"Everolimus-associated pulmonary toxicity: High-resolution CT Imaging Findings"

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Aims and objectives

Pulmonary toxicity is a serious and well known complication of sirolimus, an inhibitor of the mammalian target of rapamycin (mTOR) which is a protein kinase involved in cell growth, proliferation, metabolism and angiogenesis, used in solid-organ transplantation (1, 2).

Everolimus (Certican® in Europe, Zortress® and Afinitor® in USA; Novartis) is a more recently developed mTOR inhibitor, derived from sirolimus. This drug is currently used to prevent allograft rejection after solid organ transplantation (3) and in the treatment of some malignancies not amenable to surgical intervention (4), such as advanced renal cell carcinoma (5), subependymal giant cell astrocytoma associated with tuberous sclerosis (6), progressive or metastatic pancreatic neuroendocrine tumors (7) and advanced hormone receptor-positive, human epidermal growth factor receptor 2-negative breast cancer (8).

There are several adverse effects of everolimus, being the most important and frequent the following: increased risk of infection (including opportunistic infections), noninfectious pneumonitis, stomatitis/oral mucositis, peripheral edemas, diarrhea and hematopoietic disorders (9). An incidence of 13.5% of clinical pneumonitis has been reported in patients with advanced renal cell carcinoma receiving everolimus (10) and up to 25% in a retrospective independent review in patients with advanced lung cancer (11). In the majority of cases, the pneumonitis is relatively unaggressive and reversible with discontinuation of the therapy, but may lead to significant toxicity.

To the best of our knowledge, few isolated cases of everolimus pulmonary toxicity in renal transplant patients have been published (12-14). Studies with a larger number of patients (10,11) have been performed in oncologic patients with advanced disease. We believe that post-surgical and post-radiotherapy changes, tumor progression and pulmonary toxicity caused by other drugs may simulate everolimus pneumonitis in this population of patients. The spectrum of imaging findings was not clearly established on these studies.

Transplant patients are especially susceptible to pulmonary infections, which makes extremely difficult the clinical suspicion and definitive diagnosis of toxicity pneumonitis. Clinicians in charge of transplanted patients should be aware of this new entity of mTOR-associated pneumonitis as an alternative diagnosis of an opportunistic infection, especially in the absence of detectable infectious agent and response to antibiotic treatment, and presence of compatible imaging findings. Therefore, knowledge of
radiological signs of everolimus-associated pneumonitis is essential to establish the correct diagnosis, although it can be challenging sometimes.

The objective of our study was to describe the high-resolution CT findings of everolimus-associated pulmonary toxicity in renal transplant recipients.
Methods and materials

Patients:

The medical histories of 89 renal transplant recipients (transplanted at our institution from 1998 to 2012) receiving everolimus therapy were retrospectively reviewed. Twenty-six patients had high-resolution CT available for review. The CT was performed for different clinical indications; toxicity pneumonitis was clinically suspected in 11 of them.

The diagnosis of pulmonary toxicity was achieved after appropriate work-up to exclude infection and other pulmonary diseases. Three patients were excluded (one death due to sepsis and two patients with multifocal pneumonia). Finally, eight patients fulfilled the following diagnostic criteria of everolimus-associated pulmonary toxicity: exposure to everolimus before the onset of pulmonary symptoms, exclusion of infection or other pulmonary disease, and clinical and radiological improvement after drug withdrawal.

Clinical and laboratory data:

Clinical and laboratory data, such as symptoms, results of bronchoalveolar lavage (BAL), microbiological culture and/or biopsy, plasma everolimus concentration, as well as other underlying medical conditions, and history of smoking, were recorded.

Imaging acquisition:

High-resolution CT studies were obtained using a 64 detector row CT (Brilliance, Pips Medical System, Best, The Netherlands) or a 128 detector row CT - 128-detector rows × two focal spot positions- (Brilliance iCT , Philips Medical System, Best, The Netherlands) with helical acquisition technique (collimation, 64x0.6mm and 128x0.6mm respectively; tube voltage 120 kVp; tube current-time product, 70-200 mAs). Attenuation-based dose modulation was used in all cases to ensure delivery of lowest radiation dose and production of diagnostic scans. Reconstructions with appropriate mediastinal and lung filters were obtained (2mm thickness, 1mm overlap) as well as high resolution reconstructions (high spatial resolution algorithm, 1mm thickness, 10 mm gap).

