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The Course of COVID-19 Infection in Patients After Pancreas and Kidney Transplantation: A Single-Center Observation

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ABSTRACT

Solid graft recipients are at an increased risk of serious complications and death. Out of 130 out-patient recipients of pancreas grafts at our Clinic, 20 patients (15.73%) had a confirmed severe acute respiratory syndrome coronavirus 2 infection (SARS-CoV-2). Each patient had a different course of the disease, and the forms of infection varied from mild to severe and lethal. According to recommendations, after confirmation of the infection, mycophenolate mofetil was withdrawn and the immunosuppression was based on steroids and a calcineurin inhibitor. In this study, we performed an analysis of the course of COVID-19 infection in patients after pancreatic transplantation. Twenty pancreas recipients were confirmed to have COVID-19 infections; 4 of whom required hospitalization owing to severe complications. Patients reported weakness, excessive intensity of fatigue, shortness of breath with exertion, cough, and periodically increased temperature. Weakness and fatigue persisted in these patients for about 6 weeks. In 2 patients there was a need for oxygen supplementation and empirical antibiotic. Mortality was 5%, and there was 1 graftectomy. Deterioration of either kidney or pancreas graft were not observed in any other patients.

The course of SARS-CoV-2 infection in solid graft recipients is similar to that of the rest of the population. Because of immunosuppression, recipients were accustomed to avoiding crowds and complying with obligations to wear masks.

THE number of individuals confirmed to be infected with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus has exceeded 398.6 million worldwide. More than 5.7 million patients have died of COVID-19 since the start of the pandemic. The most affected regions in the world are Europe (more than 136.9 million cases), Asia (more than 104.9 million cases), and North America (more than 91.8 million cases). Europe is the region where COVID-19 has the highest death toll. Of all those who died of COVID-19 worldwide, 28.5% died in Europe. Fatalities in Asia are 22.7% percent of all deaths related to COVID-19 [1].

People on dialysis become infected with COVID-19 8 times more often than the general population. According to the report of the National Nephrology Consultant in September 2021 [2], 1 person in 2500 hemodialysis patients developed COVID-19, whereas the incidence in the entire population of our country was then 1 person in 50,000. On the other hand, the number of dialysis patients in Poland fluctuated during the pandemic

between 20,000 and 22,000. At the beginning of the pandemic, the incidence was 10 times higher, but almost 90% of dialyzed patients were vaccinated against COVID-19, hence a significant decrease in the incidence in this group of patients [3]. Due to the reduced immunity in dialysis patients and patients after organ transplantation, in Poland and other countries, it is recommended to perform booster vaccinations in this group of patients [4,5].

The recommendations of the Polish Transplant Society at the beginning of the SARS-CoV-2 pandemic resulted in a significant reduction in the number of organ transplants in Poland. The number of hospitals in which transplantations took place decreased, as

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did the number of organ donors. According to Poltransplant data [6], 4 pancreatic transplants were performed in 2020 and 20 were performed in 2021. Our center was transformed into a COVID-19 hospital that did not perform any pancreatic transplantation from March 2020 to May 2021; in previous years, we performed more than 20 such procedures annually.

The aim of this study was to describe the experience of our clinic with pancreas graft recipients with confirmed COVID-19 infection and to evaluate the effect of the infection on graft function.

METHODS

A retrospective analysis of pancreas recipients with confirmed SARS-CoV-2 infection was performed. We analyzed the time from transplant, age, sex, and data on symptoms of the infection.

We have previously described our surgical technique and comprehensive management [7–10]. We perform a longitudinal midline incision and anastomose pancreas arterial Y-graft and portal vein to the right iliac vessels of the donor. We create a double-layered handsewn side-to-side junction between duodenum and proximal jejunum. We transplant the kidney from the same median incision into retroperitoneal space behind the left iliac vessels. We use a 3-drug immunosuppression scheme with induction with polyclonal antibodies thymoglobulin—a total dose of 1.5 mg/kg. According to recommendations, after confirmation of a COVID-19 infection, mycophenolate mofetil was withdrawn and the immunosuppression based on steroids and a calcineurin inhibitor. During the SARS-CoV-2 infection, we did not change anticoagulant treatment in a group of patients with mild symptoms. Three months post-transplantation, recipients were administered 75 mg of acetylsalicylic acid daily. In a group of patients with moderate or severe infection symptoms, low molecular weight heparin in a prophylactic dose was administered.

