Life-Threatening Cutaneous Bleeding in Childhood Klippel-Trenaunay Syndrome Treated With Oral Sirolimus
Didier Bessis, Hélène Vernhet, Michèle Bigorre, Isabelle Quere, Jochen Rössler

To cite this version:
Didier Bessis, Hélène Vernhet, Michèle Bigorre, Isabelle Quere, Jochen Rössler. Life-Threatening Cutaneous Bleeding in Childhood Klippel-Trenaunay Syndrome Treated With Oral Sirolimus. JAMA Dermatology, American Medical Association, 2016, 152 (9), pp.1058-1059. 10.1001/jamadermatol.2016.1008. hal-01868352

HAL Id: hal-01868352
https://hal.archives-ouvertes.fr/hal-01868352
Submitted on 17 Jan 2019

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers. L’archive ouverte pluridisciplinaire HAL, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d’enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.
Su M. Lwin, MRCP, MBBS, BSc (Hons)
Chao-Kai Hsu, MD
James R. McMillan, PhD
Jemima E. Mellerio, MD, FRCP, MBBS, BSc (Hons)
John A. McGrath, MD, FRCP, FMedSci

Author Affiliations: St John's Institute of Dermatology, King's College London, Guy's Campus, London, England (Lwin, Hsu, Mellerio, McGrath); Viapath, St Thomas’ Hospital, London, England (McMillan).

Corresponding Author: John A. McGrath, MD, FRCP, FMedSci, Dermatology Research Laboratories, Floor 9 Tower Wing, Guy’s Hospital, Great Maze Pond, London SE1 9RT, England (john.mcgrath@kcl.ac.uk).


Conflict of Interest Disclosures: None reported.

Funding/Support: This study was supported in part by the Department of Health via the UK National Institute for Health Research (NIHR) Comprehensive Biomedical Research Centre award to Guy’s and St Thomas’ National Health Service (NHS) Foundation Trust in partnership with King’s College London and Biomedical Research Centre award to Guy’s and St Thomas’ National Health via the UK National Institute for Health Research (NIHR) Comprehensive Biomedical Research Centre award to Guy’s and St Thomas’ National Health Service (NHS) Foundation Trust.

Role of the Funder/Sponsor: The funding institutions had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Additional Contributions: We thank the patient for granting permission to publish this information. We also thank Lu Liu, PhD, Viapath, St Thomas’ Hospital, London, England, and Rashida Pramanik, BSc (Hons), St John’s Institute of Dermatology, King’s College London (Guy’s Campus), London, England, for technical support; and Debra E. Lomas, MA MB BChir. MRCPath, Department of Dermatology, Great Ormond Street Hospital for Children NHS Foundation Trust, London, England, for administrative and material support. None received any compensation for their contributions.


Life-Threatening Cutaneous Bleeding in Childhood Klippel-Trenaunay Syndrome Treated With Oral Sirolimus

Klippel-Trenaunay syndrome (KTS) is characterized by the triad of cutaneous capillary malformations (port-wine stains), asymmetrical disturbed growth of soft tissues and/or bone, and venous and lymphatic malformations. Prolonged and recurrent cutaneous bleeding from ulceration of the capillary and/or venous and/or lymphatic malformation can be life-threatening. We report for the first time to our knowledge a case of Klippel-Trenaunay syndrome treated by oral sirolimus.

Report of a Case | A 13-month-old boy from Conakry, Guinea, was referred for assessment of recurrent cutaneous bleeding of the right lateral thigh complicated by chronic anemia. The parents had noted bleeding, either spontaneous or during dressing change, for 2 months despite the application of hemostatic dressings. Physical examination revealed a hypertrophic lower right limb with multiple port-wine stains centered by tumefactions 2 to 13 cm long composed of grouped hemorrhagic vesicles and crust (Figure 1A). Laboratory investigations revealed the following: hemoglobin level, 8.8 g/dL (normal range [NR], 10-14 g/dL), hematocrit, 29% (NR, 30%-42%), platelet count of 403 x 10^3/μL (NR, 150 x 10^3/μL to 400 x 10^3/μL), fibrinogen, 30 mg/dL (NR, 150-400 mg/dL), and D-dimer, greater than 4 μg/mL (NR, <0.5 μg/mL). (To convert fibrinogen to micromoles per liter, multiply by 0.0294; D-dimer to nanomoles per liter, multiply by 5.476.) Magnetic resonance imaging (MRI) of the right leg showed a microcystic lymphatic malformation with muscular infiltration of the posterior compartment of the thigh and hypoplasia of the deep veins associated with a persistent embryonic lateral marginal vein of the thigh (Figure 2A). A diagnosis was made of KTS complicated by chronic cutaneous bleeding induced by extensive microcystic lymphatic cutaneous malformation and lateral thigh vein. Due to the partially atretic deep venous system and the extensive muscular infiltration of the lymphatic malformation, treatment by surgery, sclerotherapy, catheter embolization, and compression were ruled out. Photocoagulation using the Nd:YAG or fractional carbon dioxide laser was infeasible due to the need for multiple sessions under general anesthesia and the risk of recurrence.

