Molecular Genetics and Metabolism Reports 29 (2021) 100802

Contents lists available at ScienceDirect

Molecular Genetics and Metabolism Reports

journal homepage: www.elsevier.com/locate/ymgmr

Case Report

Severe manifestations and treatment of COVID-19 in a transplanted patient with Fabry disease

Ryan Mahoney [a], Grace K. Lee [a], Joaquin Ponce Zepeda [b], Christopher Gabriel [c], Kathy Hall [a], Rob Edwards [b], Virginia Kimonis [a,*]

[a] Division of Genetics and Genomic Medicine, Department of Pediatrics, University of California, Irvine, CA, USA
[b] Department of Pathology, University of California, Irvine, CA, USA
[c] Department of Psychiatry & Human Behavior, University of California, Irvine, CA, USA

ARTICLE INFO

Keywords:
Fabry disease
COVID-19
Kidney transplant
Cytokines
Aspergillosis
Pneumonia
Migalastat

ABSTRACT

Fabry disease is an X linked disease caused by pathogenic variants in the *GLA* gene. The cardiovascular and renal systems are most affected in Fabry patients and may require heart or kidney transplants in the late stages of the disease depending on severity of manifestations. Enzyme replacement therapy (ERT) has proven to delay progression of Fabry disease considerably, especially when started early in life. Current research has shown that individuals who have received cardiac or renal transplants or are currently on dialysis have the greatest probability of developing severe manifestations of COVID-19. It has also been shown that people who contract COVID-19 experience a rapid increase in cytokine levels which can lead to a prothrombotic state and have a greater risk in the presence of comorbidities. A history of cardiac or renal transplants as well as the naturally elevated cytokine levels in Fabry disease make it likely that COVID-19 could have a greater impact on the health of these patients. We report the case of a 67-year-old male with diabetes mellitus, history of kidney transplant, and Fabry disease treated late in progression of the disease first with agalsidase beta ERT, then oral migalastat who developed severe manifestations of COVID-19. The autopsy findings showed acute and organizing hyaline membrane disease consistent with COVID-19 pneumonia and secondary invasive bronchopulmonary aspergillosis with cavitary lesion formation. The sections of the heart showed scattered subendocardial fibrosis, and the transplanted kidneys showed thyroidization and interstitial nephritis potentially secondary to COVID-19, in addition to his long-standing renal disease. This case report serves to chronicle complications in a complex patient with late stage Fabry disease and multiple COVID-19 related complications who succumbed from respiratory failure despite the advanced management for the COVID-19 infection.

1. Introduction

Fabry disease is a rare lysosomal storage disease caused by a pathogenic variant in the *GLA* gene. This pathogenic variant results in deficient α-galactosidase A enzyme and as a result, deficient breakdown of globotriaosylceramide (GL-3). Improper breakdown leads to accumulation of GL-3, which eventually causes cellular damage, dysfunction, and organ failure. We report a patient with Fabry disease and other comorbidities such as diabetes mellitus post renal transplantation who contracted COVID-19 pneumonia. He developed invasive bronchopulmonary aspergillosis with cavitary lesion formation and died from respiratory failure. Existing literature indicates an overlap in the ways COVID-19 and Fabry disease affect the body, including but not limited to increased risk for stroke, risk for cardiovascular and lung disease, severe kidney disease, and inflammation [1]. As these patients may be immunosuppressed from organ transplantation, this poses a unique challenge as the mainstay of treatment (steroids) with COVID-19 can often cause reactivation of opportunistic infections such as aspergillosis. The potential nephrotoxicity of some commonly utilized antiviral medications and the significantly decreased immune responses in recipients of organ transplants are just two of the many factors to be taken into consideration when treating COVID-19 patients with Fabry disease.

