Diffuse liver angiosarcoma and cerebral cavernous angiomas in a young patient

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Abstract

A case of a thirty-nine year old woman with cerebral cavernous angiomas who developed anaemia and thrombocytopenia secondary to diffuse liver angiosarcoma is reported. This unique association of liver angiosarcoma and cerebral cavernous angiomas may suggest that this tumour may potentially develop from benign vascular lesions. Hematologic abnormalities in angiosarcomas are moreover reviewed based on recent literature search. (Acta gastroenterol. belg., **1999**, 62, **446-449**).

Key words: angiosarcoma, cavernous angioma, radiological diagnosis, thrombocytopenia.

Case report

A thirty-nine year old woman was admitted for pallor, fever and abdominal pain. Her previous history was unremarkable except for three episodes of cerebral trunk bleeding related to cavernous angiomas which let her with a right fascial paralysis. She was taking no medication except for an oral contraceptive pill (Mercilon®) taken for the last ten years.

Two weeks before admission, she experienced a dry cough together with a progressive pain and swelling of the right upper quadrant. Her general physician felt a large hepatomegaly at abdominal examination, subsequent ultrasound showed multiple solid liver tumours and she was referred to our hospital.

Upon admission, temperature was 37.6°C, hepatomegaly was measured at 18 centimetres ; there was no sign of liver failure or ascitis. The rest of the physical examination was normal.

Pertinent laboratory included : CRP 14 mg/dl (N < 0.8 mg/dl), WBC 23360/µl (N = 4-10000/mm^3), haemoglobin 7.5 gr/dl (N = 12-17 gr/dl), MCV 71µ3 (N = 85-95µ3), platelets 36000/µl (N = 150-350000/mm^3). Fibrinogen was increased at 568 mg/dl (N = 150-400 mg/dl) as well as factor VIII (197%). Fibrinogen degradation products level was 20 (N :0-20 µg/ml). β2 thromboglobulin was increased at 258 ng/ml (N :15-40). Liver enzymes were slightly increased : AST 43(N = 15-25), ALT 20 (N = 4-32), γGT 89 (N = 5-45), ALK. Phosph. 189 (N = 10-60) and LDH 695 UI/L (N = 100-340). Bilirubin, albuminemia and INR were in the normal range. Tumoral markers were slightly elevated : Ca 125 (× 4), Ca 15.3 (× 2), Ca 19.9 (× 1.5), NSE (× 1.5). CEA and alpha-foeto protein were normal. Serology for A, B and C viral hepatitis and anti-platelets antibodies were negative. The schizocyte count and a blood smear was normal, bone marrow biopsy revealed regenerative hyperplasia, and numerous megacaryocytes.

Upper abdominal tomodensitometry showed multiple and diffuse liver tumours, the largest one involving segments IV and VIII (5 × 8 × 15cm) without hypervascularisation at the arterial phase. Liver MRI (fig. 1,2)

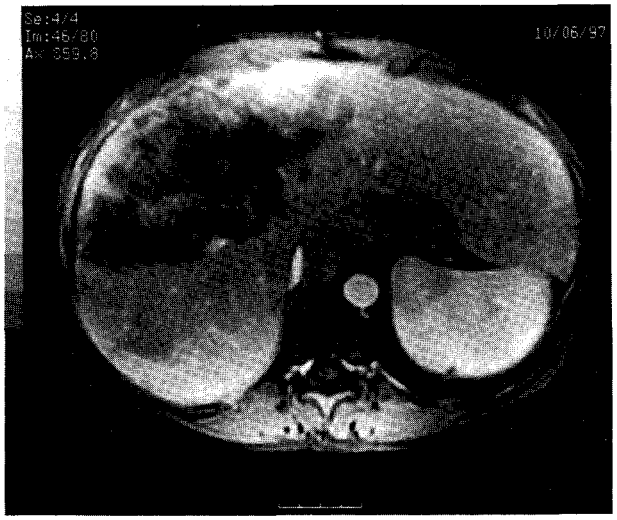

Fig. 1.

