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Rivaroxaban in the treatment of TEK-related venous malformation

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Title Page

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Short running title: Rivaroxaban in venous malformation

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Abstract: Low flow vascular malformations are rare congenital anomalies due to errors in vascular development and may be associated with known pathogenic genetic variants. Slow flow through the blood vessels can lead to localized intralesional thromboses which can cause debilitating pain and impair quality of life. We present a case of venous malformation due to a variant in the TEK gene in a 38-year-old woman in whom treatment with low dose rivaroxaban was successful in controlling symptoms of chronic localized intravascular coagulation.

Keywords: Vascular Malformations, Genetic Testing, Mosaicism, Rivaroxaban, Factor Xa Inhibitors, Quality of Life

Introduction

Vascular malformations are a heterogenous group of developmental anomalies of the vascular system which can involve arteries, veins, capillaries, lymphatics or a combination of these. They are usually present at birth and may have genetic associations (1). They can significantly impair quality of life in affected individuals due to pain, functional and cosmetic disabilities. Currently, treatment options are limited to compression bandages, sclerotherapy, surgery, analgesics and anti-inflammatory medications. Some success has been achieved with systemic treatment with sirolimus (2,3). Recently, there has been increasing discussion regarding the role of anticoagulants in low flow vascular malformations to improve symptoms and quality of life (4). We report a case of a patient with low flow vascular malformation with significant pain and localized intravascular coagulopathy who responded well to rivaroxaban.

Main text

A 38-year-old woman presented with extensive congenital vascular malformation involving the right upper limb, anterolateral chest and back. She had many years history of aching and burning pain at the site of the vascular malformation. This was associated with significant swelling and difficulties carrying any weight on the affected limb. There was no personal history of deep vein thrombosis or pulmonary embolism. She has two healthy children. On examination, there was extensive swelling of the right upper limb and anterolateral chest with several compressible blue blebs and plaques extending onto the back (Fig. 1a-c); there was evident asymmetry, with her affected arm and hand larger than the normal limb.

On investigation, magnetic resonance imaging demonstrated extensive vascular malformation involving the right upper limb from subcutaneous tissue above the shoulder and supraclavicular region to the wrist. Ultrasound of the right arm showed low flow vascular malformation with numerous phleboliths. Initial genetic testing for a vascular anomalies panel from lesional skin at a commercial laboratory detected no variants of note. A second DNA sample was extracted from affected skin, following a procedure. Testing was undertaken by exome sequencing using a detection method for somatic variants (5), and restricting analysis to a somatic vascular malformations virtual panel comprising 21 genes (ACVRL1, AKT1, AKT3, BRAF, ENG, GJA4, GLMN, GNA11, GNA14, GNAQ, HRAS, KRAS, MAP2K1, MAP3K3, MET, MTOR, NRAS, PIK3CA, RASA1, SOS1, TEK). The most frequent somatic venous malformation-causing TEK variant (6,7), NM_000459.4(TEK): c.2740C>T p.(Leu914Phe), was detected at a 3.3% variant allele frequency (VAF).

Previous treatments including compression garments, multiple debulking surgeries, long-term low dose aspirin and prophylactic enoxaparin postpartum had been ineffective. A trial of sirolimus was initiated, but the patient did not tolerate this due to debilitating lethargy and was subsequently ceased after three months. Sclerotherapy was not possible due to the size of the vascular malformation.

She was commenced on rivaroxaban 10 mg daily due to fibrinolysis (fibrinogen 2.0 g/L, normal range 2.0-5.0 g/L), chronically elevated D-Dimer (17.65 mg/L, normal range < 0.5 mg/L), phleboliths on ultrasound and ongoing debilitating pain. After one week, the patient reported improvement in her pain and quality of sleep. At three months, the patient described being almost pain free. At one year, her symptoms remained well-controlled. This

was reflected in her reduction in dermatology life quality index score from six out of thirty to three out of thirty through reduction in pain scores and impact on domestic and community activities of daily living. Objectively, D-Dimer levels decreased from 17.65 mg/L to 1.62 mg/L and fibrinogen levels increased from 2.0 g/L to 3.4 g/L pre-rivaroxaban and at four months on rivaroxaban, respectively (Fig. 2 a-b). Of note, patient reported menorrhagia while on the rivaroxaban at ten months, which resolved post levonorgestrel-releasing intrauterine device implantation.

