

## A First Case of Hepatic Angiosarcoma Treated with Recombinant Interleukin-2

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### ABSTRACT

A 60 year-old woman was admitted to our hospital because of management of multiple liver tumors. According to image findings and liver biopsy, she was diagnosed as having epithelioid hemangioendothelioma of the liver accompanied by metastases in the spleen, lungs and bones. Based on the spread of the liver tumors and the extensive systemic metastases, she was considered inoperable. Instead, she received hepatic arterial infusion therapy using recombinant interleukin-2. However, she died due to liver failure about two months after admission. Autopsy revealed that the liver tumor was angiosarcoma. It is difficult to differentiate angiosarcoma from epithelioid hemangioendothelioma based on the image findings and pathological findings of percutaneous liver biopsy. Many cases are diagnosed as angiosarcoma at autopsy. There is no established effective treatment for hepatic angiosarcoma, because the tumor stage at the time of diagnosis is often progressive. To date, immunotherapy with recombinant interleukin-2 has been reported to be effective clinically for cutaneous angiosarcoma, such as of the scalp and facial skin. To our knowledge, there have been no reported cases of hepatic angiosarcoma treated with recombinant interleukin-2. Our case is important should recombinant interleukin-2 be considered effective for hepatic angiosarcoma in the future.

**Key words:** Hepatic angiosarcoma, Recombinant interleukin-2, Hepatic arterial infusion therapy

Primary hepatic sarcomas are very rare tumors and comprise less than 1 percent of all hepatic malignancies<sup>25)</sup>. They include angiosarcoma, epithelioid hemangioendothelioma (EHE), embryonal sarcoma, and leiomyosarcoma. Because both hepatic angiosarcoma and EHE do not result in characteristic symptoms or image findings, the differential diagnosis is very difficult. Treatment of hepatic angiosarcoma includes surgical resection and systemic chemotherapy, though there is no established effective treatment because

the tumor stage at the time of diagnosis is often progressive. Several case reports have described treatment of angiosarcoma with recombinant interleukin-2 (rIL-2), and many of those cases were cutaneous angiosarcoma, such as of the scalp and facial skin. It is reported that hemangiosarcoma cells are lymphokine-activated killer (LAK)-sensitive, and LAK cells induced by rIL-2 suppress the growth of hemangiosarcoma<sup>15)</sup>. rIL-2 is considered to be effective against EHE based on a similar mechanism. Our case was

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**Abbreviations:** EHE; epithelioid hemangioendothelioma, rIL-2; recombinant interleukin-2, LAK; lymphokine-activated killer, CT; computed tomography, MRI; magnetic resonance imaging

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diagnosed as EHE upon presentation and the patient underwent arterial rIL-2 infusion therapy. After her death, autopsy showed that the correct diagnosis was hepatic angiosarcoma. Thus, the case was treated as EHE, but turned out to be the first case of hepatic angiosarcoma treated with rIL-2. Although the response to treatment was poor, we think it is an important case as it could lead to the investigation of an alternative treatment for hepatic angiosarcoma.

### CASE REPORT

The patient was a 60-year-old Japanese female. She had no history of contact with Thorotrast (thorium dioxide), vinyl chloride and arsenic. Her appetite had diminished since September 2006 (at the age of 59 years). She presented with both lower-limb edema in December 2006 (at the age of 60 years) and with abdominal fullness in January 2007. She consulted her local physician and computed tomography (CT) of the abdomen showed multiple liver tumors. She was referred to our hospital for admission and further examination of the liver tumors.

On her admission, physical examination showed icteric conjunctiva and skin, hepatomegaly and both lower-limb edema. Her laboratory data

