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ALKALINE PHOSPHATASE (ALP) ELEVATION IS A BIOMARKER FOR CHOLESTASIS, EPSTEIN-BARR VIRUS (EBV) AND OSTEOSARCOMA (REVIEW)

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ABSTRACT

Alkaline phosphatase is a "metalloenzyme" which at alkaline pH catalyze the hydrolysis of "organic phosphate ester". Different studies were done to find the function of SALP in Osteosarcoma patients. On analysis it was seen that increased SALP levels are linked with existence of metastasis. The elevated level of SALP is particularly linked with deprived rate of "overall survival" or "event free survival" (OS & EFS). SALP levels hence act as a useful, efficient and suitable biomarker for osteosarcoma. Decreased level of Dickkopf-1 by bortezomib; cause stimulation of osteoblasts, which then cause increase in formation of bone. Increased level of "bone specific alkaline phosphatase" (bALP) and "osteocalcin" specifies the increased bone formation. Elevation of ALP, bilirubin and GGT act as the indicator or marker for cholestasis according "primary lab evaluations". ALP levels can also rise in late pregnancy because of a "different form of enzyme" produced by placenta but GGT levels are normal here. Common type of "primary EBV hepatitis" is that in which "biochemical abnormalities" of increased ALP are predominant. In almost 75% cases ALP levels are so high that they can be easily detected and calculated. It can be then concluded that ALP when rise from its normal level can act as an indicator for EBV, cholestasis and osteosarcoma.

KEYWORDS: Alkaline Phosphatase Biomarker Cholestasis *Epstein-Barr Virus* (EBV) Osteosarcoma.

INTRODUCTION

Previous studies showed the function of alkaline phosphatase in cholestasis, osteosarcoma and EBV. It was observed by different experiments that in all the three diseases mentioned above; the level of alkaline phophatase was high and hence it can act as "biomarker" for these three diseases. Literature showed that hepatitis caused by primary "Epstein-Barr Virus" in adults, is usually "benign" and resolve unexpectedly almost in 5 weeks.[1] However, few clinical characteristics and natural route of "primary EBV hepatitis" in children are known.[2]

Alkaline phosphatases (ALPs)

Alkaline phosphatases (ALPs) belong to metalloenzymes and can catalyze hydrolysis of "organic phosphate ester" at an alkaline PH.[3] There are four different genes which encodes for alkaline phosphatase, first is the "tissue non-specific ALP" (TNAP) which is present on "1P36.12" and is expressed in hepatocytes, early placenta kidney and osteoblast tissue then there are 3 "tissue specific ALP genes" which are located on "2q37" and are expressed in placenta (PLAP), intestine (IAP) and germ cells (GCAP).[4]

ALP elevation in osteosarcoma

"Bone tumor" also known as "osteosarcoma" is one of the major causes of cancer-related death in children and teens because of the development of "fatal matirialasis" in lungs.[5] Commonly it has been observed that "SALP levels" are higher in osteosarcoma patients than healthy individuals.[6] Moreover SALP levels are greater in children as compare to adults.[7] Serum alkaline phosphatase (SALP) is mostly obtained from kidney, hepatic tissue in healthy person.[8] "40%-80%" osteosarcoma patients with high SALP levels were reported in early studies.[9,10,11,12] The study showed that patients have high SALP levels considerably correlate with increased metastasis presence ratio at diagnosis which is an indicator of relation between osteosarcoma metastasis and higher levels of SALP.[13] According to Kim *et al.* (2014)[14] there might be some relevance between metastasis development and SALP levels in patients with localized osteosarcoma. Higher levels of SALP in "metastatic osteosarcoma" patients can give "clinical outcomes" more proficiently.

Previous studies suggested that osteosarcoma which was transformed from osteoblasts can disturb the "tight control of proliferation" and gradually express those genes which are linked with the "cell differentiation". This can cause a constant high level of alkaline

phosphatase.[15,16] It was also stated that "osteoblastic subtype" of osteosarcoma has higher levels of SALP than any other subtype.