Imaging Interpretation:

Baseline and follow-up CT exams were reviewed by two blinded radiologists (with 8 and 2 years of experience in thoracic imaging); the decision was reached by consensus. All patients but one had a follow-up CT study; one patient was followed up with chest radiograph.
The following imaging findings were recorded: airspace consolidation, ground-glass opacities, bronchiectasis, septal thickening and centrilobular nodules. The distribution of imaging findings was assessed (apicobasal gradient, perihiliar vs subpleural, unilateral vs bilateral). Additional imaging findings such as pleural effusion or changes of chronic obstructive pulmonary disease were also recorded.

Descriptive statistics were obtained.
Results

Patients:

Among the 89 renal transplant recipients included in the study, eight patients (9%) (5 male, 3 female; mean age, 64 years, age range 55-77 years) developed everolimus-induced pulmonary toxicity. The underlying disease that led to renal transplantation was: polycystic kidney disease in 5 patients (62.5%), IgA nephropathy in one patient (12.5 %), chronic glomerulonephritis in one patient (12.5 %) and nephropathy due to long-standing hisorty of cystine kidney stones in one patient (12.5%) (Table 1).

None of the patients were current smokers. Two patients (25%) were former smokers who have quit more than 5 years ago; none of them showed findings of emphysema on CT.

Seven patients (87.5%) presented with respiratory symptoms, being the most common: dry cough (n= 6), low-grade fever (n=5), expectoration (n=2), and dyspnea (n=1). One patient was asymptomatic and the CT was performed for renal carcinoma follow-up.

Blood everolimus levels at the moment of clinical presentation ranged from 4.4 ng/ml to 13.2 ng/ml (mean 8.52 ng/ml) (normal value: 3-8 ng/ml). Patients had received everolimus for 32 months (range, 1-61 months) before symptom onset (Table 1). None of the patients received concomitant treatment with other drugs that may cause pulmonary toxicity.

Patient characteristics, underlying disease, time interval between everolimus therapy initiation and onset of symptoms, and the concentration of everolimus in plasma are shown in Table 1.

<table>
<thead>
<tr>
<th>Patient num.</th>
<th>Age (yrs)</th>
<th>Sex</th>
<th>Underlying disease</th>
<th>Everolimus therapy duration (months)</th>
<th>Plasma Everolimus concentration (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>63</td>
<td>M</td>
<td>IgA nephropathy</td>
<td>49</td>
<td>4.4</td>
</tr>
<tr>
<td>2</td>
<td>60</td>
<td>F</td>
<td>Polycystic kidney disease</td>
<td>51</td>
<td>13.2</td>
</tr>
<tr>
<td>3</td>
<td>60</td>
<td>M</td>
<td>Polycystic</td>
<td>61</td>
<td>9.6</td>
</tr>
</tbody>
</table>
Table 1: Patient population characteristics. M= male, F=female

<table>
<thead>
<tr>
<th>Patient Num.</th>
<th>Airspace consolidation</th>
<th>GGO</th>
<th>Centrilobular nodules</th>
<th>Septal thickening</th>
<th>Bronchiectasis</th>
<th>Distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>--</td>
<td>+</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>Diffuse</td>
</tr>
</tbody>
</table>

Imaging findings:

The main CT findings were: ground-glass opacities (GGO) n=7 (87.5%) (Fig. 1 on page 9), airspace consolidations n=5 (62.5%) (Fig. 2 on page 9, Fig. 3 on page 10, Fig. 4 on page 11) septal thickening n=4 (50%) (Fig. 4 on page 11), bronchiectasis n=4 (50%) (Fig. 3 on page 10), and centrilobular nodules n=1 (12.5%) (Fig. 5 on page 12).