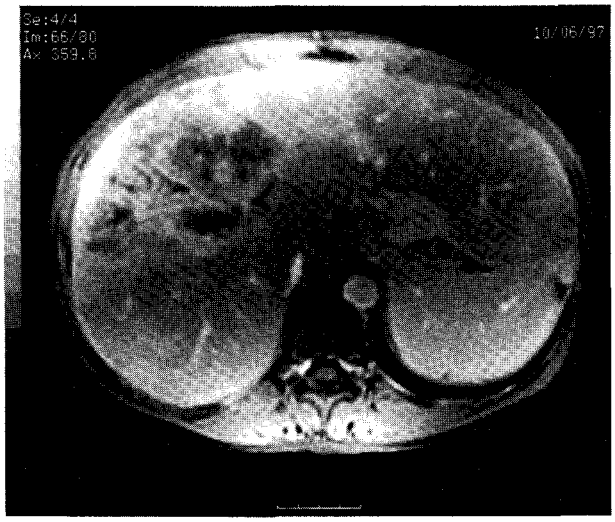

Fig. 2.

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showed multiple hypovascularized heterogenous tumours in all liver segments. After administration of gadolinium DTPA as contrast agent, heterogenous enhancement of the periphery of the tumour was observed with delayed centripetal fill in and persistence of hypointense necrotic region. The hepatic and portal veins were narrowed but free of thrombus. No characteristic signs of cavernous hemangioma were seen (i.e. homogenous marked hyperintensity on T2-weighted images and globular peripheral enhancement on gadolinium enhanced images). At arteriography, the arteries supplying the tumour were of normal size and some peripheral stain late in the arterial phase was observed. Isotopic tests showed that platelets half-life was markedly decreased to 3h (N :96 $\pm$ 12h) and that their destruction mainly occurred in the right hepatic lobe. An aminopyrin breath test showed that liver microsomal function was decreased at 0.24% (N $>$ 2.8%). Cerebral MRI showed the presence of five truncal hemangiomas, while ophtalmological examination did not disclose any retinal angiomas. No metastatic nodules were observed at CT of the lung (thin sections). Ponction of ascitis showed 21 gr/l of protein but was negative for tumoral cell. Progressively, the patient's general status declined while jaundice, purpura and leg oedema appeared.

During the third week, repeated tomodensitometry and MRI showed an increase of the size of the tumours extending to segments VI and VII. During the fourth week, clinical and biological signs of acute liver necrosis occurred. A surgical biopsy of the liver was then performed by laparoscopy. Macroscopic examination showed a marqued hepatomegaly with foci of necrosis and hemorrhagics zones. A little part of the liver (caudate lobe) was free of lesions. Microscopic examination showed diffuse invasion by endothelial tumoral cells which formed together to form tumoral vessels. These tumoral cells were positive for factor VIII and vimentin immunostaining. There were no signs of cirrhosis or hemochromatosis in the remainig tissue. This pattern was typical of angiosarcoma. We didn't find benign hemangioma inside the tumor but liver was diffusely invaded and lysis was present. We couldn't conclude on the presence or absence of this type of lesion.

Encephalopathy and hyperkaliemia progressively developed and the patient died after six weeks of hospital stay.

Post mortem examination showed an enlarged and hard liver (3654 g) with numerous masses and multiple areas of necrosis scattered in the parenchyma without visible cavernous hemangioma. There was a metastatic adenopathy in the liver hilum, the peritoneal cavity remaining free of cancer dissemination. Liver histology showed malignant cells invading the liver and multiple vascular channels in all hepatic segments. Immunostaining of tumoral cells for CD34 and coagulation factor VIII was positive. Five benign cavernous hemangiomas were found in the cerebral trunk.