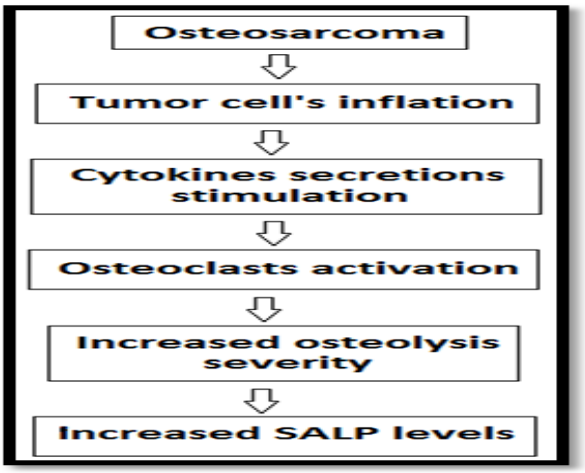

Fig. i: Increase of SALP levels by osteosarcoma

Osteosarcoma metastasis is also related to infiltration and expansion of "tumor cells" which cause stimulation of cytokines secretions to initiate osteoclasts activation. The activation of osteoclasts increases the osteolysis severity and hence increases the levels of SALP.[17] Han *et al.* (2012)[18] stated, the secretion of "matrix metalloproteinases (MMPs)" from cancer cells to dissolve or break extracellular matrix, can also increase the levels of SALP. It was assumed that progression or intrusion of osteosarcoma can increase osteolysis and rise SALP levels. After "preoperative chemotherapy" SALP levels decrease to normal in most of the patients who had initial increased SALP.[18,19] The decreasing levels of SALP while clinical therapy can be an indicator of positive reaction to the treatment and disease cure. If SALP levels remain same after treatment this could be a sign of poor response to treatment.[18] Presence of metastasis and poor "overall survival (OS) or "event-free survival (EFS)" is related to increased SALP levels. SALP is a suitable and useful biomarker of osteosarcoma prognosis.[13]

Increased bone destruction leads to myeloma which cannot be compensated for by new bone formation.[20] The study of myeloma bone disease shows that myeloma cells, osteoblasts and osteoclasts are related to each other. The activity of osteoblasts is repressed whereas bone resorption activity of osteoclasts is supported by myeloma cells because of which a discrepancy is caused between bone formation process and bone resorption process and that is the property of myeloma bone disease.[21,22,23] In normal conditions RANKL "(Receptor activator of nuclear factor-kappa B ligand)" and its receptor osteoprotegrin (OPG) regulates the formation of osteoclast their activity and "bone resorption". "Myeloma cells" disrupt the balance of "OPG" expression whereas increase expression of "RANKL".[24,57] Increase of "RANKL" and presence of "MIP-1α and MIP-1β protein" produced by myeloma cells increase "osteoblastic bone resorption".[25,26,27] Growth factors and cytokines are released in bone destruction by myeloma cells which increase survival and growth of myeloma cells hence cycle of dependence is established between "tumor cells" and "osteoblastic bone destruction".[28]

Bortezomib is an inhibitor (reversible) of proteosome and has ability to treat relapsed as well as newly diagnosed multiple myeloma (MM).[29,30] Oyajobi and co-workers (2004)[31] conducted research and stated that bortezomib has ability to stimulate "new bone formation" in "neonatal mouse calvarias organ culture". Mukherjee and co-workers (2006)[32] reported that bortezomib has no effect on the number of osteoblastic colony-forming units but can promote an increase in their size. CD45-/CD51+ express "collagen type1" and "ALP" and form "bone nodules" which proves that they are of osteoblastic lineage.

Zengari *et al.* (2003)[9] reported that SALP levels show a noticeable increase in patients treated with bortezomib and Shimazaki *et al.* (2005)[33] said that bone-specific ALP (bALP) and serum ALP levels increase if a patient of MM is treated by incardonate, dexamethazone and bortezomib which suggest that there is a direct effect of bortezomib on osteoblastic activity. It was also noticed that the combination of dexamethazone and bortezomib along with thalidomide can also increase ALP levels in patients who respond to these medicines.[9] After 3 therapy cycles of bortezomib an increase in "ALP" levels was spoted in patients who respond (complete or partial (CR/PR) to it. Increase of "parathyroid hormone" and bALP levels shows the relation between bortezomib and osteoblast activation. ALP levels were not elevated in patients who respond to dexamethasone may be because of its toxic effect on osteoblasts. Progression of myeloma for a long time and patient's response (CR/PR) are linked with 25% elevation of ALP levels at 6 week.[11,34]

