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P. Tangkijvanich

N. Paritpokee

V. Wiwanitkit

P. Tosukhowong

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Clinical association of high serum alkaline phosphatase levels in hospitalized patients

Pisit Tangkijvanich* Nara Paritpokee **
Viroj Wiwanitkit ** Piyaratana Tosukhowong*

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Objective : *To determine the etiology and clinical significance of a high alkaline phosphatase (ALP) level in hospitalized patients*

Design : *Retrospective descriptive study*

Methods : *Review of medical records of inpatients with high ALP levels above 1000 IU/L in Chulalongkorn University Hospital between January and December 1998. Excluded were patients younger than 20 years old, patients with pregnancy and patients who had bone involvement with malignancies.*

Results : *A total of 163 inpatients with complete medical records were identified (88 male and 75 female, mean age 52.3 $\pm$ 15.5 years). The ALP levels ranged from 1001 to 8057 IU/L. Fifty patients had biliary obstruction as the cause of the elevated ALP, 39 with malignant obstruction and 11 with common bile duct stones. Fourteen patients had hepatocellular carcinoma and 24 had metastatic hepatic cancers. Twenty - four patients had AIDS with superimposed infection or malignancy. Sepsis from extrahepatic origins in HIV-negative patients were also identified in 36 cases. Finally, fifteen patients had miscellaneous causes including drug-induced hepatotoxicity (3 cases), hematologic malignancies (6 cases), alcoholic cirrhosis (3 cases) and liver abscesses (2 cases).*

* Department of Biochemistry, Faculty of Medicine, Chulalongkorn University

**Department of Laboratory Medicine, Faculty of Medicine, Chulalongkorn University

Conclusions : *High levels of ALP in hospitalized patients were most frequently found in four groups having obstructive biliary disease, infiltrative liver disease, AIDS with superimposed infections and sepsis in HIV-negative patients.*

Key words : *Alkaline phosphatase, Abnormal liver function tests, Hepatobiliary tract disease.*

Reprint request : Tangkijvanich P, Department of Biochemistry, Faculty of Medicine, Chulalongkorn University, Bangkok 10330, Thailand.

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พิสิฐ ตั้งกิจวานิชย์, นารา ผริตโภคี, วิโรจน์ ไววานิชกิจ, ปิยะรัตน์ โตสุโขวงศ์. ความสัมพันธ์ทางคลินิกของการตรวจพบเอนไซม์ alkaline phosphatase ระดับสูงในเลือดของผู้ป่วยที่รักษาในโรงพยาบาล. จุฬาลงกรณ์เวชสาร 2542 ก.ค; 43(7): 485-94

วัตถุประสงค์ : *เพื่อศึกษาสาเหตุและความสำคัญทางคลินิกของการตรวจพบเอนไซม์ alkaline phosphatase(ALP) ที่มีระดับสูงในเลือดของผู้ป่วยที่รักษาตัวในโรงพยาบาล*

รูปแบบการศึกษา : *การศึกษาเชิงพรรณาแบบไปข้างหลัง*

วิธีการวิจัย : *ทำการศึกษาผู้ป่วยในของโรงพยาบาลจุฬาลงกรณ์ ที่มีผลการตรวจเลือดพบว่าระดับของ ALP สูงกว่า 1000 IU/L ระหว่างเดือนมกราคมถึงเดือนธันวาคม 2541 ทั้งนี้ไม่รวมผู้ป่วยที่มีอายุน้อยกว่า 20 ปี ผู้ป่วยที่ตั้งครรภ์หรือผู้ป่วยที่มีการลุกลามของมะเร็งไปที่กระดูก*

ผลการศึกษา : *พบผู้ป่วยภายใต้เงื่อนไขข้างต้นจำนวน 163 คน (88 คนเป็นผู้ชายและ 75 เป็นผู้หญิง อายุเฉลี่ย 52.3 $\pm$ 15.5 ปี) โดยมีระดับของ ALP ตั้งแต่ 1001 ถึง 8057 IU/L. ผู้ป่วยจำนวน 50 คนมีการอุดตันของท่อทางเดินน้ำดี (จากโรคมะเร็งชนิดต่าง ๆ 39 คนและจากนิ่วในท่อทางเดินน้ำดีอีก 11 คน) ผู้ป่วย 14 คนเป็นมะเร็งตับปฐมภูมิชนิด hepatocellular carcinoma และ 24 คนเป็นมะเร็งตับชนิดทุติยภูมิซึ่งลุกลามมาจากอวัยวะอื่น ๆ นอกจากนี้พบว่าผู้ป่วย 24 คนเป็นโรคเอดส์ที่มีการติดเชื้ออื่น ๆ หรือมะเร็งแทรกซ้อนและผู้ป่วยอีก 36 คนที่มีระดับของ ALP ในเลือดสูงกว่า 1000 IU/L มีการติดเชื้อนอกตับอย่างรุนแรง ส่วนผู้ป่วยอีก 15 คนที่เหลือเกิดจากผลข้างเคียงของยา 3 คน จากโรคมะเร็งของเม็ดเลือดหรือมะเร็งของต่อมน้ำเหลือง 6 คน จากตับแข็งที่เกิดจากโรคสุราเรื้อรัง 3 คนและจากโรคฝีในตับจำนวน 2 คน*