Our center transformed into a COVID-19 hospital in March 2020. To continue observing the recipients, outpatient care during the pandemic was under telemedicine services and on-demand in person. Controls and laboratory examinations took place in an ambulatory area created exclusively for patients on immunosuppression. The aim creating the ambulatory area was to limit possible contact with SARS-CoV-2 positive patients.

Since changes in restrictions, it was mandatory to perform a polymerase chain reaction (PCR) test for SARS-CoV-2 infection and a chest high resolution computed tomography (CT) in each solid graft donor. Also, recipients were obliged to have a PCR test and chest radiograph. Currently, after a series of vaccinations against COVID-19, the population of potential organ recipients is less vulnerable to infection, and we are slowly withdrawing from restrictions. In May 2021, at our clinic, the pancreas transplantation program was reactivated.

RESULTS

Out of 130 recipients in the outpatient observation, 20 recipients (15.3%) were diagnosed with SARS-CoV-2. Table 1 summarizes the clinical data of the recipients. There were 14 women and 6 men, and 17 patients (85%) underwent simultaneous pancreas and kidney transplantation (SPK) and 3 patients had only a pancreas transplantation. The mean time from the transplantation to COVID-19 infection was 3.88 years.

All infected patients were advised to discontinue mycophenolate for approximately 2 to 3 weeks. Three patients after

COVID-19 infection had digestive tract disorders, including diarrhea, which resolved after conservative treatment.

Four patients from the observation developed COVID-19 infection after 2 doses of mRNA vaccination, and 11 patients were vaccinated after recovery from the infection. During infection, patients reported weakness, excessive fatigue, shortness of breath with exertion, cough, and periodically increased temperature. Weakness and fatigue persisted in these patients for about 6 weeks.

Among the patients, 20% presented moderate symptoms of the infection. In a single patient, the course of SARS-Cov-2 was serious. The overall mortality was 5%, and there was 1 graftectomy. No deterioration of either the kidney or the pancreas graft in any other patients was observed. One patient vaccinated before their SARS-CoV-2 infection required hospitalization owing to severe diarrhea and need of intravascular fluid administration. In 2 patients there was a need for oxygen supplementation and empirical antibiotic. The 3 other hospitalized patients are described below.

Patient 6: Aged 51 Years

The patient underwent SPK transplantation on September 28, 2017, and afterwards qualified for our study owing to insulin-dependent diabetes, chronic renal disease, and dialysis for 18 months before the transplant. Table 2 summarizes the most important data regarding transplantation and treatment.

In March 2021, the patient was diagnosed with COVID-19. The initial symptoms included weakness, fatigue, cough, headache, and muscle pain. No shortness of breath, decrease in saturation, or fever were observed. Conservative treatment was carried out in home isolation conditions. The drug modification included the withdrawal of mycophenolate mofetil. Maintaining the regimen of the rest of the drugs, steroids, tacrolimus, and acetylsalicylic acid was prescribed.

After 3 weeks, the PCR test was still positive. Because of increasing dyspnea, the patient was referred to an infectious hospital and hospitalized for 7 days. The thoracic CT revealed bilateral scattered irregular areas of the frosted glass type, with a predominance of peripheral segments, locally with visible densities and thickening of interlobular septa (a symptom of paving stones), moderate lesions affecting 25% to 50% of the lungs (Fig 1). No deterioration of kidney or pancreas graft function was observed. Table 3 presents the results at admission to the hospital.

The patient was treated with low molecular weight heparin in a prophylactic dose, as well as empirically administered ceftriaxone and amoxicillin with a beta-lactamase inhibitor. After improvement of her general condition, she was discharged from the clinic and sent home.

In May, June, and September 2021, the patient was vaccinated with the mRNA (Moderna) vaccine and obtained the level of Ig > 2080 BUA/mL in the tests.

