THREE CASES OF HEPATOCELLULAR CARCINOMA WITH UNUSUAL PRESENTATION

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Primary carcinoma of the liver is one of the commonest neoplasms seen in Singapore. Shanmugaratnam (1956) found that it constituted 20% of all carcinomata seen at necropsy and Muir (1961) found that primary liver tumours formed 16.2% of 1,096 malignant tumours during the period 1948 to 1958. It is known that primary liver carcinoma is commonly associated with liver cirrhosis and that examination of grossly cirrhotic livers often may show one or more small tumours undiagnosed clinically. Steiner and Davies (1957), in a study of cirrhosis and primary liver carcinoma in Uganda Africans, found an associated liver cirrhosis in 79% of the 70 cases of primary liver carcinoma studied. Also, in 100 cases of advanced liver cirrhosis a primary liver carcinoma was found in 50 of them.

Three cases of hepatocellular carcinoma presenting in unusual ways are described.

Case No. 1

A male Chinese, age 45 years, was first admitted to the Outram Road General Hospital, Singapore, on June 11, 1964, with one day's history of haematemesis and melaena. He also gave a history of having taken half a glassful of brandy daily for the previous 20 years. At the time of admission, he was in shock and pale. His liver and spleen were not palpable. He was resuscitated and investigations revealed a haemoglobin of 9.0 gm per cent and a packed-cell volume of 27 per cent. The prothrombin, bleeding and clotting times were normal, but he had a platelet count of 70,000 per cu. mm. His serum bilirubin was 0.2 mg%, thymol turbidity 2 units, alkaline phosphatase 10.0 units and serum proteins 7.1 gm% (Albumin 4.3 gm% and Globulin 2.8 gm%).

As he continued to bleed and the source of bleeding was uncertain a laparotomy was undertaken. A grossly cirrhotic liver and an enlarged spleen were found. The stomach was normal. A biopsy taken from the inferior edge of the liver showed, on histological examination, post-necrotic cirrhosis (Fig. 1).

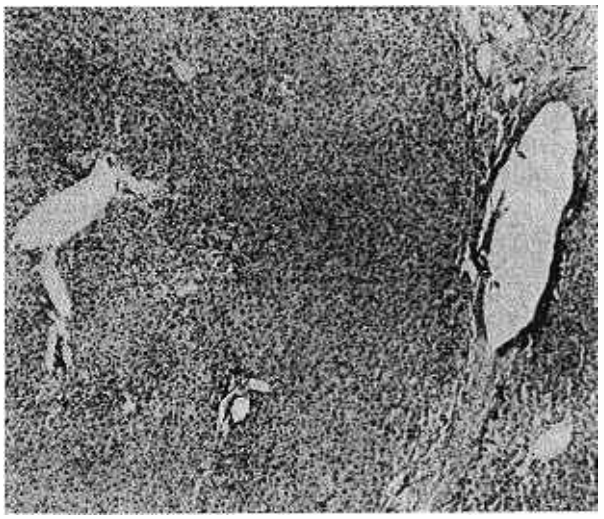

Fig. 1. *Liver Biopsy.* This microphotograph shows evidence of post-necrotic cirrhosis. The large nodule contains two central veins and a portal tract. There is also a thick fibrous band surrounding this nodule.
H & E × 45.

There were two subsequent admissions into hospital in 1965 for recurrent gastro-intestinal bleeding. Conservative treatment was instituted. Clinical findings and laboratory investigations were unchanged. A bromsulphthalein test showed 17 per cent retention of the dye at 45 minutes. Barium meal examination showed the presence of oesophageal varices. In addition, the terminal part of the oesophagus was found to taper sharply into a constricted segment, resulting in marked oesophageal stasis. The stomach itself looked normal.

The patient attended the unit outpatient follow-up clinic until early February 1966, when he developed pain in the right ear and weakness of the muscles of the face on the same side. Clinical examination revealed a lower motor neurone

right facial nerve palsy. Aural examination revealed no abnormality.

