Short Report

Hepatic manifestations of tuberous sclerosis complex: a genotypic and phenotypic analysis


A retrospective review of the clinical records and radiological images of 205 patients with tuberous sclerosis complex (TSC) was performed to evaluate the prevalence and progression of hepatic lesions; examine the association of hepatic phenotype with genotype, age, and gender; and investigate the relationships between hepatic, renal, and pulmonary involvement. Hepatic angiomyolipomas (AML), cysts, and other benign lesions were identified in 30% of the cohort, and some lesions grew significantly over time. However, no patient had clinical symptoms or complications from hepatic lesions.

TSC2 patients exhibited a higher frequency of AML compared to TSC1 patients (p = 0.037), and patients with no mutation identified exhibited a higher frequency of cysts compared to TSC2 patients (p = 0.023). Age was positively correlated with frequency of hepatic involvement (p < 0.001), whereas hepatic phenotype was independent of gender. Presence of hepatic AML was associated with presence of renal AML (p = 0.001). These findings confirm a high rate of asymptomatic hepatic lesions in TSC and further characterize the TSC phenotype.

Conflict of interest
The authors have no conflicts of interest to disclose.

Tuberous sclerosis complex (TSC) is an autosomal dominant genetic disorder that arises from germline mutations in either TSC1 (chromosome 9q34.3) or TSC2 (chromosome 16p13.3), which encode hamartin and tuberin, respectively (1, 2). These protein products function as tumor suppressors by forming a heterodimer that inhibits the mammalian target of rapamycin complex 1 (mTORC1) pathway. Loss or dysfunction of either protein results in the growth of hamartomatous lesions in multiple organ systems (3).

Renal lesions, including cysts and angiomyolipomas (AML), are the most common abdominal manifestation of TSC, occurring in 50–80% of all patients, more frequently and severely in female patients and those bearing TSC2 mutations (4–6). Renal AML can lead to complications such as pain, hemorrhage, and impaired renal function (7). They are also strongly associated with pulmonary lymphangioleiomyomatosis (LAM) (6, 8). Periodic abdominal imaging is therefore standard care in all TSC centers (9), which has in turn led to increased detection of hepatic lesions.

While the renal manifestations of TSC have been well described in large population-based studies, little has been reported on hepatic manifestations. A mutational analysis of 224 TSC patients observed hepatic AML in 6% of the cohort (10), while smaller sample studies have observed hepatic AML in up to 45% of TSC patients (11–13). The majority of hepatic AML have been observed in patients with renal AML (12, 13), but this relationship has not been well investigated. To date, one genotype–phenotype correlation study has assessed hepatic AML, but no correlations were found (10).

The following study evaluates the prevalence and progression of hepatic lesions in a large TSC patient cohort, examines the association of hepatic phenotype...
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with genotype, age, and gender, as well as investigates the relationships between hepatic, renal, and pulmonary involvement. By further characterizing the hepatic phenotype, we hope to gain insight into the pathophysiologic mechanism of visceral lesion development in TSC.

Materials and methods

A retrospective review of the clinical and radiological records of all 426 patients seen at the Herscot Center for TSC at Massachusetts General Hospital (MGH) between January 2002 and June 2009 was performed. Only patients with a definite clinical diagnosis of TSC and at least one abdominal computed tomographic (CT) or magnetic resonance (MR) study were included, resulting in a sample size of 205 patients. This study was approved by the institutional review board of MGH.

Genetic testing of TSC1 and TSC2 included detection of large deletions and rearrangements of TSC2. Patients whose genetic testing results were normal or revealed a benign polymorphism were classified as having no mutation identified (NMI). All abdominal images were independently evaluated by two board-certified radiologists (S. S. H. and M. H.) and findings were recorded as consensus, including number of lesions, lesion type, and lesion size. Size was measured in millimeters (mm) in two dimensions on axial sections, and the longest diameter of the largest lesion for each lesion type was recorded. Findings from each patient’s most recent scan (or last scan before initiation of sirolimus treatment) were used in statistical analysis. When available, serial images were compared for changes in lesion size over time. A change of 5 mm or greater was interpreted as significant, given that slice thickness was 5 mm for both CT and MR imaging. For all patients, radiology reports from abdominal imaging and chest CT scans were reviewed for renal AML and LAM.