Currently, both grafts have sufficient function (creatinine 1.36 mg/dL, eGfr > 60 mL/min/1.73 m²). The patient is independent from insulin (HbA1c -5.7%). No further episodes of fatigue or shortness of breath were reported.

Table 1. Clinical Data of Pancreas Recipients After SARS-Cov-2 Infection

	Sex	Type of Tx	Time (y) From Tx to COVID-19	Age	COVID-19 Date of Infection	mRNA Vaccine I Dose Date	mRNA Vaccine II Dose Date	mRNA Vaccine III Dose Date	Hospitalization Due to SARS-CoV-2 Infection	Symptoms	Pancreas Graft Function After SARS-CoV-2 Infection
1.	Woman	SPK	7	50	12.20	06.21	07.21	-	No	Mild	Good
2.	Woman	SPK	9	33	01.21	03.21	05.21	-	No	Mild	Good
3.	Woman	PTA	5	34	11.20	03.21	05.21	-	No	Mild	Good
4.	Man	SPK	8	55	10.20	08.21	09.21	-	No	Mild	Good
5.	Woman	SPK	6	26	12.20	03.21	05.21	10.21	No	Mild	Good
6.	Man	SPK	3	51	03.21	05.21	06.21	09.21	Yes	Moderate	Good
7.	Woman	SPK	5	34	12.20	03.21	04.21	11.21	No	Mild	Good
8.	Woman	SPK	3	45	11.20	03.21	04.21	12.21	No	Mild	Good
9.	Woman	PTA	2	36	12.21	03.21	05.21	-	No	Moderate	Good
10.	Woman	SPK	2	37	02.20	-	-	-	No	Mild	Good
11.	Man	SPK	4	41	12.21	03.21	04.21	09.21	No	Mild	Good
12.	Man	SPK	2	29	12.21	03.21	05.21	-	No	Mild	Good
13.	Woman	SPK	1	37	05.21	03.21	06.21	10.21	No	Mild	Good
14.	Man	SPK	0.5	46	11.20	03.21	04.21	-	No	Mild	Good
15.	Woman	SPK	2	37	11.20	03.21	05.21	09.21	No	Mild	Good
16.	Man	SPK	0.5	40	12.21	03.21	04.21	09.21	No	Mild	Good
17.	Woman	PTA	6	41	04.21	-	-	-	Yes	Moderate	Graft loss (graftectomy due to venous thrombosis)
18.	Woman	SPK	7	48	01.20	-	-	-	Yes	Severe	Death
19.	Woman	SPK	9	42	01.22	-	-	-	Yes	Moderate	Good
20.	Woman	SPK	5	48	04.21	-	-	-	No	Mild	Good

PTA, pancreas transplantation alone; SPK, simultaneous pancreas and kidney transplantation; Tx, transplantation.

Table 2. Case 6: History of Transplantation for Man Aged 51 Years

Donor	Deceased
Warm ischemia time	30 min
Cold ischemia time	380 min
Induction	Polyclonal antibodies at a dose of 1.5 mg/kg
Immunosuppression	Steroids, tacrolimus, mycophenolate mofetil
Transplant complications	Reoperation due to intra-abdominal abscesses
Surgical site infection	Wound

Table 4. Case 17: History of Transplantation for 39-Year-Old Woman

Donor	Deceased
Warm ischemia time	25 min
Cold ischemia time	300 min
Induction	Polyclonal antibodies at a dose of 1.5 mg/kg
Immunosuppression	Steroids, tacrolimus, mycophenolate mofetil
Transplant complications	None
Surgical site infection	None