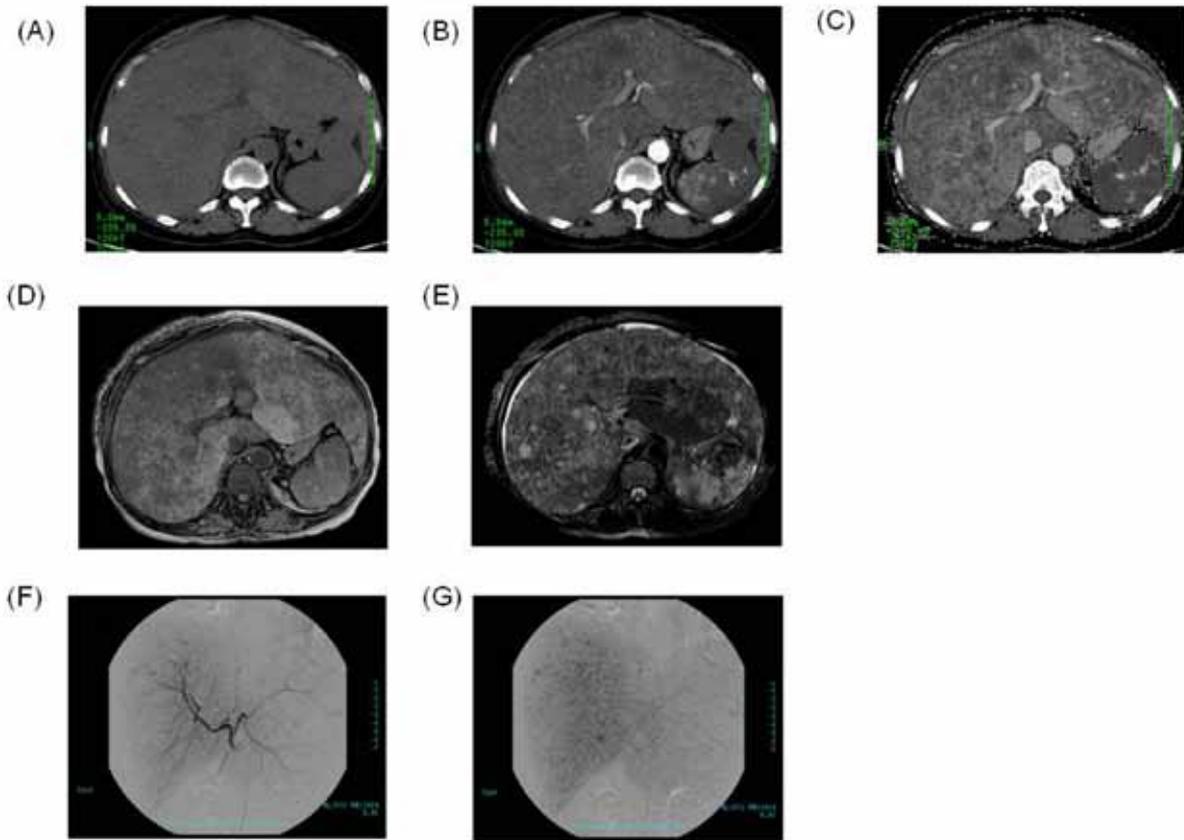
(Table 1) showed high total bilirubin, low serum albumin, mild increase in factor VIII, and negativity for hepatitis B and C viruses. CT of the whole body showed considerable hepatomegaly, numerous liver tumors (Fig. 1A, 1B, 1C), splenomegaly and multiple tumors in the spleen. The liver and spleen tumors were slightly hyperdense on hepatic artery phase and hypodense on hepatic parenchymal phase on contrast-enhanced CT. Several nodules measuring 5 mm were noted in both lungs. Osteogenic changes were recognized in thoracic vertebra 12, sacral bone and right ischial bone. Magnetic resonance imaging (MRI) of the abdomen confirmed the presence of numerous tumors in the liver (Fig. 1D, 1E). These tumors showed low intensity on T1WI and high intensity on T2WI. Angiography of the common hepatic artery showed multiple tumor stains in the liver (Fig. 1F, 1G).

Examination of ultrasound-guided liver tumor biopsy showed a proliferation of middle-sized and round-like blood vessels lacking smooth muscle, together with a proliferation of spindle-shaped cells around the blood vessels. Based on the image findings and liver pathology, the established diagnosis was EHE of the liver accompanied by metastases in the spleen, lungs and bones. Based on the spread of liver tumors and the extensive

