Rare disease

Persistently elevated alkaline phosphatase

Jitin Verma, David A Gorard

Department of Gastroenterology, Wycombe Hospital, High Wycombe, UK

Correspondence to Dr David A Gorard, Wycombe Hospital, Queen Alexandra Road, High Wycombe HP11 2TT, UK; david.gorard@buckshealthcare.nhs.uk

Summary

A 32-year-old overweight asymptomatic man was found to have a persistently raised serum alkaline phosphatase at 250–300 U/l (normal range <130). Other liver function tests were unremarkable apart from an initial marginally elevated alanine transaminase, which normalised with weight reduction. Abdominal imaging revealed a fatty liver but an extensive serological search for significant hepatobiliary disease was negative. Subsequent isoenzyme electrophoresis revealed normal liver and bone fractions of alkaline phosphatase but a grossly elevated intestinal fraction. Elevated intestinal fraction of alkaline phosphatase should be considered in the investigation of unexplained alkaline phosphatase, particularly when the usual associated hepatobiliary and bony pathologies are not present. Although an elevated intestinal fraction of alkaline phosphatase can be linked to significant gastrointestinal pathology, this case report highlights that it can be a benign biochemical finding.

BACKGROUND

Deranged liver biochemistry is commonly encountered in many clinical settings. There are specific investigative algorithms to identify the cause of elevations of different liver enzymes. Elevations of alkaline phosphatase are usually due to hepatobiliary illnesses or due to bone illnesses. A case is described where the aetiology of elevated alkaline phosphatase proved to be a rare benign condition.

CASE PRESENTATION

A 32-year-old man was referred to a gastroenterology clinic by his general practitioner following an incidental finding of a raised alkaline phosphatase on routine blood testing. His alkaline phosphatase was found to be 264 U/l (normal range (NR) 40–130) and his alanine transaminase (ALT) was marginally elevated at 65 U/l (NR 10–50). The remainder of the liver function tests including aspartate transaminase was otherwise normal. He had no symptoms at all. He was taking no regular medications and did not take any herbal remedies or illicit drugs. There was no history of previous hepatitis or liver disease. His medical history consisted of migraine and depression. He had a strong family history of thyroid disease, his father having Graves' disease and his mother having hypothyroidism. He worked in market research and consumed very little alcohol.

General clinical examination was normal, but he was overweight at 117 kg with a body mass index (BMI) of 32. Specific abdominal examination was unremarkable, with no evidence of hepatomegaly or splenomegaly.

INVESTIGATIONS

An ultrasound scan of his abdomen revealed a fatty liver but no other abnormality within the hepatobiliary system. A magnetic resonance cholangio-pancreatogram showed normal appearances of the biliary tree and no evidence of gallstones. Serological tests for hepatitis B, hepatitis C and autoimmune liver diseases were all negative. Serum

ferritin, iron and transferrin saturation were normal, as were α 1-antitrypsin and caeruloplasmin levels. Renal function tests, serum calcium, phosphate and parathyroid hormone were all normal. Thyroid function tests showed an elevated thyroid-stimulating hormone at 7.7 mU/l (NR up to 4.2), with positive thyroglobulin antibody and thyroid peroxidase antibody. The patient was started on 50 μ g thyroxine daily for subclinical hypothyroidism.

He made a concerted effort to lose weight, and his weight reduced to 110 kg. Following this weight loss and the introduction of thyroxine therapy for subclinical hypothyroidism, his previously mildly elevated ALT improved and became normal.

Despite losing weight and being on therapy for hypothyroidism, his alkaline phosphatase remained elevated at 299 U/l. Alkaline phosphatase isoenzyme electrophoresis was performed. This revealed normal liver and bone fractions of alkaline phosphatase but a grossly elevated intestinal fraction:

Total alkaline phosphatase	248 U/l (normal range 40–130)
Liver fraction	11 U/l (normal range <92)
Bone fraction	97 U/l (normal range <97)
Intestinal fraction	140 U/l (normal range <18)

Subsequent blood group testing showed that his blood group was O.

DIFFERENTIAL DIAGNOSIS

Aside from physiological elevations of alkaline phosphatase during childhood growth (bone origin) and during pregnancy (placental origin), alkaline phosphatase elevation can be broadly grouped into hepatobiliary causes and bone causes. Hepatobiliary causes of elevated alkaline phosphatase include biliary obstruction due to stones, strictures or tumours. Intrinsic liver diseases, including metastatic liver disease and the cholestatic autoimmune diseases, primary biliary cirrhosis and primary sclerosing cholangitis, are associated with elevated alkaline

phosphatase. A concurrent elevation of γ -glutamyl peptidase level would be expected in hepatobiliary causes of elevated liver disease. Fatty liver linked to obesity often causes a rise in liver transaminases but not a solitary rise in alkaline phosphatase.

