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Differential Diagnosis and Work-Up of Elevations of Alkaline Phosphatase Following Therapy for Pediatric Cancer

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To The Editor

The overlap between alkaline phosphatase (ALP) elevation related to malignancy and that related to viral illness can present a diagnostic dilemma for the pediatric oncologist. We present two cases of transient hyperphosphatasemia following cancer therapy and review the differential diagnosis and work-up.

First we present an 18-month old female who presented six months following therapy with carboplatin, etoposide, cyclophosphamide and doxorubicin for stage 4, intermediate-risk neuroblastoma with an ALP of 5527 U/L. The history of neuroblastoma raised concern for bone or liver metastases. Imaging, bone marrow aspiration, and urine VMA, HVA showed no evidence of malignancy; workup did not suggest nephropathy, endocrinopathy, hepatopathy or biliary tract obstruction. Six weeks previously, she experienced a febrile illness with upper respiratory infection (URI) symptoms and diarrhea. ALP was followed serially and 3 months later normalized to 208 U/L She remains free of neuroblastoma greater than 5 years off therapy.

The second case is a 16-month-old male who presented 6 months following therapy with cisplatin/carboplatin, etoposide and bleomycin for abdominal yolk sac tumor with ALP of 2,290 U/L. Two months prior, he had experienced a URI. Evaluation for malignancy was negative. There was no evidence of nephropathy or hepatopathy. Parathyroid hormone was slightly elevated; evaluation for rickets and decreased bone mineral density (BMD) revealed only a minimal decrease in BMD for age. Four weeks later he remained clinically well with a normal ALP of 240 U/L. He remains free of disease with normal AFP 12 months after therapy.

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ALP originates predominantly from bone and liver but also from kidney, intestine, leukocytes and placenta. The normal values for ALP vary with hormonal and bone growth status, with higher values in growing children than adults. Hyperphosphatasemia prompts concern for several pathologic conditions [1-4] (Table I). Isoenzyme fractionation of ALP can help determine the tissue of origin, refine the differential diagnosis, and direct the work-up [2, 5, 6]. Decreased BMD may manifest as elevated ALP and hyperparathyroidism and has been a well-documented late effect of childhood acute lymphoblastic leukemia and intracranial tumors; changes may also occur with solid tumors and may begin to occur early in therapy [7-13]. Benign transient hyperphosphatasemia, with ALP as high as 10,000 U/L, has been reported in children several weeks after febrile/viral illnesses [3, 4, 14-16]. Diagnostic criteria for this condition are given in Table I. The bone fraction typically exceeds the liver fraction. Specific associations have been observed with echovirus 22, enterovirus 71 and coxsackie virus B4 [3, 14, 15].

ALP elevations can be a sign of several processes concerning to the pediatric oncologist, including cancer recurrence, osseous or hepatic metastases, hepatic dysfunction and bone demineralization. However, young children may develop dramatic but benign and transient ALP elevations in the weeks to months following acute illness. For oncology patients in remission who are younger than five years (particularly with a history of recent illness) with hyperphosphatasemia but without evidence of malignancy recurrence or hepatic dysfunction, observation and close follow-up may be a reasonable initial management approach.

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References

1. Corathers SD. Focus on diagnosis: the alkaline phosphatase level: nuances of a familiar test. Pediatr Rev. 2006; 27:382–384. [PubMed: 17012488]
2. Liu PP, Leung KS, Kumta SM, et al. Bone-specific alkaline phosphatase in plasma as tumour marker for osteosarcoma. Oncology. 1996; 53:275–280. [PubMed: 8692530]
3. Suzuki M, Okazaki T, Nagai T, et al. Viral infection of infants and children with benign transient hyperphosphatasemia. FEMS Immunol Med Microbiol. 2002; 33:215–218. [PubMed: 12110484]
4. Tolaymat N, de Melo MC. Benign transient hyperphosphatasemia of infancy and childhood. South Med J. 2000; 93:1162–1164. [PubMed: 11142449]
5. Green S, Anstiss CL, Fishman WH. Automated differential isoenzyme analysis. II. The fractionation of serum alkaline phosphatases into "liver", "intestinal" and "other" components. Enzymologia. 1971; 41:9–26. [PubMed: 5116110]
6. Kraut JR, Metrick M, Maxwell NR, Kaplan MM. Isoenzyme studies in transient hyperphosphatasemia of infancy. Ten new cases and a review of the literature. Am J Dis Child. 1985; 139:736–740. [PubMed: 4014098]
7. Arikoski P, Komulainen J, Riikonen P, et al. Impaired development of bone mineral density during chemotherapy: a prospective analysis of 46 children newly diagnosed with cancer. J Bone Miner Res. 1999; 14:2002–2009. [PubMed: 10620058]
8. Athanassiadou F, Tragiannidis A, Rousso I, et al. Evaluation of bone metabolism in children with acute lymphoblastic leukemia after induction chemotherapy treatment. Pediatr Hematol Oncol. 2005; 22:285–289. [PubMed: 16020115]

