'Pseudocirrhosis' in hereditary haemorrhagic telangiectasia

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SUMMARY Telangiectasia-associated hepatic fibrosis (TAHF) in a 68-year-old woman with hereditary haemorrhagic telangiectasia (HHT) is described. The patient died of oat-cell carcinoma of the lung. In addition to the structural alterations which have been described previously in HHT, the liver exhibited focal midlobular hepatocytic necrosis and tumour metastases. The possibility that treatment of HHT was causally related to some of the hepatic abnormalities found in our patient and the differentiation of TAHF from true cirrhosis are discussed.

The occurrence of a specific hepatic pathology in hereditary haemorrhagic telangiectasia (HHT) is not established. A review of the recent literature reveals 25 cases in which liver biopsy or examination at necropsy showed telangiectases and hepatic changes variously described as cirrhosis, atypical cirrhosis, or fibrosis. The probable aetiology of the abnormalities in nine of the cases has been specified: these are congestive cardiac failure (4) (Halpern *et al.*, 1968; Pietschmann and Kolarz, 1969; Schuster, 1937); post-hepatic cirrhosis (4) (Hales, 1956; Smith and Lineback, 1954; Sussman and Sternberg, 1975; Zelman, 1962); and one case with a known history of alcohol and narcotics abuse (Van Bogaert and Scherer, 1935). Of the remaining 16 cases, the aetiology is unknown or unspecified in 10 (Angervall, 1954—own case and cited cases of Rooschuz (1937), Harding (1941), and Johnson and Nordensson (1942); Halpern *et al.*, 1968; Werner, 1942; Ytrehus, 1948); and six cases are recorded (Feizi, 1972; Martini, 1959) in which it is suggested (Feizi, 1972) that the cirrhosis is a direct result of the telangiectases. Hepatic telangiectases have also been reported in the absence of fibrosis (4) (Graham *et al.*, 1964; Michaeli *et al.*, 1968; Razi *et al.*, 1971; Smith and Lineback, 1954) or with minimal fibrosis (1) (Tedesco *et al.*, 1975). Hepatocellular carcinoma was reported in the case of Sussman and Sternberg (1975).

We report a case of HHT in which telangiectasia-associated hepatic fibrosis (TAHF) and nodular hepatocytic hyperplasia are present, together with the hitherto unreported features of focal midlobular necrosis and metastatic oat-cell carcinoma.

Case report

A 68-year-old woman with HHT was admitted to hospital in September 1976 with recurrent epistaxis, melaena, and progressive dyspnoea on exertion. During the previous 15 years she had been treated regularly for epistaxis and iron deficiency anaemia with stilboestrol, 5 mg daily, and oral and parenteral iron. In addition, blood transfusions had been required with increasing frequency during the latter years to maintain an adequate haemoglobin. The patient neither smoked nor drank and had a well-documented family history of HHT (Fig. 1).

Physical examination revealed telangiectases on the lips, tongue, buccal mucosa, and skin of the trunk. The patient appeared anaemic and exhibited finger clubbing, uniform non-tender hepatomegaly, and signs of consolidation in the lower zone of the right lung.

Laboratory investigations yielded the following results: haemoglobin 5.0 g/dl (5.0 g/100 ml); MCV 71 fl (71 μ^3); MCH 19.1 pg (19.1 pg); MCHC 27 g/dl (27%); PCV 0.18 (18%); white cell count $4.2 \times 10^9/l$ (4200/mm³), normal differential; platelets $295 \times 10^9/l$ (295 000/mm³); erythrocyte sedimentation rate 116 mm in 1 hour. Faecal occult bloods positive. Total protein 79 g/l (7.9 g/100 ml); albumin 40 g/l (4.0 g/100 ml); total bilirubin 10.2 μ mol/l (0.6 mg/100 ml); alkaline phosphatase 125 IU; SGOT 64 IU; SGPT 37 IU; LDH 600 IU. Serum iron 5.0 μ mol/l (28 μ g/100 ml); TIBC 61.7 μ mol/l (345 μ g/100 ml). Bone marrow aspirate contained clumps of neoplastic cells.