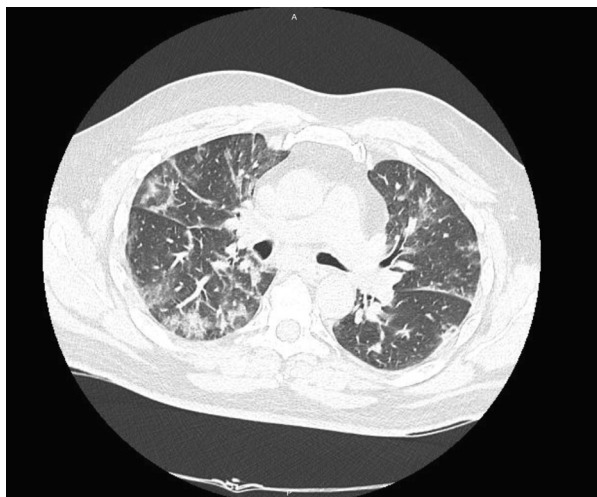


Fig 1. Case 6. Chest computed tomography. Changes in the course of COVID-19. The thoracic computed tomography revealed a bilateral scattered irregular areas of the frosted glass type, with a predominance of peripheral segments, locally with visible densities and thickening of interlobular septa (symptom of paving stones), moderate lesions affecting 25% to 50% of the lungs.

Table 3. Case 6: Laboratory Results on Discharge for Man Aged 51 Years

Creatinine	1.49 mg/dL
Estimated glomerular filtration rate	50.1 mL/min/1.73 m ²
Urea	47 mg/dL,
Anti-SARS antibodies -CoV-2 IgG	positive result (116AU/mL)
Anti-SARS-CoV -2 antibodies-IgM	positive result (10.10 INDEX)
C-reactive protein	21.8 mg
D-dimers	1.61 μ g/mL (n: 0-0.5).

Case 17: aged 41 years

The patient underwent a pancreas transplant on January 30, 2015, and qualified for our study owing to insulin-dependent diabetes without renal complications. [Table 4](#) shows transplantation details.

In April 2021, the patient tested positive for SARS-CoV-2 was detected. Initially, the patient manifested only mild symptoms. After 2 weeks, she was hospitalized because of severe muscle pain, headaches, and dry cough. The patient required

oxygen supplementation. Thoracic CT showed peripheral inflammatory lesions of matt glass and paving stones, taking up about 8% of the lungs ([Fig 2](#)). During first days of hospitalization, there was no observable graft function deterioration (creatinine 1.68 mg/dL, eGFR 46 mL/min, c-peptide 3.13 ng/mL, HbA1c -5.5%), but only leukopenia 2.38 1000/uL was found. The conservative treatment was modified according to our standard (MMF withdrawal and low molecular weight heparin in prophylactic dose). After 2 weeks, she was discharged from the hospital with a recommendation to reduce steroid therapy within 2 weeks of discharge. After 4 months, the patient reported fatigue, abdominal pain, and hyperglycemia >500 mg/dL. In an abdominal CT scan, the transplanted pancreas was enlarged, heterogeneous, with edema, arterial vascularization of the graft from the right iliac artery only in the initial segment, and venous outflow only slightly visible in the proximal part ([Fig. 3](#) and [4](#)). Conservative treatment consisted of insulin therapy, therapeutic dose of heparin, and empirical antibiotic therapy. Endoscopic examination showed mucosal necrosis of the graft's duodenum, mucosal surface without visible vessels. Patients wad qualified for graftectomy. In the histopathological examination of the specimen of the transplanted pancreas, there

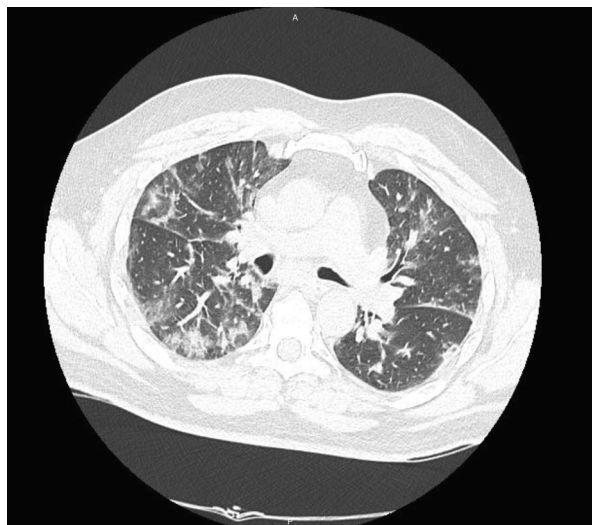


Fig 2. Case 17. Chest computed tomography. Changes in the course of COVID-19. The thoracic computed tomography revealed peripheral inflammatory lesions of matt glass and paving stones, taking up about 8% of the lungs.

