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Case report

Mycobacterium Tuberculosis Associated Immune Reconstitution Inflammatory Syndrome in a Renal Transplant Patient

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Abstract

Introduction. Solid organ transplant (SOT) recipients are at an increased risk of developing reactivation of a latent Myobacterium Tuberculosis (MTB) infection or primary infection. MTB infections in this patient group follow a more aggressive extrapulmonary course and can present with atypical symptoms. Immune reconstitution inflammatory syndrome (IRIS) is a pathological inflammatory response to a pathogen that paradoxically occurs after initiating treatment for an underlying infection. Classically, MTB associated IRIS is a known complication of highly active antiretroviral therapy (HAART) treatment in HIV patients. However, current reports indicate an increased risk for IRIS in solid organ transplantations.

Case Report. Here we describe a case of a deceased donor renal transplant recipient who developed extrapulmonary MTB and subsequently IRIS from antimycobacterium treatment.

Conclusion. IRIS is becoming more prevalent in the setting of SOT with MTB. Physicians should keep a high level of clinical suspicion if a patient begins to paradoxically deteriorate after initiating therapy.

Keywords: tuberculosis, IRIS, kidney transplant, extrapulmonary tuberculosis, immunosuppression

Introduction

Immune reconstitution inflammatory syndrome (IRIS) is a dysregulated inflammatory response that causes a paradoxical worsening of symptoms, signs and radiologic findings after treating an infection in an immunocompromised patient [1]. It is most commonly elicited by MBT with an estimated prevalence ranging from 8 to 43% [2]. Numerous literature studies describe this process occurring in advanced HIV patients with MTB after receiving HAART, causing significant morbidity and mortality [1,3,4]. However, there have been limited reports detailing IRIS related MTB in other immunocompromised states such as SOT [5]. Still, IRIS is a poorly understood condition with ambiguous diagnostic criteria in SOT, leading to delays in diagnosis with unnecessary diagnostic tests and treatment modifications.

Case Report

Our patient, a 71-year-old Croatian female with end-stage renal disease of unknown etiology was treated with hemodialysis in 2004 before receiving a kidney transplant from a deceased donor in 2007. She was discharged on an immunosuppressive therapy consisting of cyclosporine (Sandimun Neoral®), mycophenolate mofetil (Cellcept®), and prednisone (Decortin®), with a serum creatinine of 108 μmol/L. Until present symptoms, the patient had been treated for urinary tract infections.

The patient was transferred to our hospital in Zagreb after spending 3 weeks at her local hospital for suspected E.coli. urosepsis and prescribed meropenem. The presenting signs and symptoms were lumbar pain with radiation to the right groin area, subfebrility to febrility up to 39°C and a loss of appetite. Physical exam revealed bibasilar crepitations in her lungs. Labs showed an elevation in inflammatory markers with a CRP of 91.2 mg/L. The white count remained in normal range, but there was an increase in the neutrophil percentage to 79.9% and a decrease in the lymphocyte percentage to 7.7%. Cyclosporine levels were in the therapeutic range. Repeat of urine culture was negative for E.coli. The dose of mycophenolate mofetil was decreased due to the febrility; meropenem was changed to cefepine, and the patient was given IV crystalloid hydration with diuretics. A Quantiferon test performed at her local hospital was negative. CT imaging at our institution revealed centrally necrotic para-aortic and interaortocaval lymph nodes caudally from the level of the left renal vein to the bifurcation of the inferior vena cava (IVC); the mass compressed the lower portion of the IVC and had noticeably grown in size from a CT performed 3 weeks earlier at her local regional hospital (Figure 1).

CT showed diffuse reticulonodular changes with deformation of the bronchi at all levels, a lamellar pleural

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effusion with 1cm widening, and disturbed ventilation of the lower left lung lobe. There was also widening of