Discussion

Multiple pathogenic genetic variants have been identified to play a role in disrupted morphogenesis of the vascular endothelium (8). The *TEK* gene encodes the receptor tyrosine kinase TIE2, which is expressed almost exclusively in endothelial cells of rats, mice and humans. Angiopoietin-1 and Angiopoietin-2 bind to this receptor and mediates a signaling pathway that functions in embryonic vascular development (6). In this patient, after repeated skin biopsies and genetic testing, the pathogenic *TEK* c.2740C>T p.(Leu914Phe) variant was present in affected skin at a low VAF. Many commercial laboratories do not report mutations at VAF less than 10%. It is sometimes possible to obtain the sequencing data and reanalyze to detect mutations with a lower VAF. Genetic testing of vascular malformations can be valuable in inferring prognosis, risk assessment of future offspring and guide development of future therapeutic strategies (1). Our case also highlights the persistence required in obtaining an informative biopsy of the correct site with adequate lesional skin for genetic testing.

Slow flow through venous malformations can activate a consumptive coagulopathy, manifested by reduced fibrinogen and elevated D-Dimer. The inflammatory response to the formation of thrombus can cause debilitating pain (9). There are increasing reports of use of anticoagulants in the symptomatic management of patients with chronic intravascular coagulation. Rivaroxaban is an orally available direct factor Xa inhibitor that does not require routine laboratory monitoring. We achieved a satisfactory clinical response at a prophylactic dose (10 mg), which has been shown to be effective in preventing recurrent venous thromboembolism (10). Bleeding is a potential side effect and although our patient experienced menorrhagia, her symptoms resolved with insertion of a hormonal intrauterine device. Our patient achieved a marked reduction in D-Dimer levels, indicating rivaroxaban interfered with ongoing intravascular thrombosis, and suggesting this biomarker may be useful in monitoring the impact of anticoagulation on disease activity (9), together with clinical assessment.

Our case report findings are consistent with current literature by Mack, Richter and Crary where rivaroxaban was effective in controlling symptoms of consumptive coagulopathy in four patients with slow-flow vascular malformations (9). However, prospective studies are required to objectively evaluate long-term effectiveness and safety of rivaroxaban in these patients.

Conclusion

In conclusion, vascular malformations are complex anomalies that requires a multidisciplinary approach to management. Genetic testing may provide valuable information in inferring prognosis, family planning and guiding future therapies. Currently,

there are no specific guidelines for treatment which may include compression bandages, sclerotherapy, or anti-inflammatory medications. This case suggests that low dose rivaroxaban, a direct factor Xa inhibitor, may be an effective and safe alternative in the treatment of venous malformation associated symptoms due to chronic intravascular coagulation.