Bone pathology causes of elevated alkaline phosphatase include Paget's disease, hyperparathyroidism, osteomalacia, metastatic bone disease and a recent fracture.

Raised intestinal alkaline phosphatase occurs in some individuals, commonly those with blood group B or blood group O and such an elevation may not be associated with any pathological condition. Intestinal alkaline phosphatase is more likely to be elevated after a fatty meal. Sometimes elevated intestinal alkaline phosphatase may be familial.

TREATMENT, OUTCOME AND FOLLOW-UP

It was initially considered that our patient's elevated BMI leading to hepatic steatosis and his subclinical hypothyroidism could be contributing to his deranged liver biochemistry. However, fatty liver linked to obesity tends to cause a rise in liver transaminases rather than alkaline phosphatase. Weight loss and treatment of subclinical hypothyroidism coincided with normalisation of initially elevated ALT, but his alkaline phosphatase remained elevated at 299 U/l.

Once the alkaline phosphatase isoenzyme electrophoresis was performed and revealed a markedly elevated intestinal fraction, a further search for hepatobiliary disease was halted. In particular, a planned liver biopsy was deferred. The patient has been reassured that his persistently elevated alkaline phosphatase is of no pathological importance, requires no further investigation, but may cause unnecessary concern in future whenever his liver biochemistry is checked for any reason.

DISCUSSION

Alkaline phosphatase is a membrane-bound enzyme responsible for catalysing the hydrolysis of phosphate monoesters. It is present in several tissues including liver, bile ducts, intestine, bone, kidney, placenta and leucocytes. Bone alkaline phosphatase is increased at the time of physiological growth spurts, and placental alkaline phosphatase increases towards the end of pregnancy. Outside of these physiological causes of elevated alkaline phosphatase, most disease processes causing alkaline phosphatase rises are due to either hepatobiliary or bone diseases.

An intestinal fraction of alkaline phosphatase normally contributes up to around 14% of the total alkaline phosphatase.¹ Intestinal alkaline phosphatase has roles in nutrition including the breakdown of dietary cholesterol, regulating lipid absorption across the apical membrane of enterocytes and the absorption of calcium. It also has a role in intestinal defence, limiting bacterial transepithelial passage and bacterial endotoxin-induced inflammation.²

Intestinal alkaline phosphatase rises after fatty meals. Individuals with blood group B or O are most likely to display this postprandial rise in intestinal alkaline phosphatase.

Intestinal alkaline phosphatase is elevated in some pathological conditions. Major intestinal catastrophes

such as perforation of the bowel or acute infarction of the intestine will cause a release of intestinal alkaline phosphatase from the mucosa. Large erosive or ulcerative lesions of the stomach, duodenum, small intestine or colon may also result in an elevation of the serum alkaline phosphatase level. The intestinal fraction of alkaline phosphatase may sometimes be elevated in liver cirrhosis.

Our patient had no significant disease process linked to his elevated intestinal alkaline phosphatase. His intestinal alkaline phosphatase was the greatest alkaline phosphatase fraction in his serum, contributing to 56% of the total. There have been reports of other patients who have had benign elevations of intestinal alkaline phosphatase.³⁻⁴ Furthermore, there have been descriptions of families where intestinal alkaline phosphatase is elevated but there is no underlying disease.⁵⁻⁷

Clinicians need to be aware of the possibility of an elevated serum alkaline phosphatase being due to an increased intestinal fraction. In the investigation of patients with raised alkaline phosphatase, most alkaline phosphatase elevations will be turn out to be due to bone or hepatobiliary diseases. For most patients it will not be necessary to request alkaline phosphatase isoenzyme testing in the setting of other clinical, biochemical and radiological information. However, for some patients, performing isoenzyme analysis will focus the direction of investigation.⁸ In rare cases of increased intestinal alkaline phosphatase, such isoenzyme analysis will prevent further unnecessary investigation and may point to a persistent but benign finding.

Learning points

- ▶ Alkaline phosphatase is present in the liver, bone and intestine.
- ▶ Elevated levels most commonly occur in hepatobiliary and bone disease.
- ▶ Raised intestinal alkaline phosphatase occurs in some individuals without any apparent disease process, commonly those with blood group B or blood group O.
- ▶ There have been reports of familial elevated intestinal alkaline phosphatase.

Competing interests None.

Patient consent Obtained.

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Please cite this article as follows (you will need to access the article online to obtain the date of publication).

Verma J, Gorard DA. Persistently elevated alkaline phosphatase. *BMJ Case Reports* 2012;10.1136/bcr-2012-006768, Published XXX

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