* Corresponding author at: Division of Genetics and Genomic Medicine, Department of Pediatrics, University of California Irvine, 101 The City Drive South, ZC4482, Orange, CA 92868, USA.
E-mail address: vkimonis@uci.edu (V. Kimonis).

https://doi.org/10.1016/j.ymgmr.2021.100802
Received 8 August 2021; Received in revised form 11 September 2021; Accepted 11 September 2021
Available online 16 September 2021

2. Case report

We report a 67-year-old male who was diagnosed with Fabry disease at 47 years of age after he was found to have proteinuria and chronic pain in his arms, legs, and body. Diagnosis was made after GLA sequencing which found a pathogenic variant in the patient (c.1088G > A). Shortly after diagnosis, he began intravenous enzyme replacement therapy (ERT) with agalsidase beta late into the progression of the disease at the age of 49 years. He reported general improvements in his symptoms immediately after ERT initiation but continued to experience pain in his arms and legs which was exacerbated by heat. His other manifestations of Fabry disease included renal insufficiency, acute pain crises, anhidrosis, concentric left ventricular hypertrophy, abdominal pain, depression, angiokeratomas, tinnitus and osteoporosis. Unrelated comorbidities included hyperlipidemia, hypertension, and diabetes mellitus type II, managed with metformin and pioglitazone. He eventually developed kidney failure as a manifestation of Fabry disease at the age of 51 years and was placed on peritoneal dialysis for a duration of 6 months followed by renal transplantation, after which his renal function was stabilized.

He was found to have an amenable mutation for migalastat and transitioned from agalsidase beta every 2 weeks to oral migalastat on alternate days at the age of 66 years. The primary reason for this transition was to reduce social contact related to the bi-weekly infusions of ERT during the COVID-19 pandemic. Migalastat has been shown to be effective in reducing GL-3 build-up and stabilizing renal function in those with an amenable mutation [2,3]. While Migalastat is not recommended to treat Fabry patients with end stage renal disease, it was determined that this patient's renal function was sufficient post-transplant to benefit from the drug [4]. He tolerated migalastat well with no adverse side effects and his lysosomal GL-3 levels remained stable throughout the transition.

Onset of COVID-19 symptoms began with a fever, cough, fatigue, and difficulty breathing, requiring admission to hospital for two days during which he received a course of dexamethasone and convalescent plasma. He was discharged with a supply of oxygen. Nevertheless, symptoms persisted for 10 days, and he was brought back into the hospital via ambulance due to shortness of breath and hypoxia with an oxygen saturation of 77%. A chest x-ray and computed tomography (CT) at the time revealed COVID-19 pneumonia with ground glass opacities throughout both lungs (Fig. 1a).

Treatment with remdesivir and dexamethasone was administered for 6 days, and the patient eventually needed intubation for hypoxic respiratory failure resulting from COVID-19 pneumonia. He was transferred to a tertiary care center where he was placed on broad spectrum antibiotics for sepsis and the decision was made to continue tacrolimus monotherapy. He was started on high dose steroids with methylprednisolone. His oxygen requirements progressively increased, and he continued to have high fevers despite broad spectrum antibiotics. He was also treated in the prone position and paralyzed to ensure adequate ventilation given his progressively worsening oxygen requirements. CT of the chest showed a new right upper lobe cavitary nodule (Fig. 1b).

A broad infectious workup was performed, and he was found to be positive for aspergillus antigen in his sputum, suggesting invasive bronchopulmonary aspergillosis as the cause of the cavitary lesion. He was also found to have serum coccidiosis IgM positivity as well as a positive cytomegalovirus PCR test and was started on broad spectrum parenteral antifungal and antiviral therapies. Despite these therapies, the patient became hypoxic on maximal ventilator settings. After discussion with his family, he was transferred to the inpatient hospice service and it was decided to withdraw further care, and he was ultimately palliatively extubated.

An unrestricted autopsy was performed by JPZ and RE. The right lung weighed 1190 g and the left 740 g (N: $R = 450$ g, L = 425 g). The subpleural tissue was tan pink, with dark gray-black mottling. The lungs were consolidated, edematous, and congested throughout all lobes. Cut