สรุป : *ผู้ป่วยในส่วนใหญ่ที่มีระดับของ ALP สูงในเลือดมักเกิดจากกลุ่มโรคต่อไปนี้ 1. โรคที่มีการอุดตันของท่อทางเดินน้ำดี 2. โรคมะเร็งตับปฐมภูมิและชนิดทุติยภูมิ 3. โรคเอดส์ที่มีการติดเชื้ออื่น ๆ หรือมะเร็งแทรกซ้อน 4. โรคที่มีการติดเชื้อนอกตับอย่างรุนแรง*

คำสำคัญ : *เอ็นไซม์ Alkaline phosphatase ผลการตรวจการทำงานที่ผิดปกติ โรคตับและทางเดินน้ำดี*

Alkaline phosphatase (ALP; EC 3.1.3.1) comprises a group of enzymes that catalyze the hydrolysis of phosphate esters in an alkaline environment, generating an organic radical and inorganic phosphate.[1] In healthy adults, this enzyme is mainly derived from the liver, bones, and in lesser amounts from intestines, placenta, kidneys and leukocytes.[2] An increase in ALP levels in the serum is frequently associated with a variety of hepatobiliary diseases, such as extrahepatic bile duct obstruction, intrahepatic cholestasis, infiltrative liver diseases, alcoholic hepatitis and cirrhosis. Unfortunately, levels of ALP up to three times normal are considered nonspecific and usually insufficient to provide a definite diagnosis.[3]

Markedly elevated serum ALP levels are seen predominantly with more specific disorders, including malignant biliary obstruction, primary biliary cirrhosis, primary sclerosing cholangitis, hepatic lymphoma and sarcoidosis.[4] A recent study of hospitalized patients indicated that extremely high elevations of ALP are most frequently seen in cases with sepsis, malignant obstruction and acquired immunodeficiency syndrome (AIDS) with superimposed infection.[5] Whereas diffuse liver metastasis, as well as a number of benign disorders, was relatively less common causes of markedly elevated ALP.

In order to determine the etiology and clinical significance of a high ALP level among Thai patients, we reviewed the medical records of individuals in whom an ALP level of greater than or equal to 1,000 IU/L was encountered during a one-year period in Chulalongkorn University Hospital.

Methods and Materials

A retrospective case review was undertaken for hospitalized patients in whom there was an ALP level of greater than or equal to 1,000 IU/L (Boehringer Mannheim, normal 98-279 IU/L) at the Department of Laboratory Medicine of Chulalongkorn University Hospital between January and December 1998. Excluded were patients younger than 20 years old, patients with pregnancy and patients who had bone involvement with malignancies. During this period, a total of 203 inpatients were identified. After review of the patients' medical records, 163 cases had a conclusive diagnosis for further analysis. Of those, patients' data from the discharge summary were recorded and this included age, sex and additional liver function tests, i.e. bilirubin levels, as well as the final diagnosis. Descriptive statistics were calculated for patient characteristics and laboratory parameters for each etiological group. Unpaired Student's *t* test was used to assess group differences as appropriate. Statistical significance was defined as $p < 0.05$.

Results

During the one-year period, a total of 163 inpatients with elevations of ALP over 1000 U/L were identified. There were 88 male and 75 female patients with ages ranging from 21 to 93 years (mean age 52.3 $\pm$ 15.5 years). The ALP levels ranged from 1001 to 8057 IU/L.