**Table 1.** Laboratory data on admission

| Complete blood count |  | Blood coagulation     |                | Virus markers |        |
|----------------------|--|-----------------------|----------------|---------------|--------|
| WBC                  | 9300 / $\mu$ l                         | PT                    | 69 %           | HBsAg         | (-)    |
| RBC                  | 362 $\times$ 10 <sup>4</sup> / $\mu$ l | APTT                  | 31.7 sec       | HBsAb         | (-)    |
| Hb                   | 10.2 g/dl                              | Fibrinogen            | 156 mg/dl      | HBcAb         | (-)    |
| Ht                   | 30.6 %                                 | Factor VIII           | 173 %          | HCVAb         | (-)    |
| Plt                  | 134 $\times$ 10 <sup>3</sup> / $\mu$ l |                       |                |               |        |
| Blood chemistry      |  | Tumor markers         |                | ICG-R         | 36.9 % |
| T-bil                | 3.2 mg/dl                              | T-AFP                 | <5.0 ng/ml     |               |        |
| AST                  | 88 IU/liter                            | AFP-L3                | Not detectable |               |        |
| ALT                  | 40 IU/liter                            | PIVKA-II              | 24.0 mAU/ml    |               |        |
| LDH                  | 556 IU/liter                           | CEA                   | 2.4 ng/ml      |               |        |
| ALP                  | 529 IU/liter                           | CA19-9                | 63 U/ml        |               |        |
| $\gamma$ GTP         | 217 IU/liter                           | CA125                 | 241.8 U/ml     |               |        |
| TP                   | 6.8 g/dl                               | sIL-2R                | 1000 U/ml      |               |        |
| Alb                  | 2.7 g/dl                               | Autoimmuno antibodies |                |               |        |
| BUN                  | 8 mg/dl                                | ANA                   | < $\times$ 80  |               |        |
| Cr                   | 0.6 mg/dl                              | AMA (M2)              | <5.0           |               |        |
| CRP                  | 6 mg/dl                                |                       |                |               |        |
| FBS                  | 98 mg/dl                               |                       |                |               |        |
| HbA <sub>1c</sub>    | 4.8 %                                  |                       |                |               |        |
| NH <sub>3</sub>      | 17 $\mu$ g/dl                          |                       |                |               |        |

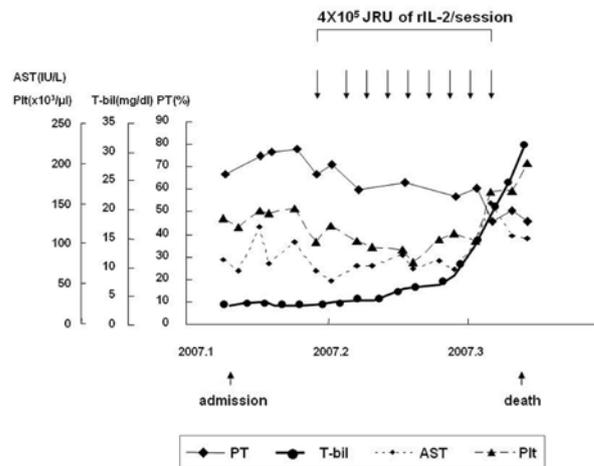
RBC; red blood cells, Ht; hematocrit, Plt; platelets, T-bil; total bilirubin, AST; aspartate aminotransferase, ALT; alanine aminotransferase, LDH; lactate dehydrogenase, ALP; alkaline phosphatase, TP; total protein, Alb; albumine, Cr; creatinine, CRP; c-reactive protein, FBS; fasting blood sugar level, PT; prothrombin time, APTT; activated partial thromboplastin time, AFP;  $\alpha$ -fetoprotein, PIVKA-II; protein induced by Vitamin K absence or antagonist-II, CEA; carcinoembryonic antigen, sIL-2R; soluble interleukin-2 receptor, ANA; antinuclear antibody, AMA; anti-mitochondrial antibody, HBsAg; hepatitis B surface antigen, HBsAb; hepatitis B surface antibody, HBcAb; hepatitis B core antibody, HCVAb; hepatitis C antibody



