



## Case Report

# LECT2 Amyloidosis and COVID-19: An Autopsy Case Report

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Citation: Bluhm L, Reisler J, Afrouzian M, Aronson J (2023) LECT2 Amyloidosis and COVID-19: An Autopsy Case Report. Ann Case Report. 8: 1437. DOI:10.29011/2574-7754.101437

Received: 31 August 2023, Accepted: 04 September 2023, Published: 06 September 2023

### Abstract

Leukocyte chemotactic factor 2 amyloidosis (ALECT2) is a recently discovered amyloidosis generally characterized by distinct globular hepatic deposits and renal involvement. The amyloidogenic protein, LECT2, is an obesity-associated hepatokine with complex associations with inflammatory cytokines; including those regulating the cytokine storm observed in COVID-19. However, no research has explored the interaction between ALECT2 and systemic COVID-19. We present a case report detailing an incidental finding of systemic ALECT2 during the autopsy of a patient who expired from complications of severe COVID-19. Amyloid deposition within the liver, kidneys, spleen, and lungs may have contributed to the declining organ function observed in this case. We propose two mechanisms by which ALECT2 potentially compounded the effects of COVID-19, including worsening hypoxia through alveolar amyloid deposition and intensifying the inflammatory response through upregulation of cytokines such as IL-6.

**Keywords:** Amyloidosis; ALECT2; COVID-19; SARS-Cov-2; IL-6; Cytokine Storm

### Introduction

Amyloidosis describes a variety of disorders exhibiting abnormally folded protein depositing as insoluble fibrils in tissue, with the two most common types being AA and AL [1]. A novel type of amyloidosis, ALECT2, was reported by Benson et al [2] in 2008 as isolated amyloid deposition in the glomerulus. The amyloidogenic protein was identified as protein leukocyte chemotactic factor 2 (LECT2), a pleiotropic cytokine produced in hepatocytes that has been implicated in various processes, including cell proliferation, neuronal development, tumor suppression, and regulation of inflammation [3-5]. ALECT2 is now recognized as the 3<sup>rd</sup> most common amyloidosis in the United States and has a high prevalence among Mexican Americans in the Southwest [7]. Initially, ALECT2 amyloidosis was only described in the kidney, with 30-40% of cases resulting in end stage renal disease (ESRD) [2,8]. However, subsequent reports have highlighted characteristic globular amyloid deposits in the liver and systemic involvement

of the spleen, bowel, adrenal glands, prostate, gallbladder, pancreas, parathyroids, and, interestingly, the lungs, specifically in alveolar septa [6-8]. Here, we report a case of fatal COVID-19 with multiorgan ALECT2 amyloidosis discovered during autopsy. When SARS-CoV-2 targets respiratory epithelial of the lower respiratory tract, specifically Type II pneumocytes, the innate immune response is activated. This immune response can both damage and stimulate pulmonary capillary endothelial cells, leading to diffuse alveolar wall edema, vascular permeability, and leukocyte infiltration [9,10]. If the infection is severe, it can progress to respiratory failure and cytokine storm, with occasional multiorgan involvement including acute kidney injury, myocardial damage, and hepatic damage [9,11]. We note that the well described systemic inflammatory manifestations and multiorgan involvement characteristic of COVID-19 [12] echoes both inflammatory functions of LECT2 and distribution of systemic ALECT2. Several authors have posited linkages between systemic amyloidosis and COVID-19 disease severity [13-16], but to our knowledge, there are no previously reported cases of ALECT2 amyloidosis and COVID-19. We report a detailed clinicopathologic

evaluation of a case of ALECT2 amyloidosis with concurrent COVID-19 and explore potential pathogenic interactions between the two conditions.

