INTRODUCTION

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

Coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that mainly affects the lungs and can produce diverse clinical manifestations ranging from asymptomatic forms to severe lung involvement and even multi-organ dysfunction (3–5). Thus, the fatality rate of COVID-19 is 13–30% (6–8), with the highest in Peru (8). Risk factors associated with a severe COVID-19 disease include old age, diabetes, hypertension, obesity, and chronic kidney disease (9–11).

Patients who have an increased risk of serious clinical manifestations due to COVID-19 are those who have had a previous lung disease and comorbidities, causing a major concern in patients with FD (2). On the other hand, SARS-CoV-2 has the angiotensin converting enzyme type 2 (ACE-2) receptor, which is its main host cell receptor. ACE2 mRNA is expressed in the lungs, heart, blood vessels, and kidneys, among others. The genetic regulation of this receptor is controlled by the genes present in the X chromosome (12), a chromosome that is altered in FD (1,13). To date, the significance of this mutation for the COVID-19 infection has not been elucidated. Therefore, whether it favors the infection or generates protection against COVID-19 is unknown. Low expression of ACE2 mRNA is also associated with hypertension, dyslipidemia, and/or heart failure in patients with COVID-19 (12).

Thus, the aim of this study is to present 2 patients with FD who were infected with the COVID-19 virus. Although it is unknown whether the X chromosome mutation in patients with FD affects the development of severe COVID-19, it is suggested that it may play a protective role against COVID-19 infection. Based on these cases, we suggest that FD is not a risk factor for severe COVID-19.

MATERIALS AND METHODS

Two patients who had both FD and COVID-19 were treated at the National Hospital in Lima, Peru.

RESULTS

CASE 1: A 49-year-old woman was diagnosed with FD 7 years ago, as she was suffering from proteinuria and paresthesias for 6 months. The diagnosis involved a genetic tests that detected a likely pathogenic mutation...
c.389A > C (p.Lys130Thr). Her kidney biopsy showed typical FD lesions on electron microscopy (EM), and histopathological damage was accompanied by undescended kidney function, which indicates stage 1 chronic kidney disease. The patient was subjected to enzyme replacement therapy (ERT) with 1 mg/kg of agalsidase beta every 15 days. Moreover, the patient was treated with 5 mg QD of intravenous (IV) enalapril.

Thirty-three days before hospitalization, the patient complained of fever (39°C) for 3 consecutive days and odynophagia for 6 days, malaise for 10 days, dry cough for 26 days, which was more persistent in the first 15 days, and anosmia and ageusia. These were not accompanied by shortness of breath or any other symptoms (Fig. 1).

On day 33, the patient was admitted for ERT administration, with normal vital signs and no pathological findings on physical examination. Following the hospital protocol, a serological test was performed, which revealed IgG-positivity for SARS-CoV-2; subsequently, a real-time reverse transcription polymerase chain reaction (RT-PCR) test was performed, with a negative result. The laboratory data on admission are presented in Table 1. Thorax computed tomography (CT) revealed bilateral ground glass-like subpleural lesions compatible with COVID-19 CO-RADS 2 infection (Fig. 2A, B). Based on these findings, 1 mg/kg of agalsidase beta (Fabrazyme™, SANOFY GENZYME [Bridgewater, NJ, USA]) was infused without adverse reactions. On day 50, the patient was asymptomatic, in a good overall condition.

**CASE 2:** A 48-year-old woman was diagnosed with FD 3 years ago, due to the presence 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). A kidney biopsy showed typical

| Parameter at admission | Case 1 | Case 2 |
|------------------------|--------|--------|
| Glucose                | 97     | 96     |
| Urea (mg/dL)           | 34     | 41     |
| Creatinine (mg/dL)     | 0.58   | 0.72   |
| GFR (e) CKD-EPI        | 108.2  | 99     |
| White blood cells      | 4,870  | 7,940  |
| Lymphocytes            | 2,890  | 2,612  |
| Hemoglobine            | 12.9   | 13.1   |
| Platelets              | 249,000| 279,000|
| CRP (mg/dL)            | 0.4    | 0.5    |
| LDH (UI/L)             | 226    | 288    |
| pH                     | 7.37   | 7.44   |
| pCO2                   | 42.2   | 32.8   |
| pO2                    | 76.6   | 96.4   |
| % SatO2                | 95     | 97     |
| % FiO2                 | 21     | 21     |
| SatO2/FiO2             | 4.52   | 4.33   |
| PaO2/FiO2              | 3.65   | 4.59   |
| HCO3                   | 23.8   | 22     |
| Albumin                | 4.1    | 4.7    |
| AST (UI/L)             | 32     | 30     |
| ALT (UI/L)             | 26     | 31     |
| Ferritin (ng/dL)       | 97     | 113    |
| D-dimer                | 0.56   | 0.67   |
| IgM SARS-CoV-2         | No reactive | Reactive |
| IgG SARS-CoV-2         | Reactive | No reactive |
| RT-PCR SARS-CoV-2      | No detected | Detected |
FD lesions on EM, and histopathological damage was accompanied by undescended kidney function, which corresponds to stage 1 chronic kidney disease. The patient was undergoing an ERT with IV agalsidase beta (1 mg/kg every 15 days), she also took 50 mg QD of losartan.

Three days before the admission, the patient was complaining of odynophagia for 2 days, as well as of dry cough for 3 days. She denied fever, malaise, ageusia, anosmia, or respiratory distress.

