WHEN FREQUENT (PANDEMIC) OCCURS IN A NON-FREQUENT DISEASE: COVID-19 AND FABRY DISEASE: REPORT OF TWO CASES

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Running Title
COVID-19 and Fabry disease
SUMMARY

Fabry disease (FD), like COVID-19, can affect multiple organs, including the lungs. Patients with FD would be expected to develop severe forms of COVID-19, not only because of lung involvement but also because of renal involvement and other comorbidities. We present two cases of patients with Fabry disease who had an infection by COVID-19. In the two cases presented, they presented mild forms of COVID-19. Although the role of the X chromosome mutation in FD on the development of severe forms of COVID-19 is unknown; in the cases presented, it is suggested that it may play a protective role in the development of COVID-19. Two cases are presented; it is suggested that FD would not be a risk factor for severe COVID-19.
INTRODUCTION

Fabry disease (FD) is a lysosomal storage disease caused by deficiency of the enzyme alpha galactosidase A, it is a secondary to a genetic mutation of the X chromosome(1). Depending on the level of involvement and the expressed genetic variant, it has various clinical presentations. It is known that FD can affect multiple organs, such as the kidneys, heart or lungs, among others (1,2).

The disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), called coronavirus disease 2019 (COVID-19), mainly affects the lungs, and can produce diverse clinical manifestations, ranging from asymptomatic forms to severe lung involvement, even multi-organ dysfunction(3–5), resulting in a fatality ratio case of 13-30%(6–8), highest mortality cases in Peru(8). Risk factors for severe disease as previously reported(9–11) are: advanced age, diabetes, hypertension, obesity and chronic kidney disease.

Patients who are at increased risk of presenting serious clinical manifestations due to COVID-19 are those who have had previous lung disease and comorbidities, this has generated great concern in patients with FD (2).

On the other hand, it is also known that COVID-19 has the angiotensin converting enzyme type 2 (ACE-2) receptor, (it is the main host cell receptor of SARS-CoV-2). ACE2 mRNAs are found to be expressed in different organs, including the lungs, heart, blood vessels, and kidneys. The genetic regulation of this receptor is controlled by the genes contained in the chromosome "X" (12), a chromosome that is altered in FD (1,13).

To present, the true role of this mutation in COVID-19 infection is unknown whether it favors the infection or generates protection against COVID-19. Low expression of ACE2 mRNA was associated with Hypertension, dyslipidemia and/or heart failure also in patients with COVID-19(12).
The reason for this communication is to present two cases of patients with FD who had Covid-19, so that together with other case reports could be submitted in the world literature they contribute to the knowledge of the clinical course of patients with this disease association.

**MATERIAL AND METHODS**

We present two cases from a National Hospital in Peru, who had both FD and COVID-19 as a case presentation.

**RESULTS**

**CASE 1:**

A 49-year-old woman was diagnosed with Fabry disease 7 years ago, because of six months of proteinuria and paresthesias, confirmed by genetic tests that detected a likely pathogenic mutation, c.389A> C (p.Lys130Thr). Her kidney biopsy showed typical FD lesions on electron microscopy (EM), histopathological damage is corroborated with undescended kidney function, which corresponds to stage 1 chronic kidney disease. She was on treatment with enzyme replacement therapy (ERT) with agalsidase beta 1mg / Kg every 15 days Intravenous (IV), she also took enalapril 5 mg qd.

33 days before hospitalization, she complaint of fever (39°C) for 3 consecutive days and odynophagia for 6 days, malaise for 10 days, dry cough for 26 days, this was more demanding in the first 15 days, anosmia and ageusia. Which lasted for 30 days, she did not have any shortness of breath or other symptoms. (Figure 1).

She was admitted for ERT administration, on day 33rd, with normal vital signs, without any pathological finding on physical examination. By hospital protocol, a serological test was performed, which was IgG positive for SARS-Cov-2 and subsequently she had an RT-PCR (real-time reverse transcription polymerase chain reaction test), which was negative. Laboratory data on admission are presented in Table 1. A Thorax computed
tomography (CT scan) showed bilateral ground glass-like subpleural lesions compatible with COVID-19 CO-RADS 2 infection (Fig. 2 A, B). After these results, agalsidase beta 1mg/kg. (Fabrazyme ™) was infused without adverse reactions. The evolution of the patient at day 50th was good, asymptomatic.