A chest radiograph showed consolidation in the right middle and lower lobes, and tomography

Fig. 1 Family tree of our patient (arrowed), showing autosomal dominant inheritance of the gene for HHT. The fourth generation has not yet shown the trait: □ ○ = normal members; ■ ● = affected members. Diagonal stroke indicates death.

revealed narrowing of the lower lobe bronchus at the hilum suggestive of a neoplasm. Barium studies were normal. A liver scan using ^{99m}Tc showed enlargement of the organ but no evidence of focal disease. A coeliac axis arteriogram revealed abnormally tortuous vessels in the liver. Focal aggregations of contrast medium throughout both lobes of the liver suggested either multiple small arteriovenous fistulae or tumour deposits.

A diagnosis of bronchogenic carcinoma with metastatic spread to bone and possibly liver was made. The melaena was assumed to be due to epistaxis and possibly bleeding gastrointestinal telangiectases.

In spite of further transfusion the patient deteriorated and died.

NECROPSY

In addition to the external telangiectases already noted there were florid telangiectases in the mucosa of the stomach, duodenum, and proximal 4 cm of the jejunum. The right pleural cavity was obliterated by fibrous adhesions. The right lung weighed 1640 g and contained a large grey-white tumour mass at the hilum. There was extensive tumour infiltration of the middle and lower lobes, predominantly peribronchial and perivascular (Fig. 2). Both right and left hilar lymph nodes were replaced by tumour. The left lung was normal. Numerous tumour metastases were present in the vertebral column, the hilar lymph nodes, and nodes in the porta hepatis.

The liver (Fig. 3) weighed 2150 g and had a yellow-green nodular external surface. Multiple telangiectases were visible through the capsule. The cut surface of the liver showed numerous nodules of hepatic parenchyma, ranging in size from 0.2 to 0.5 cm

diameter. Hepatic venous radicles were unduly prominent. White tumour deposits, measuring up to 0.8 cm diameter, were scattered throughout both lobes. The hepatic artery, portal and hepatic veins, and extrahepatic bile ducts were normal. The spleen was normal. The remainder of the necropsy was unremarkable.

Microscopy

The lung tumour showed the features of a typical oat-cell carcinoma, and similar tumour was present in the affected lymph nodes and vertebral marrow. Sections of the stomach and duodenum (Fig. 4) showed multiple dilated thin-walled vessels resembling venules present principally in the submucosa but seen also in the mucosa in some areas. In the liver, telangiectases were present subcapsularly and scattered throughout the right and left lobes (Fig. 5). They consisted of tortuous, thin-walled vessels resembling veins, with one or several arterioles, embedded in dense fibrous tissue. Bile ducts were present in relation to some of the telangiectases, and the fibrous tissue contained a sprinkling of lymphocytes. In many areas linkage of the fibrous tissue component of the telangiectases had produced isolated nodules of hepatocytes, some of which showed hyperplastic changes (Fig. 6). However, central veins were evident in many of these nodules (Fig. 7). Foci of coagulative necrosis were present within the nodules (Fig. 8) in a mid to centrilobular distribution and also in areas where the hepatic parenchyma was diffusely hyperplastic but not nodular. Metastases of oat-cell carcinoma with peripheral sinusoidal spread were scattered throughout the liver but bore no topographic relationship to the telangiectases. The liver showed no evidence of

Fig. 2 Macroscopic appearance of right lung (oblique sagittal section) showing hilar tumour (T) with peribronchial and perivascular spread to pleura (black arrows). (Actual size $\times 0.5$)

Fig. 3 Macroscopic appearance of liver showing nodularity of surface (long arrows), prominent venous radicles (open arrows), metastatic tumour nodules (white), and fine nodules of hepatic parenchyma (short arrows). (Actual size $\times 0.7$)

Fig. 4 Microscopic appearance of duodenal submucosal telangiectasis showing thin-walled venules (V) with related arterioles (a). (Elastic van Gieson $\times 23$)

Fig. 5 Microscopic appearance of hepatic telangiectasis showing many thin-walled tortuous venules (V) with feeding arterioles (a) embedded in dense fibrous tissue which is moderately infiltrated with lymphocytes. The lesion is bounded by lobules of liver cells (LOB). (Haematoxylin and eosin $\times 25$)

Fig. 6 Microscopic appearance of hyperplastic liver nodules showing doubling of liver cell plates. (Reticulin stain counterstained with neutral red $\times 40$)

Fig. 7 Hepatic nodule carved out by fibrous tissue, containing a distinct central vein (CV). (Haematoxylin and eosin $\times 40$)

Fig. 8 Mid to centrilobular coagulative hepatocyte necrosis with polymorph infiltration (CV = central vein; BD = bile ductule). (Haematoxylin and eosin $\times 23$)

siderosis, and multiple sections stained by the Orcein method for hepatitis B antigen (Shikata *et al.*, 1974) were negative.