The most common diagnosis of patients with high ALP levels in our series was malignant biliary obstruction in 39 patients. Twenty-five of these cases had cholangiocarcinoma (CCA), six pancreatic cancer,

one gallbladder cancer, one ampullary cancer, two metastatic cancers and four periampullary cancers. The ALP levels ranged from 1003 to 4753 IU/L (1754.7 ± 741.4 IU/L). The bilirubin was elevated in most, but not all, patients in this group and total bilirubin values ranged between 0.3 and 40 mg/dl(16.6 ±12.8 mg/dl). In addition, benign bile duct obstruction from choledo-cholithiasis was found in eleven patients, six of whom were complicated by ascending cholangitis. The ALP levels in this group ranged from 1014 to 2774 IU/L (1557.0 ± 522.6 IU/L) and total bilirubin values ranged between 0.5 and 11 mg/dl (4.1 ± 3.1 mg/dl).Comparing these two groups, the mean bilirubin levels in benign obstructions was significantly lower than in malignant obstructions ($p = 0.003$), whereas the mean ALP levels were comparable (Table 1).

Regarding infiltrative liver disorders with high levels of ALP, there were 14 patients with hepatocellular carcinoma (HCC) diagnosed based on histology and/or based on clinical features combined with serum AFP levels above 400 IU/ml. The ALP and bilirubin levels in this group ranged from 1020 to 2244 IU/L (1397.8 ± 373.7 IU/L) and 0.4 to 19.3 mg/dl (5.6 ± 7.0 mg/dl), respectively. There were also 24 cases with liver metastasis in which a variety of primary cancers were identified, including ovary, colon, stomach, esophagus, lung and breast cancer. The ALP and bilirubin levels in this group ranged from 1108 to 3684 IU/L (1764.6 ± 137.9 IU/L) and 0.1 to 21.6 mg/dl (7.2 ± 10.1 mg/dl), respectively. Among these, half of the patients (12 cases) had a normal total bilirubin. The mean ALP level in metastatic cancer cases was significantly higher than in HCC ($p = 0.04$). (Table 1).

In our series, there were 19 patients who had AIDS superimposed with a variety of opportunistic infections, including mycobacterium tuberculosis (TB, 8 cases), histoplasmosis (2 cases), penicillosis (2 cases), norcardiosis (1 case), pneumocystosis (1 case), cryptococosis (1 case) and cytomegalovirus (CMV, 1 case). Another three patients with AIDS had sepsis from urinary tract infection (UTI) and one had sepsis from salmonellosis. The one remaining patient with AIDS was superimposed with Non-Hodgkin's lymphoma (NHL). The ALP and bilirubin levels in this group ranged from 1004 to 3318 IU/L (1569.6 ± 711.5 IU/L) and 0.3 to 9.9 mg/dl (2.4 ± 2.8 mg/dl), respectively.

High levels of ALP above 1000 IU/L were also frequently found in non-AIDS patients with systemic infection or sepsis. Our data revealed 36 such patients in whom the evidence of the biliary obstruction or liver abscess was not demonstrated by imaging techniques. In this group, both gram-positive and gram-negative bacteria, such as *Staphylococus aureus, Escherichia coli* and *Pseudomonas aeruginosa*, were among the most frequently identified organisms. In addition, another five neutropenic patients with concurrent bacterial and fungal infections following systemic chemotherapy exhibited high ALP levels. Of interest, various tropical infections prevailing in Thailand were also identified, including melliodosis (2 cases), leptospirosis (1 case), scrub typhus (1 case) and typhoid fever (1 case). Furthermore, there were five patients with disseminated tuberculosis and one patient infected with cytomegalovirus after bone marrow transplantation. The ALP and bilirubin levels ranged from 1005 to 3251 IU/L (1652.0 ± 771.8IU/L)

and 0.6 to 43 mg/dl (5.6 ± 9.4 mg/dl), respectively. In this group, there were only 24 cases whose serum ALP levels were elevated proportionately when compared with the serum bilirubin levels. Nonetheless, the mean bilirubin level in this group was significantly higher than in the HIV-positive group ($p = 0.0013$). (Table 1).

The miscellaneous group consisted of patients with high levels of ALP following various disorders, including six patients with hematologic malignancies [two cases with acute non-lymphoblastic leukemia (ANLL), both in blast crisis stage; one chronic myelocytic leukemia (CML) cases, and three Non-Hodgkin's lymphoma (NHL) cases], four alcoholic cirrhosis cases, two pyogenic liver abscess casesand three drug-induced cholestasis cases (allopurinol in two cases and diphenylhydantoin in one cases) (Table 1).

Moreover, to emphasize the disorders associated with extreme elevations of ALP above 2000 IU/L, the clinical characteristics of these 37 patients have been summarized in Table 2.

