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A Rare Case of Progressive Malignant Triton Tumor With Rare Somatic Mutation in *TSC2* Gene

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Abstract. *Background: Malignant triton tumor (MTT) is a rare subtype of malignant peripheral nerve sheath tumor with additional rhabdomyolysis differentiation that shows rapid progression and poor clinical outcomes. Case Report: We report the case of an adult male with a metastatic MTT. Despite extensive counseling, the patient initially refused recommended treatment. Upon disease progression, the patient was admitted to our institution and multiple distant organ metastases were found. The patient underwent an above-knee amputation followed by palliative chemotherapy. The patient died a few months later due to rapid disease progression. Conclusion: To our knowledge, this is the first report of a case of MTT with multiple splenic metastases. We also describe the first finding of a frame-shift mutation in the tuberous sclerosis complex 2 (TSC2) gene in a patient with MTT. Because of limited clinical experience and the lack of clinical trials, the effects of chemotherapy and radiation therapy for MTT remain controversial. However, given the aggressive nature of these tumors and the tendency for early recurrence and metastasis, prompt diagnosis and early surgical treatment are crucial for the best outcomes.*

Malignant triton tumor (MTT) is an extremely rare histological subtype of malignant peripheral nerve sheath tumor (MPNST) with rhabdomyoblastic differentiation (1). This tumor type is thought to arise from the Schwann cells of peripheral nerves or nearby cells or within pre-existing neurofibromas (2). In general, the prognosis of patients with MTT is poor, and this entity has an aggressive nature with a very high rate of local recurrence and early distant metastasis (3). Worse prognosis is mainly associated with tumor location (trunk, buttocks, retroperitoneal and central nervous system), extent of surgical excision, degree of differentiation (undifferentiated, invading ones), and Ki67 labeling index (4). Although the association of genomic alteration and prognosis of MTT has not been fully investigated, however, there have been a few studies that evaluated such a relationship, and associated pooerr survival with tumors having gains and loss of particular genes (5, 6). Here we present a rare case of MTT with multiple distant organ metastases, including the spleen and colon, in a patient without neurofibromatosis type 1 (NF1). We also performed sequencing analysis for prognostic evaluation that revealed a shift mutation of tuberous sclerosis complex 2 (*TSC2*). To our knowledge, this is the first report of a case of MTT with multiple splenic metastases, and of a frame-shift mutation in the *TSC2 ge*ne in a patient with MTT

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Case Report

A 49-year-old Hispanic man presented to the Emergency Room of our Institution in March 2020 with severe leg pain secondary to a mass in his left leg. The patient's medical history was significant for type II diabetes mellitus, essential hypertension, and cerebral ischemic stroke with residual right hemiparesis. His history was remarkable for smoking (90-100 packs per year) but there was no history of alcohol consumption or recreational drug use. There was no significant family history of cancer or any inherited conditions. He had initially presented to the orthopedic surgery clinic in November 2019 with a slowly enlarging mass on his left leg associated

with moderate pain. At that time, physical examination revealed a tender and firm mass, measuring approximately 10×10 cm, with no significant overlying skin changes. There were no clinical signs of neurofibromatosis type 1 (NF1), such as café au lait spots or subcutaneous nodules. Computerized tomography (CT) of the left leg showed a larger mass just inferiorly that involved the proximal leg and the popliteal fossa, measuring up to 14×10×16 cm with encasement of the popliteal vessels and proximal anterior tibial, peroneal, and posterior arteries and veins (Figure 1A).

He subsequently underwent a CT-guided biopsy of the left leg mass. The pathology report showed connective tissue fibers infiltrated by diffuse sheets of neoplastic spindle cells consistent with rhabdomyosarcoma. During the further staging examination with CT, only two irregular solid pulmonary nodules were identified in the right upper and middle lobes, measuring 1.0×0.8 cm and 0.7×0.5 cm (Figure 1B). The patient refused all recommended treatment and discharged himself from the clinic. He presented again to the Emergency Room in March 2020 due to worsening of left leg pain, swelling, and drainage from the infected leg mass. He underwent further diagnostic workup. A positron-emission tomography/CT scan showed multiple lung lesions, and also a new hypodense mass 3.2×2.9 cm was discovered in the lower pole of the spleen (Figure 1C).