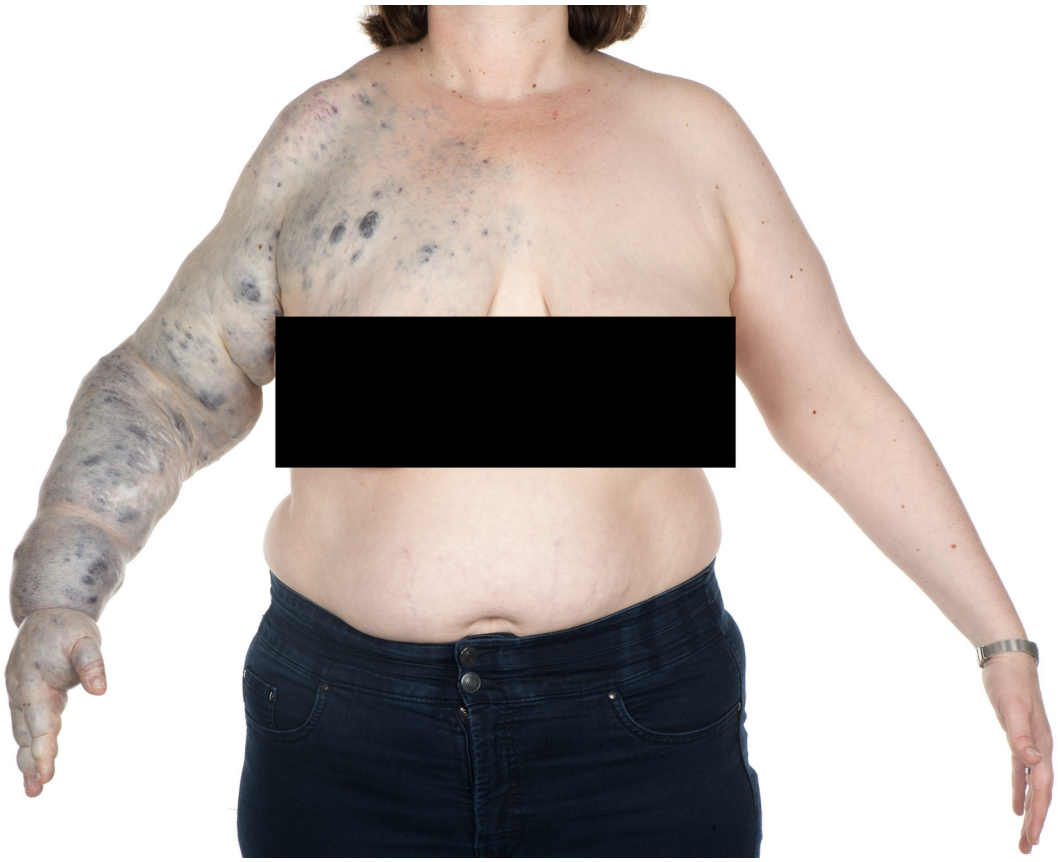
References

1. Doolan BJ, Robinson AJ, Regan M, Ragunathan A, Winship I. Genetic mosaicism in dermatology: Clinical utility of genetic testing of skin lesions. Vol. 61, Australasian Journal of Dermatology. Blackwell Publishing; 2020. p. 92–4. doi:10.1111/ajd/13149.
2. Boscolo E, Limaye N, Huang L, Kang KT, Soblet J, Uebelhoer M, et al. Rapamycin improves TIE2-mutated venous malformation in murine model and human subjects. Journal of Clinical Investigation. 2015 Sep 1;125(9):3491–504. doi:10.1172/JCI76004.
3. Hammer J, Seront E, Duez S, Dupont S, van Damme A, Schmitz S, et al. Sirolimus is efficacious in treatment for extensive and/or complex slow-flow vascular malformations: A monocentric prospective phase II study. Orphanet Journal of Rare Diseases. 2018 Oct 29;13(1). doi:10.1186/s13023-018-0934-z.
4. Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, et al. Standards and guidelines for the interpretation of sequence variants: A joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genetics in Medicine. 2015 May 8;17(5):405–24. doi:10.1038/gim.2015.30.
5. Cibulskis K, Lawrence MS, Carter SL, Sivachenko A, Jaffe D, Sougnez C, et al. Sensitive detection of somatic point mutations in impure and heterogeneous cancer samples. Nature Biotechnology. 2013 Mar;31(3):213–9. doi:10.1038/nbt.2514.
6. Limaye N, Wouters V, Uebelhoer M, Tuominen M, Wirkkala R, Mulliken JB, et al. Somatic mutations in angiopoietin receptor gene TEK cause solitary and multiple sporadic venous malformations. Nature Genetics. 2009 Jan;41(1):118–24. doi:10.1038/ng.272.
7. ten Broek RW, Eijkelenboom A, van der Vleuten CJM, Kamping EJ, Kets M, Verhoeven BH, et al. Comprehensive molecular and clinicopathological analysis of vascular malformations: A study of 319 cases. Genes Chromosomes and Cancer. 2019 Aug 1;58(8):541–50. doi:10.1002/gcc.22739.
8. Garzon MC, Huang JT, Enjolras O, Frieden IJ. Vascular malformations. Part I. Vol. 56, Journal of the American Academy of Dermatology. 2007. p. 353–70. doi:10.1016/j.jaad.2006.05.069.
9. Mack JM, Richter GT, Crary SE. Effectiveness and Safety of Treatment with Direct Oral Anticoagulant Rivaroxaban in Patients with Slow-Flow Vascular Malformations: A Case Series. Lymphatic Research and Biology. 2018 Jun 1;16(3):278–81. doi:10.1089/lrb.2017.0029.
10. Weitz JI, Lensing AWA, Prins MH, Bauersachs R, Beyer-Westendorf J, Bounameaux H, et al. Rivaroxaban or Aspirin for Extended Treatment of Venous Thromboembolism. New England Journal of Medicine. 2017 Mar 30;376(13):1211–22. doi:10.1056/NEJMoa1700518.

