Portal Cirrhosis and Idiopathic Pulmonary Fibrosis with Generalised Moderate Haemosiderosis

by K. S. Lau,
M.B., B.S., F.R.C.P.A.
Professor of Pathology.

A. P. Mukherjee
M.B., M.R.C.P.E.*
Lecturer in Medicine.
*Present address:
Consultant Physician,
Shotley Bridge General Hospital,
Consett, Co. Durham, U.K.

K. Prathap
M.D.(Malaya), M.R.C.Path.
Associate Professor in Pathology.

J. C. White
M.D. (Birm.), F.R.C.Path.
Associate Professor in Pathology.
Departments of Pathology and Medicine of the Faculty of Medicine,
University of Malaya.

Introduction

A CASE is described with an unusual association of portal cirrhosis, multiple nodular fibrotic lesions in both lungs and widespread but moderate haemosiderosis.

Case Report

A Chinese Male of 38 years was admitted to the University Hospital with intermittent haemoptysis for 10 years, yellowish discolouration of the body for 6 months, polyuria and polydypsia for 3 months. There was no previous serious illness. He lived in Klang, Selangor, and worked as an odd-job labourer. He had donated blood several times previously, and drank about two pints (1200 ml) of "toddy" (an alcoholic beverage from palm) per week. There was no family history of any serious illness, including diabetes, tuberculosis or liver disease. On examination he was well-built, jaundiced, with minimal ankle oedema and many spider naevi. Apart from moderate hepato-splenomegaly there were no abnormal physical findings. The urine contained no protein or bilirubin but there was glycosuria and increased urobilinogen; porphyrins were normal. A glucose tolerance test showed a moderately severe diabetic curve. Serum bilirubin was 2.6 mg/100 ml, S.G.O.T. 57 I.U./1, alkaline phophatase 20 King-Armstrong units, plasma protein 7 g/100 ml (albumin, 3.17 g, α 1-globulin, 0.06 g, α 2-globulin, 0.26 g, β-globulin, 1.08 g, α -globulin, 2.43 g per 100 ml). Radiological examination of the chest showed multiple irregular nodular lesions with interstitial infiltrates throughout both lungs. Haemoglobin was 16.7 g/100 ml with slight variability of the red cells, WBC 4700/μl, platelets 60000/l μ. Sternal bone marrow appeared structurally normal but with moderate excess of haemosiderin in the storage reticulum cells and normal fine iron granules in the erythroblast cytoplasm. Serum iron was 187 μg/100 ml, unsaturated iron binding capacity 17 μg/100 ml and total iron binding capacity 204 μg/100 ml; folate 16 ng/ml and vitamin B12 620 pg/ml.

After a 500 mg dose of desferrioxamine urinary iron rose from 25 μg in the 6-hour control period to 3700 μg in the first 6-hour test period, falling again to 19 μg 4 days later. A repeat test after 2 months showed 288 μg of iron in the 24 hour control period, rising to 2300 μg in the first 6 hour test period and another 2300 μg in the following 18 hours.

Liver biopsy showed portal cirrhosis with granules of haemosiderin by Perl's stain in many parenchymal and Kupffer cells and in fibrous tissue. Lung biopsy showed pleura and local areas of alveoli thickened by fibrosis and collections of haemosiderin-laden macrophages. Hepatic cirrhosis with haemosiderosis, idiopathic pulmonary haemosiderosis and diabetes mellitus were considered to be present.

The patient remained well for 9 months, then contracted macular leprosy of tuberculoid type for which he received dapsone therapy. Four weeks later he was readmitted with severe epigastric pain, breathlessness and cyanosis. He died shortly after admission in circulatory failure. Haemoglobin during the second period was 18.7 g/100 ml, 15% of this being present as methaemoglobin; reticulocytes 0.2%. The red cell G6PD activity was normal. The white cell count was 1600/μl (poly-

morphs 20%, lymphocytes 76%, monocytes 4%). His blood urea was 40 mg/100 ml, serum amylase 222 Somogyi units/100 ml and bilirubin 2.2 mg/100 ml (1.4 mg unconjugated); there was no plasma methaemalbumin.

Autopsy findings: At autopsy 4 hours after death, the right lung weighed 870 g and left lung 990 g. There was brown induration in both, consolidation in the left lower lobe and chronic, mottled brown and white nodular lesions in both, located especially beneath the pleura and around arteries; similar lesions were present in the peri-bronchial and hilar lymph nodes. Microscopically these consisted of dense, relatively acellular collagen, partly encrusted with haemosiderin; they were surrounded by fibroblasts, macrophages laden with haemosiderin and some carbon pigment (Figs. 1 and 2). Examination in polarised light did not show birefringent inorganic structures in any of the sections. No acid-fast bacilli were found. Elsewhere, fibrosis was minimal and large numbers of haemosiderin-laden macrophages were present within the alveoli. The alveolar capillaries were distended with blood. There was minimal right ventricular hypertrophy but the heart, weight 280 g, was otherwise normal. The liver, weighing 1690 g, showed portal cirrhosis (Fig. 3). Excess of stainable iron was present in many parenchymal cells, in the Kupffer cells and fibrous tissue (Fig. 4). Iron was also seen in the endocrine and exocrine portions of pancreas, the gastric and duodenal mucosa, testes, (200 g) and bone marrow. The caecum was grossly inflamed; sections showed micro-ulceration of the mucosa, and a dense infiltration of the mucosa and submucosa by polymorphonuclear leucocytes. Large numbers of Gram-negative bacilli were present in multiple organs, including heart, kidneys, adrenals, lungs and blood vessels, suggestive of terminal septicaemia.

