CASE REPORT

TITLE

Exacerbation of intimal fibrosis and endarteritis in a kidney transplant recipient with chronic active antibody-mediated rejection and COVID-19: A case report

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ABSTRACT

Kidney transplant recipients are immunocompromised hosts at risk for comorbidity and mortality due to infection. Currently there are no established guidelines for the management of immunosuppressed transplant recipients with Coronavirus disease 2019 (COVID-19). The impact of COVID-19 and its therapeutic management on chronic active antibody-mediated rejection (CAAMR) are still unclear. Here, we report a case of CAAMR exacerbation with endarteritis and intimal fibrosis after COVID-19. A 41-year-old female kidney transplant recipient with CAAMR was admitted to a local hospital with moderately severe COVID-19. Her doses of tacrolimus and mycophenolate mofetil were reduced, and she was administered methylprednisolone pulse and anti-viral drugs. This resulted in a good clinical course and she was discharged in 15 days. During and after hospitalization, the immunosuppressants were gradually returned to the baseline levels. However, about 1.5 months after discharge, the serum creatinine level became elevated. An indication kidney biopsy showed CAAMR with intimal fibrosis and endarteritis in all interlobular arteries. An increase of immunosuppressant led to a decrease of the serum creatinine level. Factors contributing to CAAMR with intimal fibrosis and endarteritis may include: (1) insufficient immunosuppression due to changes in the levels of immunosuppressive drugs, (2) overlap with endothelial cell injury caused by COVID-19, and (3) an immune-activated state

associated with COVID-19. COVID-19 is a life-threatening disease that can result in unexpected changes in immunological status. Possible allograft rejection should be carefully managed in such patients.

RUNNING TITLE

INTIMAL FIBROSIS IN CAAMR AND COVID-19

WORD COUNTS

Abstract: 237 words

Main body: 1563 words

KEYWORDS

Chronic active antibody-mediated rejection, Coronavirus disease 2019, Endothelial cell injury, Intimal fibrosis, Kidney transplantation

INTRODUCTION

During the coronavirus disease 2019 (COVID-19) pandemic, solid organ transplant recipients are at a risk of developing fatal COVID-19 due to their chronic immunosuppressive status(1). An immunocompromised status, primary chronic kidney diseases, and comorbidities such as hypertension and diabetes mellitus increase the risks of COVID-19 in kidney transplant recipients, who have a higher mortality rate than the general population (20 - 28% vs. 1 - 5%)(3). COVID-19 causes not only life-threatening respiratory failure, but also kidney damage including acute kidney injury (AKI), collapsing glomerulopathy, and thrombotic microangiopathy (TMA)(4). According to a recent systematic review, 44% of kidney transplant recipients with COVID-19 develop AKI and 8% develop graft loss(5). A common treatment strategy is reduction of immunosuppressive drugs, at the risk of increasing the likelihood of allograft rejection(6). Allograft biopsies are rarely performed for transplant recipients with COVID-19 because of the patient's poor general condition and in order to prevent the spread of the infection. There are 4 documented cases of chronic active antibody-mediated rejection (CAAMR)(4,7–9), but no reports detailing histological comparisons of CAAMR before and after COVID-19. Therefore, the impacts of COVID-19 and changes in the immunosuppressant regimen on CAAMR are still unclear. Here we present a case of CAAMR exacerbation manifested as

endarteritis and intimal fibrosis of the interlobular arteries after recovery from COVID-19.

