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Sirolimus-induced Pneumonitis Complicated by Pentamidine-induced Phospholipidosis in a Renal Transplant Recipient.

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Abstract

The proliferation signal inhibitors (PSIs) sirolimus, everolimus, and temsirolimus have been associated with a non-infectious pneumonitis characterized by lymphocytic alveolitis and bronciolitis obliterans with organizing pneumonia (BOOP). This usually occurs within the first year of administration. We present a case in a deceased donor renal transplant of interstitial pneumonitis developing 6 years after switching from tacrolimus to sirolimus for chronic graft dysfunction. After the addition of intravenous pentamidine for suspicion of Pneumocystis pneumonia, there was marked clinical deterioration requiring intubation. Open lung biopsy revealed sirolimus-induced pulmonary toxicity (BOOP) with the additional finding of a drug induced phospholipidosis (DIPL) that we

ascribe to pentamidine. After cessation of both drugs and corticosteroid therapy, there was only partial improvement. Eight months later there is residual interstitial fibrosis, and the patient still requires supplemental home oxygen. We review the literature on PSI-induced pneumonitis and discuss the pathophysiology of the potential interaction with pentamidine. We caution against its use in the setting of PSI-induced pneumonitis. Whether theses same concerns apply to other more commonly used medications associated with DIPL (eg amiodarone, aminoglycosides, etc) is currently unknown.

Introduction

The immunosuppressive agents sirolimus, everolimus, and temsirolimus are known as proliferation signal inhibitors (PSIs). After binding to FKBP12, they inhibit the serine-threonine kinase mTOR in the multimeric protein complex mTORC1 (1). Upon activation, this complex promotes proliferation of T and B lymphoctes, as well as many other cell types, including vascular smooth muscle, endotheial, and epithelial cells. Sirolimus was initially approved as an immunosuppressant for use in transplantation in 1999, and the PSIs are now also being used to treat metastatic cancer, hamartomatous diseases, polycystic kidney disease (2), and to prevent restenosis of coronary artery stents.

Unfortunately, the PSIs have a high side effect profile, including bone marrow suppression, hyperlipidemia, acne, edema, aphthous ulcers, and proteinuria (3). A non-infectious pneumonitis was initially reported in solid organ transplant patients (4-8), but appears to also occur quite commonly with oncologic use. We present a case of a deceased donor renal transplant patient who was maintained on sirolimus for over 6 years. He presented with fever, dyspnea, and interstitial pulmonary infiltrates. After

nearly 2 weeks of no improvement, intravenous pentamidine was initiated. Clinical deterioration followed resulting in intubation. Open lung biopsy revealed changes typical of sirolimus toxicity, but also changes that we ascribe to concurrent pentamidine toxicity.

Case report

A 61 year-old male with a history of hepatitis C, hypertension, ESRD, and 6 years status post deceased donor renal transplantion initially presented to an outside hospital in August of 2010 with shortness of breath, lightheadedness, and pleuritic chest pain. On presentation he was afebrile with normal vital signs. The physical exam was notable for decreased breath sounds in all lung fields without wheezes or rales. Cardiac exam was normal, including no jugular venous distension. Trace lower extremity edema was noted. No evidence for myocardial infarction was found, and an echocardiogram demonstrated normal left ventricular systolic function. The initial chest radiograph showed no acute cardiopulmonary abnormality. The serum creatinine was 1.8mg/dL, the patient's baseline.

Immunosuppression on admission included mycophenolate mofetil 1500 mg, sirolimus 2 mg, and prednisone 5 mg daily. Other outpatient medications were atenolol, amlodipine, benazepril, minoxidil, aspirin, atorvastatin, buspirion, esomeprazole, and folic acid. He was first transplanted in November 2002 with a deceased donor graft that failed from a Banff IIa acute rejection after approximately nine months. He received another deceased donor graft in July 2004. He was initially treated with tacrolimus, MMF, and steroids. Due to impaired graft function, tacrolimus was switched to sirolimus

four months post-transplantion. Graft function remained stable up to the current admission.

The patient's other medical history included chronic hepatitis C viremia, hyperlipidemia, peptic ulcer disease, and post-traumatic stress disorder. He had no relevant surgical or family medical history. He is a retired Vietnam veteran. He drinks alcohol on occasion, and smoked for several years until quitting in 2008.