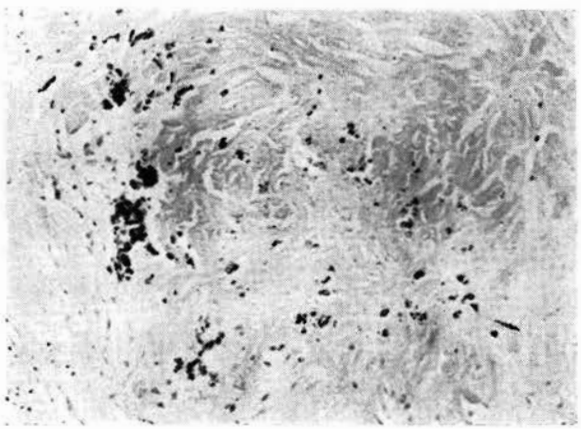

Fig. 1
Section of subpleural pulmonary nodule showing haemosiderin granules surrounded by dense acellular collagen. Prussian blue reaction, X 140.

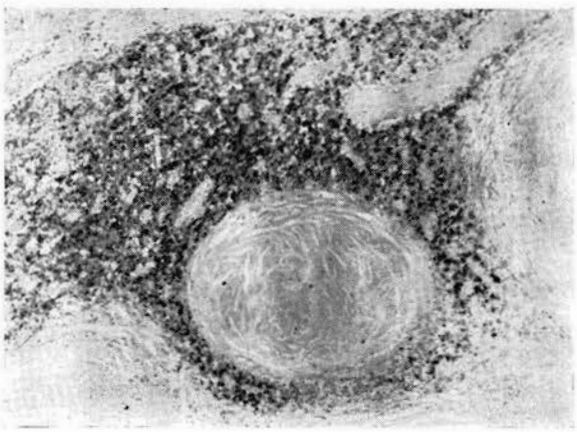

Fig. 2
Peribronchial lymph nodes showing fibrotic nodules surrounded by macrophages laden with haemosiderin and a small amount of carbon pigment. Prussian blue reaction, X 90.

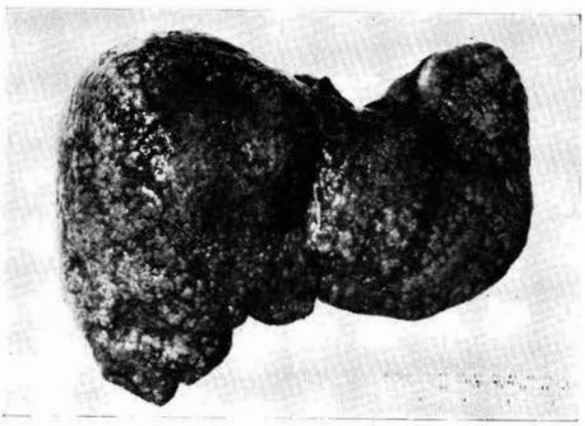

Fig. 3
Gross appearance of liver showing scarring and nodularity of the surface.

The total iron content of the wet formalin-fixed tissues was determined by bathophenanthroline after nitric-sulphuric acid digestion, and haem iron calculated from spectrophotometrically-determined pyridine haemochrome after alkaline digestion. The results are given in Table I. The copper content of the liver tissue was 3 μg/g.

A sister of the patient was examined and found to have normal levels of haemoglobin, serum iron and iron-binding capacity.

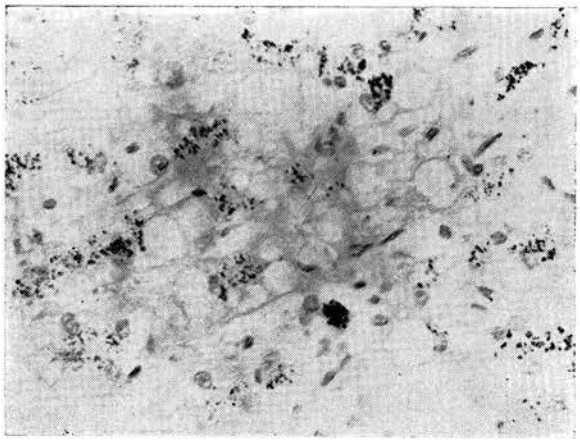

Fig. 4
Photomicrograph of liver showing haemosiderin within vacuolated parenchymatous cells and Kupffer cells. Prussian blue reaction, X 350.

