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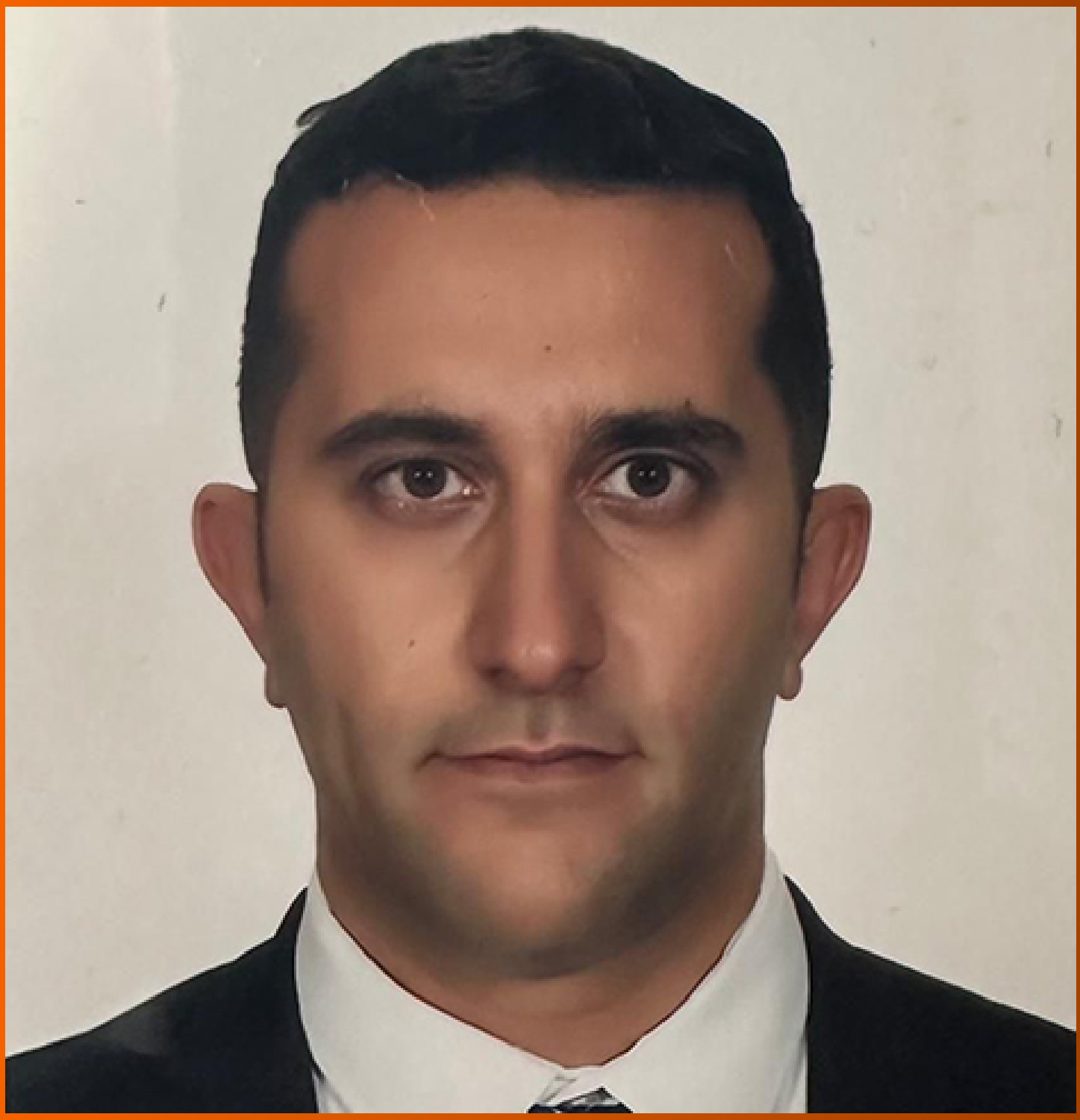

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CASE REPORT

Transient hyperphosphatasemia in a toddler with COVID-19 infection: A case report and literature review

Pemiga Sukhupanyarak, Voraluck Phatarakijnirund

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Abstract

BACKGROUND

Transient hyperphosphatasemia (TH) is a condition characterized by elevated serum alkaline phosphatase (ALP) in the clinical setting with no evidence of bone or liver disease among children under the age of 5. Typically, it will resolve spontaneously in a few months in the majority of cases. TH has been found to be associated with viral infections. Two cases of TH associated with coronavirus disease 2019 (COVID-19) infection in toddlers have been previously reported.