CASE PRESENTATION

The patient was a 41-year-old Japanese woman who had undergone living donor kidney transplantation 8 years previously due to renal dysfunction after pregnancy. The donor was healthy 33-year-old man who was her husband. ABO blood type between them was compatible. The preformed donor specific antibody (DSA) was negative. She had a history of hypertension, dyslipidemia, and post-transplant diabetes mellitus. She had developed active antibody-mediated rejection with de novo DSA (HLA-DQ7) three years after transplantation. Six years after transplantation, histological examination revealed CAAMR (Banff 2019: g2, cg2, ptc1, i0, t0, v0, cv0, ct1, ci0, i-IFTA0, t-IFTA0, mm0, ah1, aah1, C4d0) which showed microvascular inflammation with double contour of glomerular basement membrane (Fig. 1). She had been maintained on immunosuppressants including tacrolimus (Tac) 5 mg daily, mycophenolate mofetil (MMF) 1000 mg daily, and methylprednisolone (mPSL) 4 mg daily. Tac trough level had been stable at 2.4-2.8 ng/mL. Although the serum creatinine (Cre) level had been stable at 0.6-0.8 mg/dL, the mean fluorescence intensity (MFI) of DSA remained at around 20,000. At six years and four months after transplantation, MFI of DSA against HLA-DQ7 was 21,900.

Seven years and seven months after transplantation, she became aware of cough and dyspnea. On the following day, she took a polymerase chain reaction (PCR) test at a local

hospital, which revealed positivity for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, and was admitted to a local hospital. Vital signs included a body temperature of 37.5 ℃, blood pressure 137/86 mmHg, pulse 115 bpm, and SpO2 97% (room air). Laboratory test results included white blood cells (WBC) 8000/μL, blood urea nitrogen (BUN) 16.3 mg/dL, Cre 1.16 mg/dL, and C-reactive protein (CRP) 2.44 mg/dL. A chest X-ray showed bilateral lung opacities in the lower fields, and computed tomography (CT) demonstrated ground grass opacities and consolidation in both lungs. She was diagnosed as having moderately severe COVID-19. The Tac dose was decreased to 3 mg daily and MMF to 500 mg daily, and favipiravir (FAV) was started (Fig. 2). However, respiratory symptoms and pneumonia worsened on admission day 6, necessitating administration of mPSL pulse, remdesivir (REM), and antibiotics. She recovered from COVID-19 on admission day 13, and Tac was increased to 5 mg/day. The patient was discharged on admission day 15. There was no clinical picture of AKI or TMA during admission, although the serum Cre level transiently increased to 1.44 mg/dL on admission day 4.

After discharge, she remained in good general condition with renal function at the baseline level although mPSL was gradually decreased to 4 mg daily. MMF was increased to 1000 mg on day 8 after discharge. After another month, however, the serum Cre level increased to

1.43 mg/dL and the patient underwent an indication kidney biopsy on day 44 after recovered from COVID-19. Histological examination revealed CAAMR (Banff 2019: g2, cg3, ptc0, i0, t1, v1, cv3, ct1, ci1, i-IFTA1, t-IFTA1, mm0, ah2, aah2, C4d0-1) with glomerulitis, double contour of glomerular basement membrane, and marked intimal fibrosis in all the interlobular arteries (Fig. 3). C4d was faintly deposited at only one peritubular capillary vessel by immunohistochemistry (Fig. 3a, inset) but not seen by immunofluorescence. Compared to the previous biopsy specimen, the degree of endothelial cell injury was more marked, being manifested as glomerular capillary occlusion due to inflammatory cell infiltration and endothelial cell enlargement, double contour of the glomerular basement membrane, segmental sclerosis with insudation, and arterial lesions. Although tubulitis within non-scarred cortex and t-IFTA which is defined as tubulitis within scarred cortex were seen, interstitial inflammation of cortex was minimal. There was no acute tubular injury, collapsing glomerulopathy, or thrombus. The MFI of DSA against HLA-DQ7 was 21,800 and no new DSA appeared, which was no significant change before and after COVID-19. At that time, her Tac trough level was 1.6 ng/mL. Finally, we suspected CAAMR exacerbation associated with the changes in the immunosuppressant regimen during COVID-19, and MMF was increased to 1500 mg daily with reference to therapeutic drug monitoring. The serum Cre level has since stabilized at around 1.3 mg/dL, and we

continue to follow up the patient closely.

