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Rapamycin Treatment for Benign Multicystic Peritoneal Mesothelioma: A Rare Disease with a Difficult Management

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Manuscript Preparation E
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Conflict of interest: None declared

Patient: Male, 65
Final Diagnosis: Multicistic peritoneal mesothelioma
Symptoms: Strong slimming
Medication: —
Clinical Procedure: —
Specialty: Nephrology

Objective: Unusual or unexpected effect of treatment

Background: Benign multicystic peritoneal mesothelioma (BMPM) is a rare intra-abdominal tumor. Although considered by many to be benign, this tumor has a high local recurrence rate. Because of its rarity, preoperative diagnosis is difficult and its origin and pathogenesis are uncertain. There are no evidence-based treatment strategies for BMPM. It is agreed that the best treatment strategy for BMPM is the combination of surgical cytoreduction and hyperthermic intraperitoneal chemotherapy (HIPEC). An increasing body of evidence supports a pivotal role of the cytoplasmic serine/threonine kinase mTOR in the development and progression of several neoplastic diseases and specific mTOR inhibitors, including rapamycin, have been suggested as potential therapeutic options for different cancers.

Case Report: A 65-year-old male with end-stage renal disease on hemodialysis for seven years presented with BMPM. He underwent surgery to remove multiple peritoneal cysts, but four months later he experienced a recurrence of the disease. Immunohistochemistry of the cysts demonstrated a high level of phosphorylation of p70S6 kinase, a downstream mTOR target, and since a target therapy that blocks PI3K/Akt/mTOR pathway has been shown to have a scientific and logical rationale to treat this rare intra-abdominal neoplasia, we started the patient on low dose rapamycin therapy, an mTOR inhibitor. Long-term mTOR inhibition resulted in a complete and stable remission of BMPM.

Conclusions: The current case is the first report of BMPM successfully treated with rapamycin, which resulted in a long-lasting response to mTOR inhibition.

MeSH Keywords: Mesothelioma, Cystic • Sirolimus • TOR Serine-Threonine Kinases • Treatment Outcome

Full-text PDF: http://www.amjcaserep.com/abstract/index/idArt/903548

Background

Mennemeyer and Smith [1] first described benign multicystic peritoneal mesothelioma (BMPM) in 1979. Although usually considered benign, this tumor has a high rate of local recurrence [2]. Clinical presentation depends on the size and location of the cysts, and is usually represented by abdominal tenderness, dyspareunia, constipation, urinary symptoms, and the detection of a palpable abdominal mass. The etiology and pathogenesis are still largely unclear as well as its treatment [3–6]. Indeed, it is still a matter of debate whether BMPM is a neoplastic disease or a reactive process [7,8]. Based on its uncertain etiology, no uniform treatment strategy has been established. In recent years, the combination of surgical cytoreduction and hyperthermic intraperitoneal chemotherapy (HIPEC) has resulted in considerable outcome improvements, but only in selected patients, and the rate of recurrence is higher [6]. Considering the potential of BMPM to relapse or evolve into an aggressive malignant tumor, multimodality treatment may be indication.

Mammalian target of rapamycin (mTOR), a cytoplasmic serine-threonine kinase, is a key molecular switch of protein translation and cell cycle progression [9]. An increasing body of evidence suggests that this kinase may play a pivotal role in the development and progression of several neoplastic diseases [10]. Guo et al. recently demonstrated that intra-peritoneal injection in mice of Cre adenovirus with conditional alleles of TSC1 leads to the constitutive activation of mTOR and development of mesothelioma [11]. In addition, they demonstrated that more than 60% of human mesotheliomas are characterized by mTOR activation [11]. The efficacy of mTOR inhibition has been clearly demonstrated in several malignancies and in cystic diseases [12–14].

Case Report

We describe the case of a 65-year-old male with end-stage renal disease who had been on hemodialysis for seven years and who had suffered significant weight loss (20 kg) over six months with a marked increase in abdominal girth. A CT scan performed on January 2011 showed abundant ascites and a right pleural effusion, excluding neoplastic lesions of lungs, liver, pancreas, and bowel. The patient underwent a paracentesis that did not demonstrate any cytological or microbiological alterations. In consideration of these findings, he underwent an intensive, daily, hemodialysis program without benefit.