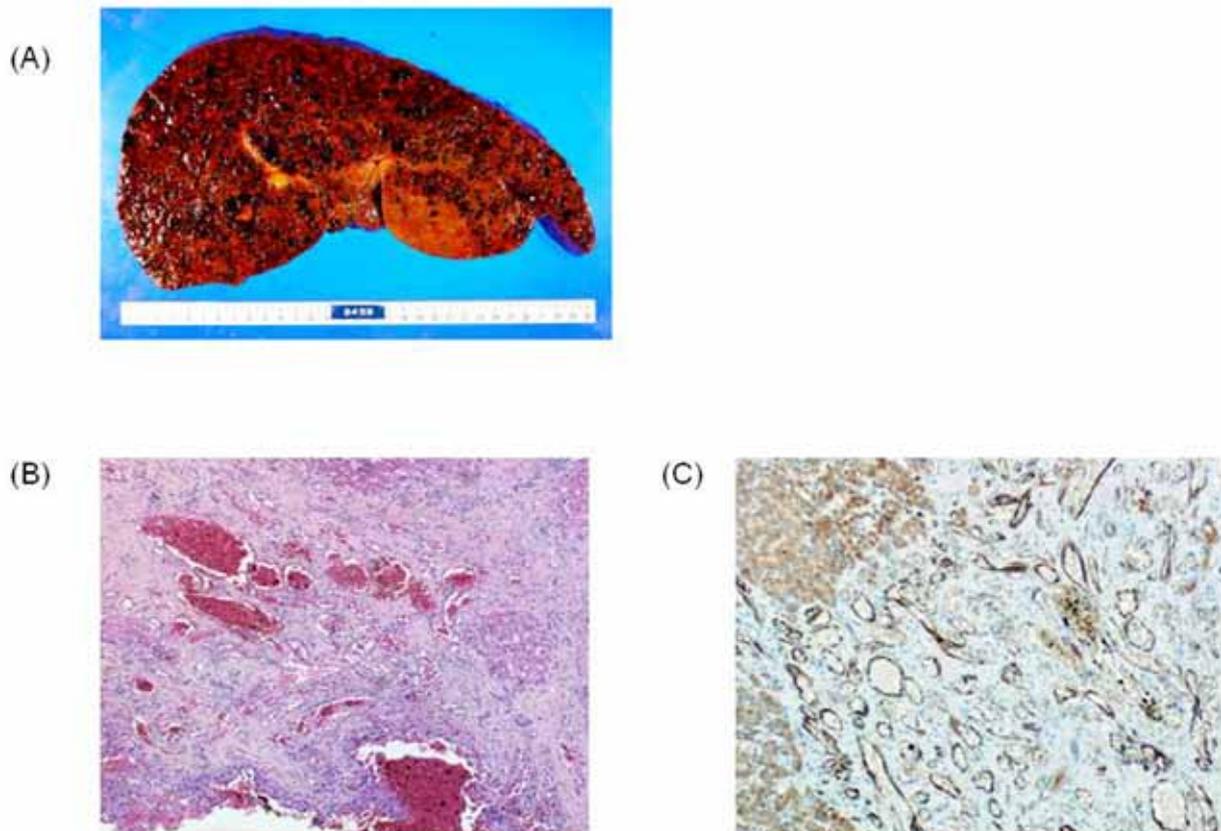
**Fig. 1.** (A) Unenhanced abdominal CT showed massive hepatomegaly and multiple hypoattenuating liver lesions. (B) Enhanced CT on the hepatic artery phase revealed multiple tumors in the liver and spleen. The tumors appeared a little hyperdense heterogeneously. (C) Enhanced CT on the hepatic parenchymal phase, tumors appeared hypodense. (D) Magnetic resonance imaging of the abdomen showed numerous tumors in liver. Tumors showed low intensity in T1-weighted images. (E) Tumors showed high intensity in T2-weighted images. (F) Angiographic findings of common hepatic artery showed multiple tumor stains in liver. Early phase. (G) Late phase.

systemic metastases, she was considered inoperable. Instead, she underwent transarterial rIL-2 infusion therapy after obtaining a written informed consent. An indwelling catheter was prepared for transarterial infusion in the common hepatic artery, and rIL-2 (celmoleukin) was infused at a dose of 400,000 JRU/session, twice a week (total 9 sessions). However, hepatic failure worsened and she died two months after admission (Fig. 2). Her autopsy was performed soon after her death. Macroscopic examination at autopsy showed marked hepatomegaly (liver weight 5 kg) and multiple tumors occupied 80 percent of the liver (Fig. 3A). Further examination showed splenomegaly (spleen weight 200 g), several tumors in the spleen, and many nodules in both lungs (maximum size, 5 mm) together with retroperitoneal lymphadenopathy.

Microscopic findings of the liver showed multiple dilated blood vessels and a proliferation of spindle-



**Fig. 2.** Clinical course after admission. rIL-2 (celmoleukin) was infused at a dose of 400,000 JRU/session through an indwelling catheter in the common hepatic artery, twice a week (total 9 sessions). Despite rIL-2 therapy, liver function worsened progressively and the patient died two months after admission.