The patient underwent a palliative above-the-knee amputation. The final pathological diagnosis described a high-grade malignant peripheral nerve sheath tumor (MPNST) with rhabdomyeloblastic differentiation, consistent with a malignant triton tumor (MTT) (pathology was submitted for additional review to a specialized sarcoma center) (Figure 2). The submitted immunostain showed that the neoplasm had focal positive staining for myogenin, desmin, smooth muscle antibody (SMA), muscle specific actin (MSA), and transducing-like enhancer of split 1 (TLE1). The tumor was negative for S100, pan-keratin, epithelial membrane antigen (EMA), cluster differentiation 34 (CD34), melanoma antigen recognized by T-cells 1 (MART-1), and signal transducers and activators of transcription 6 (STAT6). Beta-catenin exhibited a non-nuclear staining pattern.

We also submitted the sample of the tumor tissue for mutation profiling to FoundationOne© (Cambridge, MA, USA). Their analysis showed a frame-shift mutation in *TSC2* (R1474fs * 50), amplification of *MYCN* proto-oncogene, bHLH transcription factor, and splicing of chaperonin containing TCP1 subunit 6B (CCT6B) (site 615-2A>g). The patient was referred to the medical oncology clinic, and palliative chemotherapy with a single-agent doxorubicin was recommended. He completed five cycles of the chemotherapy, which he tolerated pretty well. Unfortunately, the follow-up CT scan showed significant progression of metastatic disease with development of innumerable pulmonary nodules, multiple metastatic lesions in the hepatic and splenic parenchyma, and innumerable soft-tissue density deposits along the left lateral pelvic sidewall. The patient decided to discontinue palliative chemotherapy and subsequently was referred to hospice care and died within a few weeks.

Literature review. We conducted a comprehensive literature search in PubMed using the term 'malignant triton tumor' without specifying a time period. The advanced search option extracted all MTT cases published in the English language in the databases. We identified a total of 160 articles. Case series and retrospective studies that provided updated clinical information, diagnosis and treatment guidelines were included. Single case reports, literature published in other languages and studies that lacked detail of updated diagnosis and treatment guidelines were excluded. Among the articles retrieved by this search, only seven studies met the criteria and were selected to be summarized here. We included relevant information such as study type, the study's aim, and major conclusions or outcomes as outlined in Table I.

Discussion

MTT is a rare subtype of MPNST with rhabdomyeloblastic differentiation (13). The tumor's origin is poorly understood but some research suggests that it might arise from the Schwann cells of peripheral nerves or nearby cells, or from within pre-existing neurofibromas (in NF1) (2). Interestingly, 50-70% of MTT cases have been associated with NF1, while the rest were sporadic (10, 14). NF1-associated MTTs commonly occur in males at a relatively early age (20-30 years) and often involve the head and neck region, whilst in females, sporadic cases commonly occur and in a slightly older age group (30-50 years); the most frequent location of MTT is on the trunk and extremities (9, 15). In our case, the was a 49-year-old male without NF1 or any other germline mutation.

MTT was described as a new disease in humans in 1932 by Masson and Martin after they found rhabdomyosarcomatous elements within MPNST in patients with NF1 (16). Historically, the unusual name 'triton' is derived from an experimental triton salamander which developed a neoplasm with skeletal muscle components after sciatic nerve implantation on its dorsal surface (17). Woodruff *et al.* broadened the definition of the disease in 1973, renaming it 'malignant triton tumor' for the first time because of its aggressive biological behavior (17).

Since MTT is a very rare malignancy, there are no established disease-specific signs or symptoms. Based on multiple case reports, most patients with MTT presented with a new onset of rapidly enlarging mass located on the trunk or extremity, accompanied by pain. The disease can rarely be asymptomatic and found only incidentally on imaging studies (18). There are no additional clues or signs that can help to