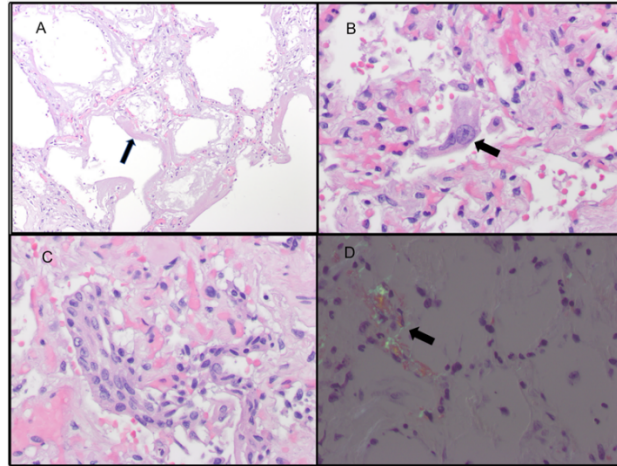
### Case Report

A 68-year-old Hispanic woman with a past medical history of essential hypertension and moderate persistent asthma presented to a major academic medical center in Southeastern Texas with shortness of breath, cough, fever, and diffuse body aches starting two days prior. Upon presentation, she was afebrile, and her vital signs were within normal limits except for a pulse oximetry reading of 86%, which improved with six liters of oxygen through nasal cannula. Physical examination and review of systems was significant for morbid obesity (BMI of 58) and dyspnea with minimal exertion; however, her lungs were clear to auscultation bilaterally. Initial laboratory studies revealed a slight leukocytosis with a white blood cell count of 12.8 K/uL, anemia with a hemoglobin of 10.1 g/dL, elevated creatinine of 1.22 mg/dL with an unknown baseline; procalcitonin of 2.14 ng/mL, mildly elevated liver enzymes with an alkaline phosphate of 169 U/L, ALT of 86 U/L, and AST of 79 U/L with no reported history of liver disease, and a positive ID Now rapid nucleic acid test for SARS-CoV-2. She was up to date on the pneumococcal and influenza vaccines and self-reported receiving two doses of the Pfizer SARS-CoV-2 vaccine prior to admission. Of note, her hemoglobin A1C was 7.1%, but she had no known history of diabetes. A CT chest showed patchy ground glass attenuation suggestive of multifocal pneumonia. She was admitted to the hospital for close monitoring and started on albuterol/ipratropium breathing treatments, a five-day course of Remdesivir, intravenous dexamethasone, a seven-day course of empiric antibiotics, and enhanced dose DVT prophylaxis. The patient's creatinine decreased to 0.88 mg/dL the next day after receiving fluid hydration. She was started on Baricitinib during hospital day one with plans to continue this medication for fourteen days. She was transferred to the ICU on hospital day two due to increased oxygen requirements necessitating BiPAP and 55 liters of high flow oxygen. The patient was unable to tolerate attempts to wean her off BiPAP. Her creatinine had been up trending during this admission, and she was found to have acute kidney injury (AKI) on hospital day eight with a creatinine of 1.86 mg/dL. On

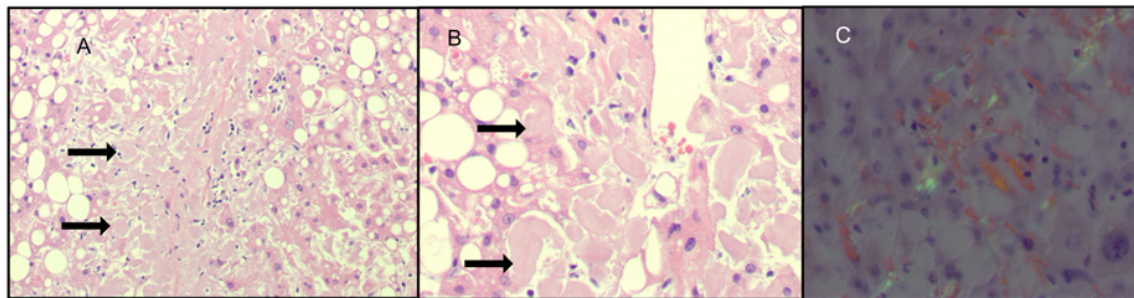
hospital day nine, the patient developed sudden onset tachycardia and hypoxia necessitating emergent intubation. An arterial blood gas showed severe acute metabolic acidosis, her creatinine peaked at 2.56 mg/dL, and she had a lactic acid of 12.23 mmol/L. She subsequently went into hypotensive shock and was started on four pressors. Nephrology was consulted and the patient was started on continuous renal replacement therapy on the same day. Although the patient has no reported history of kidney disease, nephrology suspected an AKI on chronic kidney disease stage 3. Unfortunately, the patient expired on hospital day ten with clinical impression of septic shock and multiorgan failure secondary to COVID-19 pneumonia.