**Fig. 3.** (A) Macroscopic findings of liver. Note the considerable hepatomegaly and multiple liver tumors. (B) Microscopic findings of the liver. Note the presence of multiple dilated blood vessels and proliferation of spindle-shaped cells around the vessels. Hematoxylin and eosin, magnification  $\times 100$ , (C) Immunohistochemical analysis using CD31, magnification  $\times 100$ .

shaped cells around the vessels (Fig. 3B). Immunohistochemical analysis showed positive staining for CD31 (Fig. 3C). The sarcoma cells occupied 80 percent of the liver tissue, and metastasized to the spleen, lungs, bone marrow (sternum, rib, lumbar vertebrae) and lymph nodes (around the pancreas).

### DISCUSSION

Angiosarcoma is a rare mesenchymal malignant tumor and accounts for 2 percent of all soft-tissue sarcomas<sup>13,19</sup>. Primary hepatic sarcoma is also very rare, but is the most common of hepatic mesenchymal tumors<sup>10,14</sup>. Hepatic angiosarcoma is derived from endothelial cells of Disse space and the tumor is histologically positive for vascular markers (such as factor VIII-related antigen, CD31, CD34).

Hepatic angiosarcoma occurs most commonly in patients 60-70 years of age with a 4 to 1 male preponderance<sup>2,11,24</sup>. As risk factors of hepatic angiosarcoma, Thorotrast (thorium dioxide), arsenic, anabolic steroid and vinyl chloride have been recognized<sup>17</sup>. In addition, hemochromatosis has been reported to be related to angiosarcoma<sup>4</sup>.

However, most cases have no such risk factors<sup>10</sup> and our case also had no history of exposure to the above compounds.

The diagnosis of hepatic angiosarcoma using radiographic techniques is very difficult because the image findings vary widely. On CT, angiosarcoma is often found as a huge mass, a huge mass with nodules, multiple nodules, or hepatomegaly with multiple or diffuse military micronodular tumors<sup>26</sup>. Most lesions are hypoattenuating, but some appear hyperdense on unenhanced CT. On contrast-enhanced CT, angiosarcoma may show a variety of findings. MRI also shows non-specific patterns. However, on T1-weighted images, tumors often contain irregular areas of high signal intensity, suggesting hemorrhage, and on T2-weighted images, tumors often show heterogeneous architecture<sup>10,26</sup>. Similarly, image findings of EHE are variable<sup>16</sup> and it is difficult to differentiate angiosarcoma from EHE.

Microscopic findings are helpful for diagnosis, especially immunostaining with vascular markers. However, differentiation of angiosarcoma from EHE by examination of percutaneous liver biopsy is very difficult, although the pathological

findings can show tumor of vascular origin. Liver biopsy is sometimes not diagnostic<sup>17)</sup> and many cases are diagnosed as angiosarcoma at autopsy<sup>11)</sup>. EHE is also derived from endothelial cells, like angiosarcoma. EHE usually arises in the liver, lung or bone and can be regarded as a type of low-grade angiosarcoma<sup>25)</sup>. EHE is histologically composed of dendritic and epithelioid cells with abundant eosinophilic cytoplasm and well-defined margins<sup>7,12,26)</sup>. Like angiosarcoma, immunostaining is positive for factor VIII-related antigen, CD31 or CD34. However, although tumor cells of angiosarcoma are also spindle-shaped and form vascular channels<sup>10)</sup>, they show more destructive invasion than EHE. The microscopic findings in our case showed multiple dilated distorted blood vessels and a proliferation of spindle-shaped cells around the vessels that were positive for CD31. These findings are diagnostic for angiosarcoma.

EHE is usually treated by surgical resection, systemic or intra-arterial chemotherapy, or transarterial embolization. The most adequate treatment option is surgical resection, but curative resection is often impossible because EHE often presents in multinodular diffuse manner. Therefore, liver transplantation has been recommended when lesions are limited only to the liver and surgical resection cannot be advocated<sup>7,18)</sup>. Moreover, one reported case was treated by rIL-2 with a favorable outcome<sup>6)</sup>. Based on that report, transarterial rIL-2 infusion therapy was selected for our patient.