CASE 2

A 48-year-old woman was diagnosed with Fabry disease 3 years ago, because of symptomatic sinus bradycardia that required a permanent pacemaker implant and hypertrophic cardiomyopathy, confirmed by genetic tests that detected a pathogenic mutation, c.2T>A (p.Met1Lys). Her kidney biopsy showed typical FD lesions on electron microscopy (EM), histopathological damage is corroborated with undescended kidney function, which corresponds to stage 1 chronic kidney disease. She was on treatment with enzyme replacement therapy (ERT) with agalsidase beta 1mg/Kg every 15 days Intravenous (IV), she also took losartan 50 mg qd.

The patient complained of odynophagia 3 days before admission for 2 days, as well as a dry cough for 3 days. She denied fever, malaise, ageusia, anosmia or respiratory distress. She was admitted for ERT administration on day 4th, with normal vital signs, without any pathological finding on physical examination. By hospital protocol, a serological test was performed, which was IgM positive for SARS-Cov-2, and subsequently she had an RT-PCR molecular test, which was positive, laboratory data on admission are presented in Table 1. In addition, a thorax CT scan didn’t show any COVID-19 compatible lesions (Fig 2 C, D). For this reason, the start of ERT was deferred and she was discharged for home isolation, follow up appointments were performed: 14 days later, reactive IgM and IgG were found positive, a negative RT-PCR, at day 50th and 60th, the patient remained
stable and asymptomatic. The patient was unable to receive ERT therapy due to logistical problems.

DISCUSSION

Patients with FD and COVID-19 infection in this article had the same symptoms that most infected people have (mild infection), although these patients would be expected to present moderate-severe forms.

COVID-19 infection can present as an asymptomatic form in 30-40%, mild disease 80%, moderate 14% or severe disease as 5% (4,9,10,14). Our patients are classified as mild COVID, as they were symptomatic patients with no evidence of hypoxia or viral pneumonia.

COVID-19 cases can present symptoms such as fever (83-99%), cough (59-82%), fatigue (44-70%), anorexia (40-84%), dyspnea (31-40%), myalgia (11-35%), as reported by the World Health Organization (15); our patients had the most common symptoms.

Case 1, complained of fever (Figure 1) that subsided on the 3rd day, odynophagia subsided on the 7th day, similar to the cases in Wuhan reported by Wang et al. (16) with 98% of patients with fever, 59.4% with dry cough and 17.4% with pharyngalgia; the cough in the FD patient persisted for 26 days, with the first 14 days being more intense and frequent, ageusia for 30 days and anosmia for 33 days. The prolongation of the cough could be due to the previous pulmonary condition related to FD; as it has been reported that up to 32.2% of patients with FD have altered lung function tests, mainly with altered FEV1 (obstructive pattern)(2,17); however the patient did not report wheezing or any obstructive pulmonary disease symptoms.
Likewise, she presented anosmia from the beginning of the disease, similar to the findings of Mao et al. (18) in Chinese patients with a frequency of 5.1% hyposmia and 5.6% hypogeusia, additionally Vaira et al. (19) reviewed that patients with COVID-19 ageusia and anosmia are not accompanied by nasal obstruction or other symptoms of rhinitis, probably due to the direct damage of the virus at the level of the olfactory and gustatory receptors, this characteristic was similar to the history of the first patient.

Among the radiological manifestations of lung damage in COVID-19 there were pleural thickenings. The cobblestone pattern, the predominance of ground glass opacities in bilateral involvement of the lower lobes, and the peripheral and posterior location (18,20).

In the first case presented the lesion CO-RADS 2 was presented in both lungs with peripheral and posterior location (Fig 2); however in the second patient with FD there was no lung injury evidenced by the CT scan on the 3\textsuperscript{rd} day of disease, and remained asymptomatic after, in the balance risk benefit a new Chest CT scan was not needed.

In case 1, who had serology of positive IgG, negative RT-PCR and tomography with lung injury, the evolution was clinically good 50 days after the onset of symptoms.

In case 2, only 3 days with dry cough and 2 days with odynophagia with positive RT-PCR and tomography without lung injury (14), had a good clinical evolution after 50 days, remained asymptomatic afterwards.