Table 1. Disorders associated with high level of ALP above 1000 IU/L.

Diagnosis (n)	Age (years)	TB (mg/dl)	ALP (IU/L)
Biliary obstruction (50)			
Malignant (39)	57.3 ± 14.6	16.6 ± 12.8	1754.7 ± 741.4
Benign (11)	58.5 ± 515.7	4.1 ± 3.1	1557.0 ± 522.6
	NS	$p = .003$	NS
Infiltrative disorders (38)			
Hepatocellular carcinoma (14)	56.9 ± 10.5	5.6 ± 7.0	1397.8 ± 373.7
Metastasis (24)	54.8 ± 14.9	7.2 ± 10.1	1764.6 ± 137.9
	NS	NS	$p = 0.04$
Systemic infection & sepsis (60)			
AIDS (24)	35.5 ±10.9	2.4 ± 2.8	1569.6 ± 711.5
Non-AIDS (36)	52.9 ±14.8	5.6 ± 9.4	1652.0 ± 771.8
	NS	$p = 0.013$	NS
Miscellaneous (15)			
Hematologic malignancy (6)	58.5 ± 19.1	3.2 ± 2.4	1355.8 ± 342.5
Alcoholic cirrhosis (4)	42.0 ± 1.4	2.0 ± 0.5	1267.0 ± 340.8
Drug-induced (3)	52.0 ± 1.4	20.7 ± 28.0	4055.5 ± 3721.5
Liver abscess (2)	53.0 ± 13.5	4.7 ± 2.6	1422.5 ± 632.2

ALP, alkaline phosphatase; TB, total bilirubin; AIDS, acquired immunodeficiency syndrome
NS, no statistical significance. Data expressed as mean ± standard deviations

Table 2. Disorders associated with ALP level above 2,000 U/L.

Diagnosis (n)	Sex (M/F)	Age (years)	TB (mg/dl)	ALP (IU/L)
Malignant biliary obstruction (12)	8/4	37 - 85	1.0 - 33.0	2101 - 4753
Cholangiocarcinoma (7)	6/1	37 - 80	1.0 - 33.0	2101 - 4753
Pancreatic cancer (2)	1/1	61/71	16.0/10.9	2656/2332
Gallbladder cancer (2)	1/1	85/73	3.7/10.7	2398/2495
Metastasis (1)	F	50	15.9	2632
CBD stone (2)	1/1	37/76	5.1/5.6	2774/2151
Hepatocellular carcinoma (1)	M	39	10.3	2244
Liver Metastasis (6)	3/3	44 - 77	0.3 - 4.5	2374 - 3684
Colon (3)	3/0	44 - 77	2.6 - 4.5	2374 - 2464
Ovary (2)	0/2	50/62	2.2/1.2	2772/3357
Unknown (1)	F	45	0.3	3684
AIDS (5)	4/1	24 - 34	0.6 - 4.5	2176 - 3293
Tuberculosis (3)	2/1	24 - 33	0.6 - 1.4	2176 - 2687
CMV (1)	M	34	1.0	3318
NHL (1)	M	30	4.5	3293
Systemic infection & sepsis (8)	3/5	25 - 63	0.6 - 15.5	2030 - 4575
Bacterial sepsis (5)	2/3	25 - 63	0.6 - 15.5	2030 - 3251
CMV (1)	M	39	2.4	4575
Disseminated tuberculosis (3)	1/2	23 - 36	0.7 - 3.2	2218 - 2635
Drug cholestasis (Allopurinol, 1)	F	53	40.5	8057
Alcoholic cirrhosis (1)	M	46	5.2	2365

ALP, alkaline phosphatase; TB, total bilirubin; CBD, common bile duct;
AIDS, acquired immunodeficiency syndrome;
CMV, cytomegalovirus; NHL, non-Hodgkin's lymphoma

Discussion

It has been accepted that the mechanism by which different physiological states and disease processes cause an elevation of serum ALP is that this enzyme originates only in tissues that undergo metabolic stimulation.[6] Most data indicate that the elevation occurs because of accelerated *de novo* synthesis of the enzyme and subsequent regurgitation into the serum.[1,2] At the cellular level, the increased synthesis of hepatic ALP appears to be due to increased hepatic translation of mRNA rather than to increased transcription. Thus, new protein synthesis appears to be a major factor accounting for the raised the ALP activity in hepatobiliary tract disease, as opposed to failure to clear or excrete circulating ALP.[7]

