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Short Communication

# Sirolimus and Propranolol are not Panaceas for All Vascular Anomalies

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## Abstract

Vascular anomalies are a heterogeneous group of vascular development disorders that include two broad categories: vascular tumors and vascular malformations. Sirolimus and propranolol have been selectively used to some vascular anomalies in case of accurate diagnosis. Recently, in the article entitled "Antiproliferative therapy with sirolimus and propranolol for congenital vascular anomalies in newborns (Case reports)" Cîrstoveanu et al. [1] reported four neonates with vascular anomalies treated with sirolimus and propranolol. There are some controversies regarding the diagnosis and management in the reported cases. In the article, the authors routinely used propranolol to manage lymphatic malformation, congenital hemangioma, kaposiform hemangioendothelioma and diffuse capillary malformation with overgrowth. Based on our understanding and literature review, we commented on the article. Also, we discussed some issues regarding the diagnosis and management of selected vascular anomalies. Sirolimus and propranolol should be properly used to treat selected vascular anomalies. Additionally, some errors in this publication were identified.

**Keywords:** Sirolimus; Propranolol; Lymphatic Malformation; Kaposiform Hemangioendothelioma; Kasabach-Merritt phenomenon; Hemangioma; Capillary malformation; Overgrowth

**Abbreviations:** ISSVA: International Society for the Study of Vascular Anomalies; KMP: Kasabach-Merritt Phenomenon; KHE: Kaposiform Hemangioendothelioma; TA: Tufted Angioma; IH: Infantile Hemangioma; mTOR: mammalian Target of Rapamycin; PI3K: Phosphoinositide 3-kinase; CH: Congenital Hemangioma; DCMO: Diffuse Capillary Malformation with Overgrowth; HCH: Hepatic Congenital Hemangioma; KTS: Klippel-Trenaunay Syndrome

## Introduction

Recently, in the article entitled "Antiproliferative therapy with sirolimus and propranolol for congenital vascular anomalies in newborns (Case reports)" Cîrstoveanu, et al. [1] reported four neonates with vascular anomalies treated with sirolimus and propranolol [1]. We compliment the authors for their excellent results. Nevertheless, we have a few comments on the diagnosis and management of vascular anomalies.

## Commentary

### International Society for the Study of Vascular Anomalies (ISSVA) classification for vascular anomalies was misused

The International Society for the Study of Vascular Anomalies (ISSVA) was born in 1992. Interdisciplinary and international collaboration has been the primary and guiding principle of the ISSVA, with a primary goal of improving our understanding and management of vascular anomalies. ISSVA classification has been the most widely accepted classification in the field of vascular anomalies since 1996. In the latest ISSVA document [2], vascular anomalies were broadly catergorized into vascular tumors and malformations based on biological features of endothelium [3]. Vascular tumors are true tumors with neoplastic behavior and increased mitotic activity [3]. They can be further classified into benign, locally aggressive or borderline, and malignant [2]. The term benign is confined to describe a tumor, not a malformation [2]. In the latest document, vascular malformations, not all vascular anomalies, were classified into fast-flow and low-flow [2]. The terms fast-flow and low-flow are restricted to describe vascular malformations [2], not including vascular tumors. The authors used the term fast-flow to describe vascular malformations and tumors, which should be corrected. Mixed use of terms low-flow and benign to describe vascular malformations should be avoided. Additionally, hemangiopericytoma is not considered as vascular tumor, and not

listed in the ISSVA classification [2]. The term lymphangioma was used in the diagnosis of case 1. This nomenclature is outdated and should be abandoned. The term lymphatic malformation is recommended [2].

