Clinical Case Report

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Suspected colonic cancer turns out to be disseminated tuberculosis in a kidney transplant recipient

A case report

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Abstract

Rationale: Active tuberculosis constitutes a relevant risk for kidney transplant recipients. In contrast to immunocompetent hosts, kidney transplant recipients often show atypical presentation and course of the disease impeding diagnosis. Especially extrapulmonary or disseminated infection is more frequent and can resemble malignant processes. However, reactivation of tuberculosis mostly develops within the early post-transplant course, whereas malignancies are predominantly long-term complications. We report a case of disseminated abdominal tuberculosis developing 10 years after kidney transplantation and review the underlying literature.

Patient concerns and diagnoses: A 51-year-old lady presented with epigastric pain, diarrhea, weight loss and night sweats 10 years after deceased-donor kidney transplantation. An epigastric as well as multiple peritoneal masses were found suspicious of a cancer of unknown primary. Colonoscopy revealed a colon tumor with the biopsy showing no dysplasia but histiocytic and granulomatous infiltration with acid-fast bacilli. Mycobacterium tuberculosis was detected in the biopsy and stool and disseminated abdominal tuberculosi was diagnosed.

Interventions and outcomes: With anti-tuberculosis therapy, the masses regressed, and all cultures became sterile, sparing graft function.

Lessons: This case emphasizes how variable and unspecific the presentation of tuberculosis in kidney transplant recipients may be and that tuberculosis constitutes a relevant risk also in the long-term post-transplant course.

Abbreviations: CAT = computed tomography, eGFR = estimated glomerular filtration rate, MDRD = Modification of Diet in Renal Disease, PCR = polymerase chain reaction.

Keywords: abdominal masses, colon tumor, kidney transplantation, peritoneal carcinomatosis, tuberculosis

1. Introduction

Infections such as tuberculosis as well as malignancies are 2 major complications after kidney transplantation. Despite screening and prophylaxis programs for kidney transplant candidates, the risk for primary or reactivation of latent tuberculosis is highly increased after transplantation. Depending on the geographic region, the incidence of active tuberculosis after kidney transplantation varies from 1% in developed and up to 15% in highly endemic countries.[1] Furthermore, the presentation and course of the disease differ significantly from that in immunocompetent hosts.[2] About 30% to 40% of tuberculosis after kidney transplantation are disseminated when diagnosed and involvement of extra-pulmonary organs is much more frequent than in immunocompetent hosts.[3,4] The most common extrapulmonary site is the gastrointestinal tract.[3] Symptoms of abdominal and gastrointestinal tuberculosis are often unspecific and include abdominal pain, loss of weight, and appetite, as well as fever.[5] Given these unspecific symptoms, abdominal tuberculosis is not always easy to distinguish from other abdominal diseases such as malignancies. Diagnosis is further challenged by the fact that tuberculin skin tests and interferon-gamma release assays have lower sensitivities in solid-organ transplant recipients.[6] However, reactivation of tuberculosis mostly develops within the early post-transplant course, whereas malignancies are predominantly long-term complications.[4,7–10]

Here we report a case of abdominal tuberculosis in a kidney transplant recipient resembling a metastatic colon cancer, which occurred in the long-term post-transplant course. We highlight the diagnostic challenge and review the underlying literature.

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Consent for publication: In her lifetime, the patient repeatedly signed for her approval of scientific workup and publication of her medical history.

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2. Case presentation

We report a 51-year-old woman who was admitted to our hospital 10 years after a deceased-donor kidney transplantation with epigastric pain, intermittent non-bloody diarrhea, undefined weight loss, and night sweats. She was born in the Philippines and moved to Germany as a young adult. The last oversea travel to the Philippines was 3 years ago and she denied any animal contact or intake of raw meat or unpasteurized milk. Her medical history was remarkable for end-stage renal disease of unknown origin with a 7-year hemodialysis therapy. No biopsy of the native kidneys was performed. The pretransplant screening status of latent tuberculosis is unknown and there was no history of malignancies. Her post-transplant course was complicated by 2 cellular borderline rejections within the first post-transplant year and subsequent impaired allograft function as well as anemia with iron deficiency. Her kidney function was stable with creatinine values at admission of approximately 2.1 mg/dL (estimated glomerular filtration rate [eGFR] 30 mL/min MDRD). Current medication included cyclosporine (80 mg twice per day, target levels 50 to 70 ng/mL), mycophenolic acid (360 mg twice per day), prednisolone (5 mg once per day), fluvastatin, and oral iron. The patient was in good general condition; physical examination only revealed epigastric tenderness on palpation. Laboratory testing was evident for microcytic and hypochromic anemia (hemoglobin 10.6 g/dL) as well as elevated levels of white blood cells (23.4×10^3 cells/μL), lactate dehydrogenase (677 U/L), C-reactive protein (165 mg/L), and creatinine (2.6 mg/dL).