DISCUSSION

In the present case of CAAMR exacerbation during recovery from COVID-19, changes in the immunosuppressive drug regimen may have activated CAAMR and associated endothelial cell injury, especially in interlobular arteries. Although we predicted that allograft rejection would worsen when Tac and MMF were reduced, we considered that drug reduction was necessary because COVID-19 can be life-threatening. We think that this decision was reasonable, and in fact COVID-19 was exacerbated during the patient's hospitalization. Although her serum Cre was temporarily reduced due to fluid replacement and rest during hospitalization, her serum Cre eventually increased further after discharge. When she developed renal dysfunction after discharge, we considered the possibility that COVID-19 may have affected the kidneys. However, this episode appeared after COVID-19 had resolved, and there was no histological evidence of AKI or collapsing glomerulopathy, which can appear in COVID-19. Therefore, we think that the main etiology was CAAMR activation.

Surprisingly, a small case series of kidney allograft recipients with COVID-19 found signs of rejection in 5/11 (45%) biopsies (11). To our knowledge, 10 cases of allograft rejection in patients with COVID-19 have been reported, including four cases of CAAMR(4,7–9), one case of active antibody-mediated rejection(4), five cases of T-cell-mediated rejection

(TCMR)(10,11), and one case of mixed rejection(11). Four of the TCMR cases showed endarteritis and/or intimal fibrosis, and one of the CAAMR cases showed mild intimal fibrosis. There have been no reports of endarteritis in CAAMR related to COVID-19. Compared with previous reports, the arterial lesions in the present case were more severe.

One interesting aspect of the present case was that the fibrous intimal thickening of the interlobular arteries was particularly severe. Three reasons for this can be suggested. First, the change in the immunosuppressant regimen might have worsened rejection. Although renal function and histology had been stable for the previous 3 years, the DSA had remained at an MFI of about 20,000, indicating potential activation of CAAMR. In addition, glomerulitis with capillary occlusion was clearly exacerbated, thus supporting the possibility of CAAMR progression. Second, endothelial cell injury due to COVID-19 may have been an overlapping condition. Recently, endothelial cell injury and/or vasculitis due to COVID-19 have been reported(12,13). In the kidney, endothelial cell injury encompasses a wide variety of features ranging from only endothelial cell enlargement and loss of fenestra on electron microscopy to clinicopathologically apparent TMA involving glomerular capillaries, glomerular hilar arterioles, and small arteries(4). Considering that arterial intimal fibrosis is edematous and not chronic fibrosis, contributing factors in the present case may have been not only chronic rejection, but also COVID-19 six weeks previously. Third, the immune-

activated state resulting from infection may have accelerated the rejection(14). There have been cases of COVID-19-induced de novo DSA in heart and kidney transplant patients (8,15). In addition, kidney allograft rejection can be associated with COVID-19 even if immunosuppressants are not reduced(11).

In solid organ transplant recipients with COVID-19, it is standard practice to reduce the dose of immunosuppressive drugs considering the risk of COVID-19 exacerbation. However, no appropriate immunosuppression adjustment protocol has yet been established. Recent research has shown that corticosteroids are advantageous for inhibiting the cytokine storm of COVID-19, and immunosuppressive agents such as calcineurin inhibitors (CNIs) and mammalian target of rapamycin (mTOR) inhibitors are effective in preventing SARS-CoV-2 replication in vitro(6). Thus, in the context of COVID-19, simple reduction of immunosuppression may not necessarily be beneficial for allograft recipients.

In conclusion, this is the first report to have described worsening of CAAMR with severe arterial lesions in an allograft recipient after COVID-19. We were unable to prevent CAAMR progression because it was not possible to predict the doses of immunosuppressants that would be needed in the abnormal immunological state associated with COVID-19. We hope that accumulation of further cases will clarify these relationships and aid the establishment of a suitable treatment strategy.

Statement of Ethics

This study was reviewed and approved by the Ethical Review Board of Hokkaido University Hospital, approval number 021-0009, and was conducted in accordance with the Helsinki Declaration. Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

The authors have no funding sources to declare.

Author Contributions

Takuya Otsuka, Tatsu Tanabe, and Takahiro Tsuji designed the study and prepared the manuscript. Tatsu Tanabe, Kiyohiko Hotta, Nobuo Shinohara, and Ayumu Takahashi were the physicians attending the patient and provided clinical information. Emi Takakuwa, Sari Iwasaki, Takahiro Tsuji, and Yoshihiro Matsuno supervised the histological examination and reviewed the manuscript.