Heider *et al.* (2006)[12,21] reported the stimulation of osteoblsts because of "bortezomib". He calculates the changes in levels of "bALP and osteocalcin (OC)" in different patients who were taking "borezomib ± dexamethasone" and in the group of patients who were taking "melphalan/prednisone", "adriamycin/dexamethasone" or "thalidomide containing regimens". Elevation was seen in the levels of "bALP" and "OC" in "bortezomib" taking patients. 34 patients with degenerative multiple myeloma show considerable increase in OC and increased bALP levels according to Terpos *et al.* (2006).[35] Increased levels of bALP was also observed after 4 cycles of treatment of bortezomib in 75% non responders because of decrease in serum level of Dkk1. In combination of bortezomib with thalidomide and melphalan; anti-myeloma agent bortezomib lose its effectivity on osteoblasts. Bortezomib in combination with dexamethazone shows less increase in levels of bALP than its only intake.[12,21]

ALP elevation in cholestasis

Cardiac hepatopathy (CH) is caused by "passive venous congestion" of liver which most of the time happens while chronic cardiac conditions' setting's.[36] Generally CH is asymptomatic but stretching of liver capsules may cause a little pain in "right upper quadrant", nausea and anorexia was also seen in some patients.[37,38] Physical examination shows that pulsatile liver, tender hepatomegaly, jaundice, ascites and hepatojuglar reflux are the main symptoms.[37,39] Serum cholestasis markers, like "ɤ-glutamyl transpeptidase (GGT)", "bilirubin" and "alkaline phosphatase (AP)", were found to be elevated in primary lab findings of CH.[40,41]

Within a few days after "intra-hepatic cholestasis" or "bile duct obstruction" AP and GGT elevate several times from their normal levels. The most noticeable elevation of liver AP levels are found in "diffuse infiltrative disease of liver" which includes "fungal infections" as well as "infiltrating tumors" and are usually greater than 1000U/L or might be six times more than normal levels of AP in body [46]. 90% of patients suffering from cholestasis have high levels of alkaline phosphatase and GGT than normal person.[42] Poelzl *et al.* (2012)[43] stated that GGT and alkaline phosphatase are interpreters of death from heart transplantation in patients of heart failure (HF). It was also reported by them that GGT, AP and bilirubin levels are independently associated with clinical signs of HF. Little rise of AP levels, serum bilirubin and prothrombin time prolongation are some lab findings for "differential diagnosis of alcoholic", "acute viral" or "drug-induced" hepatitis.[44,45]

Value of liver AP might be raised because of LFT abnormalities, high 5'nucleotidase level and high GGT level. Chronic "inflammatory disorder of small bile duct" also known as "primary biliary cirrhosis" could be a reason for high levels of AP in "asymptomatic patients" particularly in females.[46] Enzymes produced by serum AP (commonly produced by bone & liver) are slightly different from normal enzymes. Levels of serum AP can rise in pregnancy as a result of an enzyme produced in placenta moreover, in patients who are taking Phenytoin can have a little increased levels of GGT and AP.[47] According to a study by Lieberman & Phillips 1990[48] little rise in AP levels can be cured in 6 months but high increase in AP levels have obvious reasons found by regular clinical assessment.

ALP elevation in EBV

Kofteridis *et al.* (2011)[1] stated that 59% patients suffering from EBV hepatitis had temporary cholestatic liver disease which had major hepatic contribution with "biochemical abnormalities" of increased alkaline phophatase (ALP) and ɤ- glutamyl transpeptidase (GGT), whereas only 6% had clinical jaundice.

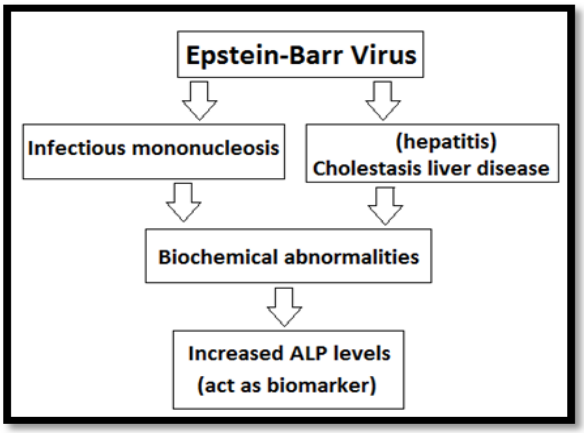

Fig. ii: EBV increase levels of ALP

Study by Soo *et al.* (2014)[2] also showed that hepatitis with "biochemical abnormalities" of raised GGT and ALP levels happened in 39% patients. "Primary EBV hepatitis" in which ALP and GGT levels are increased because of "biochemical abnormalities" can characterize a benign disease which is not accompanied by jaundice but liver function recovery is delayed. "Primary EBV hepatitis" in which ALP and γ-GT levels are increased occurs commonly.