About two weeks later, he was re-admitted for a fourth gastro-intestinal bleed. The general physical examination was essentially the same. Neurologically there was still a right facial nerve palsy of the lower motor neurone type, but now a weakness of his right limbs had become evident. There was no sensory loss and his tendon reflexes and plantar responses were normal. A lumbar puncture showed normal cerebrospinal fluid and the chest X-ray was normal.

On 12th May 1966, the patient was again admitted to hospital for haematemesis and melaena. The right facial nerve palsy had remained unchanged. There was now increased weakness of his right upper and lower limbs, and difficulty in swallowing; the food entered the trachea each time he swallowed, causing him to cough. He was found to be pale and jaundiced. Lower motor neurone lesions of the right 7th, 9th, 10th, 11th and 12th cranial nerves were now detected. There was also wasting of the right thigh and calf muscles. The weakness of the right limbs was more marked and there was now some weakness of the left limbs. Sensation was intact. Tendon reflexes were more brisk on the right side in the upper limb, but in the lower limb the right knee jerk and ankle jerk were not elicited. The plantar response on the right could not be elicited also, while on the left, it was flexor. There was limitation of active movement at the right shoulder joint due to pain.

Laboratory investigations revealed a haemoglobin of 10 gm%, total white 5,400 per cubic millilitre with a differential count of 87% polymorphs, 10% lymphocytes, 3% monocytes and no eosinophils. His blood urea was 45 mg%, serum proteins 5.6 gm% (albumin 2.7 gm% and globulin 2.9 gm%), serum calcium 9.1 mg%, inorganic phosphate 2.8 mg% and alkaline phosphatase 21.3 units. Bromsulphthalein test revealed 44% dye retention after 45 minutes; the blood Kahn test was negative. The cerebrospinal fluid was normal except for a very slight increase in protein (50 mg%).

X-ray examination of the spine showed a pathological fracture of the 3rd cervical vertebra. Tomographic studies confirmed an osteolytic deposit in the body of the same vertebra, producing a partial collapse. The anterior cortical layer was eroded and there was a localised swelling in the prevertebral soft tissue wall. X-ray examination of the right shoulder showed a large osteolytic secondary in the upper extremity of the humerus with a pathological fracture, that of the paranasal sinuses showed slight opacity of both frontal sinuses and slight mucosal thickening of the left maxillary sinuses.

An examination of the ears, nose and throat showed no growth in the naso-pharynx. There was paralysis of the right laryngeal nerve.

On the 27th day of hospital stay, he developed a motor-paralysis of the right trigeminal nerve. Five days later he suddenly bled from the right ear. A growth was seen deep in the right external auditory meatus and on histological examination showed a group of carcinomatous cells which had an acinar arrangement; some of the cells tended to differentiate into liver cells with a central vein. The picture was consistent with a secondary from a hepato-cellular carcinoma (Fig. 2).

The patient made rapid downhill progression and developed a loss of hearing with diminution of sensation over the right face, involving the right VIII cranial nerve, and ophthalmic and maxillary divisions of the trigeminal nerve respectively. For the next week following, he developed paresis and finally paralysis of the right III, IV and VI cranial nerves. On the 39th day of hospital stay, he developed primary atrophy of both optic nerves.

He finally passed into coma and succumbed on the 43rd day.

A necropsy was not permitted. However, a post-mortem liver biopsy revealed a well differentiated hepatocellular carcinoma (Fig. 3).

Case No. 2

A 49 year old Eurasian male was admitted to the Outram Road General Hospital, Singapore, on 9th May, 1966, with complaints of a cough productive of brownish sputum and right-sided chest pain for three weeks and fever for one day. At the time of admission, he was slightly febrile with a pulse rate of 80 per minute. He had fine crepitations in the right lung base and a pleural rub was heard in the same area. His liver was enlarged, one inch below the right costal margin and tender. Examination of the other systems revealed no abnormality. A provisional diagnosis of hepatic amoebiasis with right basal pleurisy was made.