He presented at our Division in April 2011 in poor clinical conditions with an advanced cachectic status and abundant ascites with diffuse abdominal distension and tenderness. Hepatitis C virus and hepatitis B virus serology were negative. A new CT scan demonstrated "a voluminous peritoneal fluid cyst extending from the diaphragm to the pelvis, displacing stomach, liver and bowel" (Figure 1A, 1B). Under ultrasonographic guidance, we collected a sample of the cyst fluid. Microbiological and cytological test results were negative.

Based on these findings, the patient underwent an explorative laparotomy. Intra-operative examination showed a diffuse peritoneal thickening with one major and several minor cystic lesions. At this point, we hypothesized a diagnosis of BMPM and we removed the multiple cystic peritoneal formations. The histological and immunohistochemical evaluation of the peritoneal cysts showed positivity for mesothelial cells markers and for calretinin and confirmed the clinical hypothesis of BMPM.

Four months after surgery, the patient presented with abdominal pain. A new CT scan demonstrated the presence of a new voluminous peritoneal cyst (Figure 1C). The patient refused a further laparotomy. Based on our findings of a significant phosphorylation of p70S6 kinase, a downstream target of mTOR, in the mesothelial cells obtained from the cyst fluid (Figure 2), and the existing literature [11–14], our Institutional Review Board approved the administration of rapamycin treatment; written informed consent was obtained from the patient. We administered the drug at an initial loading dose of 3 mg for the first day, and at a maintenance dose of 1 mg/day to obtain a blood through level of 3–5 ng/mL. After six months of rapamycin therapy, we observed reduction in the cyst volume (Figure 1D) and the patient's abdominal pain disappeared. The patient continued to take low doses of rapamycin (0.5 mg/day obtaining a mean blood trough level of 3.1±0.4 ng/mL). A CT scan performed after two years of treatment, found that the cyst had completely disappeared (Figure 1E, 1F). During the follow-up period, rapamycin was well tolerated and the patient did not present side effects.

Discussion

BMPM is a rare disease, characterized by a controversial pathogenesis and treatment. Some authors consider BMPM as a localized, benign neoplastic lesion arising from the mesothelial cells [2]. The hypothesis of a neoplastic origin is based on the slow, but progressive growth of the lesions, the tendency to recur after surgical resection, and the high disease-related mortality in advanced stages [15,16]. On the other hand, a second hypothesis suggests that the underlying cause of BMPM might be represented by a diffuse chronic peritoneal inflammation leading to the proliferation and migration of mesothelial cells and the subsequent formation of the cystic lesions.

In our case, we demonstrated an increased phosphorylation of p70S6 kinase, a downstream target of mTOR, in mesothelial