A 73-year-old lady with a background marked by "paroxysmal supraventricular tachycardia", hypertension, "partial sigmoidectomy post–colon disease" and peripheral neuropathy of the lower periphery introduced to a local hospital with fever of 1 day's span. She whined of chills, exhaustion; diffuse myalgias, tiredness and expanding sleepiness. The patient showed periodic myoclonic jerking of every one of the 4 extremities. No other important physical examination discoveries were noted. Liver chemistry tests demonstrated a bilirubin level of 0.4 mg/dL and AP of 73 IU/L (table i). The patient was exactly treated with "intravenous ceftriaxone" and "doxycycline", however her "mental status" and "temperature curve" kept on fluctuating. On the ninth day her serum bilirubin raised at 2.2 mg/dL and AP increased at 560 U/L.[49]

A 59-year-old woman with a background marked by chronic urticaria presented with 1 week of "headaches, malaise, myalgias, generalized anxiety, and insomnia". Her side effects tended to increase and decrease, and were linked with "occasional fevers". Her liver tests demonstrated a total level of bilirubin 0.9 mg/dL and of AP 509 U/L (table 1). The patient was then treated with "intravenous immunoglobulin" for 5 days. A single course of "methylprednisolone" was given but stopped because of agitation. The patient's symptoms improved within a few weeks and her liver tests showed normality in a month.[49]

Table i: Liver Chemistry Tests for Case 1 & 2

	Baseline	Day1	Day 4	Day 10	Day 12	Day 15	Day 37	Day 76
Case 1								
Total Bilirubin (0.0-1.0 mg/dL)	0.3	0.4	0.4	2.2	2.2	1.2	0.4	0.3
Alkaline Phophatase (50-136 U/L)	76	73	132	560	481	458	161	111
Case 2								
Total Bilirubin (0.0-1.0mg/dL)	0.4	0.9	1.9	1.9	0.8	0.7	0.4	0.5
Alkaline Phophatase (50-136 U/L)	74	503	742	912	850	404	169	80

EBV also known as "Epstein-Barr Virus" is a herpes virus which can cause "infectious mononucleosis (IM)". The symptoms of the disease include fever, hepatosplenomegaly, pharyngitis, atypical lymphocytosis and lymphadenopathy.[50] Rises in AP are recognizable in up to 75% of cases.[51,52] with levels as elevated as "1,440 U/L" in some cases.[53,54] In "EBV-induced infectious mononucleosis" the value of AP was assessed comprehensively and approximately 75% cases show abnormal activities of AP.[51,55] Particularly, notable rises in AP was also observed in association with "normal" or "near-normal serum bilirubin" concentration in around "65% of IM patients".[51] The dissociation of "AP-bilirubin" is not particularly for "EBV-induced mononucleosis" but it could generally be for a number of "malignant and benign infiltrative and space-occupying" hepatic diseases. Focal hepatic disease could be indicated by AP bilirubin dissociation instead of diffuse hepatic disease. This might imitate the initiation of alkaline phophatase activity as a result of "focal cholestasis".[56]

CONCLUSION

According to previous studies it can be concluded that elevated levels of "serum alkaline phosphatase" (SALP) (along with bilirubin and GGT) act as an indicator for osteosarcoma whereas increased level of "bone specific alkaline phosphatase" (bALP) along with osteocalcin is a marker for bone formation. It was also observed that levels of GGT and alkaline phosphatase are higher than normal in cholestasis patients moreover an increase in levels of ALP can also be seen during last trimester of pregnancy but in this case level of GGT is not increased. Studies suggest that about 75% cases of "primary EBV hepatitis" levels of ALP are very high and can easily be detected and calculated. So we can say that elevation of alkaline phosphatase is a prognostic marker for cholestasis, EBV and osteosarcoma.

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