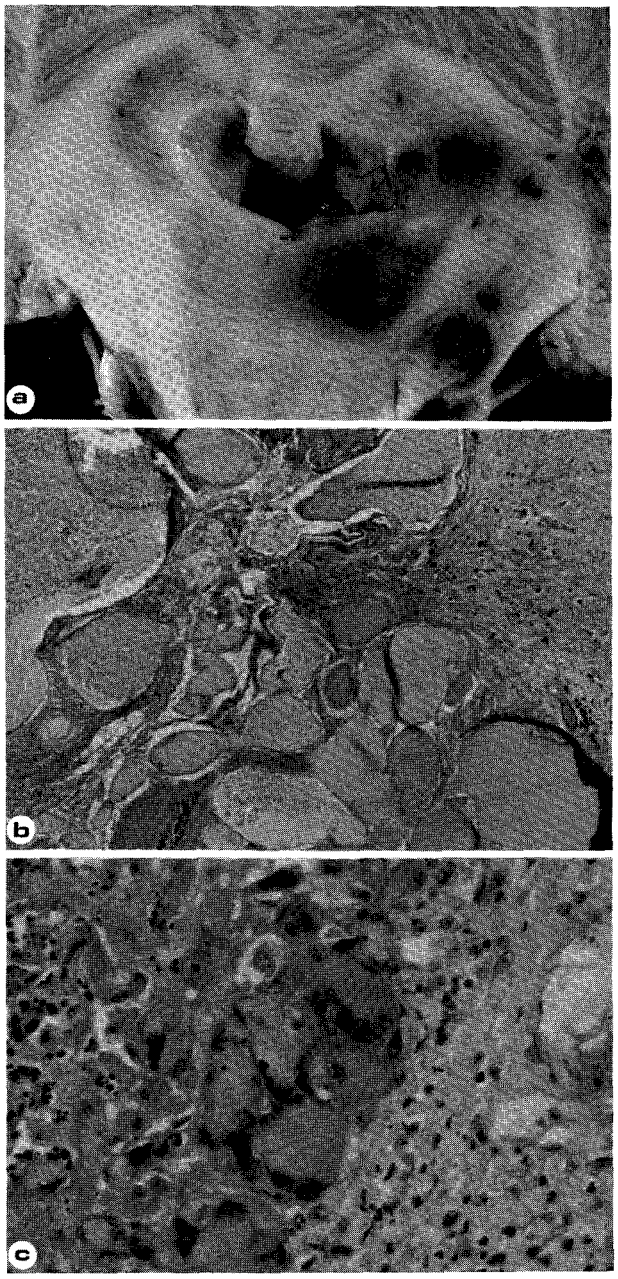

Fig. 3.

Discussion

This young patient with cerebral cavernous angiomas presented with anaemia, thrombopenia and liver tumours. The blood abnormalities were likely due to liver intravascular coagulopathy. This phenomenon, known as the Kasabatt- Meritt syndrome, has been reported in hepatic disorders such as giant cavernous angiomas of the liver (1,2) and liver hemangioendotheliomas (3). In our case, the presence of cerebral cavernous angiomas first suggested that the liver tumour might be benign giant cavernous hemangioma which

can present with fever and biological inflammatory signs (4,2). However, liver imaging showed multiple heterogenous tumours that were suggestive of a diffuse malignant process.

Liver biopsy was discussed at the end of the first week of hospital stay. According to the gastroenterologists, a transjugular or transcutaneous liver biopsy of this vascular tumour was unlikely to provide enough tissue to allow a firm diagnosis, and was at risk of tumoral dissemination if malignant. It was decided to plan a liver transplantation provided the liver biopsy at the operation time did not show an aggressive malignant disease. As the general and liver functions worsened rapidly, a surgical biopsy was obtained to rule out a treatable cancer. Biopsy showed liver angiosarcoma.

Angiosarcoma is a rare primitive tumour of the liver, accounting for about 2 % of all liver tumours (5). Only 10 to 20 new cases of angiosarcoma are reported every year in the United States, suggesting an annual incidence of about 1/10.000.000 persons (6). In autopsy series, the prevalence of this cancer is 1/100.000 (7). About 150 cases of liver angiosarcomas have been reported in the literature. Liver angiosarcoma usually occurs during the fifth or sixth decade of life (mean age of 50 year) and affects men more than women (sex ratio : 3/1).

The aetiology of liver angiosarcoma is unknown in at least 70% of the cases. Remaining cases are being clearly related to environmental carcinogenesis. Liver angiosarcoma is 10 to 15 times more frequent in workers exposed to polyvinyl chloride in plastics industries than in the general population. Other substances have also been incriminated : arsenic contained in the Fowler solution given in the past by dermatologists in the treatment of psoriasis (8) ; thorotrast used decades ago as a radiological contrast agent ; exposure to radium and a long time use of androgenic steroid or oral contraceptive (9).

Another potential aetiology of angiosarcoma is the malignant transformation of a benign liver hemangioma. This association has only been described in two patients (3,10). In our case, this association is possible, however not proved since no liver imaging was available prior to the present illness.