Multiple regression analysis was used to assess the effects of genotype, age, and gender, and pairwise comparisons of the TSC1, TSC2, and NMI populations were performed. Fisher’s exact tests were used to explore the relationships between hepatic AML, renal AML, and LAM. All analyses were conducted using Stata 11.1 (StataCorp LP, College Station, TX), and alpha was set at 0.05.

Results

Patients and imaging

A total of 685 CT and MR abdominal imaging studies, performed over a period of 18.3 years, were reviewed for 205 patients (83 males, 122 females) with TSC. The average patient age at time of most recent scan was 24.1 years (range: 0.1–76.3). In total, 61/205 (30%) patients had at least one hepatic lesion identified on abdominal imaging: 25 (12%) had AML (Fig. 1), 26 (13%) had cysts (Fig. 2), 12 (6%) had other benign lesions (including hemangioma, calcified granuloma, hamartoma, adenoma, focal nodular hyperplasia, and heterogeneous lesion with scar), and 5 (2%) had lesions that were too small to characterize.

Radiology records indicated that 117/205 (57%) patients had at least one renal AML. The presence of hepatic AML was significantly associated with the presence of renal AML (Table 1). Of the female patients imaged by chest CT, 32/72 (44%) were diagnosed with LAM. There was no significant association between the presence of hepatic AML and the presence of LAM (Table 1).

Effects of genotype, age, and gender

Genetic analysis had been performed on 161/205 (79%) patients. Three patients with somatic mosaicism of TSC2 were excluded from further analysis. Of the remaining 158 patients, 40 (25%) had TSC1 mutations, 93 (59%) had TSC2 mutations, and 25 (16%) had NMI.

A multiple regression analysis of genotype, age, and gender revealed that TSC2 patients tended to have a higher frequency of hepatic AML than TSC1 and NMI patients, and NMI patients tended to have a higher

Fig. 1. Axial (a) and coronal (b) contrast enhanced computed tomography images showing a single 16 x 16 mm² hepatic angiomyolipoma in a 42-year-old, female patient with tuberous sclerosis complex.
Fig. 2. Coronal (a) and axial (b) T2-weighted, fast spin echo magnetic resonance images showing multiple hepatic cysts, the largest measuring 7 x 7 mm², in a 44-year-old, female patient with tuberous sclerosis complex.

Table 1. Associations between renal AML/LAM and hepatic AML in patients with TSC

<table>
<thead>
<tr>
<th></th>
<th>Renal AML, n (%)</th>
<th>Hepatic AML + (n = 25)</th>
<th>Hepatic AML - (n = 180)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal AML, n (%)</td>
<td>22 (88%)</td>
<td>95 (53%)</td>
<td></td>
<td>0.001</td>
</tr>
<tr>
<td>Hepatic AML + (n = 15)</td>
<td></td>
<td>7 (47%)</td>
<td>25 (44%)</td>
<td>0.846</td>
</tr>
<tr>
<td>AML, angiomyolipoma; LAM, lymphangioleiomyomatosis; TSC, tuberous sclerosis complex.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>aThis analysis includes only females in which chest CT scans had been performed.</td>
<td></td>
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</tr>
</tbody>
</table>

