The Turkish Journal of Pediatrics 2023; 65: 124-128
https://doi.org/10.24953/turkjped.2022.254

Case Report

A rare case of Klippel-Trenaunay syndrome presenting with chronic myeloid leukemia

Çağrı Coşkun, Tekin Aksu, Fatma Gümrük, Şule Ünal

Department of Pediatric Hematology, Hacettepe University Faculty of Medicine, Ankara, Türkiye.

ABSTRACT

Background. Klippel-Trenaunay syndrome (KTS) is an overgrowth syndrome associated with capillary/venous/lymphatic malformations with limb hypertrophy and cancer risk. Various cancers, mostly Wilms tumor, have been reported in patients with KTS, but not leukemia. Chronic myeloid leukemia (CML) is also a rare disease in children, where there is no known disease or syndrome to predispose to CML.

Case. We report a case of CML incidentally diagnosed in a child with KTS when he was bleeding from surgery of the left groin for vascular malformation.

Conclusions. This case reflects the variety of cancer types that may accompany KTS and provides information about CML prognosis in such patients.

Key words: Klippel-Trenaunay syndrome, chronic myeloid leukemia, overgrowth syndrome, PIK3CA gene, vascular malformation, CVLM syndrome.

Klippel-Trenaunay syndrome (KTS) is a rare congenital vascular disorder characterized by cutaneous capillary malformations (port-wine stain), varicosities, and hypertrophy of soft tissues and long bones. KTS is also defined as an overgrowth syndrome and has recently been reclassified as capillary/venous/lymphatic malformation (CVLM) syndrome; whether it predisposes to malignancy is not clear.[1] Wilms tumor, rhabdomyosarcoma, osteoblastoma, basal cell carcinoma, squamous cell carcinoma of the skin, and angiosarcoma have been noted with CVLM, but not leukemia.[1] Chronic myeloid leukemia (CML) in children and adolescents is a rare malignancy of the hematopoietic system. Its incidence increases with age, and the incidence of CML in childhood is 0.6-1.2/million children/year.[2,3] It is characterized by hyperleukocytosis with myeloid and erythroid precursors, and increased platelets in peripheral blood.[2] Here we describe a case of CML diagnosed in a male pediatric patient with CVLM who presented with bleeding from the surgical region.

Case Report

A 14-year-old boy born of non-consanguineous parents presented with a painless mass on his left groin extending to his knee. This mass occurred initially at the age of 3 years and had been growing since. Physical examination revealed splenomegaly, limb length discrepancy, left lower extremity hypertrophy, and capillary hemangiomas over the left thigh's posterolateral skin. CVLM was suspected and confirmed with heterozygous mutation (c1634A>C/p.Glu545Ala) at the *PIK3CA* gene. He had multiple surgeries including left inguinal lymph node dissection, lymphatic lesion excision, and hematoma drainage from the wound site regarding deformities of the left limb. The patient was consulted to hematology due to hemorrhage complications occurring in the last surgery. Complete blood counts showed a hemoglobin level of 7.3 g/dL, white blood cells as $164x10^9$/L, neutrophil $76.4x10^9$/L,

✉ Çağrı Coşkun
cagri_730@hotmail.com

Received 28th February 2022, revised 15th April 2022, accepted 8th May 2022.

and thrombocytes 104x10^9/L. The differential was 20% metamyelocytes, 4% bands, 70% neutrophils, 4% eosinophils, 2% lymphocytes and 4% normoblasts, except for circulating blasts. Serum lactate dehydrogenase was 483 U/L (normal range: <248) and uric acid was 4 mg/dL (normal range: 3.5-7.2). Coagulation parameters were within normal limits. Bone marrow aspiration showed normocellular myeloid/erythroid ratio of 23:1, granulopoiesis with left shift, increased megakaryocytes were seen with normal maturation, and blasts were lower than 5%. Conventional karyotyping revealed 46 XY, t(9,22) (q34;q11.2) (20/20, 100%) without any additional cytogenetic abnormalities. The Breakpoint cluster region protein- Tyrosine-protein kinase ABL1 (BCR-ABL1) (p210) transcripts were detected as 57.7 international scale (IS) in a quantification limit of 0.0063%. Chronic phase CML (CML-CP) was diagnosed, and imatinib was initiated with a 300 mg/m^2 dose daily.

