Treatment of cystic hygroma in a young infant through multidisciplinary approach involving sirolimus, sclerotherapy, and debulking surgery

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INTRODUCTION

Cystic hygromas are macrocystic lymphatic malformations that develop during the sixth gestational week.[1,2] Cystic hygromas (CH) mostly present in the neck and comprise 20% to 25% of cervical lymphatic tumors. Mainstay treatment of CH involves complete surgical resection and sclerotherapy. Sclerotherapy has been consistently chosen over the other modalities. Oosthuizen et al[3] reported a management algorithm that incorporated sclerotherapy and surgery in the management of cervicofacial lymphatic malformation. Sclerotherapy has been consistently employed in the management of lymphatic malformations with notable reduction (30%) and sometimes complete eradication of cystic hygrma.[4] Intralesional bleomycin helped achieve complete clinical remission in 47% of patients, greater than 50% reduction in 35.8%, and less than 50% reduction in 17.1% in a 70-patient trial.[5] However, sclerotherapy has many adverse effects including swelling at the site of the lesion, scarring, pulmonary fibrosis, hemorrhage, and infection.[6] Additionally, sclerotherapy may be futile in the management of cysts not accessible for injections. Therefore, we propose a more effective approach that involves combining sirolimus to the aforementioned modalities. Sirolimus inhibits mammalian target of rapamycin (mTOR).[7-9] Specifically, sirolimus binds to FK506 to form a protein complex that avidly binds to mTOR resulting in dephosphorylation and deactivation of p70S6 kinase, which, in turn, results in the decrease of vascular endothelial growth factor C, a stimulant of lymphatic endothelial cells.[10] Blatt et al[11] reported the first successful use of sirolimus in the management of kaposiform hemangioendothelioma.

Abbreviations used:

CH:	cystic hygromas
EXIT:	extrauterine intrapartum airway intervention
MRI:	magnetic resonance imaging
mTOR:	mammalian target of rapamycin

Herein, we present remarkable reduction of extensive cystic hygroma in a 15-month-old infant through a debulking surgery followed by the administration of sirolimus in addition to reduced course of sclerotherapy.

CASE REPORT

An 8-month-old boy was hospitalized since his birth for extensive cystic hygroma. The mother is a 47-year-old healthy woman. She is gravida 9, para 6, plus 2 with no consanguinity, no chronic disease in the family, and no history of congenital anomalies. Her pregnancy was unremarkable with regular follow ups until the antenatal presentation of an enormous neck mass and polyhydramnios during the 27th gestational week. She went into labor in

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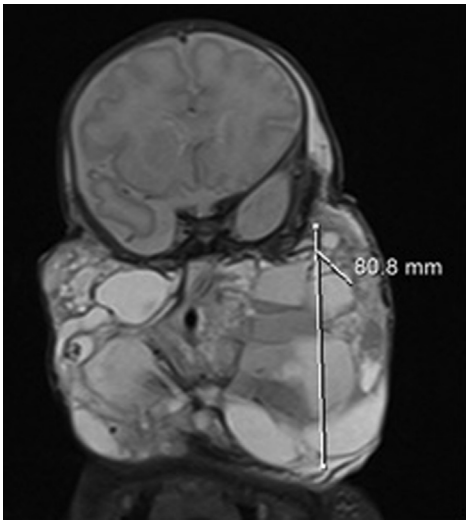

Fig 1. MRI of the face before treatment 2 days after birth. Axial T2 image with fat suppression shows numerous large bright cysts with fluid-fluid level indicating hemorrhage in the cysts. This extends through all tissues from skin on one side to the skin on the other side. The malformation volume was about 370 mL. Axial T1 image at the level of the airway confirms high signal indicating blood in the cysts.

35th week and underwent emergency cesarean section and along with extrauterine intrapartum airway intervention (EXIT) due to extensive neonatal neck mass that would potentially compromise the neonate's airway. The EXIT procedure is usually done for any fetus with a large neck mass before cutting the umbilical cord.

The patient exhibited no dysmorphism, with the large neck mass mainly involving the right side of the neck. His tongue was also involved, posing a challenge for conventional treatment with sclerotherapy. His chest, abdomen, cardiac, genitalia, and back were unremarkable. The birth weight was 3.08 kg. Baseline magnetic resonance imaging (MRI) (Fig 1) done 2 days after his birth showed a mass with a volume of 370 mL. The diagnosis was cystic hygroma.

The patient underwent 4 sclerotherapy sessions with a 1-week period between sessions a week after his birth. The sclerosing agents used include alcohol, polidocanol, and doxycycline. He then underwent debulking surgery for the cystic hygroma and gastrostomy to facilitate the administration of sirolimus. Subsequently, he underwent one more sclerotherapy session for a total of 5 sclerotherapy sessions. The cystic hygroma persisted and the veins within the tumor became sclerosed and hence difficult for injection; therefore, sclerotherapy was no longer an option for management. He was then started on sirolimus when he was 1 month old with

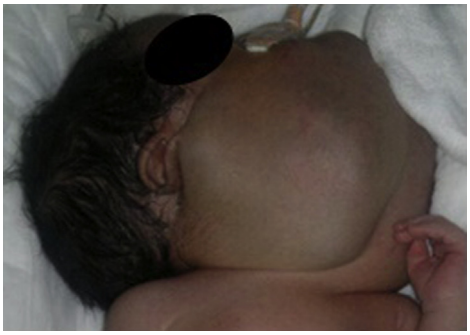

Fig 2. Patient at birth with large cystic hygroma involving neck and tongue.

an initial dose of 0.07 mg/kg given twice daily through gastrostomy tube. Sirolimus level was monitored and maintained within a range of (0.004−0.01 mg/kg). Ten days after starting sirolimus, MRI showed visual 70% to 80% improvement (about 74−110 mL). Follow-up ultrasound scans showed a decrease in the cystic components of the hygroma mass. After the administration of sirolimus for 15 months, the size of the tumor decreased to 90% of its original size before treatment, leaving a residual of 10 to 20 mL with a 79- to 110-mL reduction of original volume of 370 mL of cysts that were in the cheek, temple, and tongue that were not treated with sirolimus (Figs 1-8). The patient had laryngomalacia because of the mass effect of the cystic hygroma that compromised the airway. He is a potential candidate for future plastic surgeries to remove redundant skin.

DISCUSSION

Cystic hygromas may potentially present anywhere in the body. Some of the common sites include the cervicofacial region (80% of cases), mediastinum, beneath the tongue, axilla, and groin. Sixty percent of CH present congenitally.[6] Management of CH ideally is through surgical resection or sclerotherapy.[6] A more recent management option is an antiproliferative agent: Sirolimus.[9,12,13] Sirolimus (rapamycin) is an mTOR inhibitor that has a less drastic adverse effect profile than the preceding management modalities. It inhibits mTOR, which plays an integral role in several signaling cascades that involve cellular motility, angiogenesis, and cell growth.[10,13] Because mTOR is the final common pathway mediating most vascular tumors, sirolimus is an important target to treat lymphangiomas and hemangiomas.[8-10,13]

Pharmacokinetics associated with sirolimus varies considerably because of its metabolism by cytochrome P450 enzymes, thereby depending on the maturation of these microsomal enzymes in young infants and