Discussion

The specific hepatic pathology in HHT is difficult to delineate. In many of the recorded cases complicating factors were present which may have been causally related to the development of hepatic fibrosis, for example, congestive cardiac failure, serum hepatitis, and alcohol or drug abuse. In other cases the histology of the liver is not recorded in sufficient detail for accurate comparison.

Most authors agree on the existence of telangiectases and associated hepatic fibrosis in affected cases. Whether or not hyperplastic nodules form part of the liver lesion in HHT is a more contentious issue. Eleven cases of TAHF have been described in which the liver exhibited 'regenerative' nodules (Halpern *et al.*, 1968; Martini, 1959; Sussman and Sternberg, 1975; Zelman, 1962). Of these, two had serum hepatitis (Sussman and Sternberg, 1975; Zelman, 1962) and two suffered from congestive cardiac failure (Halpern *et al.*, 1968). The presence or absence of complicating factors was not recorded in two cases (Halpern *et al.*, 1968), and in the five

remaining cases, although transfusion hepatitis was excluded as a cause of hepatic fibrosis, alcohol abuse or congestive cardiac failure was not (Martini, 1959). Unfortunately the detailed structure of these 'regenerative' nodules was not described in any of the 11 cases.

The liver in Feizi's (1972) case contained hyperplastic lobules with normal architectural relationship of central veins to portal tracts. There were no known complicating factors in that case and the liver histology appears similar to that of the case reported here.

The pathogenesis of the parenchymal hyperplasia in our case is not clear. Abnormalities of blood flow have been postulated as the cause of nodular hyperplasia in the liver in certain conditions (Blendis *et al.*, 1974; Steiner, 1959), but the evidence is not conclusive. The vascular anomalies in our case may have a causal relationship with the hepatocyte hyperplasia but this relationship is obscured by other factors including oestrogen therapy and metastases of oat-cell carcinoma. Compensatory hyperplasia of residual hepatic parenchyma is known to occur with reduction in the total liver mass after surgical removal or replacement by tumour deposits (Edmondson and Peters, 1971). It is of interest that metastases were present in the liver of this case as the

true cirrhotic liver is less liable to metastatic disease than its normal counterpart (Ruebner *et al.*, 1961).

High-dose oestrogen therapy is used to reduce the frequency of epistaxes in patients with HHT by inducing squamous metaplasia of the nasal epithelium (Harrison, 1964). Our patient was treated in this fashion and it is possible that the hepatocytic hyperplasia may have been related to this therapy. The development of focal nodular hyperplasia (Mays *et al.*, 1974) and liver cell adenomas (Contostavlos, 1973) in patients treated with oestrogen-containing compounds has been well documented, and the association appears to be statistically significant (Edmondson *et al.*, 1976).

Peliosis hepatis is also a recognised complication of long-term oestrogen therapy (Naeim *et al.*, 1973) but vascular alterations attributable to such therapy have not been described in patients with HHT; and there does not appear to be any appreciable histological difference between the vascular anomalies of the treated and untreated patients, although Rowley *et al.* (1970) have suggested that there may be a causal relationship between oestrogens and aggravation of clinical manifestations of HHT.

The midzonal necrosis seen in some of the liver lobules in our case is similar to that recorded in the reports of Sussman and Sternberg (1975) and Zelman (1962). This phenomenon did not appear to be due to encroachment of tumour on the local blood supply as step sections failed to reveal adjacent tumour in many of the affected areas. The fact that the coagulative necrosis was confined to the mid to centrizonal portions of the lobules suggested that it was the result of hypoperfusion probably following haemorrhage from one of the gastrointestinal telangiectases.

On the basis of the findings in our case and other acceptable cases in the literature it appears that alterations in the liver in HHT constitute a specific pathological entity. The TAHF lesion is characterised by the presence of broad bands of fibrous tissue in subcapsular and portal areas in which are embedded many large, thin-walled vessels resembling veins and smaller numbers of muscular arteries. Linkage of these fibrous bands results in nodularity of the hepatic parenchyma, but within these nodules the orthodox relationship of central veins to portal areas is maintained, unlike the regenerative nodules of a true cirrhosis. We feel that the focal hyperplasia of the liver described here is not a component of the TAHF lesion but is ascribable to other factors. It is hoped that further reports of uncomplicated cases will elucidate this point.

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