

## Case Report

# Chiari I Malformation and Intramedullary Hemorrhage in a female Patient with Klippel Trenaunay Syndrome: A Rare Case Report Study

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### Abstract

Klippel Trenaunay Syndrome (KTS) is a rare vascular disorder characterized by a triad of symptoms including capillary malformations known as port-wine stains, venous varicosities, and osseous- or soft-tissue hypertrophy of the affected extremity. The etiology remains ambiguous, although genetic factors have been implicated. We present a case of a 27-year-old female with KTS who presented with progressive right sided paresis. An intramedullary hemorrhage and syringomyelia of the cervical spine, along with a Chiari I malformation were identified in brain and cervical spine MRI. Her laboratory tests revealed significant coagulopathy. Our patient was initially treated conservatively before she discharged for both a scheduled neurosurgical procedure and splenectomy.

**Key words:** Klippel Trenaunay Syndrome, intramedullary hemorrhage, Chiari I, hypofibrinogenemia, hepatosplenomegaly

### Background

Klippel Trenaunay Syndrome (KTS) is a rare congenital disorder with an incidence rate of 2-5 cases in 100000. (Ling-Li Li, 2023) It is characterized by a triad of symptoms including capillary malformation (known as port wine stain) and venous malformations, as well as bony and soft tissue hypertrophy

which mostly affects the one lower limb (Li et al., 2023). Lymphatic malformations are not always present. (Li et al., 2023) Two of the abovementioned clinical characteristics should be met for clinically diagnosing KTS. (Karmacharya, et al., 2022) Even though the anatomical distribution of KTS is mainly unilateral, affecting mostly the lower limb, sporadically can affect both lower and upper

extremities, the trunk, and the internal organs (Karmacharya, et al., (2022). Vascular malformations of the internal organs like the colon, bladder, and spleen can lead to internal bleeding. (Gubala, et al., 2023) Other complications include thrombophlebitis, deep vein thrombosis (DVT), and pulmonary embolism. (Hongna Yang, 2021) KTS has been observed predominately in males opposed to females. (Gubala, et al., 2023 2023) However, nonsignificant correlation with race and family inheritance has been reported. (Li, et al., 2023, Arasu, et al., 2022). Although the etiology was remaining unknown, recent studies revealed that individuals with KTS have a genetic basis, involving mutations in *AGGF1* (formerly *VG5Q*) gene and *PIK3CA*-gene. (Harnarayan, 2022) We present a clinical case of a young female patient with KTS who diagnosed with intramedullary hemorrhage and Chiari I malformation.

### Case report

A 27-year-old Caucasian female presented to the emergency department with sudden onset of right upper extremity paralysis, started 2 days ago. Ten days ago, she had an episode of acute onset of a moderate neck pain with radiation to the right shoulder, followed by right-sided dysesthesia and progressive onset of right lower limb paresis. Her past medical history included Klippel Trenaunay Syndrome (KTS) diagnosed at the age of four, Hashimoto disease, and iron deficiency anemia. Remarkably, she had no medical follow up of her condition since her diagnosis.

On initial assessment, the patient was alert and oriented to time, place, and person, afebrile, and clinically stable. The neurological examination revealed paralysis of the right upper extremity, and paresis of the right lower extremity, with a Grade 1 and 4 (of 5) muscle power, respectively. Left-sided hemiparesis was found with a Grade 4 (of 5) muscle power. Deep tendon reflexes were absent, and Babinski sign was positive on

both sides. The respiratory system examination had no significant pathological findings. The cardiovascular system assessment revealed normal heart sounds, and bradycardia with regular pulses. Abdominal examination showed a painless abdomen with an enlarged liver, as well as a palpable spleen below left costal margin and close to the umbilical cord, bowel sounds were present and normal. Physical examination showed soft tissue hypertrophy of both the entire lower limbs and varicose veins over the right lower limb, particularly below the knee. On skin assessment, capillary hemangiomas, known as port wine stains, were noticed on the abdominal wall bilaterally, the lower right limb, and both upper extremities. The arterial pulse was of normal character and volume, in both upper and lower extremities.

A series of routine blood tests were performed. The initial complete blood count revealed normal white blood cell count (WBCs  $6,80 \times 10^3/\mu\text{L}$ ), hypochromic, normocytic anemia [hemoglobin concentration (Hgb) of 9,20 g/L, hematocrit (Hct) level of 26,60%, mean red blood cell volume (MCV) of 83,50 fL], and moderate to severe thrombocytopenia [platelet count (PLTs) of  $80.00 \times 10^3/\mu\text{L}$ ]. The differential leukocyte count revealed 76,20% neutrophils, 12,30% lymphocytes, 0,20% eosinophils, 11,10% monocytes, and 0,20% basophils. Inflammatory markers had a slight elevation. The coagulation panel assessment revealed both a prolonged prothrombin time [PT] and activated partial thromboplastin time [aPTT], increased international normalized ratio [INR=2,07], severe hypofibrinogenemia (fibrinogen  $<0,80\text{g/L}$ ), and significantly increased D-Dimers (DD=27,82). The coagulation function was further tested with rotational thrombelastography (ROTEM), which revealed reduced clot firmness. The laboratory values were suggestive of intravascular activation of coagulation cascade. Her peripheral blood smear showed hypochromic normocytic anemia and