Nevertheless, the patient had inadequate drug compliance and follow-up visits delayed. Imatinib treatment was discontinued due to severe leg pain. Splenomegaly persisted and the complete molecular response had not yet been achieved on the 12th month of therapy, with a BCR/ABL (p210) transcript 2.68 IS. Mutation analysis for tyrosine kinase inhibitor (TKI) resistance was performed, and no BCR/ABL gene mutation was determined. The patient was switched to dasatinib therapy due to a lack of molecular response and an inability to tolerate imatinib. He used dasatinib treatment regularly and achieved a molecular response. At 18 months after diagnosis, the BCR/ABL (p210) transcript was 0.09 IS. The patient was considered to have an optimal response to dasatinib, and the therapy was continued. He is currently receiving dasatinib, now for 23 months. The BCR/ABL (p210) transcript at 32 months of treatment was negative and complete molecular response was achieved. We obtained informed consent from his family.

Discussion

Capillary venous lymphatic malformation is a rare syndrome characterized by the triad of capillary malformations, vascular anomalies, hypertrophy of bony and soft tissues.[4,5] In 1900, CVLM was defined and named by the two French doctors who described the syndrome. The estimated incidence of CVLM is 1 in 30,000 live births and it affects males and females in equal numbers.[6]

The exact pathophysiology and genetic etiology of CVLM are unknown with a sporadic occurrence, although a paradominant inheritance pattern has been suggested. A paradominant theory of inheritance tries to explain CVLM by the occurrence of a lethal mutation in a gene. Accordingly, homozygous embryos are lost, but heterozygous embryos remain alive and are normal. Familial cases are very uncommonly reported.[7,8] Chronic venous hypertension secondary to deep vein abnormality or occlusion has been suggested to play a role in the pathogenesis of CVLM. In addition, the persistence of a part of the embryological vascular system has been proposed as another underlying cause in the pathogenesis of CVLM. Mesodermal anomaly affecting angiogenesis may explain the features of CVLM syndrome.[9,10] The affected limbs tend to exhibit increased blood flow. This has been thought to be associated with vascular endothelial growth factor (VEGF) mediated angiogenesis, but there is insufficient evidence.[11] Haploinsufficiency of *AGGF1* was attributed to CVLM development through inhibition of angiogenesis by inactivating phosphatidylinositol 3-kinase (PI3K) and AKT serine/threonine kinase 1 (AKT).[4,11,12] Additionally, the *PIK3CA* gene has also been reported to be responsible from the genotype of some of the patients with CVLM.[1,13] Somatic mutations in *PIK3CA* cause many overgrowth syndromes (particularly Cloves, fibro adipose hyperplasia and megalencephaly-capillary

malformation) that have recently been identified as the *PIK3CA*-related overgrowth syndromes.[14,15]

Many types of cancer have been reported in individuals with CVLM. However, the relationship between cancer and underlying syndromes is not clear. The risk of embryonal cancer in children with CVLM does not appear to be higher than in the general population. Overgrowth syndromes such as Beckwith Wiedemann Syndrome and PTEN hamartoma tumor syndrome have increased cancer risk. Both of these syndromes are associated with genetic mutations in tumor suppressor genes. No patient with CVLM has been reported to have structural mutations in tumor suppressor genes or oncogenes. Isolated hemihypertrophy without other features of known syndromes has been recognized as an indication for childhood cancer surveillance. Therefore, it may be predicted that CVLM carries a risk of cancer on the basis of hemihypertrophy alone. Wilms tumor, rhabdomyosarcoma, basal cell and squamous cell carcinoma of the skin were identified with CVLM, except CML has not yet been associated in the literature.[1]

