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Research paper

Unravelling the Enigma: A Study on Exploring the Idiopathic Surge in Serum Alkaline Phosphatase Level

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Abstract

A 73 year old Indian female with type O blood group came for routine checkup when it was discovered she had elevated levels of serum alkaline phosphatase (600 mg/dL). Other liver function tests were within normal limits. Abdominal imaging revealed grade I fatty liver but an extensive serological search for significant hepatobiliary disease was negative. She is currently under medication for diabetes and hypertension, association with raised enzyme level couldn't be interpreted due to paucity of testing.

Keywords: *Alkaline Phosphatase; Alkaline Phosphatase Surge; Causality; Drug Induced; Raised Enzyme Level.*

1. Introduction

Alkaline phosphatases (ALPs) are a group of isoenzymes located on the outer layer of cell membrane catalyzing the hydrolysis of organic phosphate esters. The rise in level more than 3 fold raises suspicion of hepatobiliary or skeletal pathology. Rarely, it can present as drug induced especially with anti diabetics such as metformin that can lead to fatty liver in <1% of population. Familial cases are seen, some associated with blood type B and O. Reported estimates for idiopathic rise in enzyme level ranges from 1:10,000 cases to 1:100,000 cases[4]. This is a case of suspected drug induced alkaline phosphatase surge, cannot be confirmed due to paucity of testing.

2. Case Presentation

A 73 year old vegetarian Indian female came for regular checkup, a known case of diabetes mellitus type II and hypertension since 10 years and is under medication. Upon routine blood analysis, discovered her serum alkaline phosphatase level was 600 IU/L (normal- 445-129 IU/L). On examination, she had bilateral knee joint pain, but relieved on taking rest and was on homoeopathic medication (contents unknown) for arthritis for 6 years, pain under control. No history of significant weight loss (>10% weight loss in a month), no loss of appetite, no history of chronic fever (fever more than one month), no transplantation surgery, no lymphadenopathy (malignancy), no history of pain per abdomen (hepatic damage), severe joint pain, recurrent fractures, deformities of extremities and spine and limitation in movement (skeletal involvement). No history of smoking, consumption of betel nuts, lime and alcohol. She is moderately built, well nourished (BMI- 21.5 kg/m^2), conscious, oriented. Underwent plastic surgery for a gaping wound on her forehead following a fall 7 years ago, post op. uneventful. She has moderate conductive type hearing loss and is on hearing aid adjusted to 60dB level. She underwent surgery in both the eyes for cataract 15 years ago, and wears reading glasses. She had loosened teeth removed and replaced with dentures 23 years ago, exact cause unknown.

2.1. Family History

She is of blood type O positive. There is a familial history of beta thalassemia major where her youngest brother died when he was 30 years old and had no children. He had to undergo blood transfusions for every 2-3 weeks (type O). She is negative for thalassemia and upon screening her children and grandchildren, all were tested negative for thalassemia and rise in serum alkaline phosphatase. Her father was a chain smoker, smoked 20 cigarettes a day, a known case of CHD, hypertension and diabetes mellitus and he died of cardiac arrest at age 60 years, was not under medication. Her mother was a known case of chronic idiopathic depression, not under medication. Alkaline

phosphatase status unknown in both. Her younger sister has cognitive disability (exact diagnosis not made). No history of tuberculosis, epilepsy, complicated pregnancy amongst immediate family members.

2.2. Drug History

She is a known case of diabetes mellitus type II and hypertension for 10 years and is currently under the following medications (change in dosage over a period of time depending on her blood parameters).

- TAB. DAPAGLIFLOZIN 10 MG OD
- TAB. LINAGLIPTIN 5 MG OD
- FDC- TAB. GLIMEPIRIDE 2MG + METFORMIN 500MG + PIOGLITAZONE 15MG BD
- TAB. VOGLIBOSE 0.3MG TID
- TAB. TELMISARTAN 80 MG OD
- FDC- TAB. ASPIRIN 75 MG + ATORVASTATIN 10 MG OD
- FDC- TAB. CYANOCOBALAMIN 15 MCG + VITAMIN B COMPLEX 45 MG BD

She was put on injectable insulin and dosage reduced due to excessive dizziness. She was under medication for hypothyroidism (Tab. Levothyroxine) 5 years ago, discontinued.

3. Investigations

Ultrasonography - Abdomen	●	Grade I fatty change in the liver.
	●	Post-menopausal uterus posterior wall calcified fibroid.
Blood Biochemistry	●	HbA1c - 12.2%
	●	RBS - 140 mg/dl
	●	Fructosamine - 337 µmol/L (normal <=286 µmol/L) - Indicative of diabetes, poor glycemic control
	●	Lipoprotein A - 57.46 mg/dl (normal < 30.0 mg/dl) - Useful in diagnosis of Coronary Heart Disease
	●	TC/ HDL Cholesterol Ratio 2.5 (normal 3 - 5)
	●	LDL / HDL ratio 1.5 (normal 1.5-3.5)
	●	BUN 5.5 mg/dl (normal 7 - 25)
	●	Other values are within the physiological limits
Bone Mineral Densitometry	●	Osteopenia
	●	Fracture risk: 2 times increase for femoral type.
ECG, 2D ECHO		Normal for age
Liver Function Test	●	BILIRUBIN - 0.74 mg/dl (0.3-1.2)
	●	BILIRUBIN - 0.23 mg/dl (< 0.3)
	●	BILIRUBIN (INDIRECT) 0.51 mg/dl (0-0.9)
	●	GAMMA GLUTAMYL TRANSFERASE (GGT) 13U/l (< 38)
	●	ASPARTATE AMINOTRANSFERASE (SGOT) - 27 U/l (< 31)
	●	ALANINE TRANSAMINASE (SGPT) 18 U/l (< 34)
	●	PROTEIN - TOTAL - 6.72 gm/dl (5.7-8.2)
	●	Serum ALBUMIN - 4.35 gm/dl (3.2-4.8)
	●	SERUM GLOBULIN - 2.37 gm/dL (2.50-3.40)
	●	SERUM ALB/GLOBULIN RATIO - 1.84 (0.9 - 2)
Serology	●	HbSAg - Negative
	●	Anti HIV antibodies- Negative
	●	Other antibodies suggestive of hepatobiliary pathology - Negative