Laboratory investigations showed a haemoglobin of 14.6 gm%, total white 7,700 per cu. mm. with a differential count of 83% polymorphs, 13% lymphocytes, 1% monocytes and 1% eosinophils. Liver function tests revealed a serum bilirubin of 0.2 gm%, thymol turbidity

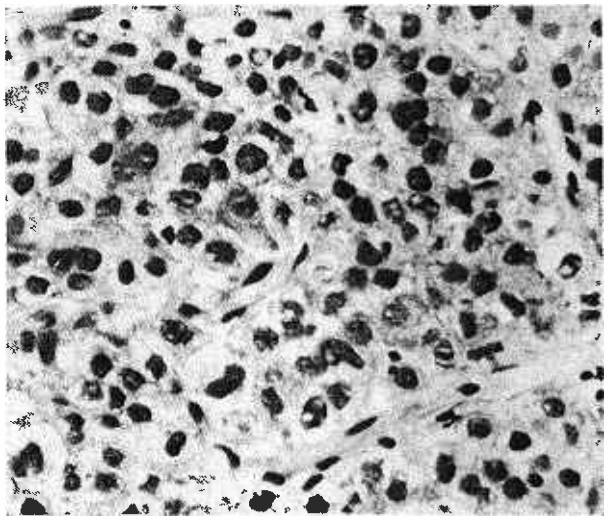

Fig. 2. *Tissue from Right Ear.* The above depicts a hepatocellular carcinoma. The cells are pleomorphic; the nuclei are hyperchromatic and these malignant cells possess abundant eosinophilic cytoplasms. They are arranged in alveolated masses around a central vein.

H & E × 500.

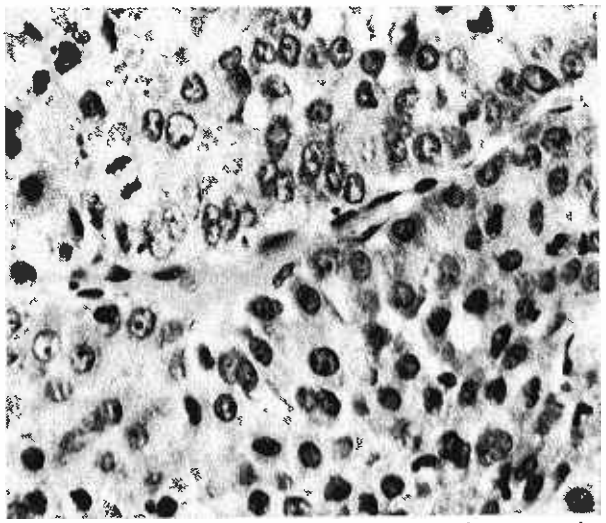

Fig. 4. *Needle Biopsy of Breast.* The picture again shows the classical alveolated form of hepatocellular carcinoma and is almost identical to Fig. 2. The "central vein" is rather elongated running across the picture. A mitotic figure is seen near the top left corner.

H & E × 500.

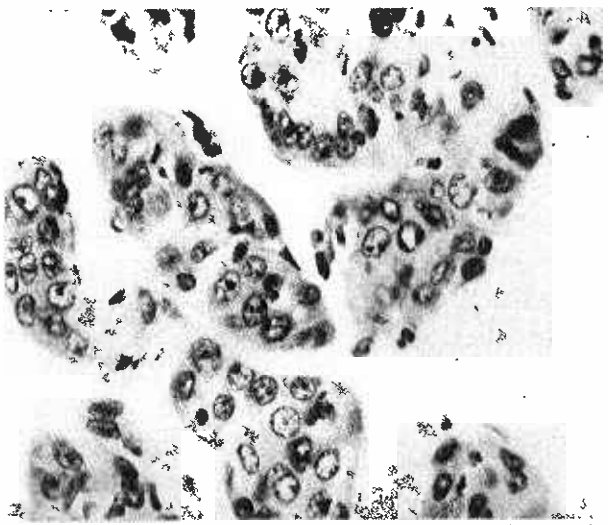

Fig. 3. *Liver Biopsy.* The hepatocellular carcinoma is seen in loose clumps and alveolated masses. The prominent nucleoli so typical of hepatocellular carcinoma are well shown in this picture.

