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Spectacular Elevations of Serum Alkaline Phosphatase: Clinical and Pathological Correlation

Roy B. Patton, M.D.*

The diseases responsible for extremely high serum alkaline phosphatase activity in 45 patients were proliferative bone disease (10 patients) and hepato-biliary tract disease (35 patients). Conditions found in these patients that are not usually thought to cause such high phosphatase levels were: drug-induced cholestasis (6 patients), non-malignant extra-hepatic bile duct obstruction (3 patients), biliary or portal cirrhosis (5 patients), and primary hyperparathyroidism with generalized osteitis fibrosa (1 patient).

Alkaline phosphatase activity is frequently determined in the clinical laboratory with increases in the serum content of this enzyme being commonly associated with bone disease in which there is formation of new bone tissue, extra and intrahepatic biliary duct obstruction and parenchymatous liver disease. Three other rather special conditions may be responsible for abnormal elevations of serum alkaline phosphatase: (1) The placenta is rich in an alkaline phosphatase and this accounts for the modest increase in the serum content of this enzyme in women in the third trimester of pregnancy.¹ (2) Human albumin for injection is prepared at least in part from placentas and persons receiving this material may have markedly high phosphatase levels from this source.² (3) Alkaline phosphatase production by a malignant tumor has been reported in a patient in whom the serum alkaline phosphatase level was elevated.³

Increases in phosphatase activity are usually in a range of two to ten times the upper limit of normal for the re-

porting laboratory; values above this range are unusual. Recently I encountered a patient with serum alkaline phosphatase levels of 73, 80 and 82 Bodansky units/100 ml. Since the reason for this was not immediately apparent, I was stimulated to find out how often spectacularly high serum alkaline phosphatase levels are found and, also, to evaluate the clinical conditions associated with these high levels.

Materials and Methods

Records of the clinical chemistry laboratory of the Henry Ford Hospital were searched for patients having serum alkaline phosphatase measurements of 50 or more Bodansky units/100 ml during the period from April 1968 thru March 1969. During this time 14,258 measurements of serum alkaline phosphatase were made. Many of these represented repeat examinations of the same patients.

The method is adapted for use in an automatic analyzer and essentially is that of King and Armstrong⁴ with modification. Results as determined are thus in King-Armstrong units. These are divided by a factor of 3.3

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Table I

Disease processes responsible for extremely high alkaline phosphatase activity in 45 patients.

Disease	Patients
Bone	10
Carcinoma of the prostate with osteoblastic metastases	6
Paget's disease of bone	2
Primary hyperparathyroidism with osteitis fibrosa	1
Carcinoma of the breast with osteoblastic metastases	1
Liver and/or Bile Ducts	35
Primary or metastatic carcinoma	21
Cirrhosis	5
Nonmalignant extra-hepatic bile duct obstruction	3
Drug-induced cholestasis	6

and reported as Bodansky units.^{5,6} The range of normal for adults is 1.5-4.0 Bodansky units/100 ml. When an abnormal value is discovered and there is sufficient specimen, it is re-tested in the chemistry laboratory for the abnormal constituent. The abnormal value is not reported if the re-test does not confirm it.

It is not possible precisely to convert units of alkaline phosphatase activity determined by a given method to units in a different method. This is due mainly to differences in substrate composition, incubation time, serum concentration and pH of the reaction mix-

ture, as well as to local laboratory modifications of original methods.

Results

Forty-five patients with serum alkaline phosphatase measurements of 50 or more Bodansky units/100 ml were found during the 12-month period of study. In all of these patients at least one other serum, assayed for this constituent, confirmed the high value. Twenty-five of the 45 patients had values between 50 and 70 units, 14 were between 70 and 100 units, and six had more than 100 units, the highest being 361 Bodansky units/100 ml. The

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clinical records of these patients were examined in order to identify the disease process accounting for the extremely high serum alkaline phosphatase. Table I shows the kinds of disease found and the number of patients in each group.