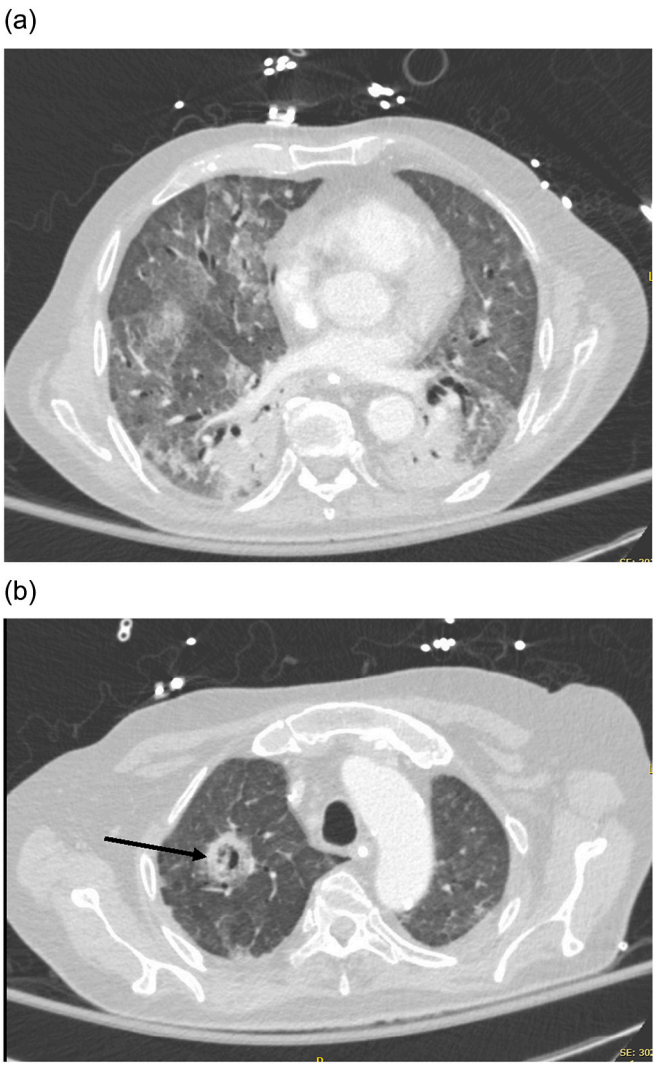

Fig. 1. Computed tomography (CT) of the chest consistent with COVID-19 pneumonia. a: CT showing diffuse ground glass opacities with patchy consolidations of bilateral lungs. b: CT of the chest showing a cavitary lesion of the right upper lobe. An arrow points to the cavitary lesion.

sections were slightly moist, tan yellow, and showed patchy consolidation. The pulmonary arteries, veins and branches were patent and showed no pulmonary emboli. On microscopy, the lung tissue showed evidence of acute and chronic hyaline membrane disease (Fig. 2a). The alveolar spaces were noted to be filled up with collagen, dead type 2 pneumocytes and dead neutrophils.

Within the lung sections, aspergillus was identified (Fig. 2b), which contained the classic septated hyphae with the 45 degree branching angles.

The autopsy reported considerable fibroadipose tissue present in the calyces, collecting duct, medulla, and renal parenchyma of his transplanted kidney (Fig. 3a).

The native kidney was shown to be fibrosed over and replaced with fibroadipose tissue (Fig. 3b).

In addition, the transplanted kidney showed interstitial nephritis on microscopy (Fig. 4a).

Microscopy of one of the native kidneys showed complete replacement by fibroadipose tissue (Fig. 4b). The native kidney had been undergoing chronic damage and began to express thyroidization of the renal parenchyma, mimicking the appearance with pseudo-follicle and pseudo-colloid formation.