The etiologies of high levels of ALP have not been previously investigated in Thailand. This study selected a specific population of hospitalized patients in Chulalongkorn Hospital. Therefore, the results may not apply to the general outpatient population. Nonetheless, several findings from this study are of interest. First, more than 90% of those patients with high ALP levels exceeding 1000 or 2000 IU/L were inclusively found in four major categories: obstructive biliary disease, infiltrative liver disease, AIDS with superimposed infections and sepsis in HIV-negative patients. In contrast with a recent study,[5] our data demonstrated that the incidence of malignant biliary obstruction occurring at a slightly higher frequency, accounted for approximately 30%, of those with extremely high levels of ALP. This discordance presumably reflected the high proportion of cholangiocarcinoma (CCA) in our study. In fact, CCA has its highest incidence rates in the northeastern provinces of Thailand where more than 70% of the population are infested with the liver fluke *Opisthorchis viverrini* [8]

Second, in most cases of malignant obstruction, the total bilirubin levels were proportionately elevated compared with the ALP levels. However, nearly 20% of the patients in this group had near-normal levels of bilirubin. Such cases implied partial biliary obstruction. For example, in Klatskin' s tumors only the left or right ductal system was obstructed. On the other hand, hepatic infiltration from primary or metastatic cancers characteristically resulted in an elevated ALP without jaundice until advanced stages, as shown in some patients in our series. Furthermore, it was noteworthy that in cases of choledocholithiasis, the bilirubin value was typically 2 to 5 mg/dl and rarely surpassed 12 mg/dl. That total bilirubin exceeded this level suggested malignant obstruction or coexisting hemolysis.[9]

Third, although liver disease is common in AIDS patients, the magnitude of clinically apparent hepatic dysfunction is small, particularly in those without opportunistic infections or drug-induced hepatotoxicity. In contrast, AIDS with superimposed infections tends to have a higher ALP and other hepatic enzymes.[10] Very high ALP levels associated with mycobacterium avium intracellulare (MAI) and cytomegalovirus (CMV) in HIV-positive patients have been reported previously.[5,11] Likewise, we found three *Mycobacterium tuberculosis* and one CMV infection responsible for the extremely high ALP levels in AIDS patients. Interestingly, we also detected one patient with non - Hodgkin's lymphoma (NHL) whose serum ALP was above 2000 IU/L without apparent abnormalities of the liver or bone. In this case, the serum ALP gradually returned to normal after the primary

tumor was treated. The mechanism of the elevation in serum ALP in such patients is still unknown.[1]

Fourth, the association of jaundice with sepsis was well documented in our study. From previous studies, in most instances, the serum bilirubin was moderately elevated (5-10 mg/dl) in accompany with mildly elevated serum ALP (1-3 times normal).[12,13] However, predominant elevations in serum ALP, but with only minimal elevations of serum bilirubin have also been observed. [5,14] Likewise, approximately one-third of sepsis from extrahepatic origins in our series had marked and disproportionately high serum ALP greater than 1000 IU/L. Moreover, some tropical diseases prevailing in Thailand were also identified to exhibit high serum ALP levels, including melliodosis, leptospirosis, scrub typhus and typhoid fever. It has previously been suggested that the development of hepatic dysfunction with jaundice in such infections, for example, in typhoid fever could indicate more severe infection. [15]

Finally, we also described three patients who had high ALP levels over 1000 U/L, presumably from drug-induced toxicity including allopurinol and phenytoin. All patients' ALP returned to baseline within a few months after discontinuation of the drugs. Interestingly, one patient with hepatic dysfunction apparently caused by allopurinol had peak ALP and total bilirubin levels as high as 8057 IU/L and 40.5 mg/dl, respectively. Indeed, hepatocellular necrosis and a mixed hepatocellular and cholestatic pattern have been previously reported with allopurinol therapy.[16] The mechanism for hepatic injury seems to be that of hypersensitivity with a relatively fixed induction period, development of fever with rash and peripheral eosinophilia, as well as the findings of tissue eosinophilia and noncaseating granuloma on liver biopsy. [16] Likewise, various patterns of liver injury have also been described associated with phenytoin hepatotoxicity. [17]

Conclusions

A number of disorders were associated with high elevations of serum ALP in hospitalized patients. The majority of the underlying etiologies in these patients were attributed to obstructive biliary disease, infiltrative liver disease, AIDS with superimposed infections and sepsis in HIV-negative patients. Our results were in concordance with those previously described from developed countries. Nonetheless, several tropical diseases unique to our region were also essential causes of marked elevations of serum ALP among Thai in patients.

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