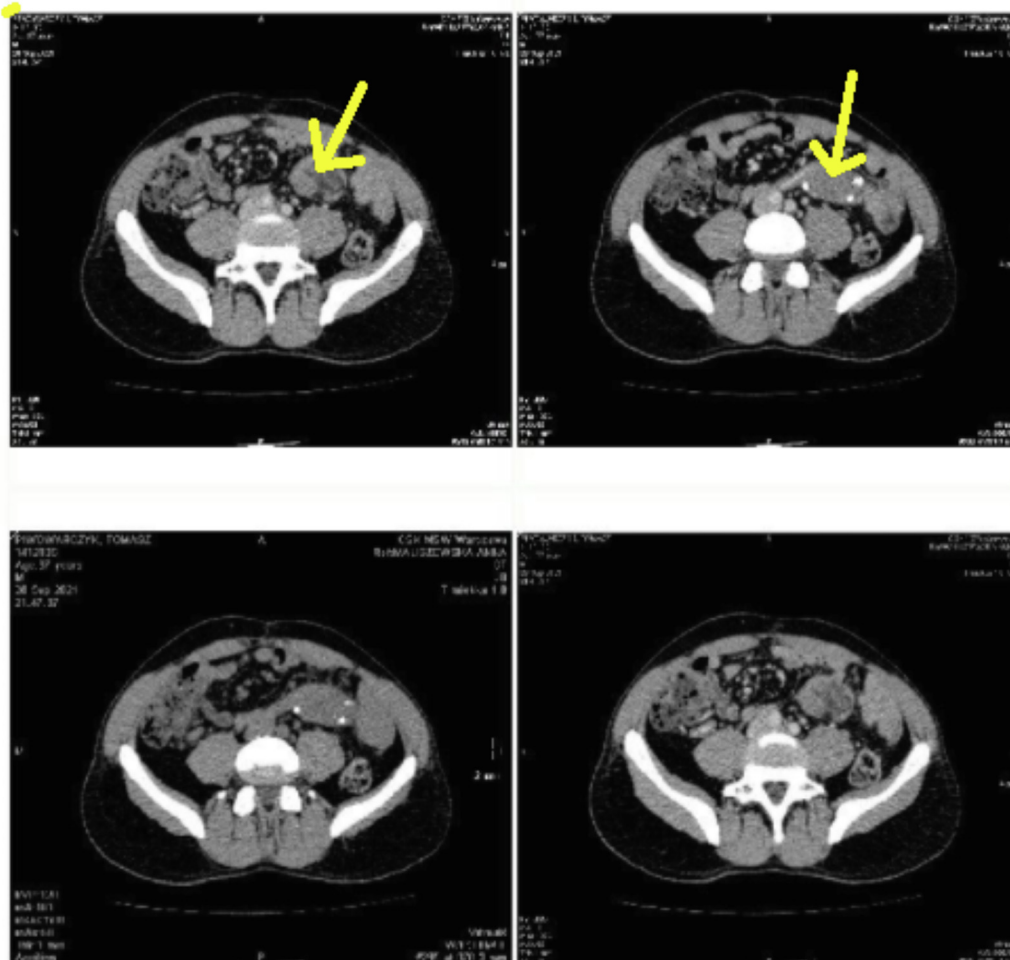


Fig 3. Case 17. Abdominal computed tomography scan. The abdominal computed tomography scan revealed that the transplanted pancreas was enlarged, was heterogeneous, had edema, had arterial vascularization of the graft from the right iliac artery only in the initial segment, and had venous outflow only slightly visible in the proximal part. The yellow arrow shows a transplanted pancreas.

was observable atrophy and fibrosis of the graft, changes related to chronic rejection, vascular thrombosis, and hemorrhagic necrosis. After the graft was removed, the patient's condition improved and the patient was discharged from the hospital and sent home. On discharge, the level of IgG was 791.0 BAU/mL, IgM 51.8 (index).