Data Availability Statement

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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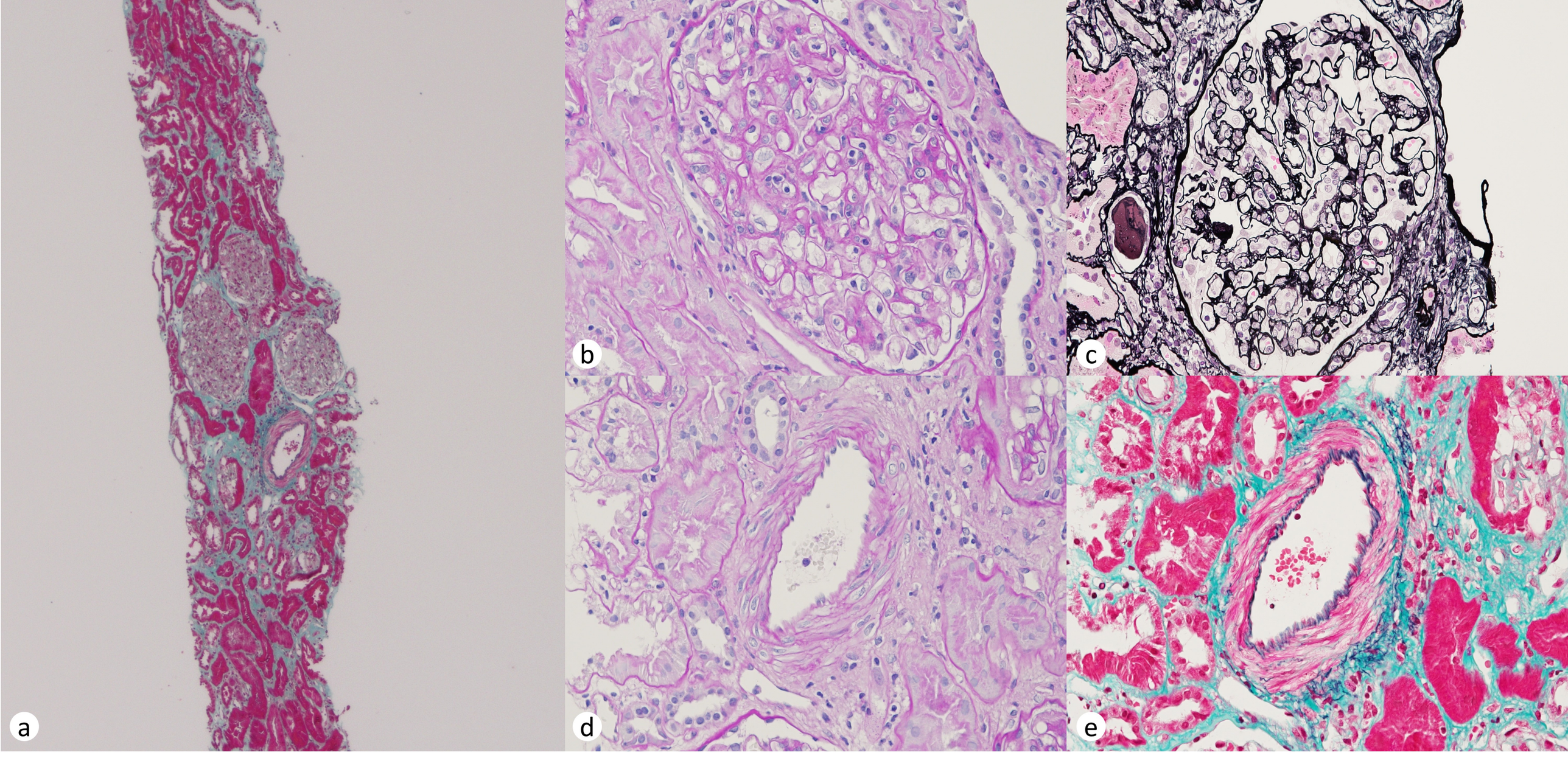
FIGURES & FIGURE LEGENDS

Fig. 1 CAAMR histology 2 years before COVID-19. (a) Low power view is shown (Elastica-Masson stain, ×100). (b) Glomerulitis with segmental endocapillary proliferation and mild endothelial enlargement are evident (PAS stain, ×400). (c) In addition to glomerulitis, segmental double contours of the glomerular basement membrane are evident (PAM stain, ×400). (d-e) There is no endarteritis or intimal fibrosis in the interlobular arteries (PAS and Elastica-Masson stain, ×400).

