

# Liver-originating isoenzymes of alkaline phosphatase in the serum: a paraneoplastic manifestation of a malignant schwannoma of the sciatic nerve

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**SYNOPSIS** A case of malignant schwannoma of the sciatic nerve is described associated with hepatic dysfunction in the absence of hepatic metastases. An elevated serum alkaline phosphatase activity was present with an isoenzyme pattern indicating hepatic involvement. These abnormalities disappeared after extirpation of the tumour. The patient is well, with no evidence of metastases, over two years later. It is concluded that the abnormality of serum alkaline phosphatase was induced by the tumour, and that the liver can be involved in the paraneoplastic syndrome.

Increased serum alkaline phosphatase activity in a patient with a malignant tumour can be due to:

- (a) increased production of alkaline phosphatase by the tumour;
- (b) metastases to bone or liver (Schwartz, 1973);
- (c) production of a new species of alkaline phosphatase by the tumour (Fishman, 1974); or
- (d) a paraneoplastic response of the liver.

We wish to describe a case with a malignant schwannoma of the sciatic nerve in the thigh in which elevation of the serum alkaline phosphatase activity was associated with an isoenzyme pattern indicating severe hepatic dysfunction that disappeared after extirpation of the tumour. We consider this a further example of the paraneoplastic response of liver which has been described as occurring with renal adenocarcinoma (Lemmon *et al*, 1965; Walsh and Kissane, 1968; Ramos and Taylor, 1972; Axelsson *et al*, 1974).

## Case History

A 57-year-old woman was admitted on 7 March 1973 because of pain of five months' duration in the left thigh. Clinical examination showed a mass the size of a grapefruit in the lower portion of the left posterior thigh and an absent ankle jerk on the left side. The liver was not palpable. Laboratory values were normal except for a markedly elevated serum alkaline phosphatase activity (as discussed below),

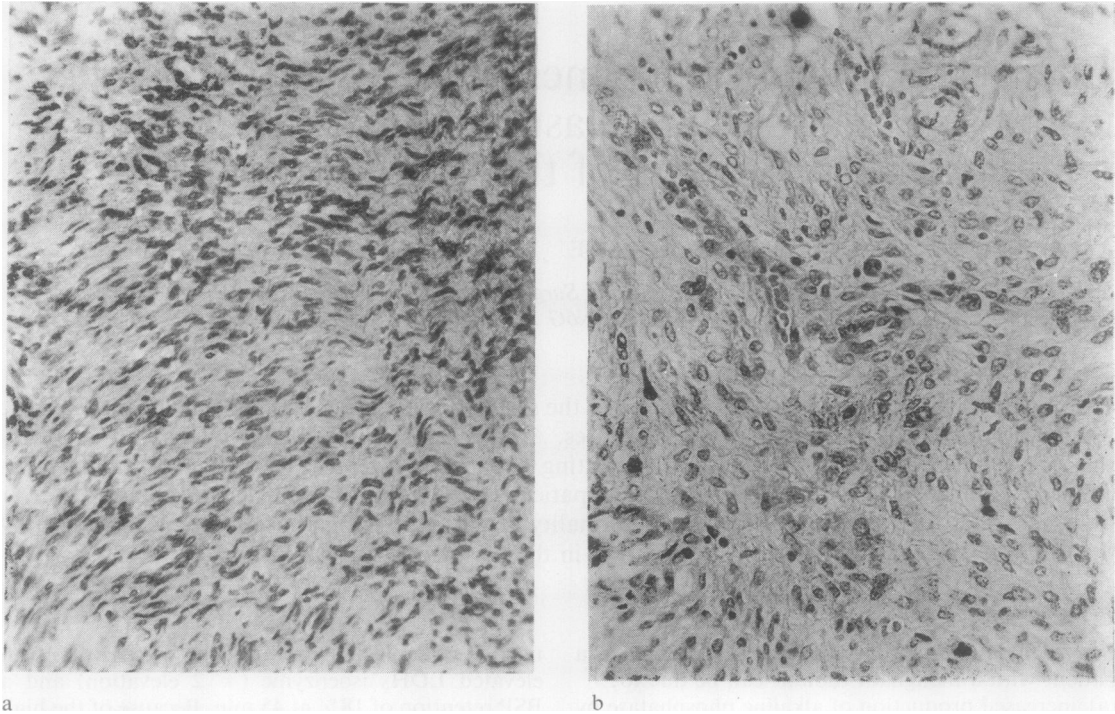
normal serum lactate dehydrogenase activity with an elevated LDH<sub>5</sub> isoenzyme ( $\times 2$  elevation) and a BSP retention of 18% at 45 min. Because of the high liver-originating isoenzyme of alkaline phosphatase, a liver scan was done and was thought to be normal. A bone scan also was normal except for increased uptake of isotope over the tumour. Biopsy of the tumour on 14 March showed an anaplastic sarcoma of uncertain origin. The only possible treatment for this lesion, which involved the sciatic nerve, was amputation of the left leg at the hip. Because of the persistent and profound increase in alkaline phosphatase there was concern about metastatic disease in spite of all other normal investigations.