The patient developed low-grade fever and urine microscopy was positive for bacteria and white blood cells. A urinary tract infection was assumed, and antibiotic therapy initiated. The fever ceased but urinary culture only showed *Escherichia coli* in nonrelevant counts. An abdominal ultrasound was evident for an epigastric hyperechogenic mass infiltrating the pancreas and a subsequent computed tomography (CAT) scan revealed multiple peritoneal lesions. A tumor in the right adrenal gland was described as well as enlarged retroperitoneal lymph nodes highly susceptive for a malignant process of unknown origin (Fig. 1A). A chest CAT scan showed no pulmonary abnormalities. Further endoscopic evaluation found an exophytic and ulcerating tumor in the right transverse colon and a metastatic colon cancer was suspected (Fig. 1B). Surprisingly, the pathological result of the biopsy taken from the colonic mass showed no dysplasia but a histiocytic and granulomatous infiltration (Fig. 2A). Acid stains detected mycobacteria and finally mycobacterium tuberculosis was identified by polymerase chain reaction (PCR) and culture (Fig. 2B). Further analysis also revealed positive tests for mycobacterium tuberculosis in the stool and sputum. All other specimens were negative for acid-fast staining and cultures, but PCR for mycobacterium tuberculosis was positive in urine and blood. Disseminated tuberculosis was diagnosed and a therapy with rifampicin, isoniazid, pyrazinamide, and ethambutol was initiated. Immunosuppressive therapy was reduced as mycophenolic acid was stopped and cyclosporine was reduced to through levels of 25 to 45 ng/mL, prednisolone was increased to 15 mg/day in compensation.

Owing to liver toxicity with highly elevated liver function tests pyrazinamide had to be stopped and therapy was continued with rifampicin, isoniazid and ethambutol. Although all cultures became sterile after 1 month, a follow-up CAT scan showed persistent abdominal masses. Thus, triple therapy was extended to 3 months. A subsequent CAT scan showed remission of the abdominal masses and the kidney transplant function improved to a creatinine of 1.7 mg/dL at discharge (eGFR 39 mL/min MDRD). Also, anemia improved, and white blood cell count as well as lactate dehydrogenase decreased to normal range. Immunosuppressive therapy was slightly increased as mycophenolic acid was resumed at 180 mg twice per day, cyclosporine was continued with target levels of 30 to 50 ng/mL and prednisolone given at 5 mg/day. The patient was discharged, and intensive antibiotic therapy was followed by 8 months of rifampicin and isoniazid.

One year later, the patient was hospitalized again and died of severe cytomegalovirus pneumonia. All tests and cultures for mycobacterium tuberculosis were negative at that time.

3. Discussion

Reactivation of latent and primary tuberculosis constitutes serious risks for immunosuppressed hosts such as kidney transplant recipients.[11] The exact frequency of active tuberculosis in kidney