Table 2. Genetic effects on hepatic involvement in patients with TSC

<table>
<thead>
<tr>
<th></th>
<th>TSC1 (N = 40)</th>
<th>TSC2 (N = 93)</th>
<th>NMI (N = 25)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, n (%)</td>
<td>17 (43)</td>
<td>39 (42)</td>
<td>8 (32)</td>
<td>0.952</td>
</tr>
<tr>
<td>Age a [mean (SD)]</td>
<td>25.8 (2.5)</td>
<td>20.3 (1.4)</td>
<td>30.3 (3.3)</td>
<td>0.058</td>
</tr>
<tr>
<td>Hepatic involvement</td>
<td></td>
<td></td>
<td></td>
<td>0.009</td>
</tr>
<tr>
<td>Frequency, n (%)</td>
<td>9 (23)</td>
<td>28 (30)</td>
<td>10 (40)</td>
<td>0.084</td>
</tr>
<tr>
<td>Multiple lesions, n (%)</td>
<td>2 (22)</td>
<td>17 (61)</td>
<td>8 (80)</td>
<td>0.074</td>
</tr>
<tr>
<td>AML</td>
<td></td>
<td></td>
<td></td>
<td>0.693</td>
</tr>
<tr>
<td>Frequency, n (%)</td>
<td>2 (5)</td>
<td>17 (18)</td>
<td>1 (4)</td>
<td>0.037</td>
</tr>
<tr>
<td>Size b [mean (SD)]</td>
<td>5.5 (0.7)</td>
<td>26.2 (19.6)</td>
<td>5</td>
<td>0.072</td>
</tr>
<tr>
<td>Cyst</td>
<td></td>
<td></td>
<td></td>
<td>0.434</td>
</tr>
<tr>
<td>Frequency, n (%)</td>
<td>5 (13)</td>
<td>7 (8)</td>
<td>9 (36)</td>
<td>0.855</td>
</tr>
<tr>
<td>Size b [mean (SD)]</td>
<td>9.7 (3.5)</td>
<td>4.3 (2.0)</td>
<td>10.2 (6.2)</td>
<td>0.698</td>
</tr>
</tbody>
</table>

AML, angiomyolipoma; NMI, no mutation identified; SD, standard deviation; TSC, tuberous sclerosis complex. 

aAge in years at most recent imaging. 

bLongest diameter of the largest lesion measured in millimeters.

Table 3. Effects of gender and age on hepatic involvement in patients with TSC

<table>
<thead>
<tr>
<th></th>
<th>Male (N = 64)</th>
<th>Female (N = 94)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatic involvement</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frequency, n (%)</td>
<td>16 (25)</td>
<td>32 (34)</td>
<td>0.512 &lt;0.001</td>
</tr>
<tr>
<td>Multiple lesions, n (%)</td>
<td>10 (63)</td>
<td>17 (53)</td>
<td>0.489 0.960</td>
</tr>
<tr>
<td>AML</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frequency, n (%)</td>
<td>5 (8)</td>
<td>15 (16)</td>
<td>0.094 0.135</td>
</tr>
<tr>
<td>Size b [mean (SD)]</td>
<td>17.0 (8.0)</td>
<td>25.0 (22.0)</td>
<td>0.122 0.317</td>
</tr>
<tr>
<td>Cyst</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frequency, n (%)</td>
<td>7 (11)</td>
<td>14 (150)</td>
<td>0.799 &lt;0.001</td>
</tr>
<tr>
<td>Size b [mean (SD)]</td>
<td>6.1 (2.5)</td>
<td>9.1 (7.1)</td>
<td>0.484 0.007</td>
</tr>
</tbody>
</table>

AML, angiomyolipoma; F, female; M, male; SD, standard deviation; TSC, tuberous sclerosis complex. 

a p values for age correspond to a positive correlation. 

bLongest diameter of the largest lesion measured in millimeters.
Table 4. Spontaneous change in hepatic lesion size in patients with TSC