Early in the hospital course, the patient became febrile and progressively hypoxic, without leukocytosis. On day 6 a non-contrast CT of the chest showed multi-focal ground glass opacities scattered throughout both lungs, predominately involving the upper lobes. Superimposed septal thickening and peripheral traction bronchiectasis, compatible with fibrosis, was also demostrated. A bronchoscopy with BAL performed on day 9 did not identify any bacterial, fungal, or viral organisms. Intravenous levofloxacin and pentamidine with dexamethasone were started for community acquired pneumonia and suspected pneumocystis pneumonia (PCP). An intravenous formulation of trimethoprim/ sulfamethoxazole was unavailable. By day 13 the patient's hypoxia had progressed with a pulse oximetry of 91% on 4 liters O^2. Repeat chest radiograph showed upper and middle lobe infiltrates with sparing of the lung bases. A ventilation/perfusion scan was normal. The patient's creatinine had increased from 1.8mg/dL on day 10 to 4.0 mg/dL by day 13.

On day 14 the patient was transferred to our hospital for further management. Within 24 hours he was intubated for respiratory distress. Antibiotics were broadened to vancomycin, pipercillin-tazobactam, and moxiflixacin. Pentamidine and sirolimus were discontinued. A repeat bronchoscopy post-intubation showed few atypical cells in a background of reactive bronchial cells, macrophages, inflammation, and debris. No

pneumocystis or other fungal elements were identified. A chest CT again demonstrated fibrosis in the upper lobes and right middle lobe. There were new dependent consolidations in both lower lobes consistent with aspiration or multifocal pneumonia. On day 15 hemodialysis was initiated for hyperkalemia (7.2 mEq/L) in the setting of oliguric renal failure.

An open lung biopsy was performed on day 16. Pathology demonsrarted marked persistently active pneumonitis varying from diffuse alveolar damage (Fig. 1a) to acute fibrinous organizing pneumonia to a lymphocytic alveolitis with organizing pneumonia (Fig. 1b) and bronchiolitis obliterans (Fig. 1c). The organizing pneumonia in many areas resembled poorly formed granulomas (Fig. 1b) in the airspaces, a feature typical of sirolimus-induced pneumonitis. Also present were finely vacuolated pneumocytes and alveolar macrophages, consistent with a drug-induced phospholipidosis (Fig. 1d).

A transplant biopsy performed on day 17 showed mild tubular damage with minimal interstitial fibrosis and tubular atrophy. Stains for C4d and BK virus are negative.

At this time the patient's steroids were changed to high dose methylprednisolone. Gradually, his pulmonary status improved. He defervesced and antibiotics were discontinued. On hospital day 20, he was extubated. He remained dialysis dependent. On day 22 low dose tacrolimus was added to mycophenolate mofetil. Methylprednisolone was gradually tapered as the patient's respiratory status continued to improve.

Several days after starting tacrolimus, the patient's platelet count declined precipitously. Heparin-induced thrombocytopenia was excluded. Despite multiple anti-hypertensive agents, the patient's blood pressure remained elevated. On day 27 the

patient became confused, reported decreased vision, and then had a generalized seizure. Brain MRI was consistent with posterior reversible encephalopathy syndrome. Tacrolimus was discontinued due to the high suspicion for a systemic thrombotic microangiopathy. A seven-day course of plasmapharesis was initiated. Eventually the thrombocytopenia resolved.

At day 40, he was still dialysis dependent. Biopsy demonstrated persistent acute tubular damage with mild interstitial fibrosis and tubular atrophy. On electron microscopy, evidence of glomerular thrombotic microangiopathy was now noted.

On day 45 he was discharged on home oxygen. Immunosuppression consisted of mycophenolate mofetil 1500 mg daily and a slow prednisone taper. Approximately one month after discharge, home oxygen was no longer required. A follow-up CT showed significant interval improvement in the fibrosis and multifocal pneumonia. Approximately three months after discharge, the creatinine decreased to 2.2 mg/dL, and dialysis was discontinued.

Discussion

Our patient developed sirolimus-induced pnuemonitis after 6 years of chronic use, the longest reported duration prior to development of this adverse event. The clinical course was exacerbated following addition of pentamidine with the requirement for mechanical ventilation. Lung biopsy showed the typical findings of sirolimus-induced pulmonary toxicity. In addition, the fine vacuolizations in type 2 pneumocytes and macrophages (phospholipidosis) were attributed to pentamidine toxicity.