On the other hand, angiosarcoma has a high malignant potential and most cases die within one year after diagnosis<sup>11,22)</sup>. The first choice of treatment for hepatic angiosarcoma is liver resection, but the reported percentage of patients who undergo resection is only 20 percent<sup>1)</sup>. The effects of systemic chemotherapy and radiation therapy are also poor. To date, immunotherapy with rIL-2, either topical or systemically, has also been reported to be effective clinically for angiosarcoma of the scalp, facial skin, nose, vagina and lung<sup>5,8,9,20,23)</sup>. IL-2 is a lymphokine secreted by activated helper T-cells, and is known to activate or enhance the proliferation of antigen-specific killer cells, natural killer cells, and lymphokine-activated killer (LAK) cells, which have cytotoxic effects<sup>3,21)</sup>. Using a SCID mouse model of human hemangiosarcoma, Masuzawa et al<sup>15)</sup> indicated that LAK cells induced by rIL-2 expressed cytotoxic activity strong enough to suppress human hemangiosarcoma. However, rIL-2 was not effective in our patient, probably due to progressive liver failure or the ineffectualness of rIL-2 for hepatic angiosarcoma.

To our knowledge, there are no reports about hepatic angiosarcoma treated with rIL-2 in the English literature. At present, due to the rarity of angiosarcoma, it is difficult to state with certainty that rIL-2 is effective against hepatic angio-

sarcoma. However, rIL-2 has been reported to be effective against angiosarcoma of other organs. Consequently, it is important to accumulate further cases with hepatic angiosarcoma and investigate the effectiveness of rIL-2.

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## REFERENCES

1. **Alrenga, D.P.** 1975. Primary angiosarcoma of the liver. Review article. *Int. Surg.* **60**:198-203.
2. **Brady, J., Liberatore, F., Harper, P., Greenwald, P., Burnett, W., Davies, J.N., Bishop, M., Polan, A. and Vianna, N.** 1977. Angiosarcoma of the liver: an epidemiologic survey. *J. Natl. Cancer Inst.* **59**:1383-1385.
3. **Damle, N.K., Doyle, L.V., Bender, J.R. and Bradley, E.C.** 1987. Interleukin 2-activated human lymphocytes exhibit enhanced adhesion to normal vascular endothelial cells and cause their lysis. *J. Immunol.* **138**:1779-1785.
4. **Fracanzani, A.L., Conte, D., Fraquelli, M., Taioli, E., Mattioli, M., Losco, A. and Fargion, S.** 2001. Increased cancer risk in a cohort of 230 patients with hereditary hemochromatosis in comparison to matched control patients with non-iron-related chronic liver disease. *Hepatology* **33**:647-651.
5. **Fukushima, K., Dejima, K., Koike, S., Tei, G., Asano, J., Ueda, M., Hyuga, M. and Oshima, W.** 2006. A case of angiosarcoma of the nasal cavity successfully treated with recombinant interleukin-2. *Otolaryngol. Head Neck Surg.* **134**:886-887.
6. **Furui, S., Itai, Y., Ohtomo, K., Yamauchi, T., Takenaka, E., Iio, M., Ibukuro, K., Shichijo, Y. and Inoue, Y.** 1989. Hepatic epithelioid hemangioendothelioma: report of five cases. *Radiology* **171**: 63-68.
7. **García-Botella, A., Díez-Valladares, L., Martín-Antona, E., Martín-Antosa, E., Sánchez-Pernaute, A., Pérez-Aguirre, E., Ortega, L., Rodríguez, R., Balibrea, J.L.** 2006. Epithelioid hemangioendothelioma of the liver. *J. Hepatobiliary Pancreat Surg.***13**:167-171.
8. **Inaba, T., Yamanaka, K., Asahi, K., Omoto, Y., Isoda, K., Hurwitz, D., Kupper, T.S. and Mizutani, H.** 2005. Complete remission in a patient with angiosarcoma by the combination of OK-432, rhIL-2, and radiotherapy. *Eur. J. Dermatol.* **15**:411-413.
9. **Kojima, K., Okamoto, I., Ushijima, S., Yoshinaga, T., Kitaoka, M., Suga, M. and Sasaki, Y.** 2003. Successful treatment of primary pulmonary angiosarcoma. *Chest.* **124**:2397-2400.
10. **Koyama, T., Fletcher, J.G., Johnson, C.D., Kuo, M.S., Notohara, K. and Burgart, L.J.** 2002. Primary hepatic angiosarcoma: findings at CT and MR imaging. *Radiology* **222**:667-673.
11. **Locker, G.Y., Doroshow, J.H., Zwelling, L.A. and Chabner, B.A.** 1979. The clinical features of hepatic angiosarcoma: a report of four cases and a review of the English literature. *Medicine* **58**:48-