## KMP specifically occurs in kaposiform hemangioendothelioma (KHE) and tufted angioma (TA), does not occur with other vascular tumors

The authors stated complex vascular neoplasms are infiltrative lesions and can cause Kasabach-Merritt phenomenon (KMP) [1]. This statement is incorrect. In 1997, Sarkar et al. revealed KMP was associated with Kaposiform Hemangioendothelioma (KHE) and not with common infantile hemangioma [4]. In the same year, Enjolras et al. found infants with KMP did not have "true" classical hemangiomas [5]. Currently, KMP is defined as a coagulopathy (thrombocytopenia) associated with KHE and TA [6]. KHE and TA are considered to be synonymous vascular tumors with similar presenting symptoms and potential for KMP [6]. Thus, KMP specifically occurs in KHE and TA, does not occur with other vascular tumors. Not all vascular tumors can cause KMP. Indeed, mild to moderate thrombocytopenia and hypofibrinogenemia can be associated with other vascular anomalies [2]. However, those hematological changes associated with non-KHE or TA have been not considered to be KMP. These hematological disorders associated vascular anomalies include rapidly involuting congenital hemangioma, venous malformations/lymphatic-venous malformations, kaposiform lymphangiomatosis, multifocal lymphangioendotheliomatosis, and cutaneovisceral angiomatosis [2]. Unlike KMP, these hematological changes are usually mild to moderate and transient [2,6]. Consequently, KMP occurs exclusively with KHE and TA.

## Infantile hemangioma has been the only vascular tumor responsive to propranolol until now

Since the discovery of excellent therapeutic effect of propranolol on infantile hemangioma (IH) in 2008 [7], propranolol and other β-blockers have emerged as the first-line agent for IH [8], and we now have more than a decade of experience with this treatment. For vascular anomalies management, β-blockers have been restricted to treat IH until now [9]. In literature, clinical trial, consensus, or guideline data supporting its efficacy for other vascular anomalies does not exist [8,9]. However, the authors used propranolol to treat four cases with vascular anomalies other than IH. To our knowledge, propranolol was misused by the authors, which should be avoided.

## Sirolimus have shown beneficial responses in various vascular anomalies other than congenital hemangioma and diffuse capillary malformation with overgrowth

Sirolimus inhibits mammalian target of rapamycin (mTOR), a serine-threonine kinase regulated by phosphoinositide 3-kinase (PI3K), which acts as a master switch in cellular processes, such as cell growth and proliferation, cellular metabolism, autophagy, and angiogenesis and lymphangiogenesis. Sirolimus was reported to be efficient in various vascular anomalies, with heterogeneous outcomes [10]. However, no evidence showed Congenital Hemangioma (CH) and Diffuse Capillary Malformation with Overgrowth (DCMO) were responsive to sirolimus management. We agreed the case 2 described in the article was diagnosed with Hepatic Congenital Hemangioma (HCH). Possible complications of a HCH include intratumoral bleeding, thrombocytopenia, hypofibrinogenemia, and high-output cardiac failure [11]. A newborn with HCH may present with significant anemia, thrombocytopenia, and hypofibrinogenemia immediately after birth [11]. The bleeding is almost always self-limited and transient, rarely requiring blood products. This should not be confused with KMP [6]. KMP is a specific phenomenon of KHE and TA, which never presents in the liver parenchyma in literature [6]. CH often regress spontaneously and do not require specific therapy [11]. Rapidly involuting CH will be ~80% reduced in size by 12-13 months old, leaving only a small, calcified remnant [11]. Consequently, the mass shrinking observed by the authors can be considered to be the result of natural history of CH. DCMO was recently defined as a distinct subtype of vascular anomaly featured by extensive capillary malformations involving more than one anatomic region with proportionate soft tissue and/or bony overgrowth [12]. Overgrowth does not correlate with capillary malformation location or intensity. The capillary malformation component of DCMO often lightened over the first several months of life [12,13]. So, the statement of port-wine stains becoming paler may be the result of natural history of DCMO.

## DCMO vs. KTS

The diagnosis of Klippel-Trenaunay Syndrome (KTS) is restricted to the triad of a capillary-lymphatic-venous malformation in a limb [2,12]. There is no diffuse capillary malformation in KTS [12]. The variably prominent subcutaneous veins in DCMO are obviously different from the persistent marginal vein and other deep venous malformation characteristic of KTS. There is no risk for cellulitis, localized intravenous coagulopathy, pulmonary embolism, and progressive overgrowth through life in DCMO [12]. None of these complications were seen in cases with DCMO [12,13]. These complications were commonly seen in patients with Klippel-Trenaunay syndrome (KTS). No patient with DCMO has true venous malformation [12,13]. Broad diagnosis of KTS lead to uncertainty in prognosis and management.