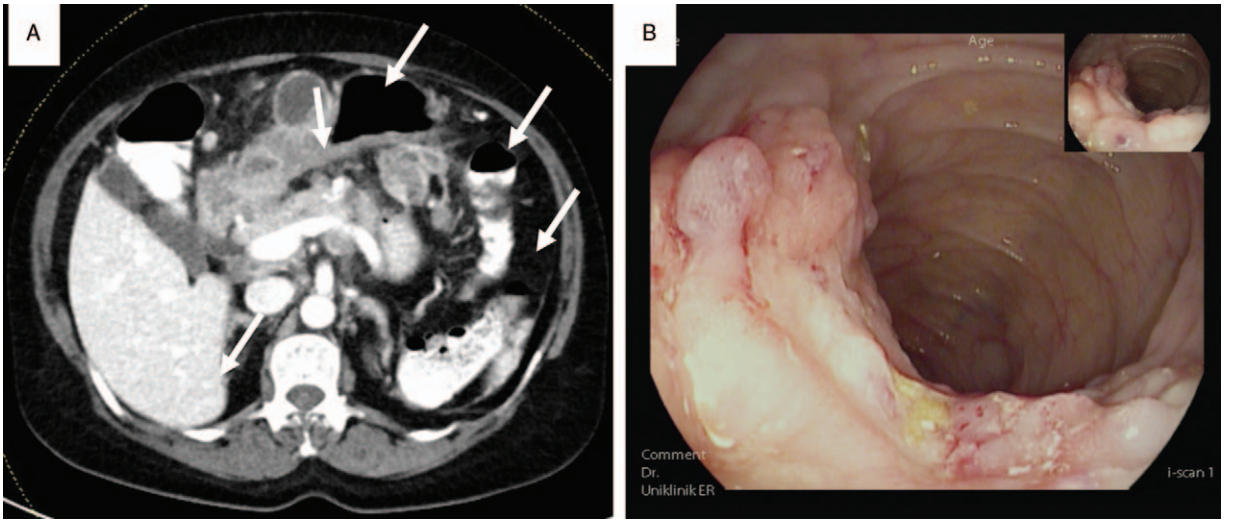

Figure 1. (A) Abdominal computed tomography scan showing multiple peritoneal lesions (white arrows) highly suspicious for a malignant process of unknown origin. (B) Colonoscopy showing an exophytic and ulcerating tumor in the right transverse colon.

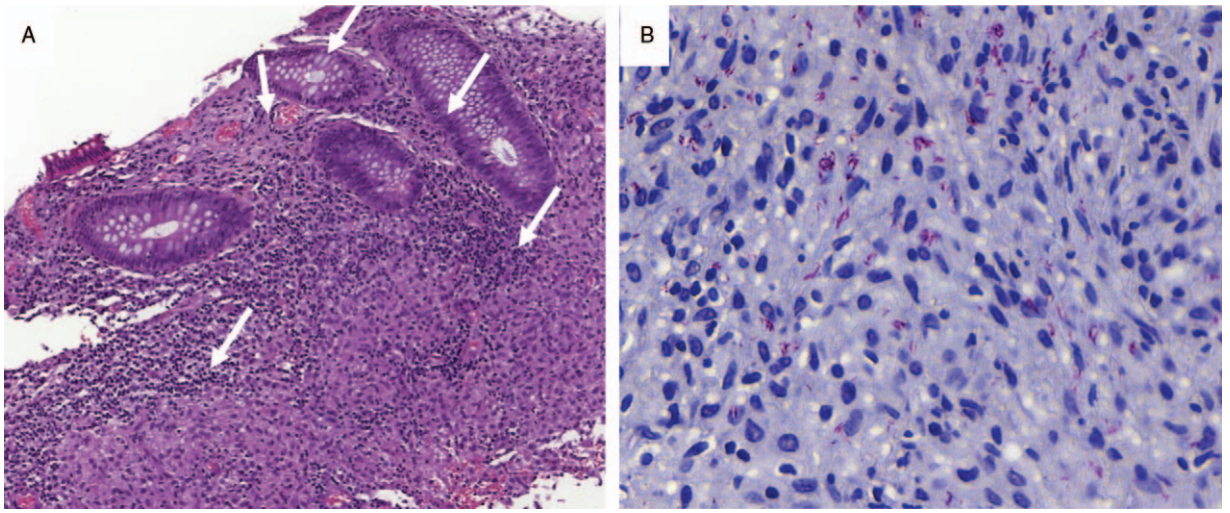

Figure 2. Colon biopsy. (A) Hematoxylin and eosin stain showing an ulcerating granulomatous inflammation (white arrows); original magnification 10×. (B) Ziehl-Neelsen stain revealing bright red acid-fast mycobacteria; original magnification 40×.