Case18: Aged 48 Years

The patient underwent an SPK transplantation on December 29, 2017, and afterward qualified for our study owing to insulin-dependent diabetes, chronic renal disease, and dialysis for 32 months (peritoneal dialysis). Table 5 shows transplantation details.

In December 2020, the patient tested positive for SARS-CoV-2. The patient required referral to the local infectious hospital owing to fever and severe diarrhea. Two weeks later, the general condition worsened, and she was referred to our clinic, the third-level hospital for COVID-19 treatment. The patient

required mask with a reservoir with oxygen flow 15l per minute. In a high-resolution CT of the chest, extensive consolidation and frosted glass changes, covering 75% to 80% of the lung volume, was found (Fig 5).

Clostridium difficile was detected in stool and vancomycin was administered orally. Empirical intravenous antibiotic therapy included piperacillin/tazobactam with antifungal drugs (voriconazole) administered orally. Increasing dyspnea and hypotension were observed. The patient developed multiorgan failure and required catecholamines as well as mechanical treatment. Increasing acidosis was an indication to start continuous renal replacement therapy. The patient died 4 weeks after the initial PCR test because of SARS-CoV-2 complications.

DISCUSSION

Since the start of the COVID-19 pandemic, the number of reported organ donors and the number of organ transplants has significantly decreased [11]. The most important reasons might