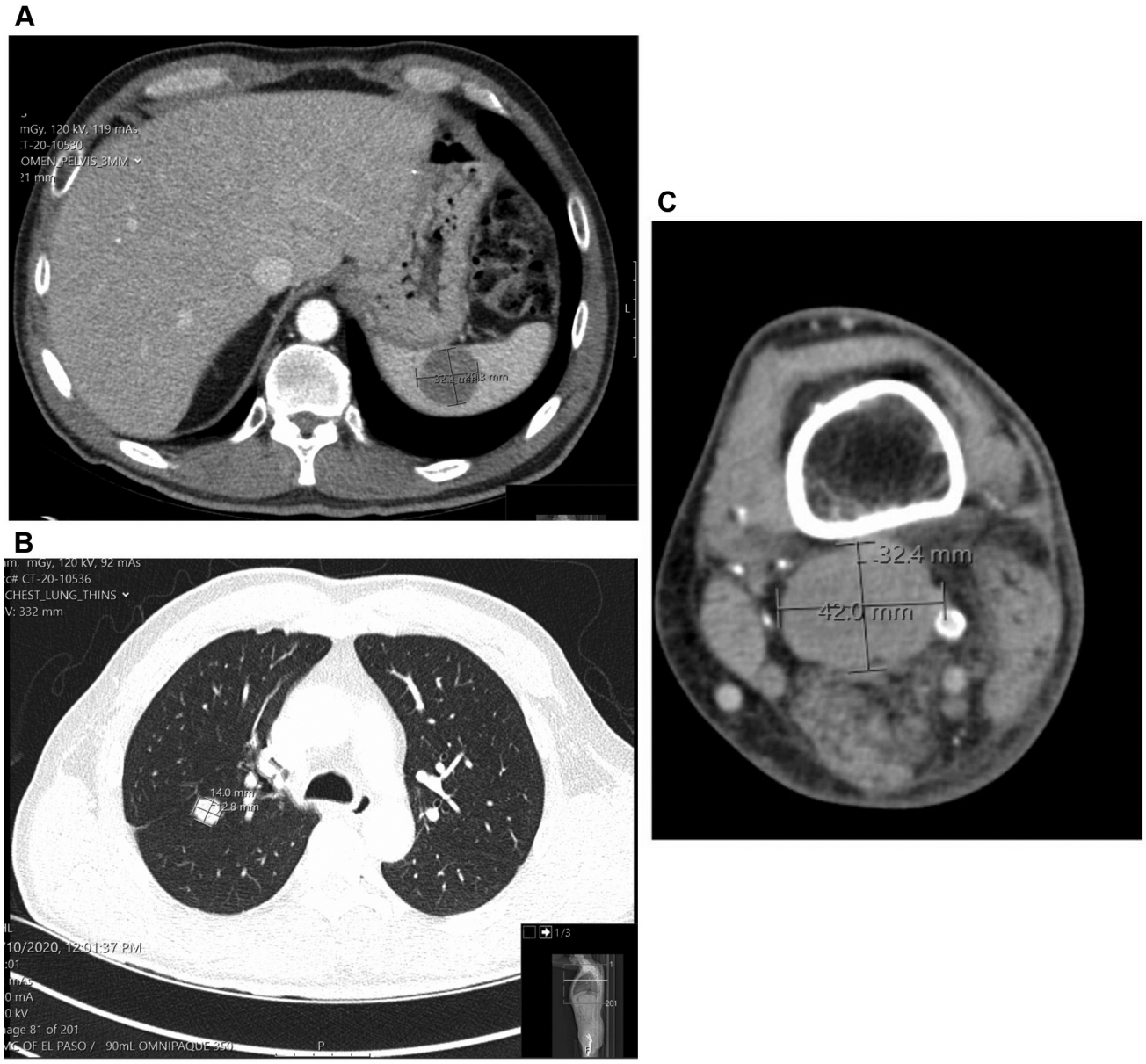

Figure 1. *Computed tomography (CT) of the tumors of the right lower extremity, spleen and lungs. A: At first presentation, CT revealed a large primary mass involving the proximal leg and the popliteal fossa, measuring up to 14×10×16 cm, with encasement of the popliteal vessels and proximal anterior tibial, peroneal and posterior arteries and veins (November, 2019). B: Two irregular/lobulated solid nodules were also found in the right upper and middle pulmonary lobes (November, 2019). The patient refused treatment. C: The patient returned and positron-emission tomography/CT showed apparent asymmetric thickening of the distal rectal wall up to 1.6 cm, an enlarged 8.5 mm right lower lobe pulmonary nodule, and an enlarged 3.2×2.9 cm hypodense splenic mass more pronounced in the lower pole of the spleen (March, 2020).*

suspect MTT. The 'gold standard' for establishing the diagnosis of MTT is biopsy of the mass. In order to confirm the diagnosis of MTT, the tumor should meet the following criteria: i) It should be connected to peripheral nerves or occur in patients with NF1; ii) most of the tumor should consist of Schwann cells; and iii) it should contain rhabdomyoblasts (19). Moreover, the diagnosis should be supported by positive staining for S-100. Imaging studies such as magnetic resonance imaging and CT help stage MTT and reveal additional tumor characteristics. In the past, some studies demonstrated the critical role of fluoro-deoxyglucose positron-emission tomography in distinguishing MTT from benign PNST (20, 21).