H & E × 500.

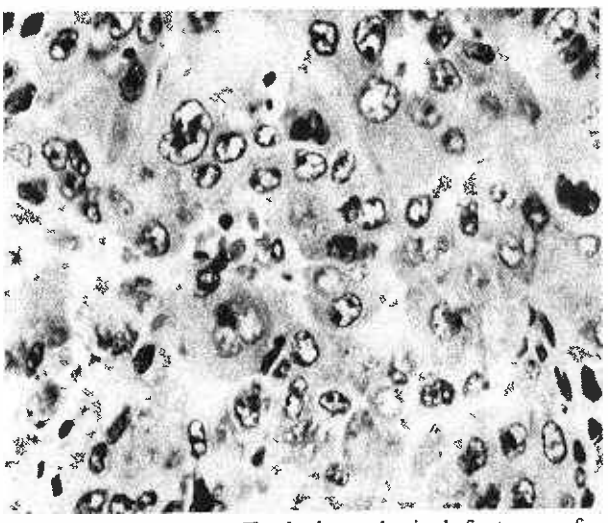

Fig. 5. *Liver Biopsy.* Typical cytological features of a hepatocellular carcinoma are shown here; the nuclei vary greatly in sizes and shapes and the nucleoli are prominent. The tinctorial hue of the cytoplasm is typically that of the liver cell.

H & E × 500.

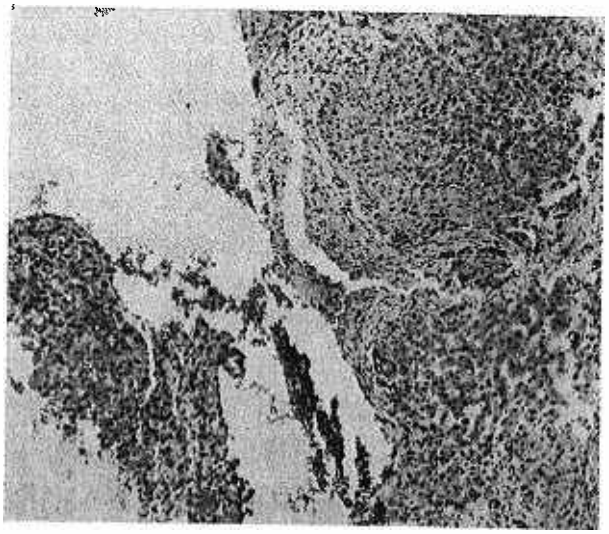

Fig. 6. *Liver Biopsy.* This is another field of the same liver biopsy as Fig. 5. The hepatocellular carcinoma is seen as a tiny fragment on the left, whilst the large piece on the right shows evidence of liver cirrhosis. There is not enough tissue to define the type of cirrhosis.

H & E × 75.

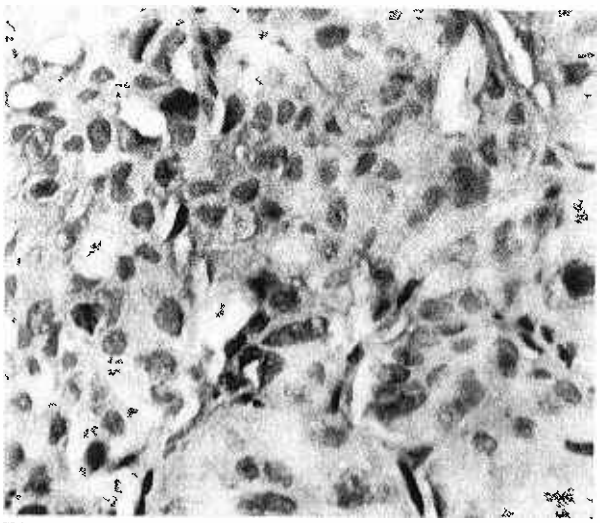

Fig. 7. *Liver Biopsy.* This microphotograph shows a liver cell carcinoma arranged in columns surrounded by sinusoids. The eosinophilic cytoplasm is typically that of the liver cell type. The nuclei are somewhat pleomorphic.

