Sirolimus for treatment of refractory capillary malformations in SMA and PROS

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Abstract

An adolescent female with ventilator-dependent spinal muscular atrophy type 1 (SMA-1) and megalencephaly-capillary malformation-polymicrogyria (MCAP) syndrome had been struggling with recurrent small to large volume hemoptysis for years secondary to complex arteriovenous malformations (AVMs) in her lungs. Despite numerous embolizations, she continued to experience hemoptysis from new AVMs. She was then started on sirolimus (rapamycin) and remains hemoptysis-free for over 12 months. To our knowledge, there are no known cases of SMA-1 with MCAP syndrome and related complex vascular malformations successfully treated with sirolimus.

Sirolimus for treatment of refractory capillary malformations in SMA and PROS

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Running Head : Use of sirolimus in a patient with SMA and PROS

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Abbreviations : *listed in order as they appear in the manuscript*

SMA-1 - spinal muscular atrophy type 1

MCAP – megalencephaly-capillary malformation-polymicrogyria syndrome

SMN1 – survival motor neuron 1

PIK3CA – phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha

PI3K – phosphatidylinositol 3-kinase

PROS – PIK3CA-related segmental overgrowth spectrum

mTOR – mammalian target of rapamycin

IR – interventional radiology

AVMs – arteriovenous malformations

CBCs – complete blood counts

LFTs – liver function tests

CT – computed tomography

VEGF – vascular endothelial growth factor

AKT – protein kinase B

CLOVES – congenital lipomatous overgrowth vascular malformations-epidermal nevi-skeletal abnormalities

pTEN – phosphatase and tensin homolog

FKBP – FK506 (sirolimus) binding protein

SRL – sirolimus

AKT – serine/threonine kinase

pKB – protein kinase B

eIF4E – eukaryotic translation initiation factor 4E

S6 – ribosomal protein

Table of Contents Summary : Case detailing use of sirolimus for treatment of vascular malformations causing recurrent hemoptysis in the first known case of SMA-1 in association with MCAP syndrome.

Contributors' Statement Page

Drs. Hanson and Ghera conceptualized and designed the study, drafted the initial manuscript,

and reviewed and revised the manuscript. Both authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Abstract :

An adolescent female with ventilator-dependent spinal muscular atrophy type 1 (SMA-1) and megalencephaly-capillary malformation-polymicrogyria (MCAP) syndrome had been struggling with recurrent small to large volume hemoptysis for years secondary to complex arteriovenous malformations (AVMs) in her lungs. Despite numerous embolizations, she continued to experience hemoptysis from new AVMs. She was then started on sirolimus (rapamycin) and remains hemoptysis-free for over 12 months.

To our knowledge, there are no known cases of SMA-1 with MCAP syndrome and related complex vascular malformations successfully treated with sirolimus.

Introduction :

SMA is an autosomal recessive genetic disorder caused by a mutation in SMN1 gene, resulting in progressive degeneration of the spinal cord and brainstem motor neurons.[1,2]

Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (*PIK3CA*) encodes the p110α isoform of phosphatidylinositol 3-kinase (PI3K).[3] Activating mutations in*PIK3CA* have long been linked to cancerous conditions and more recently linked to non-cancerous conditions such as PIK3CA-related segmental overgrowth spectrum (PROS).[3] PROS is an umbrella term that encompasses a heterogeneous group of rare, non-cancerous yet debilitating congenital conditions.[3,4]

One specific PROS presentation is MCAP syndrome, which typically presents at birth with macrocephaly and hemihyperplasia and can be progressive.[5,6] Affected individuals can have capillary malformations and consequent higher incidence of venous thrombi.[6]

Sirolimus is an FDA-approved mammalian target of rapamycin (mTOR) inhibitor.[1] Its antiproliferative, immunosuppressive and anti-angio/lymphangiogenic properties are effective in decreasing pathologic growth and vascular proliferation in children with lymphatic malformations, lymphatico-venous malformations, and kaposiform hemangioendotheliomas.[3,4,5] It has been hypothesized that the use of these mTOR inhibitors could be expanded to use as therapeutic alternatives for patients with refractory vascular anomalies such as those associated with PROS.[4,5]

To our knowledge, our patient is the first known case of SMA-1 in association with MCAP syndrome. Treatment of complex AVMs such as those associated with MCAP syndrome is difficult and may require investigational therapies. Our patient was suffering from recurrent hemoptysis episodes prior to resolution with oral sirolimus therapy.

Case Description :

An adolescent female with ventilator-dependent SMA-1 struggled for years with recurrent small to large-volume hemoptysis. She underwent various imaging studies, bronchoscopies, and interventional radiology (IR) procedures, which identified bleeding sources to be complex AVMs in her lung vasculature. The AVMs were attributed to her MCAP syndrome, diagnosed by clinical signs and symptoms (large size at birth, skin covered with capillary malformations-faded over time, right-sided hemihyperplasia) and confirmed with *PIK3CA* gene mutation in cultured skin fibroblasts.