Chronic myeloid leukemia is also rare in children and accounts for <5% of all leukemias in children less than 15 years of age, the incidence being higher among adolescents.[16] Compared to adults, children, and adolescents with CML tend to present with higher white blood cell count, larger spleen size in proportion to body size, and higher frequency of advanced phases at diagnosis.[17] Although the molecular basis of chronic myeloid leukemia is known, an etiological cause cannot be revealed in most children. Ionizing radiation is the only environmental factor involved in CML etiology. CML develops after a long latent period of exposure to radiation. There is no ethnic or genetic predisposition. However, CML is rarely observed as a secondary malignancy in some adult and pediatric cases following irradiation and chemotherapy, mostly in Hodgkin and non-Hodgkin lymphoma treatments.[3]

The therapeutic approach to CML has changed drastically since introducing the TKI, imatinib, followed by the second-generation TKI, dasatinib, and nilotinib. Treatment with imatinib has also improved outcomes in children. The second-generation TKIs (2G-TKIs), dasatinib, and nilotinib were approved recently as first-line treatment in children, and they have expanded treatment options and made allogeneic stem cell transplantation a third-line treatment.[5,18-20]

The PI3K-AKT-mTOR pathway is one of the critical pathways that control cell growth and proliferation during development. Postzygotic somatic activating mutations in *PIK3CA* are responsible for the clinical spectrum of overgrowth associated with *PIK3CA*.[15] Somatic mutations in the *PIK3CA* gene are found in many other types of cancer, including ovarian, breast, lung, brain, and stomach cancer. These mutations also play a role in colorectal cancer.[21] *PIK3CA* encodes p110a, a critical component of the PI3-kinase enzyme, which activates signaling pathways involved in cellular proliferation, survival, and growth. These mutations change single amino acids in the p110α protein. Activated in response to tyrosine kinase receptor-ligand binding, PI3K converts phosphatidylinositol (4,5)-diphosphate into phosphatidylinositol (3,4,5)-triphosphate and leads to AKT activation. This activation of AKT leads to increased cellular proliferation via mTOR.[15,21] Continuous activation of this pathway has been shown to cause venous malformations due to reduced apoptosis of endothelial cells and improper assembly of vascular smooth muscle.[21,22]

As a conclusion, it has been shown that CML may accompany CVLM. The reporting of the associated malignancies in this rare disorder may have a further impact on understanding the cancer mechanisms.

Ethical approval

We obtained informed consent from the patient's family.

Author contribution

The authors confirm contribution to the paper as follows: study conception and design: ÇC, TA, FG, ŞÜ; data collection: ÇC, TA, FG, ŞÜ; analysis and interpretation of results: ÇC, TA, FG, ŞÜ; draft manuscript preparation: ÇC, TA, FG, ŞÜ. All authors reviewed the results and approved the final version of the manuscript.

Source of funding

The authors declare the study received no funding.

Conflict of interest

The authors declare that there is no conflict of interest.