CASE SUMMARY

A previously healthy 2-year-old boy presented with fever and positive real-time polymerase chain reaction for COVID-19. Prior to his illness, the patient had been in close contact with his grandfather, who later developed COVID-19. The physical examination on admission was unremarkable. He remained asymptomatic throughout 7 d of hospitalization. On the 5th day of his illness, blood tests showed markedly elevated serum ALP (4178 U/L). Results from the simultaneous testing of the remaining liver profiles and metabolic bone panels were normal. Two months after discharge from the hospital, the patient continued to thrive well. The skeletal surveys revealed no significant abnormalities. The serum ALP declined into the normal range adjusted for his age. This evidence is consistent with the diagnosis of TH.

CONCLUSION

TH can occur in COVID-19-infected toddlers. Serial measurements of ALP levels have been shown to gradually decline into the normal range within a few months. Therefore, being aware of this transient abnormality will help clinicians to avoid additional unnecessary investigations.

Key Words: Alkaline phosphatase; Coronavirus; Pediatric endocrinology; Case report

Core Tip: Transient hyperphosphatasemia (TH) is an unrecognized condition among children under the age of 5. The only abnormality demonstrated is markedly elevated serum alkaline phosphatase (ALP) without evidence of bone or hepatic disease and spontaneous resolution occurring in several months. Numerous reports have identified various viral infections as contributing factors to the etiology of this condition. TH should be considered in coronavirus disease 2019 -infected toddlers exhibiting isolated high serum ALP. Awareness of this condition will help to avoid unnecessary investigations.

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INTRODUCTION

Transient hyperphosphatasemia (TH) is a benign and self-limiting condition characterized by a marked increase in serum alkaline phosphatase (ALP) in the absence of liver or bone disease[1]. The elevated serum ALP level usually declines into the normal range within a few months[1,2]. TH is observed in either sick or healthy infants and children under the age of 5 by finding incidentally elevated serum ALP on routine laboratory investigation for other purposes[3-8]. Although its etiology remains unclear, the propensity of TH associated with various conditions, such as post organ transplantation, hematologic malignancy, rheumatologic disease[9-11], and, in particular, infectious diseases, has been reported in the literature[5,12,13].

Coronavirus disease 2019 (COVID-19) infection is a highly contagious infection that quickly became a global pandemic disease. Endocrinopathies associated with COVID-19 infection in children, such as thyroid diseases (subacute thyroiditis, hypothyroidism, hyperthyroidism), adrenal insufficiency, diabetes mellitus, vitamin D deficiency and hypopituitarism, had been previously reported[14,15]. TH observed with COVID-19 infection in toddlers is a new discovery that was recently described in two cases[16,17]. Here, we report a case of a 2-year-old boy who developed TH associated with COVID-19 infection.

CASE PRESENTATION

Chief complaints

A previously healthy 2-year-old boy was admitted to our hospital with an acute febrile illness of 4 d duration.

History of present illness

There was a history of the patient being in close contact with his grandfather, who was later diagnosed with symptomatic COVID-19 infection. The patient had a positive test of real-time reverse transcription polymerase chain reaction for severe acute respiratory syndrome coronavirus 2.

History of past illness

He was a full-term baby with a birth weight of 2800 g, requiring no medication since his birth.

Personal and family history

No special notes.

Physical examination

The physical examination upon admission revealed that the patient was in good general condition, with no sign of respiratory distress or dehydration, body temperature 37.6°C, pulse rate 90/min, respiratory rate 22/min and O_2 saturation in room air 99%. His weight and height were 12.1 kgs (-0.7 SDS) and 86.5 cm (+0.7 SDS), respectively. The skeletal examination revealed no wrist joint swelling, rachitic rosary, knock knee or abnormal gait to suggest definite skeletal disease. There were no clinical findings of jaundice or hepato-splenomegaly to indicate hepatobiliary disease.

Laboratory examinations

The initial laboratory results showed hemoglobin 13.3 g/dL, white blood cell 10100/μL with 61.6% lymphocytes and platelet count 196000/μL. Chest X-ray revealed no infiltration. The liver function test (LFT) on the 5th day of his illness

showed a markedly elevated serum ALP of 4178 U/L (normal range: 111-277). Additionally, the occurrence of bone or hepatobiliary disease was assessed, and the results were normal as follows: Blood urea nitrogen 12.4, Cr. 0.3, calcium 9.9, phosphate 4, magnesium 2.2 mg/dL, intact-PTH 21.3 pg/mL, 25-OHD 33.6 ng/mL and gamma-glutamyl transferase 12 U/L (Table 1). The serum ALP was repeated 4 d following the initial study. It remained elevated at 4662 U/L, but the rest of the LFT was normal.

