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### Fever in a kidney transplant recipient: No Facts and Many Interactions

### Fiebre en un receptor de trasplante renal: ninguna evidencia y muchas interacciones

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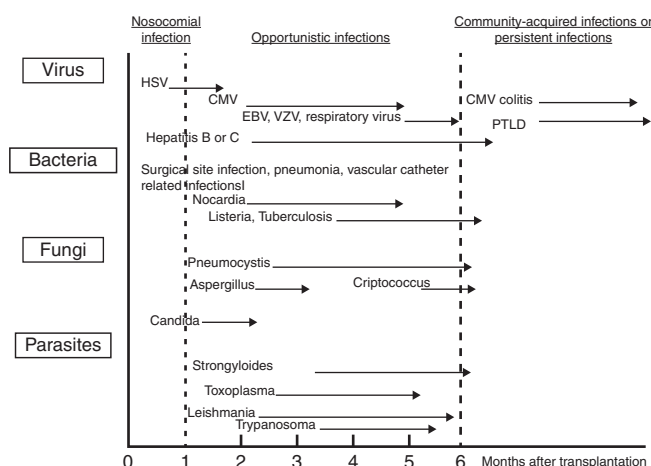
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A 69 year-old woman was admitted to hospital due to fever. She was from the South of Morocco and had been living in Spain for four years. She had a ten-year medical history of hypertension and type 2 diabetes mellitus. Nine months before admission, she received a kidney allograft from a deceased donor, due to end-stage renal disease.

The most common cause of fever in renal transplant patients is infection. However, many other factors may be responsible, such as allograft rejection, drug hypersensitivity, and malignancy. Acute rejection occurs more frequently during the first six months after transplantation. Post-transplant lymphoproliferative disorders (PTLD) occur mainly within the first year. Most infections after transplantation occur on a relatively consistent timeline, reflecting the interplay of risk factors and the net state of immunosuppression. The majority of infections occurring later than six months after transplantation are basically the common community-acquired infections encountered in patients with chronic conditions (Fig. 1). Urinary infection is frequent, especially in diabetic women. Other late manifestations may represent reactivated or chronic viral infections, particularly



**Figure 1** Chronology of infections after solid organ transplantation. Adapted from Fishman JA<sup>2</sup>. HSV – herpes simplex virus; CMV – cytomegalovirus; EBV – Epstein-Barr virus; VZV – varicella-zoster virus; PTLD – posttransplant lymphoproliferative disorders.

cytomegalovirus (CMV). Finally, patients with acute or chronic rejection and over-immunosuppression are at high risk of life-threatening infection by opportunistic pathogens.

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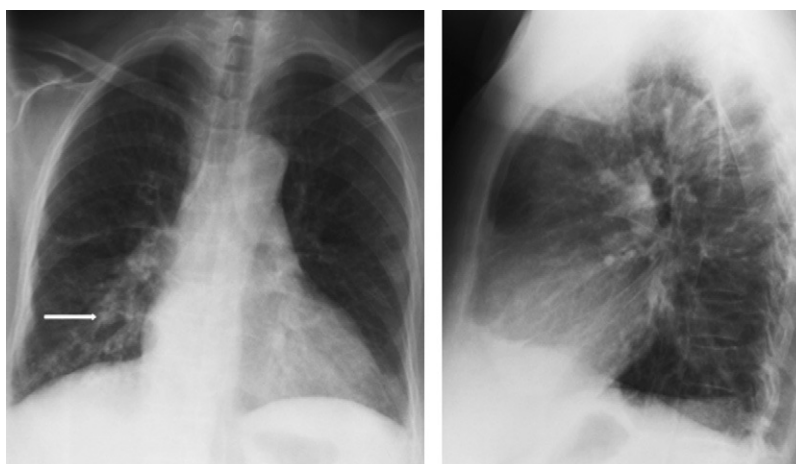


Figure 2 Chest radiography showing a right lower lobe infiltrate (arrow).