Sirolimus was first approved for use in renal transplantation in 1999. The early, multi-center trials establishing its efficacy failed to note non-infectious pneumonitis as a

significant side effect. Sirolimus-induced pneumonitis was first reported in 2000 in renal transplant patients, and subsequently with other organ transplants, including heart, lung, liver, and islet cells (4-8). In some cases, sirolimus use was *de novo* from the time of transplantation. More frequently it was added later in the course, usually to spare calcineurin inhibitor side effects, or for malignancy. Despite the apparent absence of cases in large randomized controlled trials, single-center series in kidney and heart transplantation noted incidences as high as 10 to 15% of patients taking sirolimus (7,8). The other proliferation signal inhibitors currently in use (everolimus and temsirolimus) have subsequently also been associated with a similar non-infectious pneumonitis (9,10). Outside of transplantation, these PSIs have also been used in oncology to treat various metaststic cancers such as renal cell, lung, or breast, where this pulmonary side effect is found much more frequently than in transplantation. Incidence rates as high as 25-40% have been reported, although many of these cases are asymptomatic.

Regardless of the setting or particular PSI, the clinical picture is generally similar. Symptoms include dyspnea, cough, fever, malaise, weight loss, and occasionally hemoptysis (4-8,10). Most cases occur within a few months of initiation, the longest prior reported case with sirolimus being 51 months (7). Bronchial alveolar lavage (BAL) typically reveals evidence of lymphocytic or occasionally eosinophilic alveolitis (4,7,8). Some cases initially had neutrophilic predominance suggesting infection, but on repeat BAL, lymphocytes predominated (7). Pulmonary hemorrhage occurs in a minority of cases (4,6,7,8). Radiologic features include predominantly bronchiolitis obliterans organizing pneumonia (BOOP) or interstitial infiltrates (4,6-8), typically in a ground-glass pattern. Consolidations may be found as well (4,6,7). Neither pleural-based disease

nor mediastinal involvement are features of this syndrome. When biopsy was performed, several patterns had been found. Most commonly there was bronchiolitis obliterans with organizing pneumonia (BOOP) (4,6). Other cases had simple lymphocytic intersitial pneumonitis (7). Some cases had diffuse alveolar hemorrhage (6). Granulomas may be present (4), typically poorly formed. Rarely, vasculitis has been detected, as have desquamative interstitial pneumonia and pulmonary alveolar proteinosis.

Purported risk factors for this pneumonitis include older age, male sex, dose/serum level, concomitant immunosuppression, reduced kidney function, and most especially late conversion (as opposed to *de novo* use) (7,8). A recent case series combined with a literature review of other case reports/series indicated an incidence of 14% (46 of 326 patients) (8). However, three recent randomized controlled trials specifically assessing late conversion to sirolimus (CONVERT, CONCEPT, and Spare-the Nephron) did not report this complication in nearly 800 patients treated with sirolimus for at least 1 year (11).

The pathophysiology of PSI induced non-infectious pneumonitis remains unclear. Most of the reported cases of pneumonitis in transplantation have involved sirolimus. The 3 PSIs in use have a similar mechanism of action. After binding to FKBP12 they inhibit mTOR, specifically in the multimeric protein complex mTORC1, a master regulator of cell growth, metabolism, and autophagy (1). One downstream effect of inhibition is to arrest cell progression from the G1 to S phase. The other known mTOR complex, mTORC2, is not directly inhibited by PSIs, although its activity may be indirectly reduced by their long term use. The direct relation between mTORC1 inhibition and pulmonary toxicity, if it exists, remains to be determined.

Direct toxicity is possible based on high doses and high trough levels in many reports (4). Some patients respond to dose reduction, a situation that allows for continued administration of the drug (4,8), although relapses have been reported (7,8). The high doses used in oncology with correspondingly very high incidences of pneumonitis support direct toxicity. In some cases, however, levels and doses were within the ranges currently recommended (6). This suggests alternative mechanisms, at least for some patients. One hypothesis proposes exposure of cryptic pulmonary antigens by sirolimus pulmonary toxicity, which then results in initiation of a cell-mediated reaction (4). The lymphocytic predominance in most cases, especially with CD4 cells (4), supports this concept, although others have found a normal CD4:CD8 ratio (8). It is also possible that sirolimus acts as an immunogenic hapten by binding to proteins, possibly initiating delayed type hypersensitivity (6). The presence of eosinophils and mast cells in BAL fluid is further evidence for an allergic mechanism (4,7).