Clinically, MTT is characterized by aggressive tumor behavior, frequent relapse, and resistance to chemotherapy and radiation therapy (22). For unknown reasons, the worst prognosis appears to be associated with tumor location on the trunk, buttocks, retroperitoneal, and central nervous system (23). In contrast, patients with tumors located on the upper or lower extremities have historically had more favorable outcomes (probably because of the increased likelihood of complete surgical resection). But regardless of the tumor location, the overall prognosis is poor (24). In one extensive retrospective analysis of 124 cases of MTT, the overall 5-year survival rate was 14%, with median survival of only 13 months. The rate of local recurrence or systemic progression was 50%. The study also showed that 31.4% of patients had metastatic disease at initial presentation, with metastases predominant in the lung, followed by bone, liver, peritoneum, and the central nervous system (25).

In the modern era of individualized medicine, the genetic analysis of tumor somatic mutations has become a standard of care and changed the paradigm of cancer management. We now use small molecules to inhibit oncogenic proteins, tyrosine kinase enzymes, or even whole pathways in tumor cells. At present, however, we do not have much data about the association of specific genomic alterations and outcomes for MTT. Only a few studies have evaluated gene mutation profiles in MPNST. They reported that the most frequent somatic alterations in MPNST were in neurofibromin 1 (*NF1*) (92%), cyclin dependent kinase inhibitor 2A/r B (*CDKN2A/r B*) (58%), polycomb repressive complex 2 (*PRC2*), suppressor of zest 12 (*SUZ12*) (42%), and tumor protein 53 (*TP53*) (50%) (26). The association of genomic alteration with prognosis of specific soft-tissue tumor subtypes has not yet been extensively investigated (27). Several studies have attempted to evaluate such relationships. Importantly, those studies showed that mutation in *CDKN2A* or *CDKN2B* resulted in poorer survival among patients (5, 28, 29).

To better understand the biology of MTT and in the attempt to identify a targetable mutation, we examined the tumor mutation profile of the presented patient. We identified a low tumor mutational burden (one mutation per megabase) for this microsatellite-stable tumor. We also identified a frame-shift mutation in the tumor-suppressive protein *TSC2 (*R1474fs*50), which is associated with the loss of TSC2 function. Based on the literature, the loss of TSC2 protein function has been associated with the activation of the mammalian target of rapamycin (mTOR) pathway (30). The mechanism of mTOR regulation by TSC2 is not well understood. However, the most accepted explanation is that mTOR activation is controlled by the protein Ras homolog enriched in brain (RHEB) (Figure 3). The TSC2 and TSC1 complex proteins activate GTPase, keeping RHEB inactive and thus preventing mTOR activation (31).