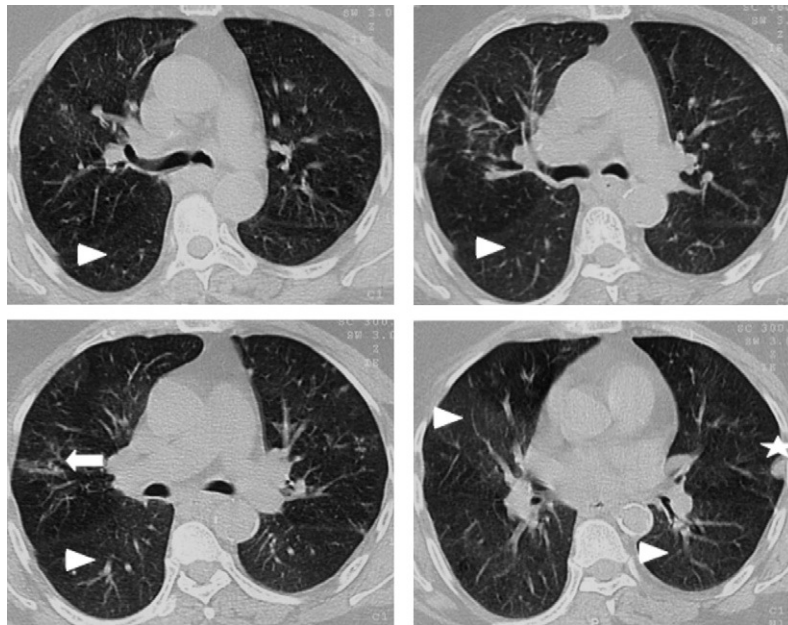
Pretransplant anti-HLA panel reactive antibodies were 52%. She was seropositive for CMV. Immunosuppression comprised tacrolimus, mycophenolate mofetil and steroids. Prophylaxis with intravenous cefuroxime (2 days), oral cotrimoxazole (9 months), and intravenous ganciclovir (10 days), followed by oral valganciclovir (3 months) was administered. At hospital discharge creatinine clearance was 71 mL/min. Four months after transplantation, a biopsy-proven acute vascular rejection (grade IIB according to the Banff classification) was established. It was successfully treated with thymoglobulin, six sessions of plasmapheresis, and human polyvalent immunoglobulin. The patient developed several infections, including *Escherichia coli* lower urinary tract infection, varicella-zoster virus (VZV) monometameric cutaneous infection and a viral syndrome due to CMV. At discharge, her creatinine clearance was 50 mL/min.

Given that pre-transplant panel reactive antibodies were above 50%, this patient should be considered as having high immunological risk. Although the presence of donor-specific antibodies and C4d staining in the biopsy is not mentioned, the information available suggests that she suffered from an acute antibody-mediated rejection. Despite being successfully treated, this episode of acute rejection reduced the glomerular filtration rate by 21 mL/min. Moreover, during admission there were infections related to immunosuppression, namely VZV cutaneous infection and a late CMV viral syndrome. CMV has been shown to raise rates of allograft rejection and other opportunistic infections. The current fever episode could be due to recurrence of acute humoral rejection or, either alternatively or concomitantly, to complications related to over-immunosuppression, mainly PTLD and infection. My infectious disease differential diagnosis includes CMV reactivation, tuberculosis and other opportunistic infections. I would inquire about the results of screening for latent tuberculosis infection prior to transplantation and findings on chest radiography.

On admission, examination showed the patient to be severely ill. Axillary temperature was 39°C and blood pressure was 150/80 mmHg. Pulmonary auscultation revealed mild bibasal crackles. The rest of the physical examination was unremarkable. Hematological

laboratory tests showed hemoglobin 13 g/dL, white-cell count 2,600 per mm<sup>3</sup> (neutrophils 76%, lymphocytes 10%), and platelets 132,000 per mm<sup>3</sup>. Abnormal serum laboratory results were creatinine 2.5 mg/dL and lactate dehydrogenase 399 U/L (normal range, 90-230 U/L). Figure 2 shows the patient's chest radiography. An abdomen ultrasound revealed atrophic native kidneys, without any other pathologic findings, even in the renal allograft. Urine culture grew *E. coli* (>10<sup>5</sup> colony-forming units/mL). Despite antibiotic treatment for urinary infection, the patient remained febrile and her general condition worsened.

The presence of fever and creatinine increase raises the possibility of a new acute rejection episode. However, the information provided is more suggestive of a renal dysfunction due to poor clinical condition. Rather than a urinary infection, the lack of response to antibiotic therapy suggests *E. coli* asymptomatic bacteriuria, which is common in women with diabetes mellitus and patients with kidney transplant. The chest radiography showed a right lower lobe infiltrate, associated with a pleural reaction, and some small-calcified lesions. The concurrence of high fever, a lung infiltrate and crackles heard during auscultation suggests that the patient may have a pulmonary infection. The absence of lymphadenopathies on both chest radiography and abdominal ultrasound makes the diagnosis of PTLD unlikely. The chest radiological pattern would be unusual for *Pneumocystis jiroveci* pneumonia and, since the patient was receiving cotrimoxazole prophylaxis, this diagnosis can be ruled out. Although leukopenia may be drug-related, the occurrence of CMV viremia should be ruled out by antigenemia or polymerase chain reaction (PCR). The finding of calcified lesions on chest radiography may indicate past tuberculosis infection. In this regard, the possibility of tuberculosis reactivation should be strongly considered. Other conditions that should be ruled out include nocardiosis and fungal infection, especially aspergillosis. The two latter infections frequently cause pulmonary nodules that are not observed on chest radiography. Nevertheless, a computed tomography (CT) of the chest could be useful to identify lesions missed on plain radiography. At this juncture, it would be appropriate to perform a bronchoscopy with bronchoalveolar lavage