H & E × 500.

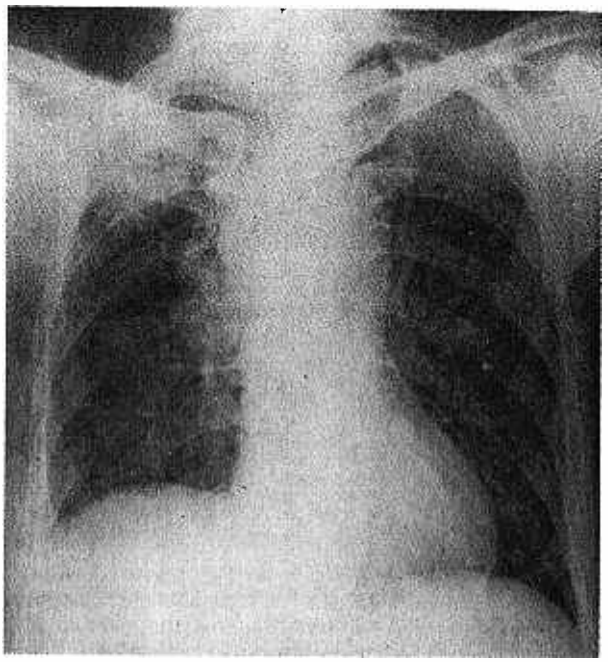

Fig. 8. The right hemidiaphragm is elevated. Opacities are seen in the right upper zone and the right hilum. The left 4th and the right 8th ribs are eroded.

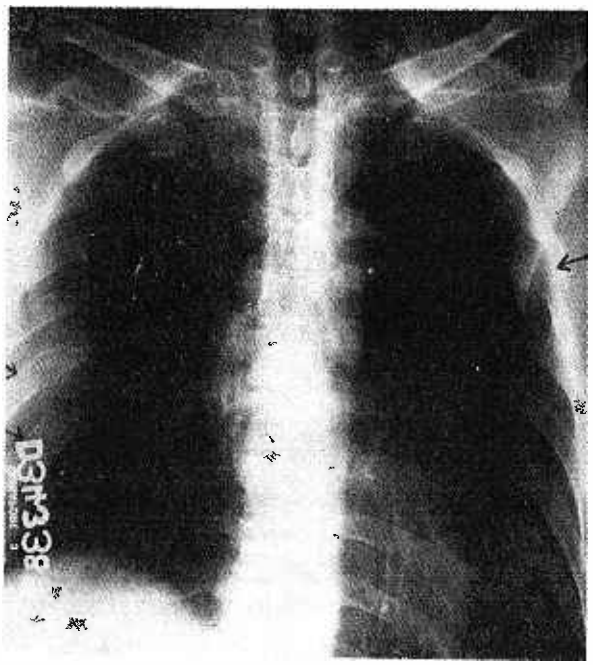

Fig. 9. There are pathological fractures of the left 4th and the right 6th and 7th ribs.

1 unit alkaline phosphatase 14.8 King Armstrong Units and a total serum protein of 7.3 gm% (3.3 gm% albumin and 4.0 gm% globulin). A bromsulphthalein test showed 21% dye retention at 45 minutes. A chest X-ray showed a slightly elevated right hemidiaphragm, consistent with an upward enlargement of the liver.

The patient was treated as for hepatic amoebiasis commencing with a course of emetine injections. The fever subsided and he was discharged, well, on the 23rd day of hospital stay.

Three days after he was discharged, he tripped and fell on to his left knee and experienced a tingling sensation around the waist, and backache. However, he did not seek medical help until two weeks later. By this time he found that both his lower limbs were a little weak and he needed the aid of a walking stick in order to walk around.

On examination he was noticed to be in pain, but his general condition was satisfactory. There was a hard nodular mass, fixed to the underlying bone, just beneath the right nipple. His liver was enlarged one inch below the right costal margin. Tenderness was elicited over the 10th and 11th thoracic vertebrae. The power in the left limb was diminished. No other abnormality was detected.