Table 1 Laboratory tests of our patient during coronavirus disease 2019 infection and follow-up

Parameters	At admission		Follow-up after illness	
	5th day of illness	9th day of illness	2nd month	6th month
ALP (U/L)	4178	4662	252	229
AST (U/L)	35.8	30.8	37.7	29.3
ALT (U/L)	17	15.9	16.5	18.8
TP (g/dL)	7.1	6.8	6.7	6.8
Alb (g/dL)	4.9	4.8	4.6	4.6
TB/DB (g/dL)	0.25/0.12	0.17/0.11	0.37/0.12	0.24/0.11
GGT (U/L)	12	-	-	-
Cr (mg/dL)	0.3	-	-	-
Ca (mg/dL)	9.9	-	9.7	-
P (mg/dL)	4.0	-	4.9	-
Mg (mg/dL)	2.2	-	2.26	-
iPTH (pg/mL)	21.3	-	26.4	-
25-OHD (ng/mL)	33.6	-	23.4	-

ALP: Alkaline phosphatase (normal range: 111-277 U/L; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; TP: Total protein; Alb: Albumin; TB: Total bilirubin; DB: Direct bilirubin; GGT: Gamma-glutamyl transferase; Ca: Calcium; P: Phosphate; Mg: Magnesium; iPTH: Intact parathyroid hormone.

Imaging examinations

No special notes.

FINAL DIAGNOSIS

At this point, the diagnosis of TH was strongly considered. The entire 7 d of his hospital course was uneventful without fever, diarrhea or respiratory tract symptoms.

TREATMENT

The management was symptomatic and supportive care with oral antipyretic, anti-emesis and oral rehydration solution.

OUTCOME AND FOLLOW-UP

Two months after discharge, the patient was re-evaluated at the outpatient endocrine clinic. His physical examination was normal. Serum ALP became normal at 252 U/L. The other investigations, including LFT, calcium, phosphorus, magnesium, 25-OHD and skeletal survey radiography, were completely normal. A six-month follow-up study with the same parameters as the 2-month follow-up study revealed that everything remained within the normal range (Table 2).

Table 2 Clinical characteristics and laboratory tests in hyperphosphatasemia associated with coronavirus disease 2019 infection: our patient and previous reports

Clinical characteristics	Our patient	Erat *et al*[16], 2020	Tchidjou *et al*[17], 2020
Ethnicity	Thai	Turkish	French
Gender	M	F	M
Age (mo)	26	16	9
Symptom of COVID-19 infection			
Fever	Yes	Yes	Yes
Upper respiratory tract symptom	No	Yes (Cough, oropharyngeal hyperemia)	Yes (Rhinitis)
Lower respiratory tract symptom	No	No	No
Gastrointestinal symptom	No	Yes (Nausea, diarrhea)	No
Laboratory tests			
Peak ALP (U/L)	4662 (Normal: 111-277)	1860 (Normal: 145-420)	3384 (Normal: 46-116)
ALP ratio[a]	16.8	4.4	29
Cr (mg/dL)	0.21	0.22	0.43
AST (U/L)	36	34	37
ALT (U/L)	17	14	39
GGT (U/L)	12	13	8
Ca (mg/dL)	9.9	9.8	NA
P (mg/dL)	4	5.5	6.8
iPTH (pg/mL)	21.3	28.1	NA
25-OHD (ng/mL)	33.6	32	NA
Resolution of TH			
Time turned to normal ALP level	Two months	One month	One month
ALP (U/L)	252	254	371

[a]ALP ratio: The measured ALP level divided by the upper limit of normal. ALP: Alkaline phosphatase; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; GGT: Gamma-glutamyl transferase; Ca: Calcium; COVID-19: Coronavirus disease 2019; P: Phosphate; Mg: Magnesium; iPTH: Intact parathyroid hormone; TH: Hyperphosphatasemia; NA: Not available.

DISCUSSION

ALP is a membrane-bound phosphomonoesterase enzyme consisting of four isoenzymes, three tissue-specific ALPs (intestinal, placental and germ cell) and the tissue-nonspecific ALP (TNSALP)[18]. TNSALP is abundant in the bone, liver and kidney and accounts for 95% of total ALP activity in serum[19]. Therefore, abnormally high ALP levels are an important marker for skeletal and hepatobiliary diseases.