**Figure 3** Computed tomography of the chest showing a patchy airspace consolidation in the medium field of the right lung (arrow), centimetric nodules (star), and a tree-in-bud bilateral pattern with small centrilobular nodules (arrow heads).

(BAL). Samples should be submitted for direct microscopic examination, cytological analysis, galactomannan detection, and bacterial, viral, fungal, and mycobacterial cultures. Moreover, blood, urine, and stool samples should be obtained and processed for specific mycobacterial cultures.

Blood cultures were repeatedly negative. CMV antigenemia was also negative. Three sputum and urine specimens were negative for acid-fast bacilli. A tuberculin skin test (TST) was nonreactive. Fundoscopic examination was normal. The patient developed a progressive respiratory failure, precluding bronchoscopy with BAL. Thoracoabdominal CT was performed. Figure 3 shows chest CT findings. CT revealed no significant abdominal abnormalities.

The negativity of several blood cultures provides further evidence against the presence of bacterial infections. In addition, the negative antigenemia makes the diagnosis of CMV disease unlikely. CT of the chest shows a patchy airspace consolidation in the medium field of the right lung, some calcified mediastinal small nodules, two centimetric nodules, and a tree-in-bud bilateral pattern with small centrilobular nodules. Both the clinical picture and CT findings are suggestive of endobronchial spread of *Mycobacterium tuberculosis*, although the diagnosis of aspergillosis cannot be totally ruled out. As the sensitivity of acid-fast bacilli sputum and urine smears is low, the negativity of these tests does not rule out tuberculosis. Similarly, it is well known that TST has a low efficacy due to false-negative results after transplantation. At this point, in a patient with progressive respiratory failure, I would perform a percutaneous CT-guided needle aspiration of the left lung subpleural nodule. The samples should be properly processed. Meanwhile, I would start antituberculosis treatment and voriconazole to cover *Aspergillus*. Voriconazole dose should be adjusted to obtain trough levels within the therapeutic range (1 to 5.5 mg/L). Close monitoring of the

levels of immunosuppressive drugs is important due to the significant risk of pharmacokinetic interactions.

Empirical antituberculosis treatment with isoniazid, rifabutin, pyrazinamide and ethambutol was initiated. Double dose of tacrolimus was administered. The patient became afebrile in two days. Her general clinical condition also presented a significant improvement, meaning that a bronchoscopy with BAL could be performed. Cytological analysis was negative for malignant cells. Gram and acid-fast staining as well as bacterial and viral cultures were negative in BAL smears. Toluidine blue staining for *P. jiroveci* was negative. PCR test for *M. tuberculosis* was also negative. BAL culture grew *Aspergillus terreus*.

Isolation of *A. terreus* from BAL has a high predictive value for invasive infection in severely immunocompromised patients. Invasive aspergillosis is an uncommon but extremely serious complication in renal allograft recipients. Prompt administration of appropriate antifungal therapy is essential to a successful outcome, as is reduction of the overall level of immune suppression, particularly corticosteroids. Most isolates of *A. terreus* are resistant *in vitro* and *in vivo* to amphotericin B. Therefore, an antifungal triazole such as voriconazole should be used. The negativity of acid-fast bacilli smear and PCR results from BAL does not rule out the diagnosis of active tuberculosis. Dual infection is not uncommon among immunocompromised hosts with pulmonary infiltrates. Interestingly, the patient became afebrile and her clinical condition improved soon after antituberculosis treatment was initiated. In this patient from a developing country, I would be concerned about the possibility of drug-resistant tuberculosis. So, pending the results of the Löwenstein culture and susceptibility tests, I would maintain the four-drug antituberculous therapy. I am particularly worried about pharmacokinetic interactions and nephrotoxicity. Isoniazid is a CYP3A4 inhibitor and may increase tacrolimus exposure. Rifabutin, like rifampin,

induces CYP3A4 and decreases tacrolimus levels, although rifabutin is a less potent inducer of microsomal P450 enzymes. In any case, as the net effect favors rifabutin, it is advisable to increase the tacrolimus dose and to monitor blood levels closely. Voriconazole is a CYP3A4 inhibitor. It has been suggested that when voriconazole is initiated, the tacrolimus dose should be reduced by 50%. Therefore, I would adjust rifabutin, pyrazinamide and ethambutol doses to renal function and I would monitor tacrolimus blood level twice a week. I would also maintain a degree of hydration sufficient to prevent hyperuricemia-induced renal dysfunction.