### Autopsy Findings

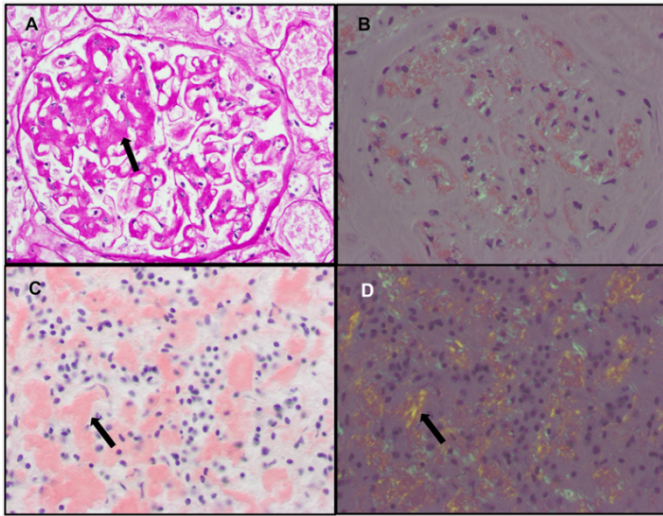
On gross examination during autopsy, the lungs were markedly heavy (790 g Right, 670 g Left) with diffuse parenchymal consolidation bilaterally. Microscopic examination revealed severe diffuse alveolar damage, exudative and proliferative phases, with diffuse thickening of the alveolar septa and prominent hyaline membranes. There was scarce type II pneumocyte proliferation but more marked foci of squamous metaplastic epithelium in the bronchi and alveoli (Figure 1). No thrombi or thromboemboli were identified. A small subacute peptic ulcer was found in the gastric antrum with an associated 650 cc of blood in the gastrointestinal lumen. GI bleeding was deemed a contributory cause of death and may have been responsible for her terminal decompensation in the setting of severe lung disease. The liver exhibited steatohepatitis with extensive macrovesicular steatosis, periportal and bridging fibrosis, and rare lobular foci of inflammation (steatohepatitis activity score 4/8, fibrosis score 3/4) [17]. An additional striking finding was prominent globular amorphous eosinophilic extracellular deposits, most prominent surrounding the terminal hepatic venules, and focally appearing as globules surrounded by zone 3 hepatocytes. These deposits were amphophilic on trichrome stain and positive on PAS. Congo Red staining demonstrated the requisite apple-green birefringence (Figure 2). This unusual appearance raised the possibility of ALECT2 amyloidosis [18]. Paraffin sections were therefore sent to Mayo Clinic for evaluation by mass spectrometry, confirming the diagnosis of LECT2 amyloidosis.



**Figure 1:** Lung pathology in COVID-19 with systemic LECT2 amyloidosis. A: The lungs exhibit prominent hyaline membranes (arrow) and interstitial edema with cellular infiltration (H&E X200). B: Atypia of hyperplastic type 2 pneumocytes (arrow). C: Squamous metaplasia of terminal airways (H&E X400). D: Under polarized light, there is evidence of focal alveolar septal birefringent amyloid deposits (arrow) (Congo Red X400).



**Figure 2:** Characteristic globular amyloid on liver histology. A: Steatohepatitis and eosinophilic globular extracellular deposits (arrows) (H&E X200). B: Globular extracellular deposits (arrows) are seen more clearly at 400x magnification (H&E X400). C: Polarized light shows apple-green birefringence and typical reciprocal orange birefringence characteristic of amyloid deposition (Congo Red X400).



**Figure 3:** Kidney and spleen pathology characteristic of LECT2 amyloidosis. A: Renal glomerulus shows expanded mesangium (arrow) with PAS positive deposits (PAS X400). B: Renal glomerulus exhibits apple-green and orange birefringence under polarized light indicating diffuse amyloid deposition (Congo Red X400). C: Amorphous eosinophilic material (arrow) within the splenic sinuses (Congo Red X400). D: Polarized light shows apple-green and reciprocal orange birefringence (arrow) characteristic of amyloid in splenic sinuses (Congo Red X400).

Histopathological examination revealed the presence of amyloid deposits in various other organs. Amyloid deposits were most prominent in the kidneys, with glomerular subendothelial, intramembranous and mesangial distribution. Amyloid was also present in the cortical interstitium, tubular basement membranes, and arteriolar intima (Figure 3). Of note, collapsing glomerulopathy and other changes normally reported in COVID-19 were absent. Both lungs exhibited subtle but multifocal amyloid deposits in the alveolar interstitium, visualized only on Congo Red staining (Figure 1). Additionally, amyloid was present in the splenic sinuses (Figure 3), intramyocardial arteries and pulmonary arteries. Amyloid was not detected in the bone marrow, pancreas, stomach, salivary gland, thyroid, hilar lymph nodes, tongue, or omental fat. Adrenal glands and parathyroid glands were not examined.