## Vincristine and methylprednisolon played important roles in the management of KHE with KMP

In the article, authors reported a case with KHE and KMP was managed with sirolimus, propranolol and methylprednisolone. In the section discussion, authors stated vincristine was also introduced into during the 13th week of combined sirolimus and propranolol therapy. After vincristine, leg swelling improved, subcutaneous tissue became softer. So, this patient received four drugs administration actually. With a high response rate of more than 70%, vincristine or vincristine plus corticosteroids has been recommended as first-line therapy for KHE/KMP in consensus-derived guidelines [6,14]. Consequently, vincristine and methylprednisolon played important roles in the management for case 3 reported in article. Sirolimus alone also has been used as

first-line therapy for KHE/KMP [14,15]. Sirolimus also has shown very excellent response for KHE/KMP, even multimodal-resistant [14,16]. Until now, no response to sirolimus has never been reported in confirmed KHE/KMP in literature. Furthermore, improvement of leg swelling may be the result of sirolimus, not vincristine [17].

### Management of lymphatic malformation.

In the article, lymphatic malformation of case 1 was macrocystic, with intracystic hemorrhage. For macrocystic lymphatic malformation, sclerotherapy has been the first-line and mainstay treatment [18]. Retrospective studies have compared sclerotherapy to surgery, which demonstrated that sclerotherapy alone is highly effective in the treatment of macrocystic lymphatic malformation [18,19]. Surgery is more effective in the treatment of microcystic and mixed lesions, with or without combination sclerotherapy [18,19]. For the case 1 reported in the article, draining and sclerotherapy is recommended. Adequate drainage of macrocystic lymphatic malformation in this case can shrink the lesion immediately, to avoid excessive skin due to persist expansion. Sclerosants can be administered via the drainage tube. No evidence has confirmed the therapeutic effect of propranolol on lymphatic malformation until now. Propranolol is not used to treat macrocystic lymphatic malformation. Generally, sirolimus is used to manage complicated microcystic lymphatic malformation and complex vascular anomalies other than macrocystic [18,20]. Additionally, the shrinking of lesion may be largely due to absorption of hemorrhage. Furthermore, natural regression of macrocystic lymphatic malformation has been observed occasionally [21].

### Some errors in the article

General abbreviation for Kasabach Merritt phenomenon is KMP, not KMM. This error is in the abstract section of the article. Reference 2 and 3 were duplicated. Reference 10 "Sirolimus for the treatment of complicated vascular anomalies in children" is a journal article of Pediatric Blood Cancer [22], not the journal Clin Med Insights Blood Disord.

## Conclusion

Based on our understanding and literature review, we commented on the article by Cîrstoveanu et al. Also, we discussed some issues regarding the diagnosis and management of selected vascular anomalies. No all vascular anomalies are infantile hemangiomas which are responsive to propranolol. Sirolimus and propranolol should be properly used to treat selected vascular anomalies.