Laparotomy was carried out on 23 March and showed a normal liver with a normal liver biopsy. Inguinal lymph nodes were histologically normal. Hip disarticulation was then carried out and recovery was uneventful. Final sections showed a malignant schwannoma arising from the sciatic nerve (fig 1). Since then the patient has learned to use a prosthesis and over two years later she is well with no sign of malignant disease.

## INVESTIGATIONS

Serum alkaline phosphatase activity and isoenzyme patterns were determined as previously described (McKenzie and Henderson, 1975).

On admission the total serum alkaline phosphatase was elevated to three times the upper limit of normal with an abnormal isoenzyme pattern (fig 2). Two days after hip disarticulation (and handling and



**Fig 1** Histological sections from the tumour. (a) View of the tumour showing palisading with wavy nuclei typical of a schwannoma. In this area the cells appear quite uniform and no mitoses are present. (b) High-power view of another area of the tumour showing highly atypical cells, several of which are in mitosis. This pattern, along with clear evidence of venous invasion, led to a diagnosis of malignant schwannoma. (Histological sections and reports were provided through the courtesy of Dr A. C. Wallace, Department of Pathology, University Hospital.)

biopsy of the liver) the serum alkaline phosphatase activity rose to five times the upper limit of normal with an intensification of the 'slow' liver-originating isoenzyme. All these abnormalities had disappeared by September 1973 and all biochemical tests have since remained normal.

Examination of the tumour itself showed little alkaline phosphatase activity with the isoenzymes located in the positions of bone and intestinal bands on polyacrylamide gel electrophoresis (fig 2).

### Discussion

Metastatic infiltration of the liver will, if sufficiently advanced, almost always give a characteristic serum alkaline phosphatase isoenzyme pattern that is also seen in many hepatobiliary diseases. Using polyacrylamide gel electrophoresis, this pattern consists of an increase in the normal (fast) liver-originating isoenzyme and the appearance of appreciable quantities of the 'origin' isoenzyme (Jennings *et al*, 1970; Walker and Pollard, 1971; Price and

Sammons, 1974). This origin isoenzyme corresponds to the 19S protein fraction obtained on sucrose density gradient separation (Jennings *et al*, 1970; Price and Sammons, 1974). Several authors have described this origin isoenzyme as being composed of two fractions—a slow liver-originating isoenzyme and a biliary-originating isoenzyme (Johnson *et al*, 1972; Dingjan *et al*, 1975). This has also been our experience (fig 2).

In the present case it seemed very likely that there was hepatic infiltration by metastases from the malignant schwannoma. Clearly, such an occurrence would have considerably altered the clinical management of this case. But the lack of further evidence of metastatic spread (ie, negative liver biopsy, liver scan, visual examination and palpation of the liver, lymphatic node examination) suggested that alternative explanations should be sought for the abnormalities detected.

Several tumour-synthesized alkaline phosphatases have been described in serum. The Regan isoenzyme was first observed in a patient with metastatic bron-

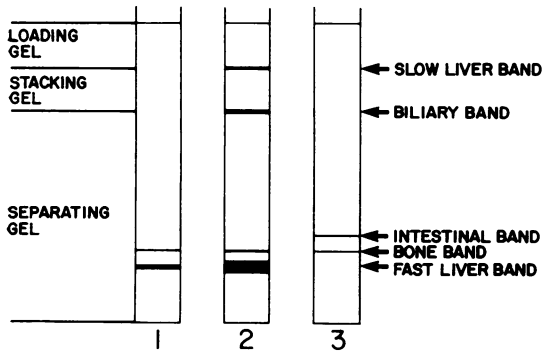


Fig 2 Serum alkaline phosphatase isoenzyme patterns obtained in the present study. (1) Normal pattern obtained after extirpation of tumour and still present over two years after operation. (2) Pattern obtained at the time of initial complaint. Note the increased fast liver band and the appearance of the slow liver and biliary bands. (3) Pattern obtained from the malignant schwannoma.