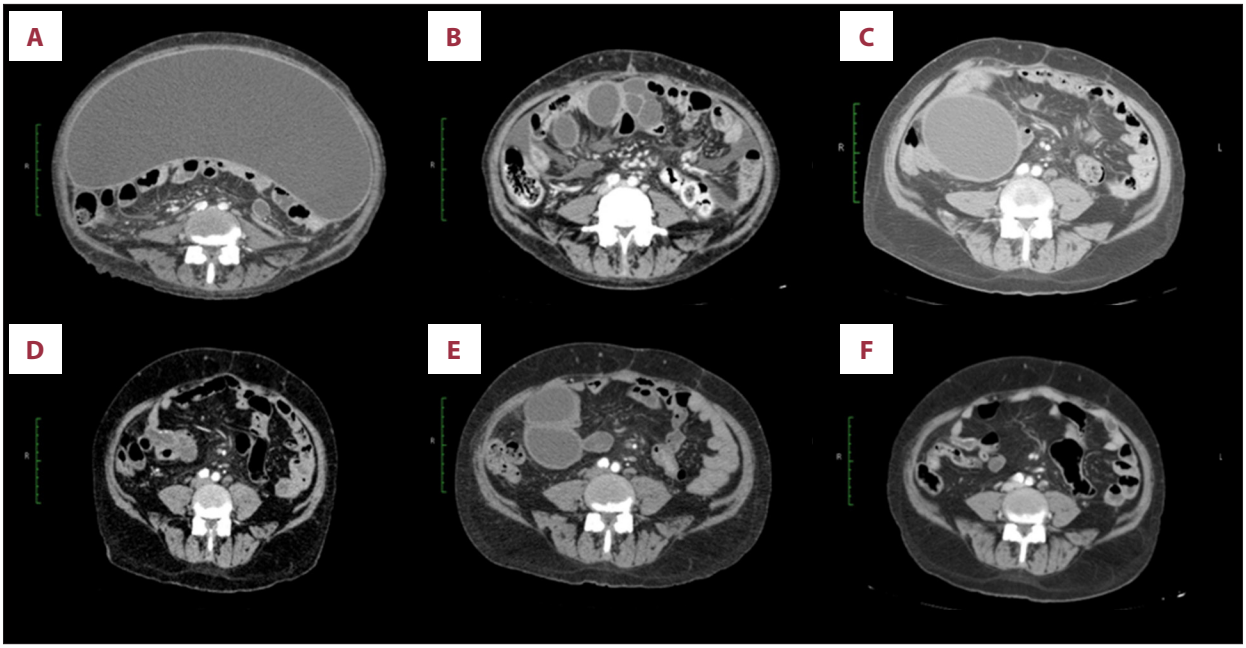

Figure 1. (**A, B**) CT scan image of the voluminous peritoneal cyst at the arrival in our Division. (**C**) CT scan image after four months laparotomy to remove the multiple cystic peritoneal formations performed. (**D**) CT image six months after rapamycin therapy. (**E, F**) The last CT image 24 months after rapamycin therapy.

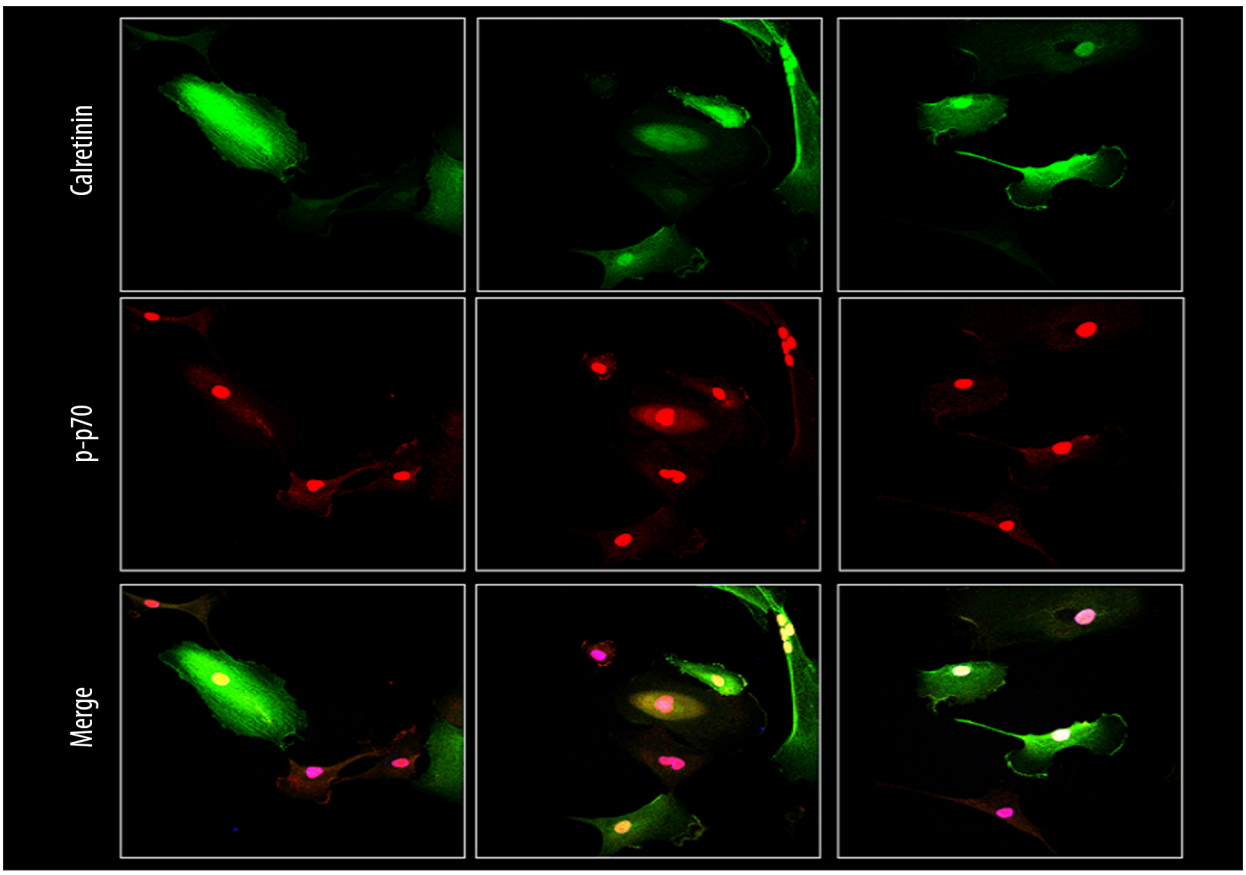

Figure 2. Confocal microscopy demonstrates the co-expression of specific mesothelioma cell markers (calretinin) and p70SK phosphorylation in cells obtained from the cyst fluid examined.