REFERENCES

1. Blatt J, Finger M, Price V, Crary SE, Pandya A, Adams DM. Cancer risk in Klippel-Trenaunay syndrome. Lymphat Res Biol 2019; 17: 630636. https://doi.org/10.1089/lrb.2018.0049
2. Tanizawa A. Optimal management for pediatric chronic myeloid leukemia. Pediatr Int 2016; 58: 171179. https://doi.org/10.1111/ped.12876
3. Suttorp M, Millot F, Sembill S, Deutsch H, Metzler M. Definition, epidemiology, pathophysiology, and essential criteria for diagnosis of pediatric chronic myeloid leukemia. Cancers (Basel) 2021; 13: 798. https://doi.org/10.3390/cancers13040798
4. Wallace SA, Ignacio RC, Klugh A, Gates G, Henry MCW. An unusual presentation of pediatric osteoblastoma in a patient with Klippel-Trenaunay-Weber syndrome: case report. J Neurosurg Pediatr 2015; 15: 638640. https://doi.org/10.3171/2014.11.PEDS13478
5. Jabbour E, Kantarjian H. Chronic myeloid leukemia: 2018 update on diagnosis, therapy and monitoring. Am J Hematol 2018; 93: 442459. https://doi.org/10.1002/ajh.25011
6. Billington AR, Shah J, Elston JB, Payne WG. Klippel-trenaunay syndrome. Eplasty 2013; 13: ic64.
7. Singhal V, Kamath N, Rao S. Klippel-Trenaunay syndrome and type 1 neurofibromatosis: a chance association? Indian J Paediatr Dermatol 2013; 14: 92-94. https://doi.org/10.4103/2319-7250.122178
8. Sharma D, Lamba S, Pandita A, Shastri S. Klippel-trénaunay syndrome - a very rare and interesting syndrome. Clin Med Insights Circ Respir Pulm Med 2015; 9: 14. https://doi.org/10.4137/CCRPM.S21645
9. Asghar F, Aqeel R, Farooque U, Haq A, Taimur M. Presentation and management of Klippel-Trenaunay syndrome: a review of available data. Cureus 2020; 12: e8023. https://doi.org/10.7759/cureus.8023
10. Lee BB, Vaghi M. Review on target treatment of klippel-trenaunay syndrome. Ital J Vasc Endovasc Surg 2021; 28. https://doi.org/10.23736/S1824-4777.21.01500-X
11. Wang SK, Drucker NA, Gupta AK, Marshalleck FE, Dalsing MC. Diagnosis and management of the venous malformations of Klippel-Trénaunay syndrome. J Vasc Surg Venous Lymphat Disord 2017; 5: 587595. https://doi.org/10.1016/j.jvsv.2016.10.084
12. Fay A, Fynn-Thompson N, Ebb D. Klippel-Trénaunay syndrome and rhabdomyosarcoma in a 3-year-old. Arch Ophthalmol 2003; 121: 727729. https://doi.org/10.1001/archopht.121.5.727
13. Harnarayan P, Harnanan D. The Klippel-Trénaunay Syndrome in 2022: unravelling its genetic and molecular profile and its link to the limb overgrowth syndromes. Vasc Health Risk Manag 2022; 18: 201209. https://doi.org/10.2147/VHRM.S358849
14. Vahidnezhad H, Youssefian L, Uitto J. Klippel-Trenaunay syndrome belongs to the PIK3CA-related overgrowth spectrum (PROS). Exp Dermatol 2016; 25: 1719. https://doi.org/10.1111/exd.12826
15. Hughes M, Hao M, Luu M. PIK3CA vascular overgrowth syndromes: an update. Curr Opin Pediatr 2020; 32: 539546. https://doi.org/10.1097/MOP.0000000000000923
16. Hijiya N, Maschan A, Rizzari C, et al. Phase 2 study of nilotinib in pediatric patients with Philadelphia chromosome-positive chronic myeloid leukemia. Blood 2019; 134: 20362045. https://doi.org/10.1182/blood.2019000069
17. Hijiya N, Schultz KR, Metzler M, Millot F, Suttorp M. Pediatric chronic myeloid leukemia is a unique disease that requires a different approach. Blood 2016; 127: 392399. https://doi.org/10.1182/blood-2015-06-648667
18. de la Fuente J, Baruchel A, Biondi A, et al. Managing children with chronic myeloid leukaemia (CML): recommendations for the management of CML in children and young people up to the age of 18 years. Br J Haematol 2014; 167: 3347. https://doi.org/10.1111/bjh.12977

19. Hijiya N, Suttorp M. How I treat chronic myeloid leukemia in children and adolescents. Blood 2019; 133: 23742384. https://doi.org/10.1182/blood.2018882233

20. American Society of Clinical Oncology. Leukemia - Chronic Myeloid - CML: Diagnosis. 2016. Available at: https://www.cancer.net/cancer-types/leukemia-chronic-myeloid-cml/diagnosis (Accessed on May 15, 2018)

21. Yuan TL, Cantley LC. PI3K pathway alterations in cancer: variations on a theme. Oncogene 2008; 27: 54975510. https://doi.org/10.1038/onc.2008.245

22. Zhang T, Yao Y, Wang J, et al. Haploinsufficiency of Klippel-Trenaunay syndrome gene Aggf1 inhibits developmental and pathological angiogenesis by inactivating PI3K and AKT and disrupts vascular integrity by activating VE-cadherin. Hum Mol Genet 2016; 25: 50945110. https://doi.org/10.1093/hmg/ddw273