The first patient with FD and COVID-19 presented positive IgG on the 30th day of illness, probably because the majority of patients with COVID-19 present positive serology since day 17\textsuperscript{th} - 19\textsuperscript{th} after the start of symptoms(21), in addition to this, it has also been described that the sensitivity of serology was 79.8% (69.9-87.6%) after 15 days (22).

The patient in the second case had positive serology for Ig M (with a sensitivity of 43.8%), probably due to the short time since the onset of her symptoms (3 days). The RT-PCR in
nasopharyngeal samples can be positive from the 3rd day of the onset of symptoms and are also found in asymptomatic patients (23).

These two cases share the same clinical characteristics, evolution and prognosis of the general population, despite having FD. Although it is true that two isolated cases cannot be generalized, we believe that they can be used to search for an explanation on why patients with FD did not have a severe form of COVID-19 disease. It is known that in general population, comorbidities are associated with more severe outcomes from COVID-19, and both of the presented cases had chronic kidney disease stage 1 and case 2 had cardiomyopathy, but neither of them presented a severe form of COVID-19, this scenario make us hypothesize that the underlying mechanism that causes FD (mutation on the X chromosome), and the sex difference in renal ACE2 activity (24) could have a role leading to a mild form of COVID-19.

Likewise, no exacerbation of FD symptoms were reported during the time of viral infection, especially in the respiratory system. (wheezing, dyspnea, hemoptysis or pulmonary thromboembolism) Generated by loss of lung elasticity, hyperreactivity bronchial, inflammation of the airway due to accumulation of glycosphingolipids and hyperplasia of smooth muscle cells and respiratory epithelium in FD (1,12,21)), which, if present in the reported cases, would be indistinguishable from determining the etiology between the two entities: FD and COVID-19.

Another point observed is the potential safety to infuse ERT when the patient doesn’t have COVID-19 symptoms and when the molecular test is negative, as the first case, who did not have any complication.

A previous report had evaluated the impact of the COVID-19 emergency in patients with FD receiving ERT (22), and found, as in the second case, difficulties in infusing the ERT and this due to multiple factors such as reorganization of infusion centers, fear of infection,
symptoms in patients. The reality observed in Italian centers does not differ from the experienced by the second case in Peru, who was unable to receive her ERT doses in the midst of the pandemic.

LIMITATIONS
The case report is not a categorical source for recommendations, however, in rare diseases such as FD, the isolated case report helps to some extent to generate scientific knowledge. More cases of COVID-19 and FD need to be evaluated globally.

CONCLUSIONS
Two cases of mild SARS-CoV-2 infection in patients with Fabry disease are presented. It is suggested that FD would not be a risk factor for severe COVID19, but to establish this relationship, further studies are required.

ACKNOWLEDGMENTS
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CONFLICT OF INTERESTS
Investigators declare no conflict of interest.
REFERENCES


FIGURE LEGENDS

**Figure 1:** Evolution of the disease of reported cases

**Figure 2.** Chest CT Scan of both reported cases.

Case 1 (A, B): Bilateral subpleural ground glass opacifications, CO-RADS 2. Case 2 (C,D): Normal CT.
### Table 1. Laboratory findings at admission of both cases

<table>
<thead>
<tr>
<th>Parameters at Admission</th>
<th>Case 1</th>
<th>Case 2</th>
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<tbody>
<tr>
<td>Glucose</td>
<td>97</td>
<td>96</td>
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<tr>
<td>Urea (mg/dl)</td>
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<td>Creatinine (mg/dl)</td>
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<td>GFR (e) CKD-EPI</td>
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<tr>
<td>Hemoglobin</td>
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<td>Platelets</td>
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</tr>
<tr>
<td>RT-PCR SARS-CoV-2</td>
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<td>Detected</td>
</tr>
</tbody>
</table>
Clinical Timeline

**Case 1**
- Day 0: Fever
- Day 3: Odynophagia
- Day 6: Malaise
- Day 10: Dry cough
- Day 15: Agcsia
- Day 30: Anosmia
- Day 33: Serology COVID IGG+
- PCR COVID Negative
- Enzyme Replacement Therapy

**Case 2**
- Day 0: Odynophagia
- Day 3: Dry cough
- Day 2: PCR COVID Positive
- Day 18: PCR COVID Negative

Time (Days)