Liver angiosarcoma presents rarely as a single and localised mass but is rather diffuse. It behaves most frequently as a local malignancy. It can spread to the whole liver, the diaphragm or the duodenum and can rupture in the peritoneum and cause severe haemorrhage. Its clinical presentation is unspecific (5,11). Frequent symptoms include abdominal pain, fatigue, weakness and weight loss. Clinical examination shows hepatomegaly, as well as ascitis and jaundice in some cases. The biological abnormalities are also unspecific : inflammatory signs, mild elevation of alkaline phosphatase and aminotransferase levels. Alpha-foeto protein is normal in this tumour. In some patients — as it was the case here — haemolytic anaemia, thrombocytopenia or localised intravascular coagulation are present, due to consumption of blood cells and activation of the coagulation cascade by the angiosarcoma (1,12).

No imaging test is specific for angiosarcoma. Ultrasound shows heterogeneous non- liquid mass(es) in the liver. Dynamic CT scan with intravascular contrast material shows liver lesions with hypodensity before injection, variable enhancement during the arterial phase sometimes with foci of necrosis. Progressive enhancement from the periphery to the center may be seen. Magnetic resonance imaging is useful to rule out liver hemangioma which appears markedly hyperintense in T-2 weighted images and shows globular peripheral enhancement on gadolinium-enhanced images. However, a case of angiosarcoma mimicking cavernous hemangioma has been reported (13). Red blood cell scintigraphy may show accumulation in the vessels of the tumour, a feature sometimes shared by cavernous angioma (6). Liver arteriography may show peripheral stain with central hypoattenuation and puddling.

The yield of liver biopsy in vascular tumours is controversial. Through the percutaneous route, the risk of bleeding is usually high. Angiosarcoma can mimic benign vascular tumour. Immunostainig is informative. Factor VIII antigen is expressed on the endothelial cell membranes, and most frequently present in angiosarcoma. Factor VIII is neither very sensitive as it can be absent in poorly differentiated forms of angiosarcomas (14) nor very specific as it is expressed in other tumours, e.g. hemangioendothelioma (11,15). Angiosarcomas and other sarcomas also express vimentin, a cytosolic myofilament. However prekeratin which is expressed in carcinomas is absent in angiosarcomas (16). It was recently suggested that a mutation of the P53 gene is present in angiosarcomas induced by the exposure to vinyl but absent when it is induced by thorotrast (17). Sporadic angiosarcomas, i.e. angiosarcoma in the absence of toxic exposure, seem to have a mutation of the K-RAS-2 oncogen (18).

The prognosis of liver angiosarcoma is very poor with a median survival of six months (19). It is essentially an incurable disease, unresectable at the time of diagnosis. Surgery is only indicated in rare cases when the tumour is localised. Liver transplantation might be an option but little is known about post transplant survival (20). Chemotherapy has also been tried (19) improving median survival from 6 to 13 months (21). Hepatic angiosarcoma is relatively radioresistant and radiotherapy doesn't improve survival (22). Hepatic embolisation can be useful to control abdominal bleeding.

Angiosarcoma of the liver is a rare primitive malignant tumour derived from endothelial cells of the hepatic sinusoids. The diagnosis is difficult because its clinical, biological and radiological presentations are unspecific. The tumour has often spread to most hepatic segments at the time of diagnosis. Liver biopsy does not always offer a firm diagnosis as angiosarcoma

can share features with other vascular tumours. Biopsy is also risky as far as bleeding and malignant cell dissemination are concerned. The prognosis is poor with a median survival of six months. We report the first association of extrahepatic benign hemangiomas and liver angiosarcoma. This association raises the hypothesis of the transformation of a liver benign hemangioma in a malignant angiosarcoma.