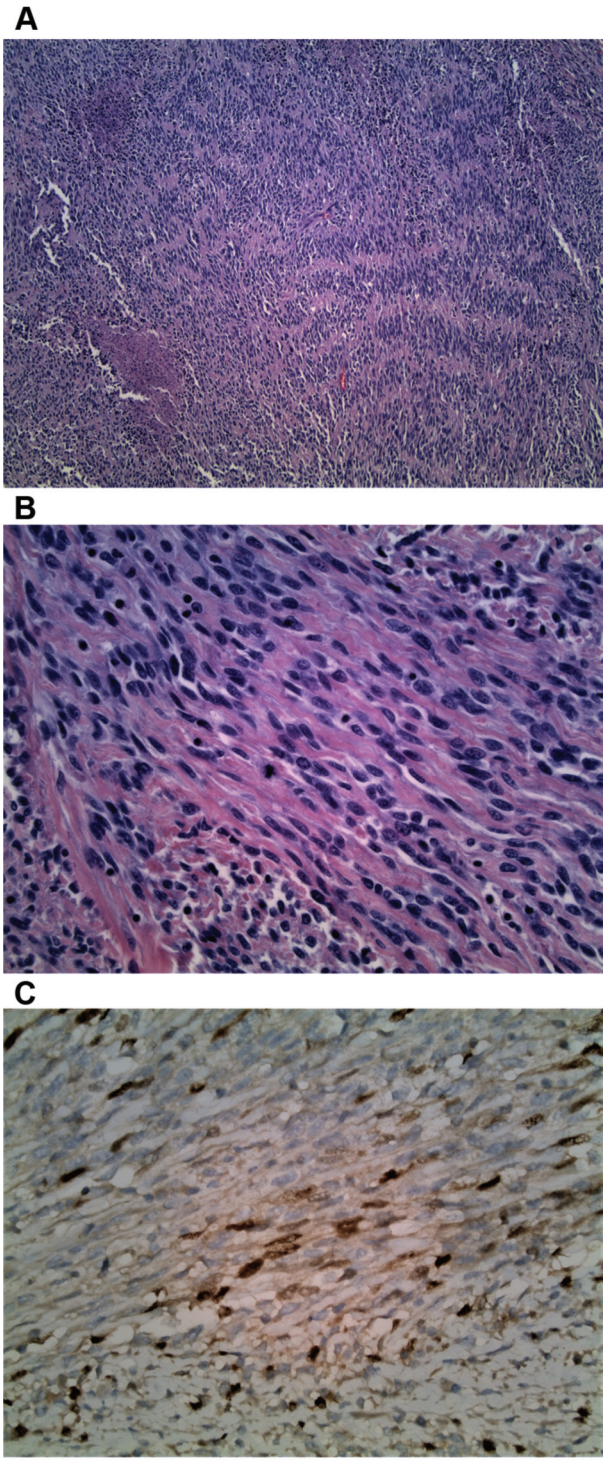

Figure 2. *Histopathological examination of the resected primary tumor. A: Low-power view showing a cellular tumor with palisaded nuclei of tumor cells consistent with the neural origin. There is also focal necrosis in the lower left portion of the image [hematoxylin and eosin stain, original magnification ×100]. B: High-power view showing large and spindle nuclei with occasional mitoses (hematoxylin and eosin stain, original magnification ×400). C: Some tumor cells show nuclear staining for myogenin (immunohistochemical stain, original magnification ×400).*

Table I. *A summary of seven case series and retrospective studies of malignant triton tumor (MTT) that provide detailed and updated clinical information, diagnosis and treatment guidelines.*

Reference	Cases, n	Type of study	Aim of study	Major conclusion
Bian *et al*. (7)	10	Retrospective review and outcomes	Describe the largest number of cases characteristic	Neoplasm associated with pain was the primary manifestation. Patients had a poor prognosis. The overall local recurrence rate was 50%. Immunohistochemical staining helps identify the origination of tumor cells – positivity for desmin, actin, and myogenin in the confirmation of rhabdomyoblastic differentiation. Complete surgical excision of the tumor is the only treatment. Additional radiation or chemotherapy shows little effect.
Bridge *et al*. (8)	38	Retrospective study	Characterize the cytogenetic features of MTTs and MPNSTs	Cytogenetic analysis revealed predominantly complex karyotypes. Overall, loss of chromosomal structure was more common than gain. Gains and losses were distributed equally between MPNST and MTT, confirming these tumors are similar with respect to recurrent genomic alteration. None of the recurrent chromosomal imbalances was restricted to either NF1-associated or sporadic MPNST. FISH analysis was negative for amplification.
Rekhi *et al*. (9)	10	Case series	Describe clinical and morphological features of MTT, diagnosed over a 10-year period	Average age of patients was 30 years, with a predominantly male population. More cases were associated with NF1. On histology, 80% of cases were of high grade, with distinct rhabdomyoblastic cells identified in PNSTs. Neurogenic differentiation with varying S-100 expression and rhabdomyoblastic differentiation with desmin and myoglobin positivity in all cases were confirmed by immunohistochemistry. Surgery with adequate margins constituted the treatment mainstay with adjuvant chemotherapy and/or radiotherapy in individual cases.
Alina *et al*. (10)	2	Case report	Report MTT associated with NF1 in two sisters	This study concluded that there are conflicting recommendations in the literature regarding the optimal treatment of MTTs. Further investigations and case reports are necessary in order to continue contributing to our knowledge of MTTs, their clinical courses, and treatment outcomes.
Tsagozis *et al*. (11)	24	Retrospective review	Analyze the association of surgical margins with overall and tumor recurrence-free survival	Surgery remains the mainstay of treatment for MTTs. Patients with MTT of the trunk and the extremities have a poor prognosis, with a high rate of metastatic disease. Local resection with a surgical margin of at least 1 mm is important for the outcome of curative treatment.
Chaudhry *et al*. (12)	3	Case series	Report a case series according to surgical case series criteria.	MTT of the mediastinum has a poor prognosis because it is difficult to obtain a wider tumor-free margin.
Li *et al*. (1)	2	Case report with retrospective literature review	Describe clinical features and identify potential prognostic factors	Complete resection and metastases were associated with mortality, indicating that complete resection may lead to a longer life span and that the existence of metastasis suggested a worse prognosis for patients with MTT.

