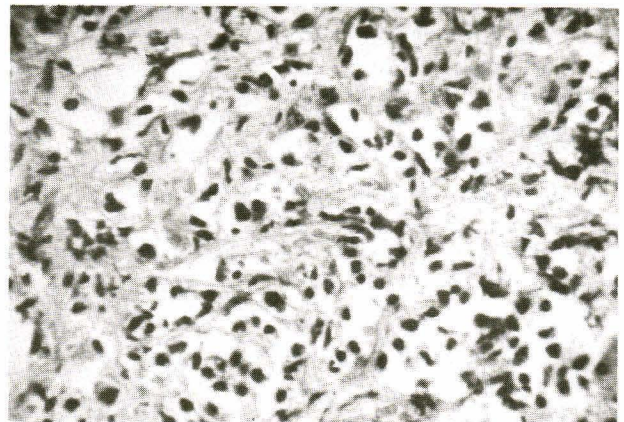


Figure 2. (case 1). Showing vascular channels lined by atypical cells invading liver parenchyma. (H & E, x 100)

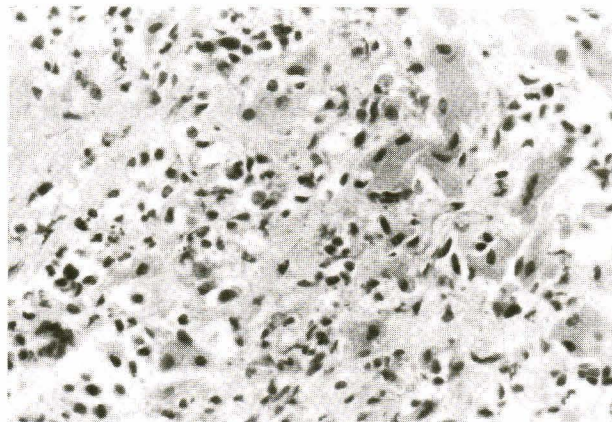


Figure 3. (case 1). Showing infiltration of hepatic sinusoids by the malignant cells. (H & E x 100)

Case 2

This 53 year old married female was admitted because of abdominal pain below the right costal margin and fever experienced for 2 weeks prior to admission. Two weeks earlier, she had been seen at OPD because of abdominal pain and fever. An ultrasonogram of the hepatoliliary tract showed no abnormality. She had been given supportive treatments which provided some relief. She was then admitted to the hospital. Physical examination revealed a toxic, stightly obese female with a body temperature of 39^oc, BP 120/70 mmHg, PR 100/min, RR 28/min. No icteric sclera seen. The abdomen showed mild

guarding and tenderness at the right upper quadrant. The liver was 6 cm below the right costal margin, It was tender with a smooth surface and firm consistency.

Laboratory investigations were as follows: hemoglobin 10.1 g/dl; white blood cell count 24,700/mm³ with 83% neutrophils, 7% band, 9% lymphocytes and 1% monocytes. Platelets were adequate. Urine and stool examinations were negative. The blood chemistry showed plasma glucose 102 g/dl BUN 12 mg/dl, Cr 2 mg/dl. A liver function test showed total bilirubin 2 mg/dl, direct bilirubin 0.8 mg/dl alkaline phasphatase 110 I.U., SGOT 135 I.U., SGPT 75 I.U. Albumin was 2.85 gm/dl, globulin 3.15 gm/dl

protrombin time 16.2 seconds (control 10.8). Serum amylase 90, urine amylase 5,810. Alphafetoprotein was negative. Hemoculture was negative.

An ECG showed non-specific ST-T change. Chest x-rays and plain abdomen showed evidence of right subpulmonic effusion. An ultrasonogram of the hepatobiliary tract showed a thick, edematous-walled gall bladder and moderate hepatomegaly. The spleen was prominent.

During hospitalization antibiotics and vitamin K were given. She remained febrile and developed oliguria with dyspnea and stupor. Jaundice was remarkably noted on the 7th hospital day. She had

pitting edema of the lower extremities with flapping tremor. She died on the 10th hospital day.

Autopsy Findings

Autopsy showed a 3,000 g noncirrhotic liver with yellowish discoloration and multiple ill-defined hemorrhagic areas, especially in the right lobe (Fig.4). Histologically, bizarre and multinucleated malignant cells were seen infiltrating the hepatic sinusoids (Fig 5,6).

Immunoperoxidase staining was weakly positive for Factor VIII related antigen. The pathologic diagnosis was angiosarcoma involving the liver, parapancreatic lymph nodes, and bone marrow.

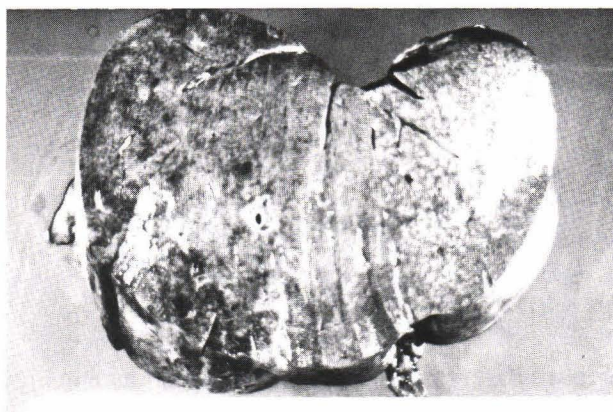


Figure 4. (case 1). Showing a solid liver tumor with ill-defined hemorrhagic areas in the right lobe.

