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Research Article

# Increased Activity of Alkaline Phosphatase in COVID-19: Potential Mechanisms

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## ABSTRACT

Clinical manifestations of Coronavirus disease 2019 (COVID-19) are multisystemic and associated with a wide range of laboratory abnormalities. Abnormalities in serum liver profile are common, however, increased serum activity of alkaline phosphatase has not been frequently reported. Two cases of PCR confirmed Sars-CoV-2 infection and high alkaline phosphatase serum activity are presented. Cholestasis from sepsis and a specific viral effect are proposed as possible mechanisms.

## INTRODUCTION

Coronavirus disease 2019 (COVID-19), first discovered in Wuhan, China in December 2019, was subsequently declared a pandemic with over 1 million cases in the United States [1,2]. With respiratory symptoms being the most common, patients have been reported to present with a myriad of extra-pulmonary symptoms including abnormalities related to liver, reportedly one of the most common organs involved in the disease outside of the respiratory system [3,4,5]. Although elevations in serum activity of transaminases and bilirubin concentration have frequently been reported in COVID-19, increased serum activity of alkaline phosphatase (ALP) has not. We present two cases found to have elevated alkaline phosphatase of hepatic origin and propose some potential mechanisms for such finding.

## CASE 1

A 49-year-old Hispanic male was hospitalized with acute hypoxic respiratory failure secondary to multi-lobar pneumonia associated with Sars-CoV-2 virus infection, confirmed by positive viral PCR testing. The patient was started on azithromycin, ceftriaxone and hydroxychloroquine as part of the initial treatment regimen. At baseline, the serum activity of alkaline phosphatase (ALP) was 250 U/L (normal 45-115 U/L), and that of gammaglutamyl transferase (GGT), 322 U/L (normal range 8-61 U/L) suggesting hepatic origin of the former. The serum activity of alanine (ALT) and aspartate (AST) transaminases was of 295 and 271 U/L, respectively. The liver disease work up was unrevealing. A liver ultrasonography suggested fatty infiltration, and excluded bile duct dilatation and space occupying lesions. The patient improved substantially in association with treatment of COVID-19, achieving resolution of pneumonia with normal follow-up radiographs. Serum activity of ALT and AST trended downwards, however that of ALP remained elevated, ranging from 187 U/L to 231

U/L on the day of discharge. The patient was given outpatient follow-up appointment with gastroenterology clinic.

## CASE 2

A 75-year-old Hispanic male presented to the emergency room with complaints of fever, fatigue and shortness of breath for four days. He reported no recent travel or sick contacts. On arrival to the emergency room, he was hypoxemic, saturating at 88% on ambient air. He was also tachypneic and desaturated to 80% with minimal exertion. He was afebrile and normotensive. Physical examination was notable for decreased air entry to the lungs with bibasilar rales and right upper quadrant tenderness. Initial tests revealed a serum activity of ALP of 673 U/L (normal 45-115 U/L), and that of GGTP of 949 U/L (normal range 8-61 U/L), suggesting hepatic origin of the former, and normal serum activity of ALT and AST and normal serum bilirubin concentration. A liver disease work up was unrevealing. Additionally, the patient had lymphopenia, a high serum d-dimer to 6900 ng/mL (normal level < 500 ng/ml), ferritin of 988 ng/mL (normal 12 to 300 ng/mL), and procalcitonin of 2710 ng/mL, with a serum lactate of 2.6 mmol/L (normal value 0.5-1 mmol/L). The Sars-CoV-2 virus PCR test was positive. Chest X- ray revealed bilateral airspace disease consistent with viral pneumonia. Abdominal imaging showed mild dilatation of extrahepatic biliary ducts with no obstructing calculus or mass. There was no history of methadone use, which can be associated with dilatation of common bile duct. The patient was started on azithromycin, ceftriaxone and hydroxychloroquine to treat pneumonia, and enoxaparin because of the risk for thrombotic disease, as suggested by a high D-dimer. A Magnetic Resonance Cholangio Pancreatography (MRCP) excluded biliary obstruction.

On subsequent days the serum ALP activity continued to increase reaching a peak of 896 U/L without substantial changes in the rest of the liver profile. Patient's condition deteriorated with progressive respiratory failure requiring continuous, high oxygen supplementation and mechanical ventilation. ALP remained high (>800 U/L). Over the next few days, the patient improved, was extubated, and was eventually discharged home in improved and stable conditions with outpatient gastroenterology follow-up.

## DISCUSSION

The two cases presented here are characterized by increased activity of AP in COVID-19, which has not been the typical finding in this disease. Both patients had a normal alkaline phosphatase prior to COVID-19 infection.

Cholestasis is defined as impaired secretion of bile. Alkaline Phosphatase (AP) is a glycosylphosphatidylinositol (GPI)–anchored ectophosphomonoesterases with multiple isoforms, mainly derived from the liver, bone and intestinal tract. Reduced canalicular secretion and hepatocellular retention of BAs increases liver alkaline phosphatase synthesis, also causing possible release into the bloodstream, rather than into bile [6]. Increased activity of serum AP is an indirect marker of cholestasis [6].

Cholestasis in the patients described above may be secondary to sepsis, which is mediated, in part by the effect of cytokines on hepatic transporters, decreasing their function [7]. In this regard, one of the cytokines released in sepsis is IL-6, documented to be increased in COVID-19 and considered a driver of the cytokine storm seen in this disease. IL-6 is secreted by neutrophils, monocytes and macrophages upon stimulation of Toll-Like Receptor 4 (TLR) by lipopolysaccharide (LPS) toxin, however, IL-6 is reported to have a protective effect on the liver as a mediator of liver regeneration [8]. Accordingly, the effect of IL-6 could be dual: down regulation of hepatic transporters, e.g ABCB11, and protection from liver failure, which has not been reported in association with COVID-19.

Another possibility for cholestasis in patients with COVID-19 is the direct exposure of the liver to the virus, an idea supported by the presence of SARS-CoV-2 RNA in stool and blood samples [9]. In this regard, SARS-CoV-2 enters the cells by the Angiotensin-Converting Enzyme 2 (ACE2) receptor [10], also found in hepatocytes and biliary epithelial cells [11], and through which the virus could cause a form of cholangiopathy; however, pathological examination of liver tissue from limited autopsy reports have not demonstrated this type of liver injury or viral inclusions in liver cells [12].

In summary, increased AP activity was a notable feature in two patients with COVID-19. A component of fatty liver as background, as suggested by imaging studies in the first case may have contributed to the rise in AP activity but not in the second case. Although hepatobiliary injury caused by the virus

itself cannot be excluded unequivocally, cholestasis secondary to the cytokine storm typical of the disease is most likely the reason for increased activity on AP in this disease.

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