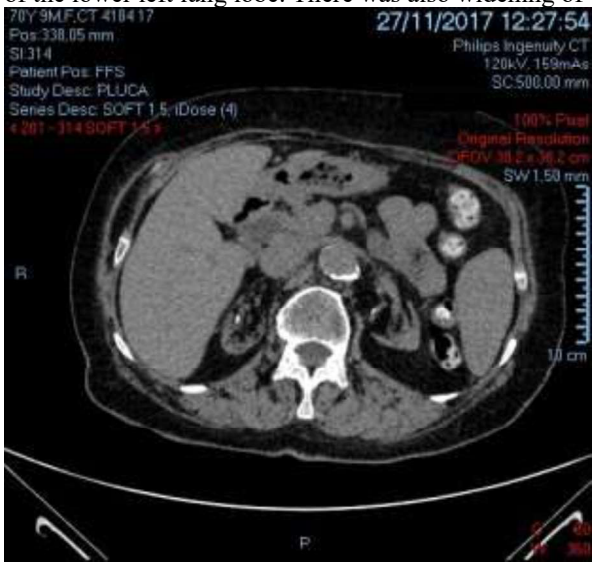

Fig. 1. Central necrotic mass with inhomogeneous infiltrate and vascularized edges. While there is compression of the IVC, it cannot be definitively concluded that there is invasion into the vasculature.

the fat tissue surrounding the ascending to the transverse colon suggesting inflammatory changes but without a definite cause. The patient had positive IgM and IgG to Toxoplasma gondii and was empirically started on pyrimethamine, sulfadiazine and leuocovorin. Subsequent testing revealed that the patient had negative PCR testing for EBV DNA and MTB DNA, but a mildly detectable level of polyomavirus BK DNA. Serology showed negative HSV2 immunoglobulins, but a borderline result for HSV1 IgM. Aspergillus galactomannan antigen also tested negative.

A few days later, an exploratory laparotomy aspirated and drained 23 ml of purulent fluid from the enlarged interaortocaval lymph node. The lymph node contents tested positive for acid fast bacteria and MTB was isolated on culture media. Pyrazinamide, rifampicin and isoniazid were subsequently started. A repeat Quantiferon ELISA was positive for MTB. Review of records showed that the patient's father died because of MTB in 1952.

Six weeks later, the patient's symptoms were still persistent and showed a lack of clinical improvement. Ethambutol, ciprofloxacin, metronidazole and fluconazole were added to the therapy.

Two weeks after adjusting the therapy, the patient began to deteriorate with increasing fatigue, weakness, nausea and vomiting, inspiratory crepitations, abdominal tenderness, tachycardia, fevers up to 39.6^{o}C and a 10 kg weight loss. Labs showed an abrupt increase in leukocytes to 26.7x10^{9}/L, with an elevated neutrophil percentage of 91.1% and a decreased lymphocyte percentage of 1.8%, mild normocytic anemia, CRP of 151.9 mg/L, and a subtherapeutic level of cyclosporine. Creatinine levels rose to 149 µmol/L.

The patient had been consuming an enteral formulation, Ensure® Plus Advance, since the onset of her symptoms 3 months ago. She complained of dysphagia to solid foods, but did tolerate fluids. In an effort to address the rapid weight loss, hypoproteinemia and hypoalbuminemia, we added the enteral formulation, Diben Drink®. Pending the oral intake of this trial, we were considering switching the patient to total parenteral nutrition.

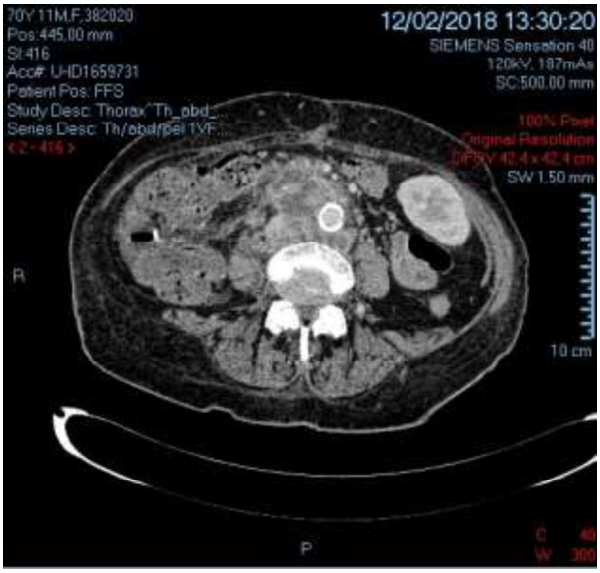

Fig. 2. Conglomerate of lymph nodes with vascularized edges and necrotic center that is extending from the great vessels to the right psoas major. The largest dimension is 7.6x5.7cm. The iliac lymph nodes remain unaffected

Control CT showed an increase in mass of the previously noted interaortocaval lymph nodes. The lymph nodes encircled around the aorta and most of the IVC extending into the right psoas major (Figure 2). There was some involvement of the lymph nodes in-between the portal vein and IVC, which increased in size from the previous CT scans. The pleural effusion had disappeared from previous CT; however the lungs showed more diffuse reticular peripheral changes, especially on the lung borders (Figure 3). There was also a poorly demarcated hypovascular area in the spleen, which was not seen on previous films. In an effort to explain this deterioration, MTB cultures were sent for multidrug-resistance testing.