- 64.
12. **Lyburn, I.D., Torreggiani, W.C., Harris, A.C., Zwirewich, C.V., Buckley, A.R., Davis, J.E., Chung, S.W., Scudamore, C.H. and Ho, S.G.** 2003. Hepatic epithelioid hemangioendothelioma: sonographic, CT, and MR imaging appearances. *Am. J. Roentgenol.* **180**:1359-1364.
  13. **Maddox, J.C. and Evans, H.L.** 1981. Angiosarcoma of the skin and soft tissue: a study of forty-four cases. *Cancer* **48**:1907-1921.
  14. **Maeda, T., Tateishi, U., Hasegawa, T., Ojima, H., Arai, Y. and Sugimura, K.** 2007. Primary hepatic angiosarcoma on coregistered FDG PET and CT images. *Am. J. Roentgenol.* **188**:1615-1617.
  15. **Masuzawa, M., Mochida, N., Amano, T., Fujimura, T., Hamada, Y., Tamauchi, H., Sakurai, Y., Nishiyama, S. and Katsuoka, K.** 2001. Evaluation of recombinant interleukin-2 immunotherapy for human hemangiosarcoma in a SCID mice model(WB-SCID). *J. Dermatol. Sci.* **27**:88-94.
  16. **Miller, W.J., Dodd, G.D., 3rd, Federle, M.P. and Baron, R.L.** 1992. Epithelioid hemangioendothelioma of the liver: imaging findings with pathologic correlation. *Am. J. Roentgenol.* **159**:53-57.
  17. **Molina, E. and Hernandez, A.** 2003. Clinical manifestations of primary hepatic angiosarcoma. *Dig. Dis. Sci.* **48**:677-682.
  18. **Mucha, K., Foronczewicz, B., Zieniewicz, K., Nyckowski, P., Krawczyk, M., Cyganek, A. and Paczek, L.** 2006. Patient with liver epithelioid hemangioendothelioma treated by transplantation: 3 years' observation. *Transplant. Proc.* **38**:231-233.
  19. **Naka, N., Ohsawa, M., Tomita, Y., Kanno, H., Uchida, A. and Aozasa, K.** 1995. Angiosarcoma in Japan. A review of 99 cases. *Cancer* **75**:989-996.
  20. **Ohguri, T., Imada, H., Nomoto, S., Yahara, K., Hisaoka, M., Hashimoto, H., Tokura, Y., Nakamura, K., Shioyama, Y., Honda, H., Terashima, H., Moroi, Y., Furue, M. and Korogi, Y.** 2005. Angiosarcoma of the scalp treated with curative radiotherapy plus recombinant interleukin-2 immunotherapy. *Int. J. Radiat. Oncol. Biol. Phys.* **61**:1446-1453.
  21. **Rosenberg, S.A.** 1984. Adoptive immunotherapy of cancer: accomplishments and prospects. *Cancer Treat. Rep.* **68**:233-255.
  22. **Stambo, G.W. and Guiney, M.J.** 2007. Hepatic angiosarcoma presenting as an acute intra-abdominal hemorrhage treated with transarterial chemoembolization. *Sarcoma* **2007**:90169.
  23. **Takeuchi, K., Deguchi, M., Hamana, S., Motoyama, S., Kitazawa, S. and Maruo, T.** 2005. A case of postirradiation vaginal angiosarcoma treated with recombinant interleukin-2 therapy. *Int. J. Gynecol. Cancer* **15**:1163-1165.
  24. **Tamburro, C.H.** 1984. Relationship of vinyl monomers and liver cancers: angiosarcoma and hepatocellular carcinoma. *Semin. Liver Dis.* **4**:158-169.
  25. **Weitz, J., Klimstra, D.S., Cymes, K., Jarnagin, W.R., D'Angelica, M., La Quaglia, M.P., Fong, Y., Brennan, M.F., Blumgart, L.H. and Dematteo, R.P.** 2007. Management of primary liver sarcomas. *Cancer* **109**:1391-1396.
  26. **Yu, R.S., Chen, Y., Jiang, B., Wang, L.H. and Xu, X.F.** 2008. Primary hepatic sarcomas: CT findings. *Eur. Radiol.* **18**:2196-2205.