9. Holzer G, Krepler P, Koschat MA, et al. Bone mineral density in long-term survivors of highly malignant osteosarcoma. J Bone Joint Surg Br. 2003; 85:231–237. [PubMed: 12678358]
10. Kaste SC, Rai SN, Fleming K, et al. Changes in bone mineral density in survivors of childhood acute lymphoblastic leukemia. Pediatr Blood Cancer. 2006; 46:77–87. [PubMed: 16106430]
11. Kaste SC, Ahn H, Liu T, et al. Bone mineral density deficits in pediatric patients treated for sarcoma. Pediatr Blood Cancer. 2007
12. Kelly J, Damron T, Grant W, et al. Cross-sectional study of bone mineral density in adult survivors of solid pediatric cancers. J Pediatr Hematol Oncol. 2005; 27:248–253. [PubMed: 15891558]
13. Nysom K, Holm K, Michaelsen KF, et al. Bone mass after treatment for acute lymphoblastic leukemia in childhood. J Clin Oncol. 1998; 16:3752–3760. [PubMed: 9850018]
14. Crofton PM. What is the cause of benign transient hyperphosphatasemia? A study of 35 cases. Clin Chem. 1988; 34:335–340. [PubMed: 3342506]
15. Eboriadou M, Skouli G, Panagopoulou P, et al. Acute laryngotracheobronchitis and associated transient hyperphosphatasemia: a new case of transient hyperphosphatasemia in early childhood. J Paediatr Child Health. 2006; 42:149–150. [PubMed: 16509919]
16. Posen S, Lee C, Vines R, et al. Transient hyperphosphatasemia of infancy--an insufficiently recognized syndrome. Clin Chem. 1977; 23:292–294. [PubMed: 832398]

Table I

Differntial Diagnosis and Work-Up of Elevated Alkaline Phosphatase Following Therapy For Pediatric Malignancy

Condition	Elevated ALP Profile				Other Work-up (as clinically indicated)
	Bone	Liver	Kidney	Leukocyte	
Medications	+	+	+/−	−	Review med list
Sepsis	+	+	+/−	+/−*	Metabolic panel LAP*
Osseus Malignancy	+++	+/−	+/−	−	Tumor markers Bone Scan Imaging
Bony Injury	+++	+/−	+/−	−	Plain radiography
Rickets	+++	+/−	+/−	−	Elevated PTH TSH/FT4 may be elevated 1,25 and 25-OH Vitamin D levels
Osteopenia/ Osteomalacia	+++	+/−	+/−	−	QCT DXA
Hepatic disease Or malignancy	+	+++	+/−	−	Liver/gallblader US/imgaing Hepatic Enzymes Hepatitis Serologies Tumor Markers
Biliary Obstruction	+	+++	+/−	−	Liver/gallbladder US Hepatic Enzymes GGT markedly elevated
Germ Cell Tumors	+	+	+/−	−	Rule out pregnancy AFP HCG Imaging as indicated
Benign Transient Hyperphosphatasemia	++	+	+/−	−	Recent viral illness Age<5 years ALP 3-50 × ULN for age

Legend: +++ Markedly elevated, ++ Moderately elevated, + Mildly elevated, +/− May be elevated or normal, −Not elevated; Abbreviations (in order of appearance):LAP=Leukocyte Alkaline Phosphatase, PTH=Parathyroid Hormone, TSH=Thyroid Stimulating Hormone, FT4=Free T4, QCT=Quantitative Computed Tomograpy, DXA=Dual Energy X-ray Absorptiometry,GGT=Gamma-glutamyltransferase, AFP=Alpha-fetoprotein, HCG=Human Chorionic Gonadotropin, ALP=Alkaline Phosphatase, ULN=Upper Limit of Normal.

* Leukocyte alkaline phosphatase may help differentiate leukemoid reaction from CML