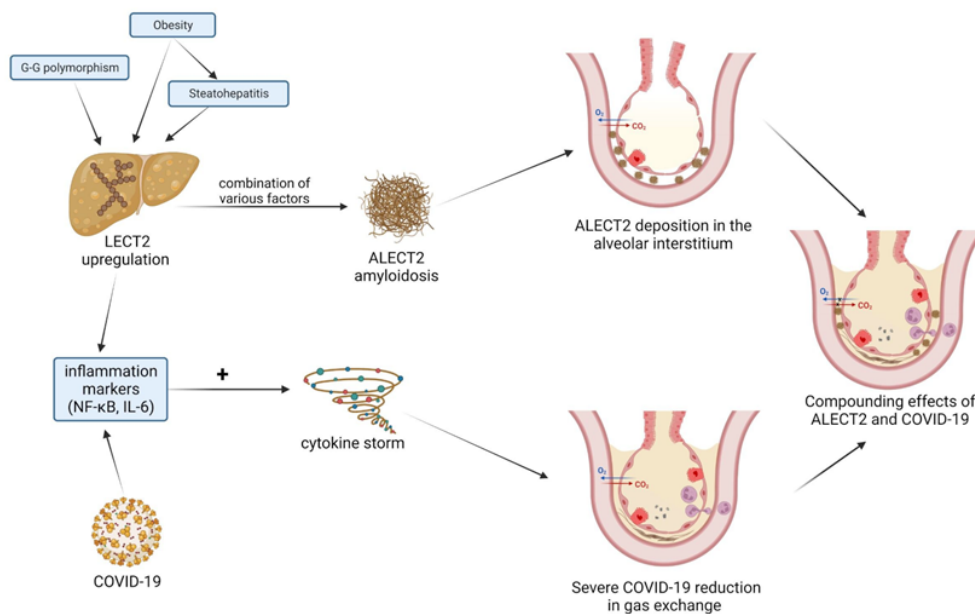
## Discussion

We describe the first reported case of ALECT2 amyloidosis, a common but often unrecognized form of amyloidosis, in association with fatal COVID-19. In this case, ALECT2 amyloidosis was discovered incidentally at autopsy and was not suspected in life. Our patient demonstrated several typically associated clinical and demographic features of ALECT2, such as obesity, advanced age, and Hispanic ethnicity [6,8,19-21].

However, researchers have identified ALECT2 amongst various ethnic groups, including Egyptians, Native Americans, First Nations people of British Columbia, Punjabis, Israelis, and Arabs [8,22-25], suggesting that ALECT2 is not isolated to one ethnicity and requires additional demographic analysis. Pathologically, the characteristic ALECT2 globular congophilic deposits were present in the liver [18,26]. Renal amyloid was seen in glomerular basement membranes, mesangium and tubulo-interstitium; this distribution is characteristic of ALECT2 amyloidosis and differs from that of other amyloid types [6]. Amyloid deposits were also found in the alveolar interstitium in the lungs, and focally in the spleen and arterial walls of the heart and lungs, consistent with previous reports of systemic ALECT2 [4,20]. While the exact pathophysiology of ALECT2 is unknown, the current understanding suggests that a combination of genetic factors, such as a polymorphism of the G nucleotide at the 172 nd position on the LECT2 gene, and environmental conditions likely lead to an upregulation in LECT2 production in the liver [3,4]. The protein, which is potentially unstable, especially when not bound with zinc, can form abnormal fibrils that deposit in organs as amyloid [4,25,27]. Interestingly, low zinc levels have been implicated in COVID-19 severity and mortality [28]. Unlike other forms of amyloidosis, ALECT2 amyloid is not the result of proteolytic cleavage or extracellular processing of a native protein; instead, the entire protein is found within deposited fibrils [25]. LECT2 is considered an obesity-associated hepatokine with various complex associations with inflammation [25]. Although there is evidence that LECT2 downregulates inflammation, and is associated with recovery from sepsis [29,30], it has also been found to promote inflammation [31,32]. Initially, LECT2 was identified as a chemotactic agent for human neutrophils [3]. In one study focused on LECT2's role in insulin resistance, the protein was suggested to enhance various inflammation pathways involving I $\kappa$ B, nuclear factor kappa beta (NF- $\kappa$ B), and IL-6 [33]. In a mouse model, Takata and colleagues demonstrated that hepatic fat accumulation may result in upregulated LECT2, which promotes liver inflammation and macrophage polarization to inflammatory M1 type [31]. This may contribute to the progression from simple steatosis to steatohepatitis [31,34], as seen in our patient. Additionally, LECT2 enhances the LPS-induced phosphorylation of c-Jun N-terminal kinase (JNK), a kinase involved in signaling leading to transcriptional activation of IL-6 gene [35,36]. IL-6 is an important cytokine in the early and localized alveolar pathology of COVID-19 pneumonitis [37] as well as the macrophage activation syndrome associated with COVID-19 [38]. Various steps in IL-6 pathways have been targeted for treatment of the cytokine storm of severe COVID-19 by medications including Baricitinib and Tocilizumab [39-41]. Specifically, our patient was treated with Baricitinib. This drug inhibits Janus-Kinase (JAK), the receptor pathway utilized by IL-6 in classic signaling [10]. We suggest that