Table 1

Tissue	Haem Iron μg/g of wet tissue	Non-haem Iron	
		μg/g of wet tissue	Estimated total in organ in μg.
Liver	15	130	220 x 10^3
Pancreas	26	129	
Spleen	138	236	47 x 10^3
Lungs	104	288	536 x 10^3

Summary of clinico-pathological findings:

1. Advanced portal cirrhosis with extensive fibrosis and abnormally-distributed haemosiderosis of parenchymal and Kupffer cells and fibrous tissue. Quantitatively the haemosiderin did not exceed the storage iron of normal liver (Morgan and Walters, 1963); the haemoglobin-iron content of this liver was low, however, and functional tissue over-shadowed by fibrosis.

2. Idiopathic pulomonary nodular fibrosis, associated with congestion and haemosiderosis. The haemoglobin-iron content of lungs was high, but there was considerable excess of haemosiderin-iron in macrophages. No acid-fast bacilli or birefringent inorganic structures found.

3. Diabetes with haemosiderosis of pancreas.

4. Haemosiderosis of stomach, duodenum and testes, with splenic and bone marrow haemosiderin increase.

5. Terminal Gram-negative septicaemia.

Discussion

Established, cryptogenic portal cirrhosis is present in the patient, and although the total haemosiderin content is not high, it is concentrated in the reduced parenchyma of the damaged organ. The nodular fibrotic lesions of the lungs are of unknown aetiology, and are associated with marginal, haemosiderin-laden macrophages in the alveoli elsewhere. The lesions are not very similar to the usual findings in idiopathic pulmonary haemosiderosis (Spencer, 1962). A more generalised haemosiderosis involves the pancreas, with diabetes, gastric and duodenal mucosa and testes.

Although the lung lesions raise the possibility of a dust disease, there is no history of exposure to iron ore or siliceous dust, and no birefringent inorganic structures present microscopically. The condition appears different to Kaschin-Beck disease in Manchuria (Hiyeda, 1939). Although surface water after rain, well water and untreated river water in West Malaysia are often highly ferruginous, the town water consumed by this patient has minimal iron content, and his dietary habits were apparently normal. The iron intake from his consumption of toddy amounted to about 3.8 mg per week.

Widespread distribution of haemosiderin in the tissues is of rare occurence here and raises the possibility of an aberrant iron metabolism; however, there is no real evidence for either genetic or acquired disturbances leading to excess of storage iron.

The amounts of iron found in the organs (Table I) are very low compared with the large quantities described in the literature on haemochromatosis (Kleckner, 1958) and on pulmonary haemosiderosis (Finch and Finch, 1955). The episodes of haemoptysis over 10 years, and also blood donation, would have some effect in reducing the total iron stores. Nonetheless, the local breakdown of red cells is likely to have maintained the lung iron. The amounts of iron found would correspond to those reported in younger subjects during the evolution of iron overload in the Bantu (Bothwell and Bradlow, 1960). Urinary excretion of iron after desferrioxamine is also much lower than is usual in idopathic haemocrhomatosis or even in transfusion siderosis (Dreyfus and Shapira, 1958). The bone marrow iron stores are qualitatively less marked than is frequently seen in hereditary haemolytic or in refractory anaemias in this region.

Kent and Popper (1968) have drawn attention to the inverse relationship between mild iron deposition and marked fibrosis in cirrhosis as compared

with haemochromatosis, where the reverse obtains. In the present case, however, both liver and lungs exhibit the same relationship of mild iron deposition with heavy fibrosis.

Whether the widespread but moderate distribution of haemosiderin in the present case is secondary to the fibrosis in lungs and liver remains unknown, as does the nature of pulmonary lesions and aetiology of the cirrhosis. In cirrhosis with secondary iron deposition, generalised deposition throughout the body is uncommon (Powell, 1971). Co-existence of idopathic pulmonary haemosiderosis and haemochromatosis have not been shown (Finch and Finch, 1955; Dubin, 1955; Zimmerman, Chomet, Kulesh and McWhorter, 1961).

MacSween (1966) reviewed abdominal crises, circulatory collapse and sudden death in haemochromatosis, and among the possible mechanisms he cited Gram-negative bacteraemia and/or endotoxin shock as a cause of the circulatory collapse, with possible origin in the gastro-intestinal tract. The present case, with terminal acute inflammatory changes in the caecum, exhibited intravascular Gram-negative bacilli in multiple organs; the terminal methaemoglobinaemia, occuring without demonstrable enzyme defect in the red cells, may also have resulted from bacteraemia.

Summary

Haemochromatosis is well-known in classical form, the secondary fibrotic changes in the tissues giving rise to characteristic manifestations. The present patient is a rare example of portal cirrhosis and nodular pulmonary fibrosis of unknown aetiology, accompanied by widespread moderate haemosiderosis of tissues. There is no positive indication of a primary disturbance of iron metabolism. The disparity between degree of iron deposition and degree of fibrosis makes it likely that the latter lesion is the primary event.

Acknowledgements

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