The patient was admitted for ERT administration on day 4, with normal vital signs and without any pathological findings on physical examination. Following the hospital protocol, a serological test was performed which revealed IgM-positivity for SARS-CoV-2. Subsequently, an RT-PCR molecular test was also positive. The laboratory data on admission are presented in Table 1. In addition, a thoracic CT scan did not show any COVID-19-related lesions (Fig. 2C, D), deferring the start of ERT. The patient was discharged for home isolation. Follow-up appointments were made 14, 50, and 60 days later. During the first follow-up (at day 14), the reactive IgM and IgG were found positive, while the RT-PCR test was negative for COVID-19.

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At days 50 and 60, the patient remained stable and asymptomatic, but was unable to receive ERT therapy due to logistical problems.

DISCUSSION

Patients with FD and COVID-19 in this report had similar symptoms as the majority of infected people (i.e. mild infection), although these patients would be expected to present moderate-severe forms of COVID-19.

Patients with COVID-19 are asymptomatic in 30–40% of cases, mild in 80%, moderate in 14%, and severe in 5% of patients (4,9,10,14). Our patients were diagnosed with mild COVID, as they were symptomatic but with no evidence of hypoxia or viral pneumonia.

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

The first patient (case 1) complained of fever (Fig. 1) that subsided on day 3 and odynophagia that subsided on day 7, 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. Cough in the FD patient persisted for 26 days, while it was more intense and persistent during the first 14 days, while ageusia persisted for 30 days and anosmia for 33 days. The prolongation of the cough could be due to a previous pulmonary condition related to FD. Up to 32.2% of patients with FD have altered lung
function tests, mainly with altered FEV1 (obstructive pattern) (2,17); however, the patient in case 1 did not report wheezing or any obstructive pulmonary disease symptoms.

The second patient (case 2) developed anosmia from the beginning of the disease, which is aligned with findings of Mao et al. (18) in Chinese patients with a frequency of 5.1% hyposmia and 5.6% hypogeusia. In line, Vaira et al. (19) reported that patients with COVID-19-related ageusia and anosmia do not suffer from nasal obstruction or other symptoms of rhinitis, probably due to a direct damage of the virus at the level of the olfactory and gustatory receptors. This characteristic was similar also in the first patient.

Among radiological manifestations of the lung damage in COVID-19, pleural thickenings have been reported, including the cobblestone pattern, the predominance of ground glass opacities in bilateral involvement of the lower lobes, and the peripheral and posterior locations (18,20). In the first case, the lesion CO-RADS 2 was present in both lungs with peripheral and posterior location (Fig 2); however, in the second patient with FD, there was no lung injury as evidenced by the CT scan on the 3rd day of the disease. Since the patient remained asymptomatic, a new chest CT scan was not required.

Patient 1, who had positive IgG test, negative RT-PCR test, and tomography revealing lung injury, was in good condition 50 days after the onset of symptoms.

Patient 2, who had dry cough for only 3 days and odynophagia for 2 days, with a positive RT-PCR test and tomography without lung injury (14), was also in good condition 50 days later and remained asymptomatic afterwards.

The first patient with FD and COVID-19 presented positive IgG on day 30 of the illness, probably because the majority of patients with COVID-19 present positive serology from day 17–19 after the start of symptoms (21). Moreover, the sensitivity of serology is reportedly 79.8% (69.9–87.6%) after 15 days (22).

The patient in case 2 had positive serology for IgM (with a sensitivity of 43.8%), probably due to short time since the onset of her symptoms (3 days). RT-PCR tests from nasopharyngeal samples can be positive from the day 3 following the onset of symptoms and are also found in asymptomatic patients (23).

Both cases described here share the same clinical characteristics, disease progression, and prognosis of the general population, despite having FD. Although it is difficult to generalize based on 2 isolated cases, our observations indicate that patients with FD do not have a severe form of the COVID-19 disease. In the general population the presence of comorbidities is associated with more severe forms of 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. Based on this finding we hypothesize that the underlying mechanism that causes FD (mutation on the X chromosome), and the sex difference in renal ACE2 activity (24), could contribute to a mild form of the COVID-19 disease.

Likewise, no exacerbation of FD symptoms was reported during the time of viral infection in the described cases, especially in the respiratory system (e.g. wheezing, dyspnea, hemoptysis, or pulmonary thromboembolism triggered by loss of lung elasticity, bronchial hyperreactivity, inflammation of the airway due to accumulation of glycosphingolipids and hyperplasia of smooth muscle cells and respiratory epithelium [1,12,21]). Had such symptoms been present in the reported cases, the etiology of the 2 entities, i.e. FD and COVID-19, would have been indistinguishable.

Another important observation is related to potential safety of ERT infusion when a patient does not have COVID-19 symptoms and when the molecular test is negative, as in the first case, who did not develop any related complications.

A previous report 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. This was due to multiple factors such as reorganization of infusion centers, fear of infection, and COVID-19 symptoms present in patients. Here, the second patient was unable to receive her ERT doses, which reflects the situation of healthcare in the midst of the COVID-19 pandemic, also in other countries, e.g. in Italy.

This case report is not a categorical basis for any clinical recommendations; however, in rare diseases such as FD, isolated case reports help expand the scientific knowledge of a given condition. More cases of COVID-19 and FD need to be evaluated globally in order to draw further conclusions on the topic.

In conclusion, we described 2 cases of mild SARS-CoV-2 infection in patients with FD. Our observations indicate that FD is not a risk factor for severe COVID19, but further studies are required to fully explain this association.

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Conflict of interest None to declare.

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