<table>
<thead>
<tr>
<th>Patient</th>
<th>Gender</th>
<th>Agea</th>
<th>Mutation</th>
<th>Lesion type</th>
<th>Change (%)</th>
<th>Timeb</th>
<th>Initial sizec</th>
<th>Final sizec</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>19</td>
<td>TSC2</td>
<td>AML</td>
<td>+310</td>
<td>2.1</td>
<td>10</td>
<td>41</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>21</td>
<td>TSC2</td>
<td>AML</td>
<td>+250</td>
<td>3.5</td>
<td>6</td>
<td>21</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>35</td>
<td>TSC2</td>
<td>AML</td>
<td>+110</td>
<td>2.5</td>
<td>10</td>
<td>21</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>18</td>
<td>TSC2</td>
<td>Hemangioma</td>
<td>+90</td>
<td>2.7</td>
<td>10</td>
<td>19</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>25</td>
<td>TSC2</td>
<td>Adenoma</td>
<td>+77</td>
<td>2.6</td>
<td>31</td>
<td>55</td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>8</td>
<td>TSC2</td>
<td>AML</td>
<td>+73</td>
<td>3.3</td>
<td>22</td>
<td>38</td>
</tr>
<tr>
<td>7</td>
<td>F</td>
<td>14</td>
<td>TSC2</td>
<td>AML</td>
<td>+37</td>
<td>1.3</td>
<td>27</td>
<td>37</td>
</tr>
<tr>
<td>8</td>
<td>F</td>
<td>50</td>
<td>NMI</td>
<td>Cyst</td>
<td>−24</td>
<td>0.8</td>
<td>21</td>
<td>16</td>
</tr>
</tbody>
</table>

AML, angiomyolipoma; F, female; M, male; NMI, no mutation identified; SD, standard deviation; TSC, tuberous sclerosis complex.

aAge in years at most recent imaging before lesion size change.
bTime in years over which change occurred.
cLongest diameter of the largest lesion measured in millimeters.
dLesions were biopsied for confirmation.

Table 5. Change in hepatic AML size in response to sirolimus treatment in patients with TSC

<table>
<thead>
<tr>
<th>Patient</th>
<th>Gender</th>
<th>Agea</th>
<th>Mutation</th>
<th>Sizeb Baseline</th>
<th>Sizeb On sirolimus</th>
<th>Change (%)</th>
<th>Sizeb Off sirolimus</th>
<th>Change (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>24</td>
<td>TSC2</td>
<td>21</td>
<td>11</td>
<td>−48</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>39</td>
<td>TSC2</td>
<td>29</td>
<td>22</td>
<td>−24</td>
<td>27</td>
<td>+23</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>38</td>
<td>TSC2</td>
<td>43</td>
<td>43</td>
<td>0</td>
<td>50</td>
<td>+16</td>
</tr>
</tbody>
</table>

AML, angiomyolipoma; F, female; TSC, tuberous sclerosis complex.

aAge in years at baseline imaging.
bLongest diameter of the largest lesion measured in millimeters.
cImaging performed at completion of 1 year of treatment, except for patient 2 (imaging performed at 5 months).
dImaging performed 6 months after completing treatment.

Lesion progression and regression

Of the 61 patients with hepatic lesions, 50 (82%) had multiple abdominal imaging studies available for review, and 8/50 (16%) experienced spontaneous change in lesion size over time (Table 4). Of the 25 patients in our cohort with hepatic AML, 5 (20%) were treated with sirolimus. Four of these five patients had enrolled in a phase II multicenter trial of sirolimus to treat renal AML (14), three of whom experienced change in hepatic AML size during or after treatment (Table 5). Apart from the aforementioned clinical trial, a 16-year-old female patient with a TSC2 mutation was treated with sirolimus for neurologic indications. After 6 months of treatment, routine imaging revealed that her largest hepatic AML had partially responded, as defined by RECIST criteria (15), with a 54% decrease (37 to 17 mm; Fig. 3), which has to date remained stable over 2 years of continuous therapy.

Discussion

This study has further characterized the hepatic phenotype in TSC by describing lesion progression, predictive variables, and relationships between hepatic, neurologic, and renal manifestations of the disease. The use of sirolimus for the treatment of hepatic lesions has shown promise, with some patients experiencing partial responses to therapy. Further studies are needed to evaluate the long-term efficacy and safety of sirolimus in the management of hepatic AML in patients with TSC.