cells of the cystic lesions in our patient. This cellular event has often been used a reliable marker of mTOR activation and has been suggested as a potential phamacodynamic target to monitor the efficacy of mTOR inhibition. Our observation of a hyper-phosphorylation of p70S6 kinase in the cells obtained from the BMPM cysts may support the neoplastic hypothesis suggesting an activation of mesothelial cells resembling the one observed in mesothelioma. In addition, the observation in our patient of a prompt and stable response to rapamycin treatment clearly suggested a key role for mTOR in the pathogenesis of the disease and further supported the hypothesis of a neoplastic nature of BMPM. Indeed, the PI3K/Akt/mTOR pathway has been shown to play a role in the development and progression of several neoplastic diseases [17–19]. mTOR sits at an intersection of several inputs to the cell, integrating signals from both growth factors and nutrients and mediating its effects through two main effectors, p70S6 kinase and 4E-BP1/eIF4E, with a well-defined role in the regulation of protein translation [17,18,20]. The mTOR pathway can, indeed, promote neoplastic cell survival and proliferation through the phosphorylation and sequestration of the pro-apoptotic Bad [21], upregulation of FLIPs [22], translation of anti-apoptotic proteins, and support of the mitochondrial energy production [17,23,24]. Thus, great interest has arisen in the potential benefits of mTOR inhibition in tumors. In an interesting and elegant study, Wilson et al. suggested that mTOR was the key effector of mesothelioma cells survival, suggesting a therapeutic role for mTOR inhibition in mesothelioma [25]. Altomare et al. [26] reported that 65% of their cases of mesothelioma were characterized by an elevated phosphorylation and subsequent activation of AKT, the serine kinase upstream of mTOR in the signaling cascade. In addition, they demonstrated, for the first time, a homozygous deletion of PTEN in one of their patients [26]. Zhou et al. [27] reported the activation of the PI3K/AKT/p70S6K pathways in mesothelioma but not in non-neoplastic mesothelial cells. In addition, AKT activation was directly related to the coordinated activation of receptor tyrosine kinase EGFR, MET, and AXL. The inhibition of the mTOR pathway obtained the same anti-proliferative effect observed by the concurrent inhibition of EGFR, MET, and AXL. Dual targeting of PI3K/mTOR by a combination of everolimus, a specific mTOR inhibitor, and AKT knockdown had a greater effect on mesothelioma proliferation and viability than inhibition of individual activated RTKs or downstream signaling intermediates [27]. Finally, Guo et al. [11] clearly demonstrated that constitutive mTOR activation in mesothelial cells, induced by TSC deletion, induces the development of mesothelioma in mice.

Interestingly, several studies have clearly suggested that the anti-neoplastic effect of mTOR might be, at least partially, due to its well-known anti-angiogenic action [12,28]. Since in our case we did not observe any sign of neoangiogenesis in the BMPM lesions (data not shown), it is unlikely that the beneficial effects of mTOR inhibition that we observed was correlated with the anti-angiogenic effect of rapamycin, further supporting the hypothesis of a direct effect on mesothelial cell of the cysts. Since we do not have any reliable information on the pathogenesis of cyst formation in this particular setting we cannot conclude whether the results on cysts' growth induced by mTOR inhibition might be linked only to the inhibition of mesothelial cells proliferation or to a specific effect of this signaling pathway on cell polarity and secretion demonstrated in other settings [14,29].

Interestingly, the dose of rapamycin used was extremely low when compared to the immunosuppressive doses currently employed for kidney transplantation. This observation might explain the lack of infections and side effects in our case that are often observed in the transplant setting.

Conclusions

In conclusion, based on our knowledge that mTOR pathway is activated in several malignancies and on our previous positive experiences with mTOR inhibition in cystic diseases, the use of rapamycin could be a logical option for the treatment of BMPM. Our report is the first case of BMPM successfully treated with rapamycin with a long-lasting response to mTOR inhibition. This observation suggests new opportunities in the therapy of this rare abdominal neoplasia which has been a difficult disease to manage.

Conflict of Interest

The authors have no conflict of interest to declare.

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