The patient remained afebrile and her respiratory function improved progressively. Oral steroids were tapered. Due to the favorable clinical response, treatment with four antituberculosis drugs was maintained. Serum testing for galactomannan antigen was repeatedly negative. Caspofungin was started due to the suspicion of an invasive infection caused by *A terreus*. Despite the increase in tacrolimus dose, the blood level of this drug was 3 ng/mL 6 days after the start of antituberculosis treatment. Serum creatinine level increased to 4 mg/dL and creatinine clearance fell to 16 mL/min.

Galactomannan testing has been demonstrated to be a useful tool for early diagnosis of invasive aspergillosis in neutropenic patients. The performance characteristics of serum galactomannan assay are less well defined in other populations. In solid organ transplant (SOT) recipients the sensitivity of the test is about 50%. Therefore, the repeatedly negative galactomannan result would not change my decision to administer antifungal therapy to this patient. Caspofungin is approved for use in patients with probable or proven invasive aspergillosis that is refractory to or intolerant of other therapies. Caspofungin is usually well tolerated and has fewer drug interactions than voriconazole. Nevertheless, it can reduce the area under the curve of tacrolimus by ~20%. On the other hand, inducers of drug clearance such as rifabutin may significantly reduce caspofungin concentrations.

Differential diagnosis of acute renal allograft dysfunction in this patient may be broad, taking into account the limited data available. Clinical information of urinary volume and weight gain in combination with analytical data in serum and urine would be useful. In the absence of fever and urinary symptoms, bacterial pyelonephritis may be practically ruled out. Antituberculosis therapy may be a cause of interstitial nephritis in native kidney although it is only rarely described in renal recipients receiving concomitant steroid treatment. Pyrazinamide-related hyperuricemia may cause renal dysfunction. Low tacrolimus levels and concomitant steroid dose reduction may put this patient at risk to acute rejection. Therefore I would promptly increase the tacrolimus dose and carefully review clinical and analytical data.

Daily dose of tacrolimus was increased. Pyrazinamide was discontinued because of creatinine clearance below 20 mL/min. Levofloxacin was added to the antituberculosis treatment. A new bronchoscopy with transbronchial biopsy of one of the nodular lesions was performed. The histological examination showed a negligible amount of lung parenchyma without abnormalities. Neither granulomas nor filamentous fungi were observed. Serum creatinine level decreased to 1.9 mg/dL. Blood levels of tacrolimus were maintained between 9 and 12 ng/mL.

Thereafter, the following liver function test abnormalities appeared: total bilirubin 2.27 mg/dL (normal range, 0.20-1.10); aspartate aminotransferase 807 U/L (normal range, 5-45); alanine aminotransferase 225 U/L (normal range, 5-45); alkaline phosphatase 660 U/L (normal range, 40-130);  $\gamma$ -glutamyl transpeptidase 362 U/L (normal range, 8-61). The patient was asymptomatic and receiving steroids, tacrolimus, mycophenolate mofetil, caspofungin, isoniazid, rifabutin, ethambutol, and levofloxacin.

The improvement of renal function after pyrazinamide discontinuation suggests that pyrazinamide-related hyperuricemia was the most likely cause of the renal dysfunction. More importantly, liver function test results suggest severe antituberculosis drug-induced hepatotoxicity. Isoniazid is a well-known cause of liver injury during antituberculosis treatment. Moreover, the patient had been receiving pyrazinamide, which has increasingly been recognized as a significant cause of hepatotoxicity. Rifabutin is associated with a lower potential for hepatotoxicity than isoniazid or pyrazinamide. For their part, levofloxacin and particularly ethambutol rarely cause liver injury. Hepatotoxicity is the most serious adverse effect of antituberculosis treatment and can be a life-threatening complication. Therefore, at this point, I would immediately stop all the antituberculosis drugs and closely monitor tacrolimus levels. When alanine aminotransferase returns to less than twice the upper limit of normal, I would restart the antituberculosis drugs one at a time; first ethambutol, second levofloxacin, and finally rifabutin. While awaiting the results of the Löwenstein culture, I would not administer isoniazid and pyrazinamide, since these drugs are the most frequently associated with hepatotoxicity.