Proliferative bone disease was responsible for the high serum alkaline phosphatase in ten patients, six of whom had carcinoma of the prostate gland with osteoblastic bone metastases. Only one of these patients was jaundiced. In this patient, no obstructive disease and no evidence of metastases in the liver were found during a common bile duct exploration. The jaundice, which subsequently cleared, may have been due to drug-induced cholestasis. Two of the ten patients had Paget's disease of bone, but no evidence of liver disease. One patient had a parathyroid adenoma with hyperparathyroidism and generalized osteitis fibrosa. She was never jaundiced and, at necropsy, there was no evidence of liver disease.⁷ The tenth patient had carcinoma of the breast with osteoblastic bone metastases. Three liver scans were done over a three-month interval in this patient and there was no evidence of metastases. She was not jaundiced when the alkaline phosphatase was markedly elevated.

In 35 of the 45 patients, the high phosphatase was attributed to liver and/or biliary tract disease. Malignant disease involving the liver and/or the extrahepatic biliary system was the cause in 21 patients. These cancers were primary in the following sites: colon and rectum, 7; pancreas, 3; stomach, 2; breast, 2; and gallbladder, ampulla of Vater, common bile duct,

liver, duodenum, renal pelvis and uterine tube, one each. With the exception of two patients with adenocarcinoma of the colon all of these patients were jaundiced at or near the time when the serum alkaline phosphatase was extremely high. Nineteen of the 21 patients have since died and nine had post mortem examinations. Three of these had hepatic abscesses, as well as malignancy metastatic to the liver or porta hepatis. None of the 21 patients had extensive bone metastases and, when these were present, they were not osteoblastic.

Of the 14 patients with nonmalignant disease to account for the high serum alkaline phosphatase, two had primary biliary cirrhosis, two had secondary biliary cirrhosis and one had portal cirrhosis. Extrahepatic bile duct obstruction was responsible in three, and drug-induced cholestasis was thought to be the cause in the other six. In one this was considered due to chlorpromazine and in another to novobiocin. One young woman developed jaundice and high serum alkaline phosphatase levels while taking a contraceptive drug containing an estrogen and a progestogen. These levels promptly subsided upon discontinuance of the drug. No single drug could be implicated in three patients who were taking several medications.

One of these, a 49-year-old woman with chronic pyelonephritis and renal failure, became jaundiced and had high serum alkaline phosphatase levels during the final eight days of her life. No extrahepatic biliary tract obstructive disease and no malignancy were seen at necropsy. There was no evidence of secondary hyperparathyroidism and no significant bone disease.

The second, a 70-year-old woman with Hodgkin's disease, developed jaundice and had a serum alkaline phosphatase of 76 Bodansky units/100 ml while receiving a variety of drugs. The abnormal bilirubin and phosphatase measurements promptly returned to normal after several of the drugs were stopped. Eleven months following the episode of jaundice, she was feeling well, with the Hodgkin's disease apparently under control.

A 64-year-old man with sarcoidosis, the final case, presented with jaundice and elevated serum alkaline phosphatase. No gross liver disease was seen at the time of a common bile duct exploration. The jaundice gradually subsided over a period of several weeks, although the serum alkaline phosphatase continued to be modestly elevated. In this patient, the hyperbilirubinemia

and high phosphatase were thought due to a toxin, probably a drug.

Comment

The underlying disease processes responsible for extremely high serum alkaline phosphatase activities are probably not different from those that cause more modest elevations of this enzyme. Pathologic conditions likely to be the cause are Paget's disease of bone, osteoblastic bone metastases, active rickets,⁸ primary and metastatic tumors of the liver, hepatic abscesses, granulomatous diseases of the liver and hepatic amyloidosis.⁹ The present study indicates that other causes may be drug-induced cholestasis, non-malignant extrahepatic bile duct obstruction, some forms of cirrhosis and primary hyperparathyroidism with osteitis fibrosa.

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