Figure legends

Figure 1: Extensive swelling of the right upper limb and anterolateral chest (a) with several compressible blue blebs and plaques (b) extending onto the back (c).

Figure 2: (a) D-Dimer levels pre and post rivaroxaban. (b) Fibrinogen levels pre and post rivaroxaban.



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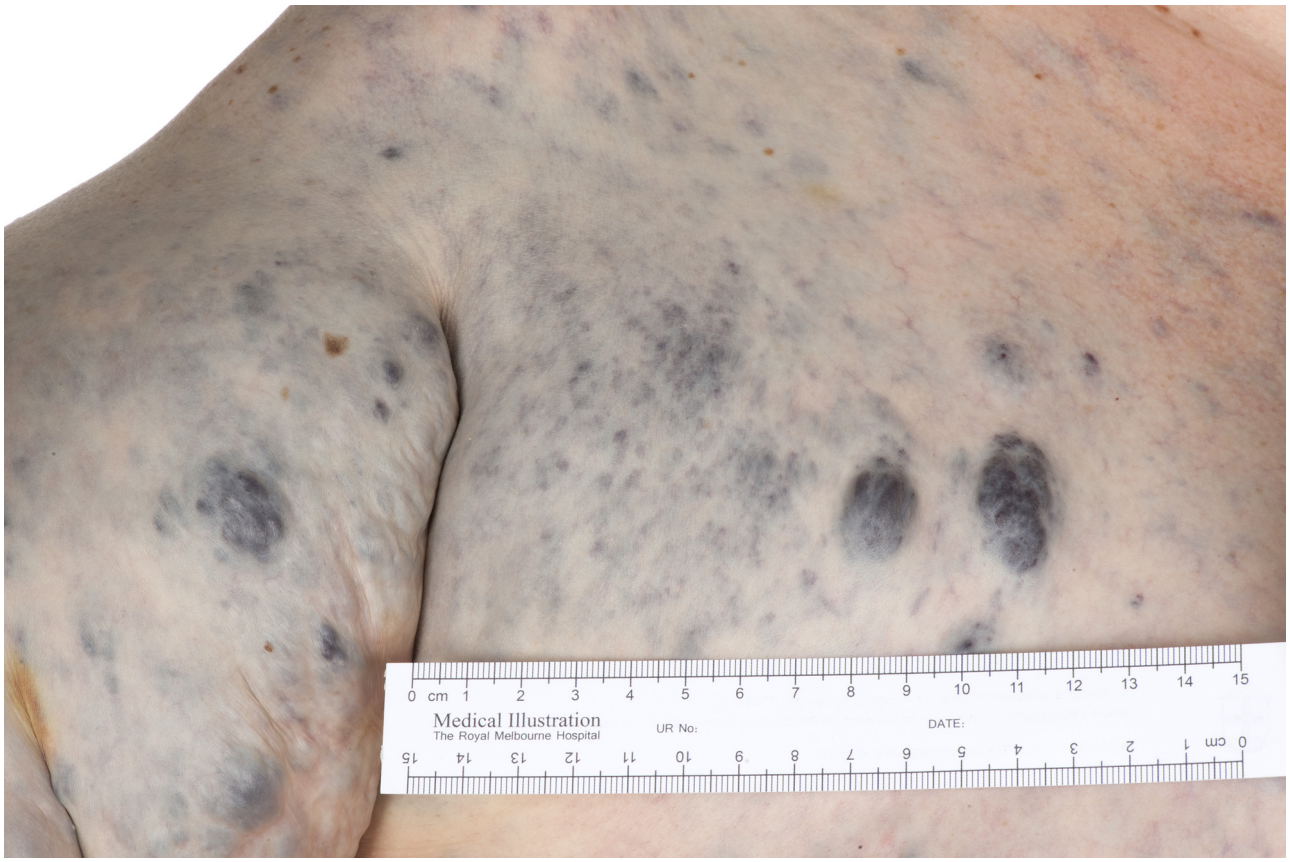

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