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Case Report

Abstract

Tuberous sclerosis complex (TSC) is an autosomal dominant genetic disorder associated with cell proliferation disarrangements and high variability in clinical presentation. Only a few cases of colon cancer involvement have been reported. We report the case of a previously healthy adult, presenting with peritonitis due to perforation of a previously unknown colon cancer. The physical exam showed Tuberous sclerosis's skin stigmas, and the CT scan revealed several renal lesions, later identified as renal cell carcinoma. We performed a PUBMED search and found no association of colon and renal cancer reported in TSC patients. We believe this is the first report of colon adenocarcinoma and synchronous renal cell carcinoma occurring in a TSC patient. Furthermore, this rare presentation regarding the patient's age and the apparent lack of the expected neuropsychological features might suggest an unusual genetic alteration. In this communication we briefly review the genetic bases of TSC, its clinical expression, the colon and renal involvement reported in the literature as well as the possible mechanisms underlying our patient's features.

Keywords: Colon cancer, Tuberous sclerosis, Renal carcinoma.

Introduction

The Tuberous sclerosis complex (TSC) is an autosomal dominant disease, characterized by mutations in TCS1 and TCS2 genes leading to over activation of the mammalian target of rapamycin (mTOR) and other downstream proteins, producing cell proliferation disorders.1,2 Some data suggest a correlation between specific TCS1 and TCS2 mutations and different phenotypes.3,4 TSC comprise a wide range of presentations.5 The neuropsychological manifestations (mental retardation and seizures) are the most common, usually presenting in childhood and progressing through the years.6 Renal alterations are the second most common finding, with angiomiolipomas presenting in about 80% of the patients and renal cell carcinoma in only 2%.7 Gastrointestinal manifestations are fairly unusual, being hamartomatous rectal polyps the most common finding. Only a few cases of colon cancer have been reported.8

To date and, to our knowledge, there are no previous reports of renal cell carcinoma and colon cancer association in TSC patients.

Here, we report the case of an apparently healthy adult presenting with synchronous colon and renal cancer, later diagnosed with TSC owing only to dermatological findings. Additionally we performed a PUBMED search, and found just 4 reports of colon cancer in TSC patients9-12, none of them associated with renal cancer (Table 1). Therefore, we believe this is the first report of a TSC patient presenting with both colon and renal cancer. Finally, we review the literature and try to explain the patient's uncommon disease presentation.

Case presentation

A 56-year-old patient with past history of high blood pressure, anaemia and tobacco smoking was referred to our hospital complaining of abdominal pain. For the past 6 months he had experienced weight loss, asthenia, and constipation. On admission the physical examination revealed hypotension and peritonitis sings.

A CT scan was performed and showed a stenosing neoplastic lesion of the cecum which invaded the terminal ileum and lead to small bowel dilation and secondary perforation. Additionally several renal lesions...
were found: in the right kidney a solid mass of 15mm suggestive of renal cell carcinoma, 2 angiomiolipomas and 1 cyst were described, and in the left kidney 3 solid lesions of 55 mm, 27 mm and 10 mm, all of them of malignant appearance. The thorax scan only revealed small sub pleural bullae.

An urgent right hemicolectomy was performed with no major complications and posterior full recovery of the patient. The pathology examination described a high grade mucinous infiltrating adenocarcinoma, which comprised all bowel layers, with metastasis in 3 of 16 nodes (pT4a pN2). No malignant lesions were found on terminal ileum examination. Molecular analysis showed a N-RAS mutation in exon 3 (p.Q61L).

Two weeks after the colon surgery a laparoscopic left nephrectomy was performed. The pathology examination showed a chromophobe renal cell carcinoma of 5cm (pT3a) and a renal oncocytoma (0.5 cm).

During hospitalization, a most extensive physical examination was performed, showing periungual fibromas (>2) facial angiofibromas (>3) and 1 forehead fibrous plaque, therefore fulfilling TSC diagnostic criteria. The patient referred that his father and two paternal uncles presenting similar cutaneous features, however his 3 sisters had no apparent skins lesions, and he lacked further family. There was no personal or familiar history of seizures or mental impairment.

Discussion

Here, we report a unique presentation of TSC, in a patient who developed both a colon adenocarcinoma and a renal cell carcinoma. The gastrointestinal manifestation of TSC are unusual, and the occurrence of colon carcinoma is really rare. Renal cell carcinoma can be found in almost 2% of the TSC patients, but its association with colon cancer has not been previously reported.

We performed a PUBMED search using the Mesh terms “tuberous sclerosis” and “colorectal cancer”, with no date or language filter and found a total of 19 reports. Of them, we only included cases reporting colorectal cancer, thus finally obtaining 4 reports. None of them associated with renal cancer of any histology. The colorectal and renal histological findings, if present, in those 4 reports are described in Table 1.

<table>
<thead>
<tr>
<th>Case</th>
<th>Colorectal findings</th>
<th>Renal findings</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Adenocarcinoma</td>
<td>None</td>
<td>9</td>
</tr>
<tr>
<td>2</td>
<td>Leiomyosarcoma</td>
<td>None</td>
<td>10</td>
</tr>
<tr>
<td>3</td>
<td>Adenocarcinoma</td>
<td>Angiomiolipoma</td>
<td>11</td>
</tr>
<tr>
<td>4</td>
<td>Adenocarcinoma</td>
<td>Angiomiolipoma</td>
<td>12</td>
</tr>
</tbody>
</table>

The mammalian target of rapamicin (mTOR) is an essential component of two distinct multiprotein complexes, mTOR complex 1 (mTORC1) and 2 (mTORC2).

mTORC1 is activated by several upstream signals (including the MAPK pathway), leading to cell growth and proliferation. Hamartin (TCS1 gene product) couples to the proximal domain of tuberin (TCS2 gene product) and then the later downregulates mTORC1 function through a distal domain interaction. Hamartin and tuberin are both inhibited by various signals (including ERK). Functional mutations in TCS1 or TSC2 genes cause TSC.

It has been shown that specific TCS2 mutations, affecting its distal domain would still allow a correct TCS1-TCS2 coupling, but still entailing an impaired mTORC1 inhibition. Those mutations may be reflected in a mild neuropsychological phenotype (less seizures and mental impairment), albeit its highly variable. It seems possible that our patient could carry a distal TCS2 mutation, explaining its mild phenotype. Within these mTORC1 deregulation background, the NRAS activating mutation could also enhance the mTORC1 function by RSK (ribosomal S6 kinase) and decrease its inhibition trough ERK (both of them downstream protein in the MAPK pathway). This fact could also contribute to colon cancer carcinogenesis.

Conclusion

Here we have reported a unique clinical presentation and a possible mechanism to explain it.

Conflict of interest

The authors declare that they have no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

References