Year of Investigation	Rise in Serum Alkaline Phosphatase (mg/dL)
2017	670
2019	634
2020	662
2021	720
2022	827

3.1. Screening for Other Causes: To Rule Out Differential Diagnosis

Investigation	Inference (normal range)
Serum creatinine	0.95mg/dL (0.51 - 0.95 mg/dL)
Serum LDH	174.1 U/L (135 - 214 U/L)
Carcino Embryonic Antigen	1.90 ng/mL (Upto 3.4 ng/mL)
Alpha fetoprotein	5.50 ng/mL (Less than 7.0 ng/mL)
CA 19.9	15.00 U/ml (0 - 30.9 U/ml)
CT Abdomen	Grade I Fatty Liver

4. Differential Diagnosis

Sepsis, Malignant obstruction within the hepatic system, Liver metastasis, Malignant bone tumors, Hypo/Hyperthyroidism, Lymphomas and Acquired ImmunoDeficiency Syndrome (AIDS). She is tested negative for all the above mentioned medical conditions.

5. Treatment

The patient has no presenting complaints and the investigations were normal for her age. She was continued on the same medications and was advised to undergo routine investigations (CBC, urine routine, HbA1c, Liver Function Test) for every 3 months. Post follow up was uneventful. She practises yoga for one hour every morning (5:00 AM-6:00 AM) followed by drinking a glass of milk. She skips breakfast, but occasionally consumes a bowl of porridge containing buckwheat (100g) with a spoonful of sugar. Lunch usually consists of white rice, sambhar (lentil stew) with cooked vegetables (100-200g) and a large glass of buttermilk (~500mL). She consumes around 2 litres of water everyday with an evening brisk walk for 30 minutes. She is a strict vegetarian, doesn't consume eggs, and is on a B12 supplement. Now, is put on a full fat, low carb diet consisting of almonds, butter tea, steamed vegetables, soups and cottage cheese.

6. Discussion

Phosphate monoester hydrolysis is facilitated by the membrane-bound enzyme alkaline phosphatase. It can be detected in the liver, bile ducts, colon, kidney, bone and others. Physiological growth spurts induce an increase in bone alkaline phosphatase. Apart from these physiological reasons for elevated alkaline phosphatase, hepatobiliary or bone illnesses account for the majority of disease processes that produce a rise in alkaline phosphatase[2]. As per Jitin Verma et al, raised intestinal alkaline phosphatase occurs in some individuals without any apparent disease, commonly those with blood group B or blood group O[1]. Relation between drug intake and rise in alkaline phosphatase could not be established as she did not undergo the investigation for a period of 10 years. However, as per Kutoh E. et al, minor enzyme elevations have been reported to occur during metformin therapy in less than 1% of patients where it may actually lower elevated aminotransferase levels in patients with fatty liver disease. Clinically, apparent liver injury from metformin is very rare, only around 12 cases have been reported so far[3]. Intestinal alkaline phosphatase helps in the breakdown of dietary cholesterol, regulating lipid absorption across enterocytes and calcium absorption. It also has a role in limiting bacterial transepithelial passage. Yujiang Liang et al. noted that the correlation between alkaline phosphatase levels and increased risk of depression differed between men and women where bone rebuilding process is increased in postmenopausal women due to estrogen deficiency and the process can be regulated by ALP levels[6].

7. Conclusion

ALP screening is useful to determine the presence of liver disease or damage and bone disease, among others. It has been shown that ALP is a reliable marker of cardiovascular disease such as stroke in hypertensive patients and spontaneous cerebral hemorrhage and in inflammatory conditions such as knee osteoarthritis[6]. She has no significant disease process linked to the elevated serum alkaline phosphatase. There have been studies conducted on other patients who have had benign elevations of alkaline phosphatase without underlying disease or drug induced that can lead to mild fatty liver disease without any clinical presentation such as right hypochondrium tenderness, jaundice and significant rise in liver function test parameters. The interaction between drugs given concomitantly is complex and challenging and complicates causality assessment. Often drugs may have reciprocal interaction such that either drug increases the potential for rise in alkaline phosphatase level of the other, such as metformin[5]. For most patients, it is not necessary to request alkaline phosphatase testing in the setting of other clinical, biochemical parameters. However, for some patients, performing isoenzyme analysis will focus the direction of investigation especially in hepatobiliary and skeletal pathology. There have been instances of familial idiopathic alkaline phosphatase surge unaccompanied by significant clinical findings.

8. Footnote

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