Despite recurrent embolizations of appropriate blood vessels, she continued to have hemoptysis not amenable to further IR interventions. She was then started on sirolimus for management of her AVMs.

Sirolimus was initiated as twice daily enteral administration of 0.8 mg/m2 through her gastrostomy tube. The dose was titrated to target trough levels of 10-15 ng/mL. The plan was to use this medication for 10-12 months while monitoring for side effects and improvement in signs and symptoms. Given her comorbid conditions, we had to stop sirolimus twice during the initial months. Co-administration of antifungal drugs (voriconazole or posaconazole) for management of chronic paronychia lead to supratherapeutic levels of sirolimus, so it was stopped for 3 months. It was stopped again for two months in order for her to get an Ommaya reservoir (spinal port) placement. Afterwards, she received uninterrupted 12 months of sirolimus therapy per plan. She was monitored for side effects related to bone marrow suppression, hepatic or renal damage via regular complete blood counts (CBCs), liver function tests (LFTs), creatinine and urine protein levels, respectively, which remained normal. Serial computed tomography (CT) chest with contrast, were obtained which showed significant improvement during the first 6 months [Figure 1] with stabilization of AVMs thereafter. She had no further episodes of hemoptysis, and sirolimus was discontinued after a duration of 12 months of treatment. Further plan is to continue to monitor for her symptoms, repeat imaging if needed, and restart sirolimus or, if possible, a similar newer drug like alpelisib with lesser side effects, if symptoms reoccur.

Discussion :

SMA-1, also known as Werdnig-Hoffman Disease, is the most common form of the disorder.[1] Affected patients may appear normal at birth prior to the development of symptoms - progressive hypotonia, symmetric limb weakness/flaccid paralysis, poor head control, and reduced/absent reflexes - by six months of age.[1]

PROS conditions are characterized primarily by asymmetric overgrowth caused by mosaic-activating *PIK3CA* variants in tissues of mesodermal origin.[2] The *PIK3CA* mutations identified in PROS are consistent with those identified in solid tumors, the H1047R mutation in the catalytic domain being the most common.[2] Somatic *PIK3CA* mutations, on the other hand, exist primarily in epithelial tissues and are mutations often implicated in cancers.[2]

PIK3CA encodes the p110α catalytic subunit of PI3K.[3] This kinase is essential to growth factor signaling and normal vascular development [Figure 2].[4,5] The PI3K pathway is regulated by mTOR [Figure 2].[4,5] mTOR is a kinase that stimulates protein synthesis, resulting in various cellular processes, including cell proliferation and increased angiogenesis [Figure 2].[8] Increases in mTOR signaling enhance expression of vascular endothelial growth factor (VEGF), a primary regulator of angiogenesis and lymphangiogenesis.[5] Thus, mTOR plays an integral role in the development of various vascular anomalies.[4,5] Activating somatic mutations in*PIK3CA* cause dysregulation of the PI3K pathway, leading to physiologically inappropriate activation of protein kinase B (AKT) and mTOR signaling with subsequent excessive/asymmetric tissue growth [Figure 2].[4] The pathologic proliferation in these*PIK3CA* -mutated patients is referred to as PROS and can be further characterized into various syndromic clinical presentations. Two examples of PROS include congenital lipomatous overgrowth vascular malformations-epidermal nevi-skeletal abnormalities (CLOVES) or our patient's diagnosis, MCAP, as described above.[3]

Laser ablation therapy is the current standard of care for treatment of vascular anomalies in MCAP syndrome, but novel approaches are needed on a case-by-case basis, like ours. Sirolimus has proved to be an efficacious and safe treatment for the majority of complex vascular anomaly patients.[5] Recent clinical trials have demonstrated its efficacy in these patients, some of which were known to have elevated PI3K/AKT/mTOR signaling.[5] This case further supports and suggests that systemic sirolimus therapy decreases morbidity associated with complex pulmonary AVMs in the setting of two rare, coexisting syndromes. Further studies are required to assess long-term treatment outcomes for specific disease phenotypes, optimum length of treatment with sirolimus, and utility of newer drugs like alpelisib.

Figure 1 : CT chest w/wo contrast (lung window). Coronal views of posterior lung fields 8/2017 (Figure 1a), 10/2018 (Figure 1b) and 4/2019 (Figure 1c). Previously-visualized tiny nodular lesions (AVM) in right and left lower lobes have significantly improved with sirolimus therapy.

Figure 2 : Mode of action of sirolimus. pTEN: *phosphatase and TENsin homolog* ; FKBP: *FK506 (sirolimus) binding protein* ; SRL: *sirolimus* ; PI3K: *phosphoinositide 3-kinase* ; AKT:*serine/threonine kinase also known as protein kinase B* (pKB); mTOR: *mammalian target of rapamycin* ; eIF4E: *eukaryotic translation initiation factor 4E* ; S6: *ribosomal protein* .[4]

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