TH is a benign self-limited condition that reportedly has a prevalence from 1.1% to 3.5% among infants aged 2-24 mo and affects both sexes equally[20,21]. This condition was first described in 1954 by Bach[22]. In 1985, Kraut *et al*[2] established the criteria for the diagnosis of TH in infancy and children, defined as an age group below 5 years, no evidence of bone or liver disease on physical examination or laboratory test, elevation of both bone and liver ALP isoenzymes and a return to normal serum AP values within 4 mo. Although the specific cutoff value of ALP level for diagnosis of TH had not been identified by the original criteria, recent studies have suggested that TH is considered when serum ALP is above 800[5,13], 1000 (6, 11, 21) or 2000 U/L[23]. However, the peak serum ALP of TH was distinctively higher than the serum ALP levels of other bone and hepatic diseases. In a review of 733 TH patients, the mean ALP level was 9 times above the upper limit of the normal range, and 71% of these patients had the highest ALP > 5 times above the upper limit of the reference value[4].

Numerous reports have identified various viral infections as contributing factors to the etiology of TH (Table 3)[13,23-27]. Suzuki *et al*[28] identified antibodies against enteroviruses, such as ECHO 22, entero-71 and coxsackie B4, in the serum of 50 TH children. Among these viruses, ECHO 22 antibody was most frequent, accounting for 32% of TH cases. Additionally, few but not all studies reported clusters of TH during the fall and winter seasons, which supported the assumption of the viral etiology[3,12,21].

Table 3 Viral infections associated with hyperphosphatasemia [13,23-27]

Respiratory syncytial virus
Influenza virus
Epstein-Barr virus
Adenovirus
Bocavirus
Cytomegalovirus
Rotavirus

The mechanism of TH is obscure. Several hypotheses have been postulated, including increased activities of ALP in plasma, increased production and impaired clearance of ALP. The most likely mechanism is decreased hepatic clearance due to the high sialic acid content of ALP, but the mechanism involved in excessive sialic acid content of the molecule is unknown[29]. Increased bone ALP production is thought to be a result of increased bone resorption triggered by virus infection, consequently increasing osteoblast activities and bone formation and hence increasing bone turnover. This was supported by evidence of transiently increased urinary hydroxyproline (bone resorption marker) excretion[30]. In contrast, the study by Kutilek *et al*[8] in 2012 showed a lack of elevated iPTH, Beta-CrossLaps and osteocalcin in TH patients. As such, the hypothesis of increased bone turnover leading to elevated ALP in TH remains controversial.

TH typically resolves without any treatment. A reduction in ALP level to the normal range occurs between 2 wk and 4 years with a median of 10 wk[4]. In 80% of cases, ALP returns to the normal level in 16 wk[4].

Our patient, who was confirmed to have an active COVID-19 infection, exhibited typical clinical features of TH, including high serum ALP levels and no clinical or laboratory evidence of bone or hepatic disease. His biochemical markers of bone metabolism were normal, including calcium, vitamin D and intact PTH. ALP isoenzyme assays were not available at our facility, nor were the other more specific tests for bone turnover markers. The markedly elevated ALP in our patient became normal within 3 mo of follow-up and remained stable at the 6-month follow-up. Given the reports of TH associated with other viral infections, we concluded that our patient developed TH related to COVID-19 infection. Recently, two cases of TH associated with COVID-19 infection in children have been reported[16,17]. All 3 cases, including ours, were aged under 3 years, in accordance with the preponderance (82%) of TH in patients aged < 36 mo in a previous report[4]. The peak level of ALP appears to have no association with the severity of the illness. In our patient, the peak ALP was at 4, 662 U/L (16.8 times to upper normal range), while his symptoms were mild only with low-grade fever. However, the other 2 previous cases had additional clinical symptoms of the upper respiratory tract and gastrointestinal symptoms, but peak levels of ALP appeared to be lower (Table 2). Nonetheless, the serum ALP levels of all 3 cases were similar to those in previous case reports, ranging from 805 to 16814 U/L[3,5,8]. Our patient had the serum ALP return to the normal range of 252 U/L at 2 mo after the acute illness, which is similar to most of the TH cases. In the 2 previous cases of TH associated with COVID-19 infection, their ALP levels declined to the normal range within a month (Table 2). This can be explained by their early schedule testing compared to ours.

In summary, we demonstrated a typical case of TH in a toddler who had been confirmed to have acute COVID-19. It is likely that a rising number of TH cases will be observed along with continuation of the COVID-19 pandemic.

CONCLUSION

Transient hyperphosphatasemia is a benign and self-limiting condition that occurs mainly in infants and children under the age of 5. This condition can be found in toddlers with COVID-19 who exhibit an isolated high level of serum ALP without evidence of bone or hepatic disease based on physical examination and laboratory testing. Therefore, follow-up monitoring of serum ALP levels to confirm the resolution of hyperphosphatasemia without additional extensive investigation and treatment is recommended.

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