It was postulated that her lack of response to therapy could be due to polymorphisms of her metabolic enzymes. Although gene analysis showed that she did have the fast metabolic variant of CYP3A4 and a high activity of N-acetyltransferase 2, the analysis recommended a normal dosing regimen.

Multiple cultures of her blood and urine proved to be negative despite rising inflammatory markers. We switched from fluconazole to caspofungin, piperacillin

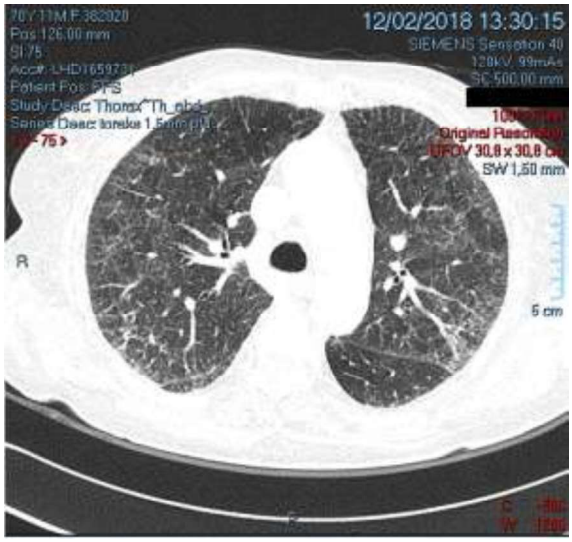

Fig. 3. Disseminated reticulonodular pattern of the lungs

and tazobactam instead of ciprofloxacin and metronidazole. Yet inflammatory markers remained constant and the lymph nodes continued to grow. The clinical picture represented IRIS secondary to MTB. We decided to stop immunosuppressive therapy except for prednisone as recommended by literature for treatment of IRIS [6], and started to prepare the patient for an eventual graftectomy upon stabilization. However, 1 week later the patient died during the sleep. Autopsy finding revealed large abscess collections in abdominal cavity with MTB content.

Discussion

The onset of MTB-IRIS usually occurs within 3 months from the start of treating the infection and is more frequently seen when there is diffuse MBT lymph node and pleural involvement [4]. The archetypal disease presentation consists of fever, weight loss, night sweats, enlarging lymphadenitis with suppuration, and worsening respiratory symptoms secondary to new or worsening pleural effusions that present with cough, dyspnea and shortness of breath [1]. Nonetheless, cases have reported less common lesions involving the central nervous system, subcutaneous tissues, abdomen (retroperitoneal lymphadenopathy and peritonitis), musculoskeletal system and obstructive endobronchial lesions [1]. Our patient's presentation was similar to findings listed in literature with abdominal tenderness, back pain, loss of appetite, weight loss, weakness, febrility and respiratory envelopment. Her MBT involvement of the retroperitoneal lymph nodes and psoas major, along with lymphopenia, anemia and rapid immune reconstitution were all risk factors for the onset of IRIS [1,3,4]. Still, this presentation in a kidney transplant recipient has rarely been reported [5]. It is possible that decreasing the mycophenolate mofetil dose and a subtherapeutic level of cyclosporine relieved the immunosuppression and triggered this severe form of IRIS. Moreover, rifampin is known to cause subtherapeutic doses of cyclosporine through drug-drug interactions [7].

Conclusion

In conclusion, physicians dealing with an idiopathic collection of inflammatory symptoms in an immunosuppressed SOT recipient should consider IRIS as a potential differential diagnosis. Additional research is needed to understand the convoluted pathogenesis of IRIS so that diagnostic and treatment guidelines can be made to prevent adverse outcomes.

Conflict of interest statement. None declared.

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