The heart weighed 450 g (M = 300 g, F = 250 g) and was moderately

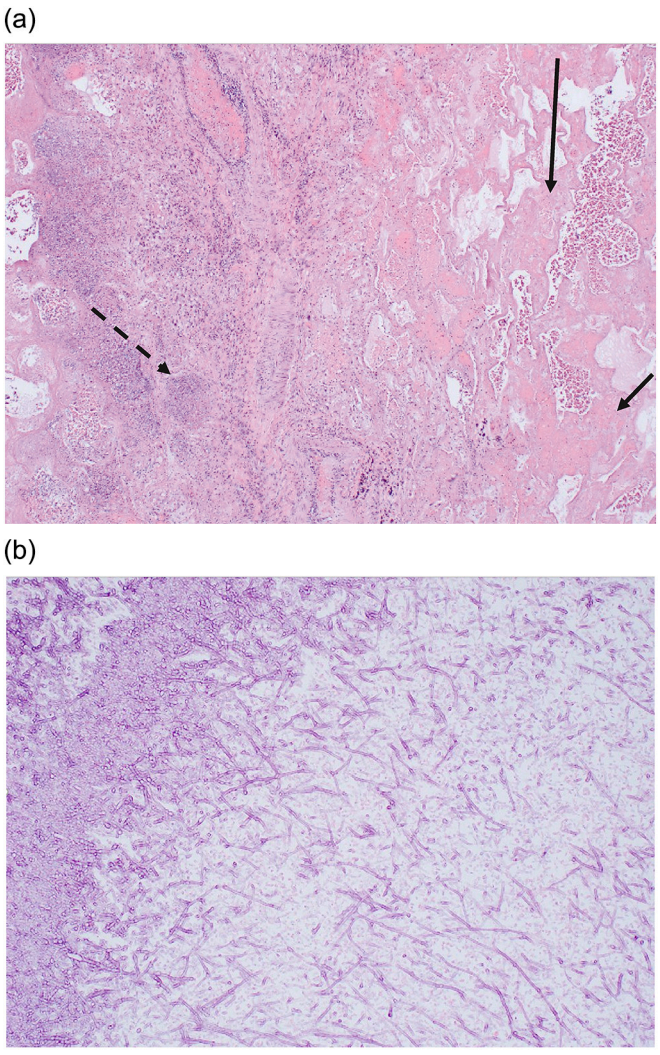

Fig. 2. a: Acute and chronic hyaline membrane disease. The right half side of this Hematoxylin and Eosin (H&E) stained slide is showing an area of acute hyaline membrane (solid arrow). The lung tissue is infarcted, however some lumen within the alveoli are still discernable and the hyaline membranes are recognizable. The left side of the H&*E*-stained slide is showing an area of chronic hyaline membrane disease, where the lumen of the alveoli are becoming occluded with collagen, dead type 2 pneumocytes and dead neutrophils (dashed arrow). b: H&E section from the lung infected with aspergillus. This H&*E*-stained slide from one of the sections taken from the lung shows septated hyphae branching at 45 degrees.

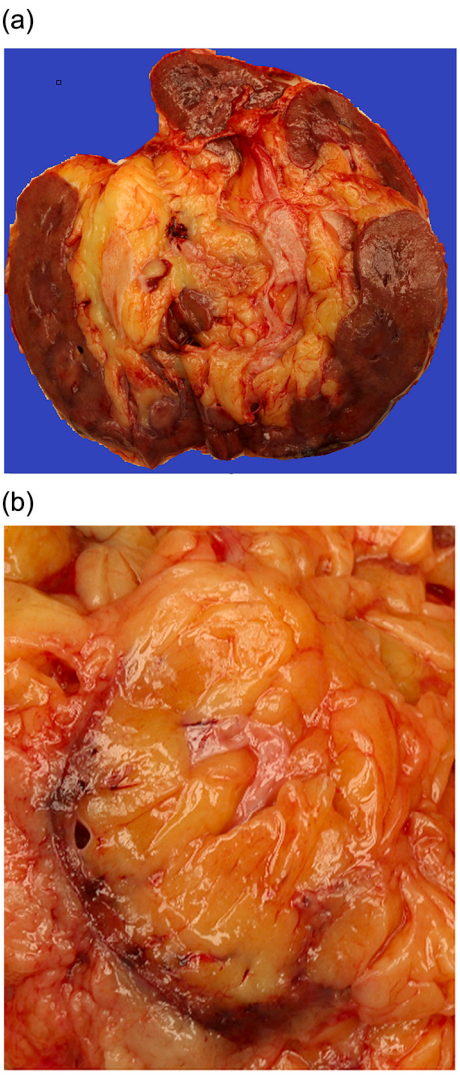

Fig. 3. a: One of the transplanted kidneys. Both kidneys had a similar appearance, where the renal parenchyma is beginning to atrophy, the majority of which has been replaced by fibroadipose tissue. b: Appearance of a native kidney. The kidney was completely fibrosed and replaced with fibroadipose tissue. The renal parenchyma was completely atrophic.

enlarged. The epicardium was smooth, thin, and transparent. The heart chambers were not dilated. One mural thrombus was identified in the right atrium, and an additional mural thrombus identified in the right ventricle. The right ventricle measured 0.8 cm in thickness and the left 1.4 cm in thickness, which provided evidence of moderately thickened muscular tissue. On microscopy, scattered subendocardial fibrosis was identified within the wall of the heart (Fig. 4c), seen in chronic ischemic heart disease and the coronary vessels were mildly occluded. These changes are somewhat nonspecific as this could be related to his long standing Fabry disease or could be related to the patient's longstanding hypertension and diabetes. There were no foamy histiocytes identified, however histiocytes and fibroblasts were identified in a morphology of chronic tissue repair as opposed to glycolipid accumulation.