thrombocytopenia, The liver and renal function tests were within the physiological limits, without any electrolytic imbalance. The blood cultures were negative. The urinalysis was not consistent with a urinary tract infection. The serological testing for infectious diseases was negative. Her immunological tests including RF, ANA, anti-dsDNA, pANCA, cANCA, CCP, dsDNA, ENA, Ro, La, Scl70, and RNP, were all negative. The hepatitis viral panel was negative. Notably, from her repeated blood tests, it was observed a significant and gradual drop in platelet levels as well as in the coagulation parameters leading to a consumptive coagulopathy called Kasabach–Merritt syndrome (KMS).

Initially, an emergency CT scan of the brain was performed which identified the descent of the cerebellar tonsils in the spinal canal. The chest X-Ray findings were unremarkable. The electrocardiogram (ECG) showed sinus bradycardia, without morphological features of ischemia. The transthoracic cardiac ultrasonography showed a normal size of the heart, no dilation of atrium and ventricles, TASPE 20mmHg, and an ejection fraction (EF) of 60%. The systolic and diastolic function of the ventricles were normal. Additionally, no abnormal reflux was noticed in any of the cardiac valves. The exclusion of a possible deep venous thrombosis (DVT) was assessed by Doppler ultrasonography of both the lower extremities. No findings consistent with deep venous thrombosis (DVT) were identified. However, it showed numerous dilated superficial veins of the right lower extremity at the level of gastrocnemius muscle. Additionally, a color doppler ultrasound of splenoportal axis did not reveal any significant findings. Later the abdominal contrast-enhanced computed tomography (CECT) scan showed hepatomegaly with cranio-caudal diameter of 21.8 cm without any distinct lesions in the hepatic parenchyma. The CT scan also depicted a massive splenomegaly with cranio-caudal

diameter of 25.8 cm. Self-limited gross hematuria, lasted for 5 days, without other related symptoms like urgency, dysuria, and frequency, was noticed on the first day of her hospitalization. The following day of her hospitalization, acute neurologic deterioration was observed, with upper right limb paresis and dysphagia. MRI of the brain and cervical spine demonstrated 1.1cm descent of the cerebellar tonsils below the McRae line causing significant medullary compression (Figure 3), and syringomyelia of the cervical spine with intramedullary hemorrhage extending from the level of C1 up to C7. (Figure 4). The above findings are consistent with Chiari I malformation.

A diagnostic cerebral angiography was performed which did not reveal any vascular malformations. The thoracic/lumbar/sacrum MRI revealed a posterior, left-sided, paracentral, lumbar disc herniation mostly at the L5-S1 level, and less at L4-L5 levels, causing spinal cord compression. An abdominal MRI was performed a week after the CT of the abdomen due to referred abdominal discomfort from the patient and the presence of mild abdominal distension. The abdominal MRI showed splenomegaly with further increase of spleen's diameters (22cm x 13cm x 29cm) causing compression of the left kidney. Neither liver nor pancreatic focal lesions were noted. A small amount of intraperitoneal fluid was found in the lesser pelvis.

The primary therapeutic aim was the correction and monitoring of coagulation parameters before proceeding to the surgical correction of Chiari I malformation. Given the persistent coagulopathy and the diagnosis of Kasabach–Merritt syndrome, she was initially started on human fibrinogen (1g IV every 8 hours). Additionally, she was transfused with packed red blood cells and fresh frozen plasma. According to her platelet count, it was not considered necessary to be transfused with platelets. Remarkably, the patient had no

response to this therapy over the next days, thus tranexamic acid (1g IV every 8 hours) was added to the initial therapeutic scheme. Therapy continued until the preoperative day, when the patient's hemoglobin and hematocrit were stable even though her coagulation profile remained abnormal. Prior to her scheduled neurosurgical procedure, she transfused with 2U of packed red blood cells, and 21 U of fresh frozen plasma.

## Discussion

According to the International Society for the Study of Vascular Anomalies 2018, KTS is a congenital disorder characterized by vascular malformations affecting the capillaries in 98%, and veins in 72%, lymphatic malformations in 11% and limb overgrowth seen in 67% of the cases (Arasu A, 2022, Saleem, et al., 2019). The diagnosis is made when the two of the three criteria are met. (Deca, et al., 2020).

Remarkably, our patient was presented with all these features.

Due to the persistent coagulopathy, we considered the diagnosis of Kasabach–Merritt syndrome for our patient. KMS is characterized by consumptive coagulopathy, thrombocytopenia, and microangiopathic hemolytic anemia in association with a certain type of hemangioma. (Osman, 2013) Common laboratory findings include low fibrinogen levels and coagulation factors like factor II, V, VIII, as well as thrombocytopenia, and prolonged PT, aPTT. (Neubert, et al., 1995) A similar laboratory profile was observed in our patient. Thus, based on both her medical history and laboratory findings, we assumed that the hypofibrinogenemia was the result of consumptive coagulopathy as a complication of KTS.