After informed parental consent, treatment with oral sirolimus was started at 0.8 mg/m² per dose twice daily along with cotrimoxazole for Pneumocystis prophylaxis. The bleeding stopped completely after 48 hours. Subsequent dosing of sirolimus was adjusted to 1 mg/m² per dose to maintain a goal drug level around 10 ng/mL. The patient’s anemia was corrected and D-dimer level normalized 1 and 5 months, respectively, after starting sirolimus treatment. In the following 6 months, a consistent and gradual reduction in the thickness of the tumefaction and its hemorrhagic component (Figure 1B) was noted and confirmed by MRI (Figure 2B). An attempt to terminate sirolimus treatment resulted in a rapid relapse of minimal cutaneous bleeding after 2 to 3 days, and sirolimus therapy was restarted promptly at the same dosage. No clinically significant adverse effect was observed after 10 months, and treatment by oral sirolimus was maintained at the same dose.

Discussion | Recent observations have shown that KTS is caused by heterozygous somatic gain-of-function PIK3CA mutations in a mosaic pattern, leading to inappropriate activation of the P13K/akt/mTOR pathway, and belongs to the PIK3CA-related overgrowth spectrum (PROS). Recent publications emphasize the potential interest of sirolimus, an inhibitor of mTOR activity, as a treatment option for cutaneous vascular malformations and PROS. Sirolimus has been used successfully with a good safety profile in more than 70 case reports of vascular anomalies with lymphatic components, and phase 2 studies are ongoing to assess its efficacy and safety in various complex vascular malformations, including KTS (clinicaltrials.gov NCT00975819, NCT02509468, and NCT01811667).
For our patient, sirolimus provided rapid and effective control of the cutaneous bleeding complicating a combined venous and lymphatic cutaneous malformation. The drug’s efficacy in treating the cutaneous lymphatic malformation appears obvious from the striking regression in the turgidity and hemorrhagic component of the lymphatic vesicles. However, a potentially antiangiogenic action on the lateral thigh vein cannot be excluded. This case report suggests that sirolimus may be an alternative medical treatment for bleeding induced by venous and lymphatic malformation associated with KTS.

Didier Bessis, MD
Hélène Vernhet, MD, PhD
Michèle Bigorre, MD
Isabelle Quéré, MD, PhD
Jochen Rössler, MD

Author Affiliations: Department of Dermatology, Saint-Eloi Hospital, University Hospital of Montpellier, Montpellier, France (Bessis); University of Montpellier, Montpellier, France (Bessis); INSERM U1058, Montpellier, France (Bessis); Department of Radiology, Lapeyronie Hospital, University Hospital of Montpellier, Montpellier, France (Bessis); Department of Pediatric Infantile Surgery, Lapeyronie Hospital, University Hospital of Montpellier, Montpellier, France (Bessis); Department of Internal Medicine, Saint-Eloi Hospital, University Hospital of Montpellier, Montpellier, France (Bessis); Department of Pediatric Oncology and Hematology, Arnaud de Villeneuve Hospital, University Hospital of Montpellier, Montpellier, France (Rössler).

Corresponding Author: Didier Bessis, MD, Department of Dermatology, Saint-Eloi Hospital, University Hospital of Montpellier, 80 avenue A Fliche, 34295 Montpellier CEDEX 5, France; d-bessis@chu-montpellier.fr.


Conflict of Interest Disclosures: Dr Rössler received research funds from Novartis, Pfizer, and Pierre Fabre. He is a principal investigator in clinical studies sponsored by Bayer, BMS, Helsinn, Infectopharm, Sanofi, Pierre Fabre, and Merck. No other disclosures are reported.

Additional Contributions: We thank the patient’s parents for granting permission to publish this information.