Fig. 2 Clinical course before, during and after admission for COVID-19. FAV; Favipiravir, REM; Remdesivir, CTRX; ceftriaxone, GRNX; Garenoxacin, mPSL; methylprednisolone, Tac; Tacrolimus, MMF; mycophenolate mofetil.

Fig. 3 CAAMR histology 1.5 months after COVID-19. (a) Low power view is shown (Elastica-Masson stain, ×100). C4d deposition was observed at only one peritubular capillary vessel (inset, immunohistochemistry). (b) Glomerulitis with global endocapillary proliferation and enlargement of endothelial cells is seen (PAS stain, ×400). (c) Double contour of the basement membrane has become global (PAM stain, ×400). (d-e) All interlobular arteries show marked intimal fibrosis, sometimes accompanied by endarteritis

(PAS and Elastica-Masson stain, ×400).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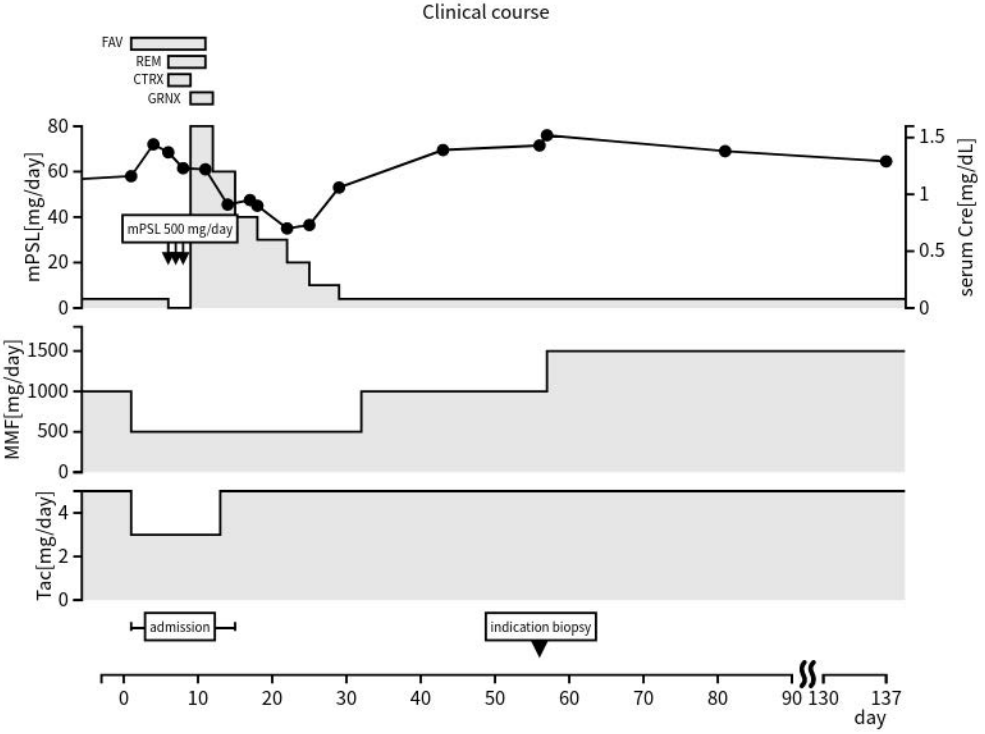
Clinical course
FAV
REM
CTRX
GRNX
mPSL[mg/day]
80
60
40
20
0
mPSL 500 mg/day
serum Cre[mg/dL]
1.5
1
0.5
0
MMF[mg/day]
1500
1000
500
0
Tac[mg/day]
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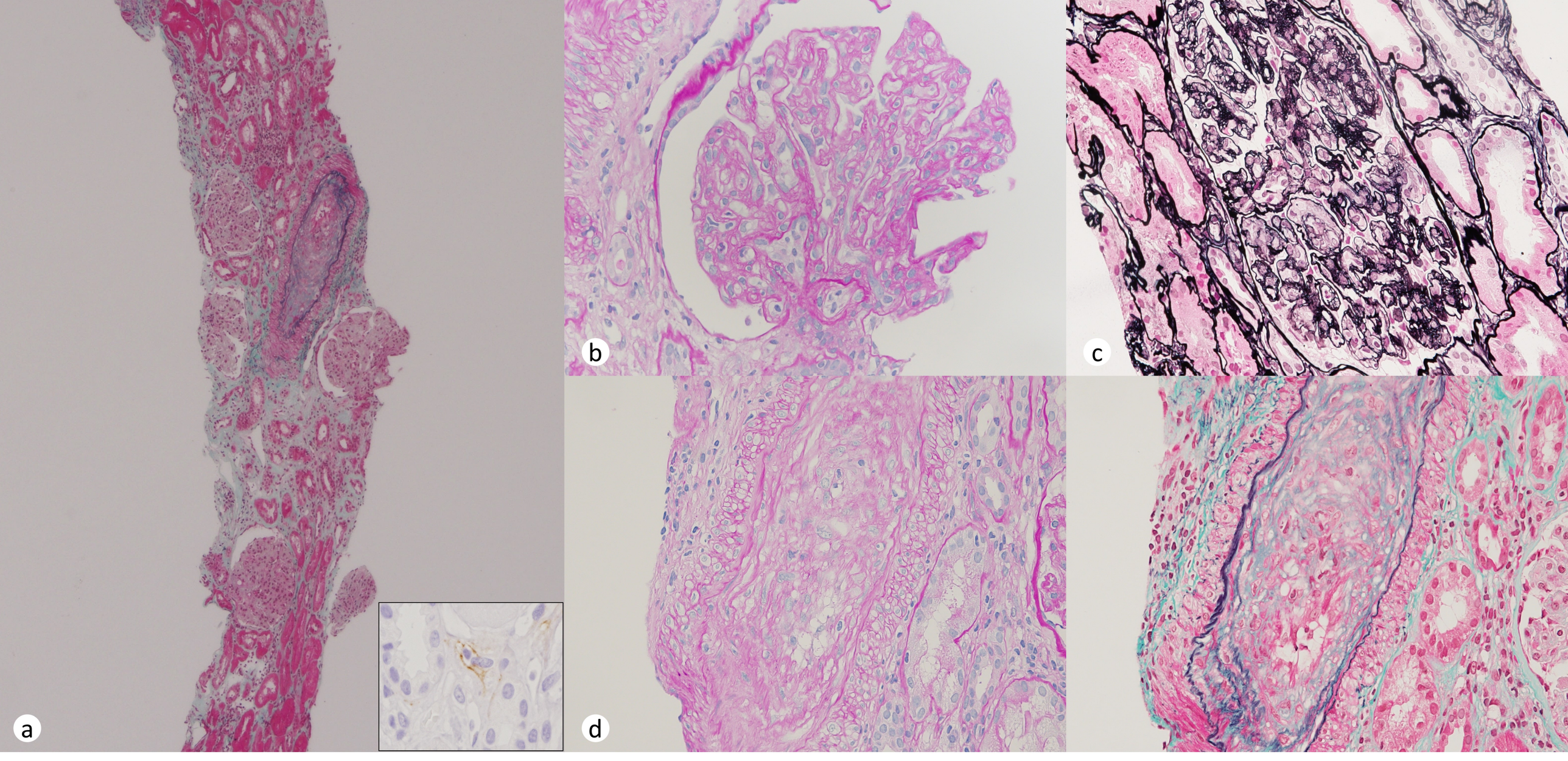
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