chogenic carcinoma (Fishman *et al*, 1968) but it has now been found in a wide variety of neoplasms, although its presence is significantly associated with tumours of the female breast and genitourinary tract (Cadeau *et al*, 1974). It is of interest to note that the use of a very sensitive immunochemical test system has demonstrated the presence of the Regan isoenzyme in normal healthy individuals (Usategui-Gomez *et al*, 1974). Another isoenzyme, the Regan variant, has been found, until recently only in patients with hepatoma (Warnock and Reisman, 1969; Higashino *et al*, 1972) but this variant has now been observed in patients with metastatic adenocarcinoma of the pancreas and stomach (Dingjan *et al*, 1975; McKenzie and Henderson, 1975), among other less well characterized pathologies. Another alkaline phosphatase isoenzyme, the Nagao type, has been investigated after being found in a case of pleural carcinomatosis (Nakayama *et al*, 1970). These possibilities could be excluded in the present case because of lack of correspondence between the tumour alkaline phosphatase isoenzymes and the serum pattern.

In recent years there has been a growing appreciation of the association of neoplasms with systemic manifestations not due to their local growth or metastases. These have been described as the paraneoplastic syndromes. For example, carcinoma of the lung can be associated with hormonal, metabolic, connective tissue, dermatological, neuromuscular, vascular, and haematological abnormalities (Nathanson and Hall, 1974).

Several presumed paraneoplastic effects have been

reported involving the liver. Thus 'toxohormone'—a toxic principle that is liberated by a variety of tumours—inhibits liver catalase activity (Busch, 1962). 'Acute phase' plasma proteins, which are synthesized in the liver (Williams, 1970), have also been observed to increase in the presence of non-hepatic neoplasms (Busch, 1962) but this plasma protein response has also been observed following many forms of pathological stress, and it is doubtful if the term 'paraneoplastic' is strictly applicable in this particular instance. In experimental animals, non-hepatic tumours have been observed to increase the liver mitotic index (Malmgren, 1956), the liver weight (Annou *et al*, 1951), and the rate of uptake of  $^{32}\text{P}$  by liver DNA (Payne *et al*, 1952).

Recently, Brensilver and Kaplan (1975) have concluded that elevation of the liver-originating serum alkaline phosphatase can occur in the absence of liver disease. In order to prove that no liver involvement had occurred they followed up their patients for many years. They suggest that the elevation of the liver-originating serum alkaline phosphatase may be a non-specific 'acute phase' reaction.

In the presence of renal adenocarcinoma there is now a considerable body of evidence to suggest that a hepatic paraneoplastic response does occur. Stauffer (1961) originally described hepatic dysfunction without liver metastases in five cases with renal adenocarcinoma, and fuller descriptions of this hepatic response have since appeared. Thus, Lemmon *et al* (1965) described a case of renal adenocarcinoma with hepatosplenomegaly who had abnormal BSP retention, serum alkaline phosphatase (and isoenzymes), transaminases, and LDH activities. All these, and other, abnormalities of hepatic function resolved after removal of the primary tumour. Others have reported similar serum enzyme abnormalities which reverted to normal following extirpation of the tumour mass (Walsh and Kissane, 1968; Ramos and Taylor, 1972). Sometimes the only abnormality detected is the serum alkaline phosphatase, all other liver-originating enzymes being normal (Axelsson *et al*, 1974), and with no hepatomegaly.

One can only speculate about the mechanism by which a distant tumour can so alter the characteristics of the hepatic cell membrane that it allows the selective leakage of high molecular weight particles into the circulation, while smaller molecules do not appear. Whatever the mechanism, its effect is only mimicked by quite severe assaults on the liver cell, such as obstructive lesions of the biliary tract, acute (and severe) viral hepatitis or actual metastatic infiltration of the liver itself—at least as regards the appearance of abnormal alkaline phosphatase isoenzymes. Axelsson *et al* (1974) showed that in their two cases



of renal adenocarcinoma there was a very marked increase in canalicular alkaline phosphatase synthesis in the hepatocyte, and possibly a similar mechanism was at work in the present case.

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