3. Discussion

This case report highlights the complications of COVID-19 in a male with late-stage Fabry disease who had several co-morbidities including immunosuppressant treatment following a renal transplant and diabetes mellitus. Initial patient reports from the beginning of the COVID-19 pandemic revealed that diabetes was one of the most common comorbidities seen in critically affected COVID-19 patients [5,6]. A metanalysis researching the mortality of diabetic patients who contract COVID-19 found that they had a two-fold increase in both their mortality rates as well as the severity of their COVID-19 infection when compared to non-diabetics [7]. Chronic kidney disease is known to be a common occurrence in late-stage Fabry disease patients [8]. A separate study reported that patients with kidney disease who contract COVID-19 are more likely to develop acute renal injuries, which significantly increased their risk of in-hospital mortality [9,10]. Although treating with remdesivir is not contraindicated in all patients with Fabry disease, it is important to consider individual patient renal function as the medication is potentially nephrotoxic [1,11]. This patient was given remdesivir and tolerated it well based on his eGFR, blood urea nitrogen, and creatinine levels.

Fabry disease may also be associated with elevated levels of pro-inflammatory cytokines [12,13]. The cytokine storms associated with COVID-19 may then potentially elevate these levels even higher and

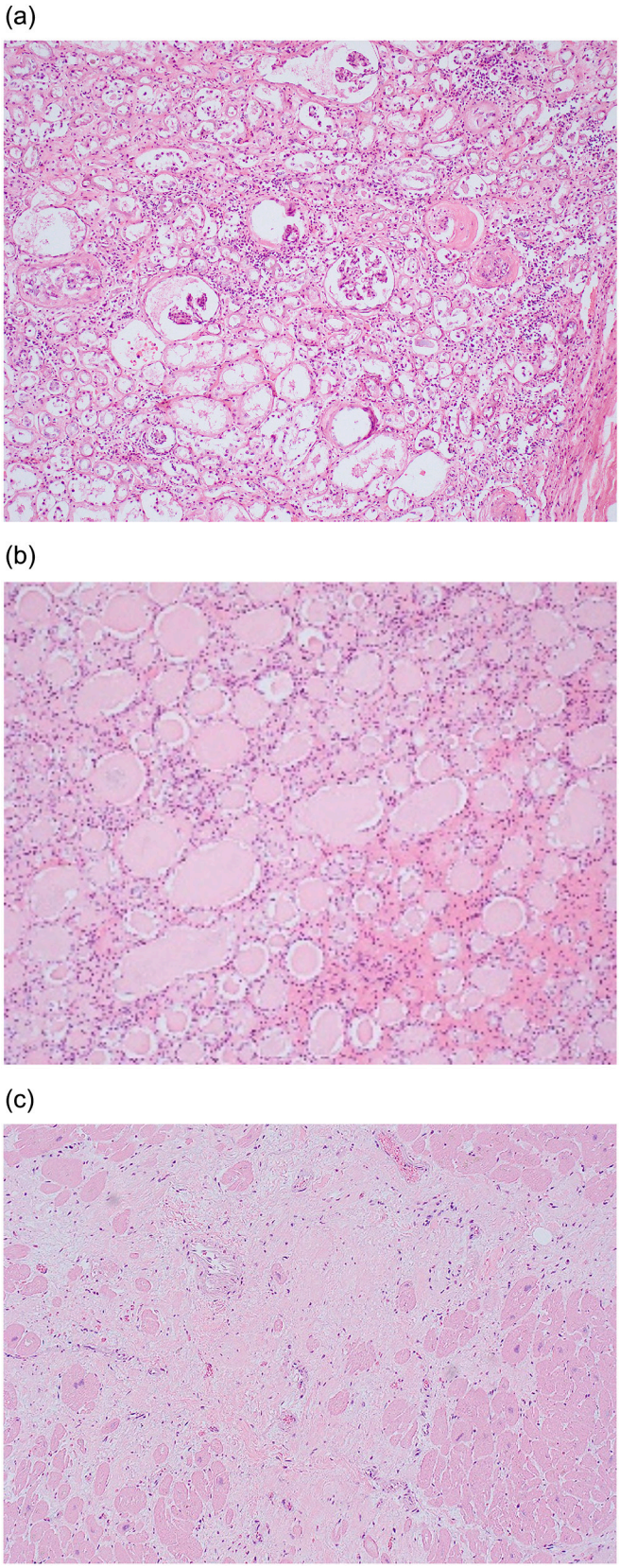

Fig. 4. a: Microscopy of the transplanted kidney. There is evidence of interstitial nephritis, which is shown here with the inflammatory cells working their way into the interstitium. b: Microscopy of a native kidney. c: H&E stain of cardiac tissue showing subendocardial fibrosis. A 10× magnification of a focus on an H&*E*-stained slide showing cardiac tissue with subendocardial fibrosis.