FISH: Fluorescent *in situ* hybridization; MPNST: malignant peripheral nerve sheath tumor; NF1: neurofibromatosis type 1.

Interestingly, mTOR pathway activation has been commonly reported in various sarcomas but the precise mechanism involved is unclear. Some studies suggested that mTOR activation in sarcomas is TSC2-independent since *TSC2* mutation or homozygous deletion is extremely rare in sarcomas and has not been reported in the large Sarcoma

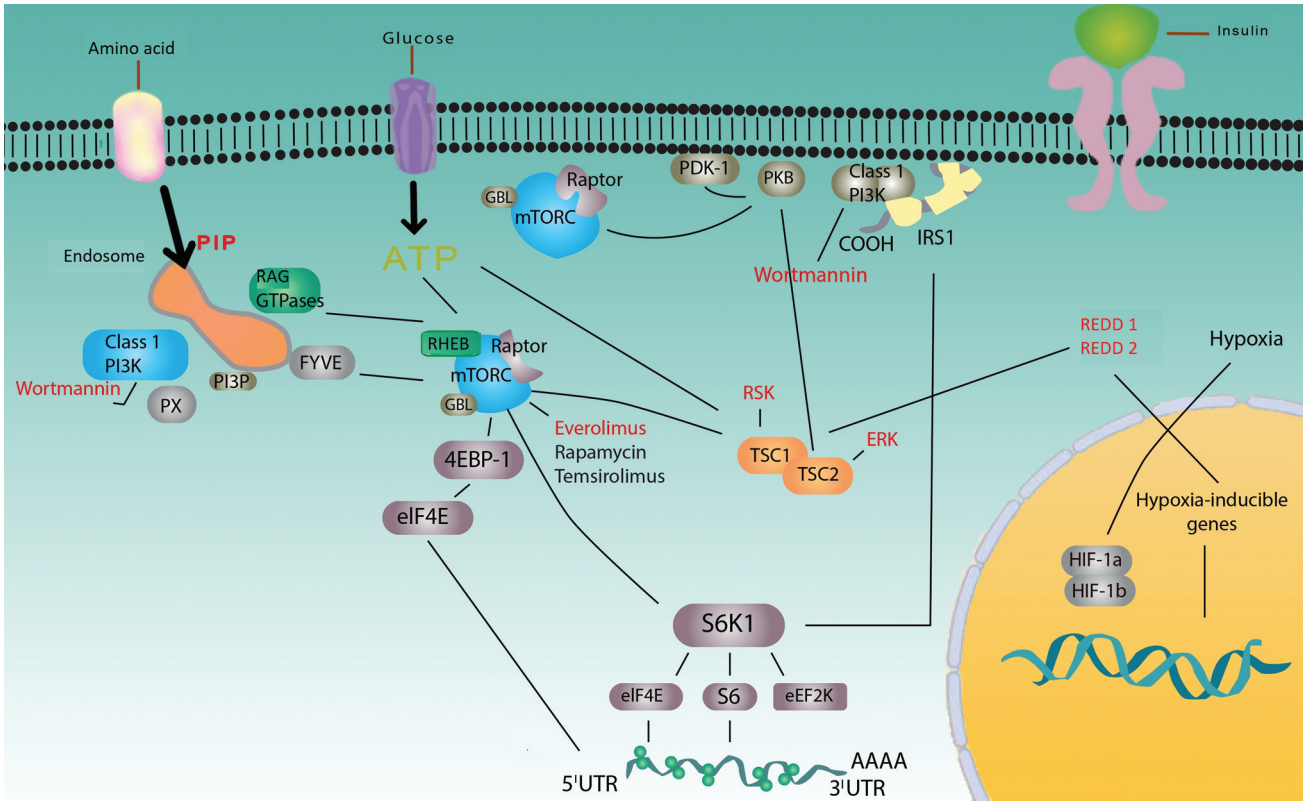

Figure 3. *The role of the mammalian target of rapamycin (mTOR) signaling pathway in the development of tuberous sclerosis complex (TSC) and inhibition by mTOR inhibitors. (With special thanks to Ahmet Cemal and Fatih Bozdogan, Orange Grove and Catalina Middle School 6th and 10th grade students, for their effort in designing this schematic image). 4EBP-1: Eukaryotic translation initiation factor (eIF4E)-binding protein 1; ATP: adenosine triphosphate; eEF2K: eukaryotic elongation factor-2 kinase; ERK: extracellular signal-regulated kinase; GBL: G-protein beta subunit-like; HIF1a/b: hypoxia-inducible factor 1 a/b; IRS1: insulin receptor substrate 1; PDK-1: pyruvate dehydrogenase kinase-1; PI3K: phosphatidylinositol-3-kinase; PIP: phosphatidylinositol-trisphosphate; PKB: protein kinase B; Rag GTPase: Rag guanosine triphosphatase; RHEB: Ras homolog enriched in brain; RSK/S6K1: ribosomal protein S6 kinase; S6: secondary 6; UTR: untranslated region.*

Genome Project data set (n=207 cases). *TSC2* mutation was sporadically reported in uterine angiosarcoma and multiple benign tumors such as hamartomas, chordomas, perivascular epithelioid cell tumors, and rhabdoid tumors (32). Therefore, the exact role of TSC2 alterations in sarcomas is unclear (33).

In clinical practice, mTOR inhibitors have been used for many years to treat metastatic breast cancer, renal-cell carcinoma, and subependymal giant-cell astrocytoma (34). Based on multiple clinical trial results, the US Food and Drug Administration has approved two mTOR inhibitors: Everolimus and temsirolimus (35). The data on the efficacy of mTOR inhibitors in other tumor types are limited to small phase I/II clinical trials and sporadic case reports. In one case report, a near-complete response was reported after using everolimus in *TSC2*-mutated anaplastic thyroid cancer (36). In the second report, a complete response was observed in a patient with *TSC2*-mutated Hodgkin's lymphoma (37).