Fig. 3. Axial, T2-weighted, fast relaxation fast spin echo magnetic resonance images showing the partial response, as defined by RECIST criteria (15), of a hepatic angiomyolipoma to sirolimus treatment in a 16-year-old, female patient with tuberous sclerosis complex. The longest diameter measured 37 mm on baseline imaging (a) and 17 mm on follow-up imaging 6 months after treatment initiation (b).
renal, and pulmonary lesions. Hepatic lesions were observed in nearly one-third of this TSC cohort. This prevalence lies within the range previously reported, however, does include other benign lesions in addition to AML (10–13).

TSC2 patients exhibited a higher frequency of hepatic AML compared to TSC1 patients (18% vs 5%, p = 0.037) and trended toward having larger hepatic AML. These findings refine the TSC2 phenotype and align with previous reports indicating that TSC2 mutations often lead to a more severe multiorgan clinical profile (10, 16, 17). The results from this study also support the notion that the clinical features of the NMI population are distinct from those of the TSC1 and TSC2 populations, thereby strengthening the possibility of an additional disease locus (18). Patients with NMI exhibited a higher frequency of hepatic cysts compared to TSC2 patients (36% vs 8%, p = 0.023), were more likely to have multiple hepatic lesions compared to TSC1 patients (80% vs 22%, p = 0.017), and trended toward having a lower frequency of hepatic AML compared to TSC2 patients. While it is possible that patients with NMI by standard sequencing have mosaic mutations in TSC1 or TSC2, the frequency of this occurrence has proven to be very low (19).

In contrast to previous reports, age and gender were not significantly associated with frequency of hepatic AML. (11–13). Previous suggestions of female predominance (12, 13) may have been influenced by unanticipated selection bias, because renal AML are more common in female patients (6) and likely prompt increased abdominal imaging in women, thereby inadvertently skewing the incidental detection of hepatic lesions toward women, as well.

Consistent with previous case reports, hepatic AML showed propensity for growth (20, 21). As sirolimus inhibits mTOR activity, the observed regression during treatment and growth after treatment suggests that hepatic AML growth and/or development may result from upregulated mTOR pathway signaling due to impaired tumor suppressor function. As has been previously suggested for renal AML, hepatic AML regression during treatment may be related to apoptosis or cell volume reduction (22).

A significant relationship was identified between the presence of hepatic and renal AML, as has been suggested in previous reports (12, 13). Because all patients seen at our center undergo routine abdominal imaging, we can conclude that this finding is not a result of selection bias. The hypothesis that renal AML and LAM share a common cellular origin and arise by means of “benign metastases,” the migration of histologically benign cells, has been supported by the detection of identical somatic TSC2 mutations and loss of heterozygosity (LOH) sequences in both renal AML and LAM cells from patients with sporadic disease (23). Given our finding, we hypothesize that hepatic AML may also arise from cells of the same origin as renal AML and LAM cells. Future studies investigating the molecular genetics of hepatic AML, renal AML, and LAM cells in patients with all three pathologies will determine if these manifestations have identical LOH and may substantiate the possibility that the visceral lesions of TSC share a common cellular origin.

Given the exploratory nature of this study, p values were not adjusted for multiple comparisons. Therefore, significant results should be validated in future studies. Also, as this study cohort includes only patients followed at a tertiary care center, these findings may be skewed toward more severely affected patients. Still, no patient in this cohort had clinical symptoms or complications from hepatic lesions. However, future prospective studies should evaluate hepatic enzyme levels to confirm that the lesions do not compromise hepatic function.

In summary, asymptomatic hepatic lesions are found in at least 30% of patients with a clinical diagnosis of TSC. Hepatic AML are more common in TSC2 patients compared to TSC1 and possibly NMI patients. Conversely, the prevalence of hepatic cysts is decreased in TSC2 and possibly TSC1 patients compared to NMI patients. The majority of patients with hepatic AML has coexisting renal AML. Hepatic AML have the ability to spontaneously grow over time, and some respond to mTOR inhibitors. Further delineation of the hepatic phenotype will help reveal the molecular mechanisms underlying visceral lesion development in TSC and may advance treatment options for symptomatic manifestations of the disease.

Acknowledgements

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References

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