## References


1. Cîrstoveanu C, Bizubac AM, Mustea C, Manolache Ş, Istrate-Bârzan A, et al. (2021) Antiproliferative therapy with sirolimus and propranolol for congenital vascular anomalies in newborns (Case reports). Exp Ther Med 22: 1097.
2. (2018) ISSVA Classification of Vascular Anomalies © International Society for the Study of Vascular Anomalies.
3. Mulliken JB, Glowacki J (1982) Hemangiomas and vascular malformations in infants and children: a classification based on endothelial characteristics. Plast Reconstr Surg 69: 412-22.
4. Sarkar M, Mulliken JB, Kozakewich HP, Robertson RL, Burrows PE (1997) Thrombocytopenic coagulopathy (Kasabach-Merritt phenomenon) is associated with Kaposiform hemangioendothelioma and not with common infantile hemangioma. Plast Reconstr Surg 100: 1377-1386.
5. Enjolras O, Wassef M, Mazoyer E, Frieden IJ, Rieu PN, et al. (1997) Infants with Kasabach-Merritt syndrome do not have "true" hemangiomas. J Pediatr 130: 631-640.
6. Drolet BA, Trenor CC, Brandão LR, Chiu YE, Chun RH, et al. (2013) Consensus-derived practice standards plan for complicated Kaposiform hemangioendothelioma. J Pediatr 163: 285-291.
7. Léauté-Labrèze C, Dumas de la Roque E, Hubiche T, Boralevi F, Thambo JB, et al. (2008) Propranolol for severe hemangiomas of infancy. N Engl J Med 358: 2649-2651.
8. Sebaratnam DF, Rodríguez Bandera AL, Wong LF, Wargon O (2021) Infantile hemangioma. Part 2: Management. J Am Acad Dermatol 85: 1395-1404.
9. Goss JA, Konczyk DJ, Alomari MH, Maclellan RA, Greene AK (2017) Propranolol Treatment of Vascular Anomalies Other Than Infantile Hemangioma. J Craniofac Surg 28: 2001-2003.
10. Freixo C, Ferreira V, Martins J, Almeida R, Caldeira D, et al. (2020) Efficacy and safety of sirolimus in the treatment of vascular anomalies: A systematic review. J Vasc Surg 71: 318-327.
11. Iacobas I, Phung TL, Adams DM, Trenor CC, Blei F, et al. (2018) Guidance Document for Hepatic Hemangioma (Infantile and Congenital) Evaluation and Monitoring. J Pediatr 203: 294-300.
12. Lee MS, Liang MG, Mulliken JB (2013) Diffuse capillary malformation with overgrowth: a clinical subtype of vascular anomalies with hypertrophy. J Am Acad Dermatol 69: 589-594.
13. Liu KX, Prajapati VH, Liang MG, Mulliken JB, Lee MS (2018) A cross-sectional survey of long-term outcomes for patients with diffuse capillary malformation with overgrowth. J Am Acad Dermatol 78: 1023-1025.
14. Ji Y, Chen S, Yang K, Xia C, Li L (2020) Kaposiform hemangioendothelioma: current knowledge and future perspectives. Orphanet J Rare Dis 15: 39.
15. Wang H, Guo X, Duan Y, Zheng B, Gao Y (2018) Sirolimus as initial therapy for kaposiform hemangioendothelioma and tufted angioma. Pediatr Dermatol 35: 635-638.
16. Wang H, Duan Y, Gao Y, Guo X (2017) Sirolimus for Vincristine-Resistant Kasabach-Merritt Phenomenon: Report of Eight Patients. Pediatr Dermatol 34: 261-265.
17. Ji Y, Chen S, Xia C, Zhou J, Jiang X, et al. (2020) Chronic lymphedema in patients with kaposiform hemangioendothelioma: incidence, clinical features, risk factors and management. Orphanet J Rare Dis 15: 313.
18. Kalwani NM, Rockson SG (2021) Management of lymphatic vascular malformations: A systematic review of the literature. J Vasc Surg Venous Lymphat Disord 9: 1077-1082.
19. Balakrishnan K, Menezes MD, Chen BS, Magit AE, Perkins JA (2014) Primary surgery vs primary sclerotherapy for head and neck lymphatic malformations. JAMA Otolaryngol Head Neck Surg 140: 41-45.
20. Adams DM, Trenor CC, Hammill AM, Vinks AA, Patel MN, et al. (2016) Efficacy and Safety of Sirolimus in the Treatment of Complicated Vascular Anomalies. Pediatrics 137: e20153257.
21. Smith RJ (2004) Lymphatic malformations. Lymphat Res Biol 2: 25-31.
22. Hammill AM, Wentzel M, Gupta A, Nelson S, Lucky A, et al. (2011) Sirolimus for the treatment of complicated vascular anomalies in children. Pediatr Blood Cancer 57: 1018-1024.

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