puts the patients at greater risk of a clotting related event brought about by endothelial inflammation and damage [14]. In this patient, fibrinogen levels were highly elevated throughout his inpatient stay, although it is unknown definitively whether they were due to the combination of pro-inflammatory cytokines and cytokine storms. He was treated with enoxaparin sodium.

The inflammatory cells in the transplanted kidney are likely due to the longstanding glycolipid accumulation within the podocytes, glomerular epithelial cells, mesangial and tubular cells. Globotriaosylceramide (GL-3) accumulation in the smooth muscle cells of the renal arterioles causes degenerative changes which promotes glomerulosclerosis and interstitial fibrosis in the later stages of Fabry kidney disease [15,16].

Dexamethasone is a mainstay of treatment in patients with COVID-19. However, in patients on long-term immunosuppressants, this carries an added risk of reactivation of opportunistic fungal and viral infections. His long history of post-kidney transplantation immunosuppressants in combination with dexamethasone and methylprednisolone administration may have contributed to his opportunistic aspergillosis infection and potential worsening of the systemic inflammatory response associated with COVID-19.

As with most rare diseases, there is limited research regarding COVID-19 and Fabry disease. A study of 129 Fabry disease patients in Italy were followed throughout the COVID-19 pandemic and no patients were known to be infected, though they experienced interruptions in their routine assessments due to physical distancing guidelines [17]. Two individuals who had both Fabry disease and COVID-19 in Lima, Peru were treated with mild symptoms of COVID-19 infection and recovered with no long-lasting symptoms within 50 days of infection [18]. Also due to physical distancing guidelines and concerns for infection, interruptions to treatment and a shift in how patients interact with healthcare professionals to telemedicine have been reported [19]. Given the complexity of late-stage Fabry disease in a patient who had a history of kidney transplant and was on immunosuppressants as well as other risk- increasing co-morbidities such as diabetes mellitus, careful consideration of the risks of routine treatment may potentially avoid complications of opportunistic fungal infections and other possible severe manifestations of COVID-19.

Declaration of Competing Interest

None.

Acknowledgements

We thank the patient for his participation in the Fabry registry, and his family for their consent to publish this case report. The Fabry registry is funded by Sanofi Genzyme. This work was also supported by the Sanofi Genzyme lysosomal storage diseases fellowship grant.

References

[1] D.A. Laney, D.P. Germain, J.P. Oliveira, et al., Fabry disease and COVID-19: international expert recommendations for management based on real-world experience, Clin. Kidney J. 13 (6) (2020) 913–925, https://doi.org/10.1093/ckj/sfaa227.

[2] D.P. Germain, K. Nicholls, R. Giugliani, et al., Efficacy of the pharmacologic chaperone migalastat in a subset of male patients with the classic phenotype of fabry disease and migalastat-amenable variants: data from the phase 3 randomized, multicenter, double-blind clinical trial and extension study, Genet Med. 21 (9) (2019) 1987–1997, https://doi.org/10.1038/s41436-019-0451-z.

[3] D.G. Bichet, R. Torra, E. Wallace, Long-term follow-up of renal function in patients treated with migalastat for Fabry disease, Mol. Genet. Metab. Rep. 28 (2021), 100786, https://doi.org/10.1016/j.ymgmr.2021.100786.

[4] Amicus Therapeutics Galafold™ (Migalastat) Capsules, for Oral Use: US Prescribing Information 2018 https://www.fda.gov/. Accessed 18 Oct 2018.

[5] J.-J. Zhang, X. Dong, Y.-Y. Cao, et al., Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China, Allergy 75 (2020) 1730–1741.