Laboratory investigations revealed a haemoglobin of 15 gm%, total white 10,100 per cu. mm. with a normal differential count. The erythrocyte sedimentation rate was 34 mm. per hour. His serum calcium was 9.2 mg%, inorganic phosphate 2.9 mg% and alkaline phosphatase 21.1 units.

X-rays showed pathological fractures of the left 4th and the right 6th and 7th ribs and also the 10th thoracic vertebral body (Fig. 9).

A biopsy of the mass beneath the right nipple revealed a metastatic carcinoma, consistent with a primary in the liver (Fig. 4).

The patient's condition deteriorated quite rapidly. Two weeks after admission, he was paralysed completely in both lower limbs and also developed urinary retention. He also had hypoaesthesia from the 10th thoracic segment downwards. The mass in the right chest wall had grown larger.

He gradually slipped into a comatosed state and died. Again, no permission for an autopsy could be obtained. A post mortem liver biopsy showed a hepatocellular carcinoma with liver cirrhosis (Figs. 5 & 6).

Case No. 3

A 49 year old male Chinese was admitted to the Outram Road General Hospital, Singapore, on 24th November, 1966, for a three month history of cough productive of small amounts of whitish sputum, worse in the mornings, with occasional blood streaking and a weight loss of 12 pounds. There was also right shoulder tip pain on occasions during the previous two weeks.

Clinical examination revealed a man in fairly good health. He was afebrile. There were few crepitations scattered in the lungs. He had palmar erythema and a few spider naevi, tender phrenic nerves and hyperalagesis in the shoulder tips on both sides. The liver was enlarged, 1½ inches below the right costal margin and it also had a systolic bruit. Examination of the other systems revealed no abnormality.

Laboratory investigations revealed a haemoglobin of 10.4 gm%, total white count of 12,200 per cu. mm., with a differential count of 92% polymorphs, 4% lymphocytes, 2% monocytes and 2% eosinophils. The erythrocyte sedimentation rate was 80 per hour. Liver function tests showed a serum bilirubin of 0.5 mg%, thymol turbidity of 1 unit, alkaline phosphatase 23.2 units and a total proteins of 6.7 gm% (3.2 gm% albumin and 3.5 gm% globulin). An X-ray of the chest showed an elevated right hemidiaphragm. There was an opacity in the right upper zone and in the right hilum. There were also erosions in the left 4th and right 8th ribs (Fig. 8).

In view of the presentation of the previous two cases, it was thought that the rib and lung lesions in this case could be due to metastasis from a probable liver cancer as the liver was enlarged.

A liver biopsy showed a well differentiated hepatocellular carcinoma, (Fig. 7).

The patient went to China to seek treatment after he was discharged from the ward.

DISCUSSION

Primary carcinoma of the liver is commoner in the East than in the West. Why this is so has not yet been fully understood.

Liver cirrhosis is very often associated with primary liver carcinoma. Of the various types of cirrhosis, portal cirrhosis has been found to be the commonest. This is borne out in the first two cases described in this paper.

Although primary carcinoma of the liver metastasises frequently, involvement of the brain and bones of the skull is not common. Muir (1961) had found three cases of metastasis to bone and brain in a study of 178 primary malignant tumours of the liver. Patton and Horn (1964) found one metastasis to the pituitary gland in 60 cases. Jorma Ervasti (1964) in an analysis of 100 cases with 93 autopsies, had two brain metastases and seven in the bones; the bones involved were the spine, sternum and os pubis.

SUMMARY

Three cases of primary hepatocellular carcinoma with brain and bone metastasis are described. The first a Chinese male aged 45 presented with recurrent attacks of bleeding oesophageal varices due to portal hypertension following cirrhosis of the liver and subsequently developing cranial nerve palsies.

The second was a male Eurasian aged 49 presenting initially with a hepatitis which appeared to respond to anti-amoebic treatment and subsequently showing up with a secondary in the rib and pathological fractures.

The third was a male Chinese aged 49 presenting with respiratory symptoms and having a large tender liver and some evidence of cirrhosis. An X-ray of the chest showed lung secondaries and rib erosion.

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