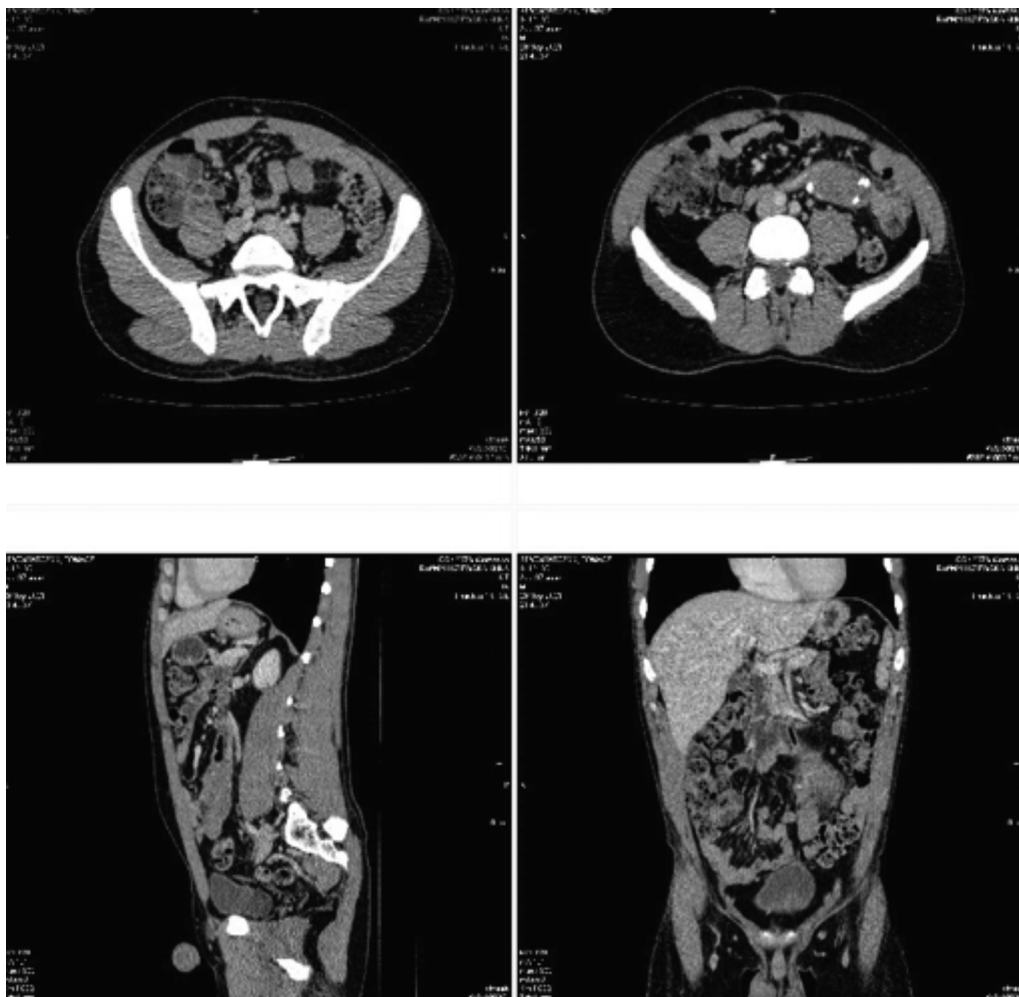


Fig 4. Case 17. Abdominal computed tomography scan of the sagittal section. The computed tomography scan revealed that the transplanted pancreas was enlarged, was heterogeneous, had edema, had arterial vascularization of the graft from the right iliac artery only in the initial segment, and had venous outflow only slightly visible in the proximal part

Table 5. Case 18: History of Transplantation for Woman Aged 47 Years

Donor	Deceased
Warm ischemia time	25 min
Cold ischemia time	360 min
Induction	Polyclonal antibodies at a dose of 1.5 mg/kg
Immunosuppression	Steroids, tacrolimus, mycophenolate mofetil
Transplant complications	Early kidney graft loss (vascular complications), HD
Surgical site infection	Intra-abdominal infection

HD, hemodialysis.

have been limited access to hospital resources and a limited number of pancreas donors, surge conditions of the pandemic with a shortage of facilities, changes in the availability of transplant centers owing to transformation into infectious centers, as well as deficiency of medical staff [12,13]. Another important

factor might have been SARS-CoV-2 infection among patients on the waiting list. Santos et al [14] reported that 4.6% of kidney-pancreas waiting-list patients were diagnosed with COVID-19. SPK transplantation is safe and feasible in patients convalescing from COVID-19 [15]. In our clinic, there was no case of disqualification owing to COVID-19 infection. Patients infected with the SARS-CoV-2 virus were taken off of the waiting list for approximately 3 months. In 2021, we performed 2 SPK transplantations in patients who recovered from COVID-19 infection, 6 months and 7 months before the transplant, respectively. The early results of organ transplantation in these cases are very good. We also described previously SARS-CoV-2 infection in a kidney recipient [16].

In a Spanish observation, pancreas recipients diagnosed with SARS-CoV-2 infection were just 1% of cases (8 cases out of 778 solid graft recipients registered). The cumulative risk of SARS-CoV-2 infection among pancreas graft recipients was 5.5 out of 1000 for the pancreas, the same as the risk in the