There is no universal therapeutic approach for KTS patients. (Karmacharya, et al., 2022). However, studies have shown that patients with KTS and significant hypofibrinogenemia who treated with fibrinogen replacement

therapy had an improvement in coagulation profile and subsequently a reduction of postoperative bleeding risk. (Coloma-Perez, et al., 2013) Treatment of KTS patients mostly involves an incorporation of conservative and surgical methods. (Karmacharya, et al., 2022) Interestingly, in our case the patient did not respond to the therapy despite the intensive fibrinogen replacement therapy and repeated transfusions with blood products. She continued to be anemic, thrombocytopenic, and coagulopathic till the preoperative day. Up to date, there is no definite therapeutic approach available for individuals with KTS. It is considered incurable and conventional treatment is mainly used. (Vahidnezhad, Youssefian & Uitto, 2016). However, novel therapies for KTS have focused on targeting the PI3K pathway. (Gubala, et al., 2023). Based on recent data, the development of direct PI3K inhibitors like sirolimus and alpelisib, has shown a favorable safety profile and promising results in the prevention of complications and improvement of vascular malformations (Gubala, et al., 2023).

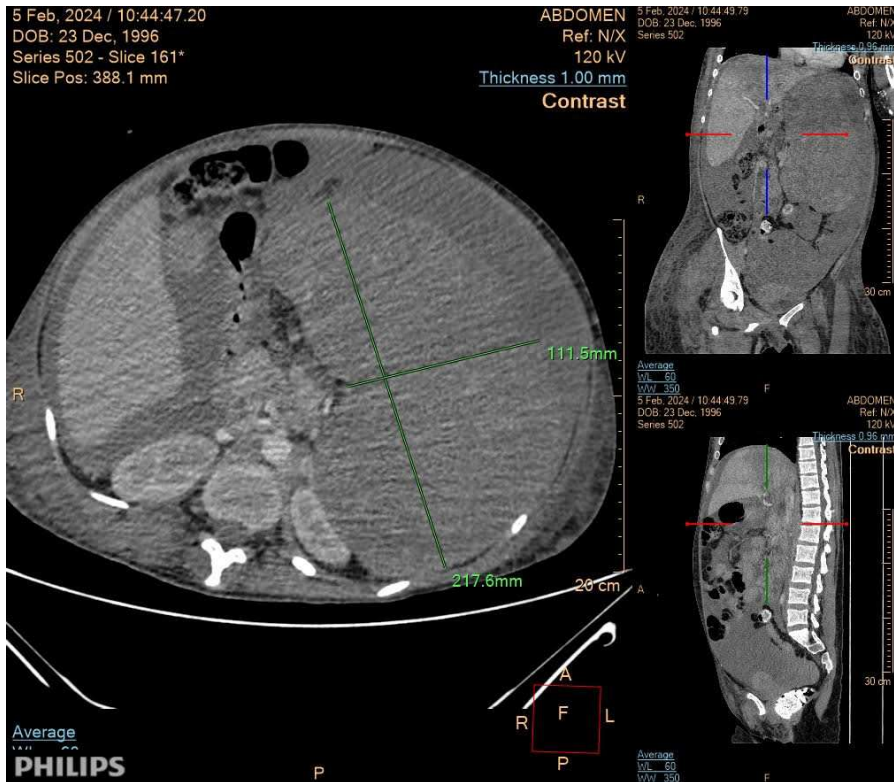
In our case, the patient received consistent medical care from a multidisciplinary team involving neurosurgeons, pathologists, hematologists, neurologists, and general surgeons.

**Conclusion:** Klippel-Trenaunay Syndrome is a rare congenital disease with a limited number of published research. Early diagnosis and recognition of the heterogeneous presentation of KTS, extended knowledge and awareness are significant for improving the therapeutic management of KTS. Until now, there has been no established therapy and no consensus regarding its management, except of following and individualized therapeutic approach. Several treatment modes have been proposed, but further research is required for testing novel agents and establishing their efficacy and safety profile.





**Figure 1.** A coronal section of the abdominal CECT scan showing hepatomegaly and massive splenomegaly with a cranio-caudal diameter of 21.18cm and 25.8 cm respectively.



**Figure 2.** An axial section of the abdominal CECT scan demonstrating an enlarged spleen with antero-posterior diameter of 21.7cm.



**Figure 3.** A sagittal T2 weighted section of cervical spine MRI showing the descent of the cerebellar tonsils 1.1 cm below the McRae line (normal value <5 mm) which causes significant medullary compression.



**Figure 4.** A sagittal T2-weighted cervical spine MRI sequence of the same patient with syringomyelia depicted at C5-C6 level (white arrow). The finding is consistent with Chiari I malformation.

**Conflicts of interest :** There are no conflicts of interest.

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