As noted, the incidences when all three PSIs are used for metastatic cancer are much higher than occurs in transplantation (10). There are several reasons why this may be true. Cancer patients are more closely watched from the pulmonary standpoint with frequent thoracic imaging. This may allow for greater detection of asymptomatic cases. Use of much higher doses without therapeutic drug monitoring is typical with oncologic use. For example, everolimus has been dosed at 10 mg/day, 3-5 times the typical daily dose used in transplantation. Steroids may be protective and are not usually co-administered in these patients. Finally, cancer patients are also more likely to have concurrent exposure to other potential pulmonary toxic drugs.

The clinical course of most cases of PSI pulmonary toxicity is generally rapid improvement upon cessation of the drug. Simple dose reduction may or may not be effective. Some cases have been treated with high dose steroids, but not in any controlled fashion (5,7,8). In general, steroids appear to have a beneficial effect. Most patients have nearly complete recovery, but several fatalities have occurred in heart transplant patients (8). Occasional cases have had pulmonary fibrosis detected later (5,6). Surprisingly, cases are reported of patients with improved symptoms upon conversion from one PSI to another (12).

Pentamidine also has a high side effect profile when given intravenously for treating PCP. Most notable are nephrotoxicity, hyperkalemia, dysglycemia,, and hepatotoxicity (13). Pulmonary toxicity has not been mentioned in this context, but the concurrent infection could obscure any direct toxicity. *In vitro* studies show significant uptake of pentamidine and metabolites by type 2 alveolar epithelial cells and macrophages with evidence of direct toxicity (14). Aerosolized pentamidine (AP) given to experimental animals (dogs and rats) produced both acute (alveolitis) and chronic (fibrosis) pulmonary toxicity, but at doses up to 5 times that given to patients (15). In the clinical setting, AP shows low systemic absorption and little proclivity for either systemic or pulmonary toxicity (16). One long term study ($\geq$ 5yrs) of AP for prophylaxis in HIV patients showed only a slight reduction in flow rates, probably at the level of small airways. This effect was seen only in smokers (16).

As a cationic amphiphilic drug (CAD), pentamidine is known to produce drug-induced phospholipidosis (DIPL) (17,18), characterized by lysosomal acuumulation of phospholipids in the form of myeloid bodies (19). Our patient had numerous vacuoles by

light microscopy in type 2 pneumocyes and macrophages that likely represent myeloid bodies. It has been postulated that this lysosomal phospholipid accumulation results in lysosomal dysfunction with increasing autophagy, an alternative form of programmed cell death (19). Activation of the mTORC1 complex is known to reduce autophagy (1), and hence, by inhibiting this complex, PSIs may likewise increase it. This may explain the synergistic pulmonary toxicity between a CAD like pentamidine and sirolimus seen in this case.

Our patient had a typical presentation of sirolimus-induced pulmonary toxicity, with the exception of its late onset (> 6 yrs). In addition, there was marked and rapid clinical deterioration following initiation of i.v. pentamidine. Biopsy showed direct evidence of sirolimus toxicity as well as evidence of injury to type 2 pneumocytes and macrophages indicating a synergistic pentamidine effect.

In any patient with suspected PSI-induced pneumonitis, PCP will also be a diagnostic consideration. If treatment for PCP is required, trimethoprim/sulfamethoxazole would be first choice. If not possible, we would caution against i.v. pentamidine for fear of synergistic toxicity. Furthermore, data indicate clindamycin-primaquine is more effective than pentamidine as second line therapy (20), without this potential pulmonary risk. Whether these same concerns apply to other more commonly used medications associated with DIPL (eg amiodarone, aminoglycosides, etc) is currently unknown.

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Figure Legend

Fig. 1a) Diffuse alveolar damage. Photomicrograph showing fibrin membranes (arrows) prominently lining thickened alveolar walls (10 X H& E).

Fig. 1b) Lymphocytic alveolitis with organizing pneumonia. The alveolar walls contain a lymphocytic inflammatory infiltrate with organizing exudates (outlined by arrows) in the airspaces (10X H & E).

Fig. 1c) Bronciolitis obliterans. The lumen of a terminal bronchial is obliterated by an organizing exudate (outlined by arrows) (10X H& E).

Fig. 1d) Pentamidine-induced phospholipidosis. The type II pneumoncytes (arrowhead) and macrophages (arrows) show fine vacuolization (20X H&E).