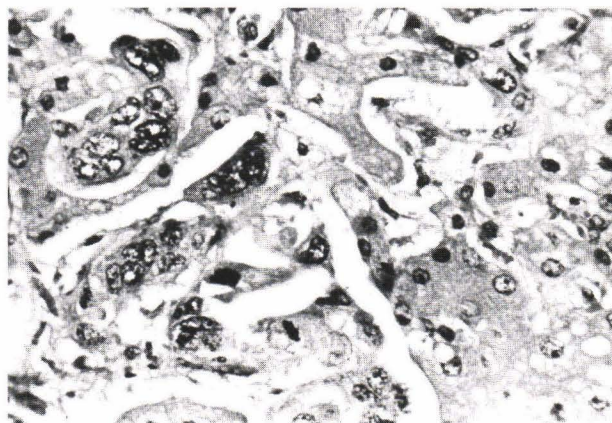


Figure 5. (case 2). Showing bizarre multinucleated cells in the sinusoids of the liver. (H & E x 400)

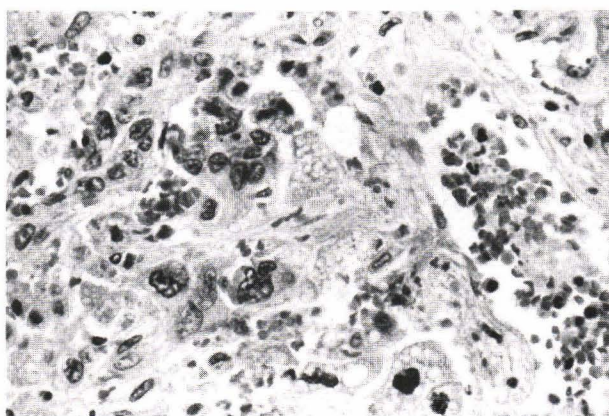


Figure 6. (case 2). Showing a blood vessel infiltrated by angiosarcoma cells. (H & E x 400)

Case 3

This 28 year old female was referred to Chulalongkorn Hospital because of slight abdominal discomfort with mild hepatomegaly. The liver function tests were as the follows: total bilirubin 0.51 mg/dl, direct bilirubin 0.25 mg/dl, SGOT 89 I.U., SGPT 124 I.U. Alkaline phosphatase 571 I.U. Serum albumin was 4 g/dl, globulin 4.5 g/dl. Prothrombin time was normal. Serum HBsAg was negative. Anti HBcIgM-negative, Anti HCV-negative, Anti HIV-negative. A CT liver scan showed diffuse inhomogeneous hypodensity with minimal



Figure 7. (case 3). Showing malignant cells infiltrating the hepatic sinusoids. (H & E x 100)

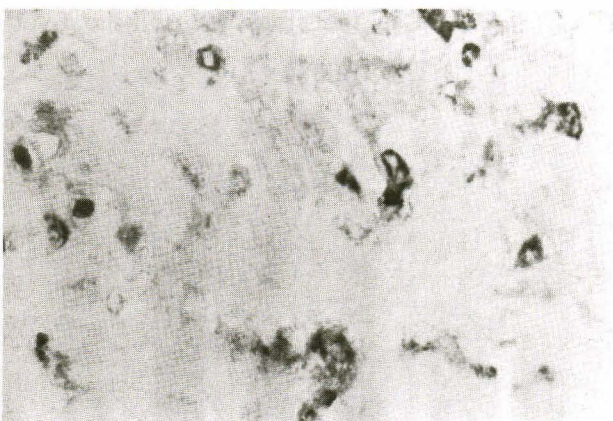


Figure 9. (case 3). Angiosarcoma cells showing strong reactivity with antibody to factor VIII-related antigen. (arrows). (Immunoperoxidase stain x 400)

subcapsular collection. A liver biopsy was performed.

Pathology

Microscopically, the noncirrhotic liver was diffusely infiltrated by dark-stained atypical cells lining the sinusoids (Fig. 7, 8). Immunoperoxidase staining was positive for factor VIII related antigen (Fig. 9). Electron microscopy also showed Weibel-Palade bodies as a marker for the endothelial cell origin of the tumor cells (Fig.10). The pathologic diagnosis was angiosarcoma involving the liver. The patient was lost to follow-up.