References

1. WATANABE M., YLASA S., TAKETA K., KONAGA E., OKAJIMA K. A case of giant hemangioma of the liver complicated by intravascular coagulopathy. *Acta Med. Okayama*, 1978, **32** : 61-8.
2. TAILLANDIER J., ALEMANNI M., VEYSSIER P., SMADJA C., MANIGAND G., FRANCO D. Angiomes géants du foie révélés par de la fièvre et un syndrome inflammatoire. *Ann. Med. Interne*, 1995, **146** : 319-321.
3. BERTRAND L., PUYEO J., PAGES A., CIURANA AJ., BLANC F., KITSCHKE B. Hémangiosarcome du foie secondaire à un angiome caverneux calcifié ; mort en coagulopathie de consommation. *Ann. Gastroenterol. Hepatol.*, 1980, **16** : 19-27.
4. PATERTON D., BABANY G., BELGHITI J. Giant hemangioma of the liver with pain, fever and abnormal liver tests. Report of two cases. *Dig. dis. Sci.*, 1991, **36** : 524-7.
5. LOCKER G.Y. The clinical features of hepatic angiosarcoma ; a report of four case and a review of the English literature. *Medicine* (Baltimore), 1979, **58** : 48-63.
6. GINSBERG F., SLAVIN J.D., SPENCER R.P. Hepatic angiosarcoma mimicking of angioma on the three-phase technetium-99m red blood cell scintigraphy. *J. Nucl. Med.*, 1986, 1861-63.
7. KANEL G.C., KORULA J., LIEW C.T., PETRES R.L. Atypical diffuse angiosarcoma of the liver. *West J. Med.*, 1987, **146** : 482-5.
8. AXELSON O. Arsenic compounds and cancer. Hemisphere publishing corporation, 1980, 1229-35.
9. HOCH-LIGETI C. Angiosarcoma of the liver associated with diethylstilbestrol. *JAMA*, 1978, **240** : 1510-1.
10. TOHME C., DROUOT E., PIARD F., BERNARD A., BRACHET A., CHAUFFERT B., VIARD H. Hémangiome caverneux du foie associé à un angiosarcome : transformation maligne ? *Gastroenterol. Clin. Biol.*, 1991, **15** (1) : 83-86.
11. FORBES A., PORTMANN B., JOHNSON P., WILLIAMS R. Hepatic sarcoma in adults : a review of 25 cases. *Gut*, 1987, **28** : 668-674.
12. TAKKAL M., KESTENS P.J., NOËL H., DELOS M., HAOT J. Angiosarcome hépatique développé cinq ans après traitement pour glomérulonéphrite subaiguë. *Acta Gastro-Enterologica Belgica*, 1995, mars avril, Vol. LVIII, 245-251.
13. ITAI Y., TERAOKA T. Angiosarcoma of the liver mimicking cavernous hemangioma on dynamic CT. Journal of computer assisted tomography september october, 1989, **13** (5) : 910-912.
14. GUARDA L.A., ORDONEZ N.G., SMITH L., JR HANSSEN G. Immunoperoxidase localisation of factor VIII in angiosarcomas. *Arch. Pathol. Lab. Med.*, 1982, **106** : 515-6.
15. ANTHONY P.P., RAMANI P. Endothelial markers in malignant vascular tumours of the liver : superiority of QB-END/10 over Von Willebrand factor and Ulex europaeus agglutinin 1. *J. Clin. pathol.*, 1991, **44** : 29-32.
16. FORTWENGLER P.H., DOUGLAS JONES J.R., ESPINOSA E., TAMBURRO C.H. Evidence for endothelial cell origin of vinyl chloride-induce hepatic angiosarcoma. *Gastroenterology*, 1981, **80** : 1415-19.
17. HOLLSTEIN M. P53 mutation at A :T base pairs in angiosarcomas of vinyl chloride exposes factory workers. *Carcinogenesis*, 1994, **15** : 1-3.
18. PRYGODZKY R.M. Sporadic and thorotrast-induced angiosarcomas of the liver manifest frequent and multiple point mutation in K-ras-2. *Laboratory investigation*, 1997, **76** : 153-159.
19. DAS GUPTA T.K., PATEL M.K., CHAUDHURI P.K., BRIELE H.A. The role of chemotherapy as an adjuvant to surgery in the initial treatment of primary soft tissue sarcomas in adults. *J. Surg. Oncol.*, 1982, **19** : 139-144.
20. GONZALES E.M. Liver transplantation in malignant primary hepatic neoplasms. *American Journal of Surgery*, 1992, **163** :395-400.
21. TAMBURRO C.H. Relationship of vinyl monomer and liver cancers : angiosarcoma and hepatocellular carcinoma. *Sem. liver dis.*, 1984, **4** : 158-69.
22. SUIT H.D., MANKIN H.J., WOOD W.C., PROPPE K.H. Preoperative, intra operative, and postoperative radiation in the treatment of primary soft tissue sarcoma. *Cancer*, 1985, **55** : 2569-67.