overexpression of LECT2 in this patient may have compounded the effects of COVID-19, leading to severe inflammation that could not be interdicted by Baricitinib. Research into the interaction between COVID-19 and amyloidosis is scarce, with no literature exploring the correlation between ALECT2 and COVID-19. A review found that AL amyloidosis patients experience an increased risk of COVID-19 infection and death due to multiple factors, including sex, age, immunosuppression, and comorbidities [15]. Similarly, research on ATTR amyloidosis revealed that patients also have increased risk of death from COVID-19 because of age and comorbidities like hypertension and diabetes mellitus [16]. Researchers hypothesized that ATTR in alveolar-septal space may make COVID-19 hypoxemia harder to tolerate [16]. This hypothesis can be extrapolated to this case of ALECT2, as amyloid was found throughout the alveolar interstitium potentially

worsening the severity of respiratory distress. Additionally, the hypothesized influence of ALECT2 on pulmonary function has been reported before, including a case of pulmonary-renal syndrome with LECT2 amyloid in the alveolar interstitium leading to diffuse alveolar hemorrhage [42]. Interestingly, a recent abstract reported a unique case of ALECT2 pulmonary amyloidosis causing acute respiratory distress syndrome with subacute hypoxic respiratory failure [43]. These findings implicate pulmonary ALECT2, seen diffusely throughout histology specimens in this case report, as a potential exacerbating factor of COVID-19 respiratory distress. In summary, we propose that ALECT2 could contribute to severe COVID-19 by twomechanisms. First, through alveolar interstitial deposition worsening hypoxemia and secondly, by heightening the dysregulated inflammatory response of COVID-19 (Figure 4).



**Figure 4:** Concept map demonstrating proposed interplay of ALECT2 and COVID-19 within alveolar interstitium. While the pathogenesis of ALECT2 is still being elucidated, several mechanisms have been implicated in LECT2 upregulation, including the G-G genotype and liver injury as seen in steatohepatitis. This upregulated and potentially unstable protein combines with various other factors and interacts with the extracellular matrix to eventually form amyloid fibrils that can deposit in organ systems, including the alveolar interstitium. While LECT2 upregulation has a complicated relationship with inflammation, studies suggest that LECT2 increases levels of inflammatory markers, including IL-6, a prominent cytokine associated with COVID-19 pneumonitis. Elevation of these inflammatory mediators may promote progression towards cytokine storm, worsening alveolar edema. ALECT2 deposition in the pulmonary interstitium could worsen the inflammatory response and hypoxia induced by COVID-19.

## Conclusion

Our report details a novel case of multiorgan ALECT2 involving the liver, kidneys, lungs, spleen, and myocardial arteries discovered incidentally during the autopsy of a patient who suffered severe COVID-19 complications. While amyloidosis could be a coincidental finding, further research on LECT2 pathophysiology is necessary to determine if a correlation exists between ALECT2 and severity of COVID-19 symptoms, especially in relation to worsening hypoxia and inflammatory response. Despite its prevalence and potential impact on patient outcomes, ALECT2 remains underrecognized and insufficiently researched.

## Disclosure

**Funding:** None.

**Ethical Guidelines:** Since this case report involved a deceased person, Institutional Review Board approval was not required. The study was instead approved by our institution's Committee on Post-Mortem Research, which oversees protection of privacy and confidentiality of the patient and next of kin.

**Conflict of Interest:** The authors have no conflicts of interest to disclose.

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