or other solid organ recipients is not well known and highly depends on the geographical tuberculosis prevalence.[3,12] Older studies suggest a 20- to 70-times increased risk of active tuberculosis for solid organ recipients compared to the general population.[3] A more recent meta-analysis found a prevalence of 0.6% in kidney transplant recipients from low prevalence countries, which translates into a 56-times increased absolute risk over the general population.[12] The risk for tuberculosis increases with the intensity of immunosuppression. Thus, previous rejections and coexisting infections such as cytomegalovirus or pneumocystis pneumonia infections are associated with an elevated risk for tuberculosis.[13] As different regimens, such as tacrolimus and cyclosporine-containing therapies, have been linked to the onset of tuberculosis it remains unclear which exact immunosuppressive regimen has the lowest risk for the development of active tuberculosis.[14,15] However, additional T-cell-depleting drugs certainly increase the risk.[13]

Diagnosis of active tuberculosis in transplant recipients is complicated, as presentation is often atypical and unspecific. Whereas pulmonary tuberculosis is less frequent as compared to nontransplant recipients, extrapulmonary infection is more common. Disseminated disease is found in up to one-third of kidney transplant recipients.[4,16] Although fever occurs in as much as 70%, other symptoms such as weight loss and weakness are only present in <50% of kidney transplant recipients.[4] This is even more accentuated for abdominal tuberculosis where unspecific symptoms like abdominal pain, loss of weight, and appetite are the most common symptoms.[5] Therefore, the time from suspicion to diagnosis of tuberculosis is thus significantly longer in kidney transplant recipients compared to non-kidney transplant recipients.[16] The symptoms as well as the radiologic or endoscopic presentation of abdominal tuberculosis can resemble that of malignancies so that distinguishing between these entities is difficult and diagnosis commonly requires biopsies as illustrated in this case. As tuberculosis mostly occurs in the early post-transplant course and malignancies are predominantly late-course complications, the timing might help to distinguish between these diseases. However, this case shows that tuberculosis can also occur many years after transplantation.

Most cases of post-transplant tuberculosis are thought to be owing to reactivation of latent tuberculosis.[11] This is supported by the fact that most cases occur within the first year after transplantation.[2] Thus, prevention with screening and treatment of latent tuberculosis is a key feature in impeding post-transplant tuberculosis. The American Society of Transplantation Guidelines as well as the European Best Practice Guidelines recommend screening all transplant candidates and consider prophylactic treatment upon positive results and risk factors.[17,18] However, screening is impaired by low sensitivities and specificities of available test in immunocompromised hosts. For hemodialysis patients, testing with interferon gamma release assays show 50% and the tuberculin skin test only 31% sensitivity.[19] Although prophylactic treatment is very effective in preventing early-onset tuberculosis, the underlying studies only had short follow-ups so that the long-term effectiveness is unknown.[20] In our case, active tuberculosis occurred 10 years after kidney transplantation, which is rather unusual. Although the screening history is unknown, and a new-onset infection cannot be excluded, the patient's origin, history, and presentation point toward a reactivation of latent tuberculosis. Perhaps regular testing of latent tuberculosis after transplantation as recommended for patients with ongoing risk factors for tuberculosis, such as those receiving biologicals for rheumatoid arthritis, could have identified active tuberculosis at an earlier stage.[21]

Furthermore, the therapy in kidney transplant recipients is complicated by drug–drug interactions with immunosuppressive agents and is associated with the development of rejections.[11,22] Owing to the difficulties in diagnosis and treatment, the mortality of active tuberculosis in renal transplant recipients is still 6% to 10%[4,15] with about 15% graft loss and a median GFR decrease of 10 mL/min during therapy.[23] In our case, the kidney transplant function even improved with therapy. This can partially be attributed to the reduction in cyclosporine doses but might also be because of renal involvement of tuberculosis,[24] which is supported by the sterile pyuria.

In conclusion, this case demonstrates the variable and unspecific presentation of tuberculosis in kidney transplant

recipients with its challenging diagnosis and illustrates that tuberculosis also constitutes a relevant complication in the later post-transplant course.

Author contributions

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