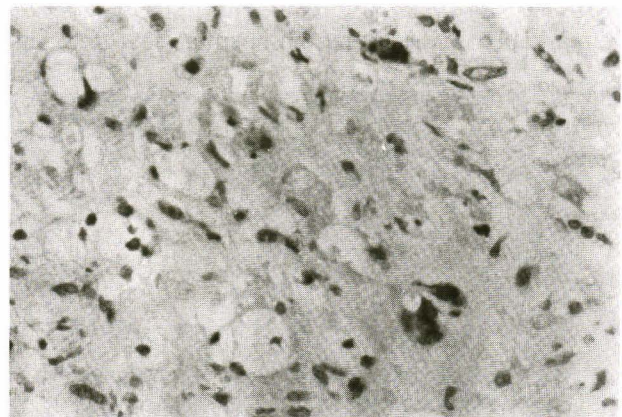


Figure 8. (case 3). Higher magnification of malignant cells in the hepatic sinusoids. (H & E x 400)

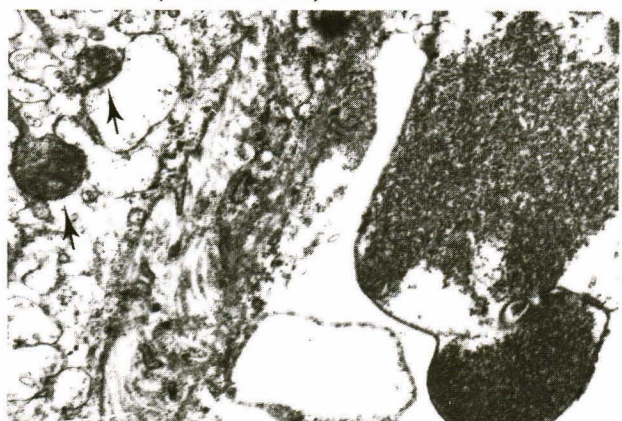


Figure 10. (cases 3). Showing two Weibel-Palade Bodies (Arrows). (Transmission electron micrograph x 15,000)

Discussion

Angiosarcoma of the internal organs is very rare in Thailand. From our review of the Thai literature we found 1 case reported involving the spleen⁽³⁾ and one other case involving the kidney⁽⁴⁾ (Table 1). Including our 3 cases, there were 4 females and 1 male. The most common presenting manifestation was abdominal distension associated with discomfort and pain for sometime. The prognosis of angiosarcoma involving the liver is usually worse than other organs such as the spleen or kidney. Angiosarcoma is characterized by formation of freely anastomosing vascular channels. Histologically well differentiated angiosarcoma is similar to peliosis hepatis or other benign vascular

lesions⁽⁵⁾ such as hemangioma or hemangioendothelioma. Poorly differentiated angiosarcoma, on the other hand, must be differentiated from other pleomorphic sarcoma and metastatic epithelial lesions. Immunohistochemically, factor VIII-related antigen is usually reactive in differentiated cases (6) and often negative in undifferentiated angiosarcoma. Angiosarcoma is most often seen in adults. The peak age is in the sixth and seventh decades of life, with a male to female ratio of 3:1. But cases reported in children have also been recorded. In our 3 cases, all were females with relatively younger ages (2 months, 53 years, 28 years). The modes of presentation are hepatomegaly, ascites, abdominal pain, vomiting and fever.⁽⁹⁾

Table 1. Reported angiosarcoma in Thailand.

Case No	Authors	Age(yrs)	Sex	Metastases	Treatment	Outcome
1	สมัย มีมงคลกุลติก (1)	43	M	None	Splenectomy	unknown
2	มณฑิรา มฤคทัต ชูศักดิ์ ปวิพัฒน์นันท	21	F	one	Nephrectomy	unknown
3	Pongseperra et al	2/12	F	Bone-marrow Spleen lymph nodes adrenals	Supportive	Died 6 days
4	Pongsepeera et al	53	F	Bone-marrow lymph nodes	Supportive	Died 10 days
5	Pongsepeera et al (present cases)	28	F	None	unknown	unknown

Laboratory findings include anemia and leucocytosis which were seen in our first 2 cases. The majority of patients with angiosarcoma die less than 6 months after diagnosis, usually from liver failure.^(7,10) Our first 2 patients died in 6 and 10 days after diagnosis.

Gross pathology of our first 2 patients show solid tumors with ill-defined hemorrhagic foci.

The predisposing risk factors in the development of angiosarcoma have been related to pigmented cirrhosis (hemochromatosis),⁽¹¹⁾ vinyl chloride,^(10,11) thorotrast,⁽¹²⁻¹⁴⁾ and arsenic.⁽¹⁵⁾ Angiosarcoma of the liver may be associated with hepatocellular carcinoma and/or cholangiocarcinoma.⁽¹⁶⁾ In the United States, from reports of 1964 through 1974, the majority of angiosarcoma was of unknown cause.^(2,17) Our 3 cases also fall into this unknown category.

Summary

Three cases of hepatic angiosarcoma, the first reported cases in Thailand, were presented. All were females aged 2 months, 53 years and 28 years. The third patient was diagnosed by liver biopsy during life. The first two cases were diagnosed at autopsy with involvement of the liver, bone marrow, lymph nodes, adrenals, and spleen. Factor VIII-related antigen are also seen in tumor cells by immunohistochemical techniques. Electron microscopy also showed Weibel-Palade bodies.

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