Treatment with isoniazid and rifabutin was stopped and pyrazinamide was reinitiated. The patient's general condition improved greatly and she was able to walk around the ward without any help. A few days later she was discharged. Although the diagnosis of tuberculosis was not microbiologically documented, treatment with ethambutol, levofloxacin and pyrazinamide was maintained. As rifabutin was no longer administered, oral voriconazole was given instead of caspofungin. Tacrolimus dose was adjusted appropriately.

Taking into account the fever resolution and the clear improvement on clinical condition, it is reasonable to maintain antituberculosis treatment and antifungal therapy while awaiting the final microbiological results. However, I would reintroduce rifabutin instead of pyrazinamide. First, at the usual doses, rifabutin hepatotoxicity is uncommon. Second, the absence of any disproportionate increase in bilirubin and alkaline phosphatase in liver function tests argue against rifabutin hepatotoxicity. Third, a regimen containing neither isoniazid nor a rifamycin should be administered for at least 18-24 months to lessen the risk of relapse. Introduction of voriconazole will increase tacrolimus exposure and put this patient at risk of calcineurin inhibitor-related hyperuricemia and acute nephrotoxicity. Thus, the tacrolimus dose should be reduced and its levels carefully monitored.

One month after the first bronchoscopy was performed, the BAL sample grew *M. tuberculosis* susceptible to all antituberculosis drugs. Treatment with voriconazole was discontinued. The patient completed a total of 18 months



under triple antituberculosis treatment. A new CT, 60 days after admission, revealed resolution of lung infiltrates. Liver enzymes remained within the normal range for the rest of the treatment period. Serum creatinine remained stable around 1.5 mg/dL and creatinine clearance remained around 50 mL/min. After 3 years of follow-up the patient remains in good health.

## Commentary

Tuberculosis is one of the most significant opportunistic infections affecting SOT recipients.<sup>1,2</sup> Toxicity of the treatment and interactions with immunosuppressive drugs makes clinical decisions very difficult in this context.<sup>3,4</sup> Clinicians in charge of this patient had to adopt challenging decisions before they had a microbiologically confirmed diagnosis. First one was to initiate empirical antituberculous treatment based on suggestive clinical, epidemiological and radiological data. In Spain,<sup>3</sup> the incidence of tuberculosis in renal transplant recipients has been estimated to be 358 cases per 10<sup>5</sup> per year, but much higher figures have been reported in developing countries.

The second crucial decision was to continue antituberculous treatment based on clinical response, despite microbiological preliminary results were against this diagnosis (negative tuberculin PPD test, negative PCR and negative acid-fast stain). As the discussant pointed out, in some cases the diagnosis of tuberculosis is made solely on the basis of respond to therapy<sup>5</sup>. This choice was even harder to adopt because the available microbiologic results pointed to other life-threatening opportunistic infections such as aspergillosis. Although the isolation of *A. terreus* from BAL cannot discriminate between colonization and infection, it has a high predictive value for invasive disease in immunocompromised hosts. The patient fulfilled criteria for probable invasive fungal disease according to revised definitions.<sup>6</sup> The decision to initiate an empirical treatment<sup>7</sup> must be based on the probability of the infection, its severity and the therapeutic threshold of the treatment. In this scenario, it was considered prudent to initiate antifungal treatment despite the clinical respond to empirical antituberculous treatment. The patient presented a high risk for hepatotoxicity of antituberculous drugs<sup>8</sup> and for difficult to manage interactions between first choice antituberculous,<sup>4,9</sup> antifungal<sup>10</sup> and immunosuppressive drugs.

The third clinically relevant decision was to adjust treatment when adverse effects and interactions developed. In this clinical context the treating physicians were dealing not only with the possibility of two severe opportunistic infections, but with the necessity of preserving the allograft,

given the poor prognosis of elderly patients under dialysis. Once the decision of initiating an empirical treatment has been adopted, the development of adverse effects or interactions should be a criterion to search for the most beneficial combination of drugs, rather than to taper off them.

In conclusion, despite continuing improvements in microbiological and imaging methods, clinicians still have to face puzzling cases in which therapeutic decisions have to be based on the clinical respond to drug administration. Maintaining this decision, despite side effects of the drugs administered, might be the key for a favorable outcome.

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