The distribution of imaging findings was diffuse in 4 cases (50%); basal predominance was found in 4 patients (50%) and subpleural distribution in 3 (37.5%) (subpleural GGO in one case, subpleural consolidations in two cases). Image findings are detailed in Table 2.
### Table 2. CT imaging findings of everolimus-induced pulmonary toxicity

<table>
<thead>
<tr>
<th>Patient</th>
<th>Diffuse</th>
<th>Subpleural</th>
<th>Basal</th>
<th>Basal/</th>
<th>Subpleural</th>
<th>Diffuse</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>--</td>
<td>--</td>
<td>Subpleural</td>
</tr>
<tr>
<td>3</td>
<td>+</td>
<td>+</td>
<td>--</td>
<td>+</td>
<td>+</td>
<td>Basal</td>
</tr>
<tr>
<td>4</td>
<td>--</td>
<td>+</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>Diffuse</td>
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<tr>
<td>5</td>
<td>+</td>
<td>--</td>
<td>--</td>
<td>+</td>
<td>+</td>
<td>Basal</td>
</tr>
<tr>
<td>6</td>
<td>--</td>
<td>+</td>
<td>--</td>
<td>--</td>
<td>+</td>
<td>Basal/</td>
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<tr>
<td></td>
<td></td>
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<td></td>
<td></td>
<td>Subpleural</td>
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<tr>
<td>7</td>
<td>+</td>
<td>+</td>
<td>--</td>
<td>+</td>
<td>--</td>
<td>Diffuse</td>
</tr>
<tr>
<td>8</td>
<td>+</td>
<td>+</td>
<td>--</td>
<td>+</td>
<td>+</td>
<td>Basal/</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Subpleural</td>
<td></td>
</tr>
</tbody>
</table>

After drug-withdrawal, clinical and radiological resolution was found in 6 patients (75%), and significant improvement in 1 patient (12.5%). Imaging findings persisted in one patient (12.5%), because therapy was decided to continue.
Fig. 1: Figure 1. 63-year-old male with history of IgA nephropathy who presented with low-grade fever, expectoration and cough. Blood everolimus level was 4.4 ng/ml. The duration of everolimus therapy was 49 months. Top row: CT scan at initial clinical presentation. Diffuse ground-glass opacities are shown. Bottom row: Two months after drug withdrawal. Images show complete resolution of ground-glass opacities.

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Fig. 2: Figure 2. 77-year-old male who underwent kidney transplant in 1998 due to polycystic kidney disease. Patient presented with fever, expectoration and dyspnea. Blood everolimus concentration was 7.8 ng/ml. Top row: Chest X-ray (posteroanterior and lateral views) at clinical presentation demonstrates bilateral multifocal air-space consolidation. Middle row: CT scan performed some days after shows extensive bilateral consolidations, ground-glass opacities and septal thickening. Bottom row: Chest X-ray, 3 months after everolimus withdrawal, shows almost complete resolution of imaging the findings.

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**Fig. 3:** Figure 3: 57-year-old female with history of polycystic liver and kidney disease, transplanted in 2009, presented with low-grade fever. Everolimus blood concentration was 8.5 ng/ml. Duration of everolimus therapy was 17 months. Top row: CT images at clinical onset show patchy bilateral airspace consolidation, some septal thickening and cylindrical bronchiectasis (black arrows) Bottom row: CT scan 5 months later, after drug withdrawal, shows complete resolution of previous findings.

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Fig. 4: 55-year-old male, with history of chronic nephropathy due to cystine stones, transplanted in 2010, presented with dry cough 23 months after initiation of everolimus therapy. Top row: CT images at disease onset, axial images and MPR coronal reconstruction, show reticular pattern with inter- and intralobular septal thickening (arrows), small subpleural airspace consolidation (arrowhead). Basal predominance is demonstrated on the coronal reconstruction. Bottom row: CT scan three months later, after drug withdrawal and steroid therapy, shows complete resolution of the findings.

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Fig. 5: Figure 5: A 60 year-old female with history of hepatorenal polycystic disease and kidney transplantation in 2006. Patient presented with dry cough, low-grade fever and bibasal crackles 51 months after initiation of everolimus therapy. Everolimus blood concentration was 13 ng/ml. Top row: CT images at disease onset show ill-defined centrilocular nodules (asterisks), ground-glass opacities (arrows), and basal subpleural consolidations (arrowheads). Polycystic liver disease is also noted on the image on the right. Bottom row: CT

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Conclusion

Pulmonary toxicity is a potential complication of everolimus therapy and presents with a varied spectrum of imaging findings. Radiologist should be familiar with CT findings, since early recognition and drug-withdrawal is paramount.
References


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