The *MYCN* amplification was the second abnormality found in our case. *MYCN* encodes MYC family proteins. Those proteins are thought to act as oncoproteins by preventing cell differentiation and promoting proliferation. A high MYCN expression level was reported in some cases of synovial sarcoma and Ewing sarcoma (38). Surprisingly, *MYCN* amplification has not been reported in the Sarcoma Genome Project data set (39). Clinically, there are no specific inhibitors approved for combating *MYCN* amplification (40). However, some preclinical studies suggest a possible role of CDK2 and aurora kinase A and B inhibitors in patients with *MYCN*-amplified tumors (38, 41).

The major challenge for medical oncologists is to develop an optimal treatment plan for patients with MTT. Given the disease's rarity and lack of evidence-based guidelines, there is a great gap in our knowledge regarding the optimal management plan. Traditionally, management is based on expert opinions and data from successfully treated patients described in case reports. In general, most experts agree that the best initial treatment for local or locally advanced MTT is radical surgical excision. There is no clear role for adjuvant

radiotherapy and chemotherapy but those approaches might be offered if radical surgery cannot achieve clear resection margins. Limited data have suggested the best outcomes are achieved for patients undergoing complete tumor resection (11). Based on analysis of published reports, postoperative radiotherapy, chemotherapy, or chemotherapy combined with radiotherapy showed a positive effect on survival; however, none of the treatment options mentioned above has been shown to reduce the recurrence or progression of MTT postoperatively (1). Therefore, further studies are needed to ascertain the exact role of chemotherapy and radiotherapy in patients with MTT.

Conclusion

MTT is a lethal neoplasm with a dismal prognosis, particularly in the advanced stage with distant metastasis. Because of limited clinical experience and lack of clinical trials, the effect of chemotherapy and radiation therapy for MTT remains controversial. However, given the aggressive nature of these tumors and the tendency for early recurrence and metastasis, prompt diagnosis and optimal treatment with clinical and radiological follow-up are crucial.

Conflicts of Interest

None of the Authors have any financial or personal bias to declare. The Authors report no conflicts of interest.

Authors' Contributions

SR Ghafouri and A Philipovskiy completed the background research, drafted and edited the article and approved publication. MN Hakim, IT Konstantinidis, and L Kafchinski edited and finalized the article.

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