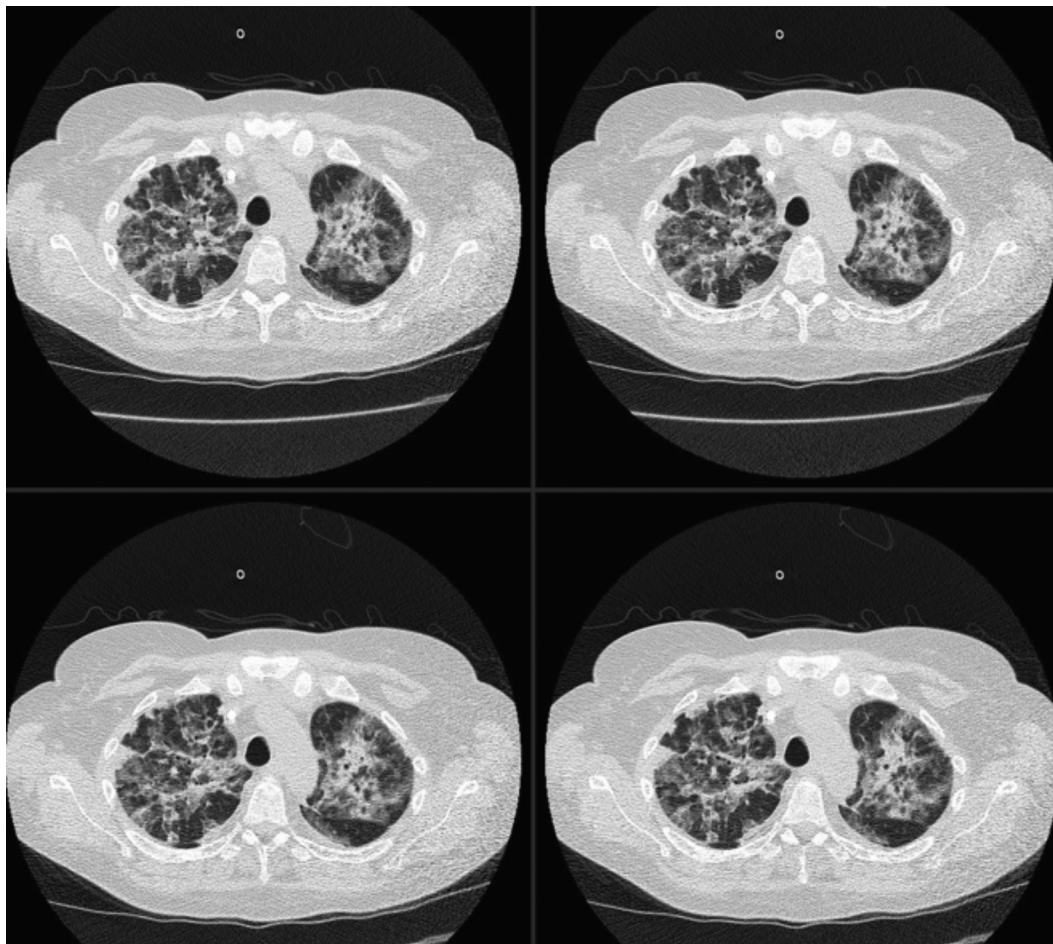


Fig 5. Case 18. Chest computed tomography scan. Changes in the course of COVID-10. The high-resolution computed tomography scan of the chest revealed extensive consolidation and frosted glass changes, covering 75% to 80% of lung volume.

Spanish population [17]. In the observation, 2 patients required intensive care unit stays, 4 patients were ventilated mechanically, and 1 patient developed multiorgan failure [17].

Dube et al [18] described 4 cases of pancreas recipients diagnosed with SARS-CoV-2; among them, 1 patient from the observation died and 50% of cases reported diarrhea as a major symptom of the disease. Diarrhea was one of the most frequent complaints in our own observation, including two cases that led to hypovolemia, hospital referral, and need of intravenous fluid administration. The reason for the increased incidence of diarrhea is unclear.

The course of COVID-19 might be serious. Yi reported the use of anakinra in a severe case and respiratory failure [19]. Heron described the successful use of mammalian target of rapamycin inhibitors as an alternative to immunosuppression that could change the course of COVID-19 owing to their antiviral features [20].

In 1 case, we observed late pancreas venous graft thrombosis (PVGT). The occurrence of PVGT varies from 10% to 20% of cases [21,22] and is the most frequent indication for graftectomy [21]. Incidence of PVGT is increased by technical issues

such as harvesting method, preservation, cold ischemia time, donor and recipient characteristics, inflammatory factors, or coagulopathy and prophylactic anticoagulant administration [23,24]. In our cohort, the incidence of graft failure due to PVGT in association with COVID-19 was 20%. More observations need to be done to verify if COVID-19 increases the risk of PVGT, but some data suggests that COVID-19 patients are predisposed to PVGT [25,26]. A case of renal allograft late infarction in a 46-year-old COVID-19-positive recipient 13 years after kidney-pancreas transplant was reported [27].

CONCLUSIONS

The incidence of COVID-19 infection among pancreas recipients is similar to that of the general population, but immunosuppression and history of dialysis might increase the risk of death and serious complications. In our study, we did not observe an increased graft loss associated with SARS-CoV-2, but, in the general population, the infection is associated with thrombotic complications. There is a need for a multicenter analysis of solid graft recipients and the creation of guidelines regarding

referrals for hospitalization, immunosuppression modifications, and anticoagulants.

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