[6] Xiaobo Yang, Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study, Lancet Respir. Med. 8.5 (2020) 475–481.
[7] Ashish Kumar, et al., Is diabetes mellitus associated with mortality and severity of COVID-19? A meta-analysis, Diabet. Metabol. Syndrome 14 (4) (2020) 535–545.
[8] S. Jaurretche, N. Antogiovanni, F. Perreta, Prevalence of chronic kidney disease in fabry disease patients: multicenter cross sectional study in Argentina, Mol. Genet. Metabol. Rep. 12 (2017) 41–43, https://doi.org/10.1016/j.ymgmr.2017.05.007.
[9] Y. Cheng, R. Luo, K. Wang, et al., Kidney disease is associated with in-hospital death of patients with COVID-19, Kidney Int. 97 (5) (2020) 829–838, https://doi.org/10.1016/j.kint.2020.03.005.
[10] S. Kissling, S. Rotman, C. Gerber, Collapsing Glomerulopathy in a COVID-19 Patient Vol 98 (2020), https://doi.org/10.1016/j.kint.2020.04.006.
[11] European Medicines Agency Summary on Compassionate Use of Remdesivir-gilead https://www.ema.europa.eu/en/documents/other/summary-compassionate-use-remdesivir-gilead_en.pdf 17 March 2021 date accessed.
[12] P. Rozenfeld, S. Feriozzi, Contribution of inflammatory pathways to fabry disease pathogenesis, Mol. Genet. Metab. 122 (3) (2017) 19–27, https://doi.org/10.1016/j.ymgme.2017.09.004.
[13] De Francesco, N. Pablo, et al., Fabry disease peripheral blood immune cells release inflammatory cytokines: role of globotriaosylceramide, Mol. Genet. Metab. 109 (1) (2013) 93–99.
[14] Z. Varga, A.J. Flammer, P. Steiger, et al., Endothelial cell infection and endotheliitis in COVID-19, Lancet 395 (10234) (2020) 1417–1418, https://doi.org/10.1016/S0140-6736(20)30937-5.
[15] F.A. Wijburg, B. Bénichou, D.G. Bichet, L.A. Clarke, G. Dostalova, A. Fainboim, A. Fellgiebel, C. Forcelini, K. An Haack, R.J. Hopkin, M. Mauer, B. Najafian, C. R. Scott, S.P. Shankar, B.L. Thurberg, C. Tøndel, A. Tylki-Szymańska, U. Ramaswami, Characterization of early disease status in treatment-naive male paediatric patients with fabry disease enrolled in a randomized clinical trial, PLoS One 10 (5) (2015 May 8), e0124987, https://doi.org/10.1371/journal.pone.0124987.
[16] A.B. Fogo, L. Bostad, E. Svarstad, W.J. Cook, S. Moll, F. Barbey, L. Geldenhuys, M. West, D. Ferluga, B. Vujkovac, A.J. Howie, A. Burns, R. Reeve, S. Waldek, L. H. Noël, J.P. Grünfeld, C. Valbuena, J.P. Oliveira, J. Müller, F. Breunig, X. Zhang, D.G. Warnock, all members of the International Study Group of Fabry Nephropathy (ISGFN), Scoring system for renal pathology in Fabry disease: report of the International Study Group of Fabry Nephropathy (ISGFN), Nephrol. Dial. Transplant. 25 (7) (2010 Jul) 2168–2177, https://doi.org/10.1093/ndt/gfp528. Epub 2009 Oct 15. PMID: 19833663; PMCID: PMC2902894.
[17] E. Riccio, M. Pieroni, G. Limonegli, A. Pisani, Impact of COVID-19 pandemic on patients with Fabry disease: an Italian experience, Mol. Genet. Metab. 131 (1–2) (2020) 124–125, https://doi.org/10.1016/j.ymgme.2020.07.008.
[18] M. Gómez-Luján, C. Cruzalegui, C. Aguilar, M. Alvarez-Vargas, P. Segura-Saldaña, When frequent (Pandemic) occurs in a non-frequent disease: COVID-19 and fabry disease: report of two cases, Jpn. J. Infect. Dis. 74 (3) (2021) 228–232, https://doi.org/10.7883/yoken.JJID.2020.729.
[19] D. Elstein, R. Giugliani, J. Muenzer, J. Schenk, I.V.D. Schwartz, C. Anagnostopoulou, Impact of the COVID-19 pandemic on the standard of care for patients with lysosomal storage diseases: a survey of healthcare professionals in the fabry, gaucher, and hunter outcome survey registries, Mol. Genet. Metab. Rep. 28 (2021), 100788, https://doi.org/10.1016/j.ymgmr.2021.100788.