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Case Series

Klippel-Trenaunay Syndrome: Case series from a university hospital of Nepal

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ABSTRACT

Introduction: Klippel Trenaunay Syndrome (KTS) is a rare congenital malformation with capillary and venous malformations and soft tissue/bony overgrowth with or without lymphatic malformation. Cutaneous vascular stain, varicosities and tissue hypertrophy represent its main clinical features. Besides, the patient can develop thromboembolic pathologies, recurrent bouts of infection, stasis eczema, limb length discrepancy and intolerable pain typical of intraosseous involvement.

Methods: Here, we report a case series of seven patients aged 10–45 who presented to our centre with clinical features suggestive of KTS. Out of them, six patients had involvement of unilateral lower limb, while only one had involvement of bilateral lower limb. They all had typical cutaneous vascular stains and underlying venous malformation, while one patient had developed complications with multiple ulcer formation.

Outcomes: An interdisciplinary team of vascular surgeons, dermatologists, interventional radiologists, orthopaedics, and physiotherapists managed the cases. We performed an individualized treatment as per the patient's presentation, which included a combination of supportive, medical, interventional radiologic, and surgical interventions. The follow-up outcomes of all the patients revealed significant resolution of symptoms.

Conclusion: Patients with KTS can have diverse presentations. Therefore, clinicians should ensure an individualized treatment with the involvement of a multidisciplinary team for proper management and prevention of complications.

1. Introduction

Klippel-Trenaunay Syndrome (KTS), also known as an angio-osteohypertrophy syndrome [1], characterised by the triad of capillary malformations, venous malformations, and limb overgrowth [1]. It is a rare disease with a prevalence of 2–5 per 100,000 population, primarily affecting the lower extremities [2]. KTS is present since birth and is mostly sporadic [2]. Recent studies suggest that it is associated with mosaic-activating mutations in the PIK3CA gene [3]. The patient can have variable outcomes depending upon the clinical presentation. Some have a good prognosis with milder symptoms like painless cutaneous stain and non-debilitating vascular malformation [2]. However, coagulopathy, major bleeding and recurrent cellulitis suggest a bad prognostic feature [2]. Therefore, their management warrants a multidisciplinary approach, centring on preventing and managing complications [2,4]. We present a case series of seven patients with Klippel-Trenaunay Syndrome (KTS) written according to PROCESS 2020 criteria [5] (see Table 1)

2. Case series

2.1. Case 1

A 10-year-old female presented to the Cardiothoracic and Vascular

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Unit of the Department of Surgery with pain in the right inner thigh for ten days, acute onset, intermittent type aggravated by walking and running. There was no history of trauma, previous surgery and family history of similar illness.

On examination, there was a diffuse red-purple cutaneous stain over the bilateral lower limb with soft tissue swelling in the right lower limb (Fig. 1). Multidisciplinary management was done, including consultation with radiologists, orthopaedics, cardiothoracic vascular surgeons, and dermatologists.

Doppler ultrasonography revealed the presence of an accessory vein over the anterior and lateral aspect of the bilateral lower limb of diameter 3.7 mm on the right side and 3.6 mm on the left side. The great saphenous vein (GSV) appeared normal in both limbs. Sclerotherapy was done in bilateral abnormal veins with advice on the use of compression bandages. A prominent dilated compressible vein was noted in the lateral part of the calf region on ten days of follow up. Dilated veins of the thigh (GSV and accessory vein) were thrombosed. In two sites, foam sclerotherapy was done in right superficial calf veins. She was also advised for physiotherapy for anklet toe pumping exercise.

In a recent follow-up, sclerotherapy was done in the superficial accessory vein of the right limb. Doppler ultrasonography done after two weeks duration showed an adequate thrombosis of the vein on the lateral aspect of the limb. A total of three episodes of sclerotherapy were done over four months.

2.2. Case 2

A 19-year-old male presented with prominent dilated veins in his left leg since childhood. It was associated with swelling and pain for a year aggravated by his job, where he had to stand for a longer duration. He added that he noticed purplish pigmentation in the left calf and foot region without ulceration for six months. He gave no history of trauma or surgical procedure involving the limb. Doppler ultrasonography revealed dilated veins in the lateral aspect of the left lower limb from ankle region to thigh with a maximum diameter of 7.3 mm. The vein had multiple perforators connecting with deep and muscular veins. However, there was no deep vein thrombosis.

CT venogram was done, which revealed an abnormal vein in the lateral part of the calf and thigh with multiple connections to deep veins, and a diagnosis of persistent embryonic lateral marginal vein of the Servelle was made. Radiofrequency ablation (RFA) of the defective veins was done with adjunct sclerotherapy of the prominent veins, and selected perforators were done (Fig. 2).

The patient was advised for physiotherapy and compression stocking. Doppler ultrasonography was done on an annual follow-up, which showed resolution of the lateral marginal vein along with the absence of incompetent perforators. He added that the symptoms had completely subsided.

2.3. Case 3

A 35-five-year-old female presented with a history of red-purple skin discolouration and prominent dilated veins in the lateral aspect of the right thigh and leg since childhood. It was associated with gradually progressive swelling and pain for two years. Doppler ultrasonography revealed persistent embryonic lateral marginal Vein of Servelle in the right lower limb, which was further confirmed by CT venogram (Fig. 3). However, the patient denied undergoing any surgical intervention and is under compression stocking and other conservative management.

2.4. Case 4

A 45-year-old female presented with multiple non-healing ulcers in the lateral part of the left ankle for two years. She gave a history of prominent dilated veins in the left lower limb since childhood and had on and off pain. She added that she noticed blue-purplish pigmentation prior to the ulceration; Doppler ultrasonography revealed multiple venous malformations in the lateral aspect of the left thigh and calf along with the presence of Persistent embryonic lateral marginal Vein of Servelle. As the lateral marginal vein of Servelle was extremely tortuous, RFA was not done. However, multiple sclerotherapy sessions were done, focusing on the essential perforators around and proximal to the ulceration. Her ulcers have healed with three sclerotherapy sessions and adequate compression therapy, as revealed on the annual follow-up.

2.5. Case 5

An 18-year-old female presented with a history of prominent dilated veins in the lateral aspect of the left thigh and calf since childhood. She added the presence of itchy blue-purple pigmentation in the lateral part

Table 1
Details of cases of patients with KTS.

Case	Gender	Age (Years)	Clinical Features	Affected region	Radiological Finding	Management
1	F	10	Port wine stain Swelling Pain	Bilateral lower limb	Accessory vein over the anterior and lateral aspect of the right lower limb	Sclerotherapy Elastocrepe bandaging Physiotherapy
2	M	19	Port-wine stain Prominent dilated veins Pain	Left lower limb	Persistent embryonic lateral marginal Vein of Servelle.	Compression stockings RFA Sclerotherapy
3	F	35	Dilated veins Pain	Right lower limb	Persistent embryonic lateral marginal Vein of Servelle	Compression stockings
4	F	45	Port wine stain Pain Multiple non-healing ulcers Prominent dilated veins	Left lower limb	Persistent embryonic lateral marginal Vein of Servelle Multiple venous malformations in left lateral lower limb	Sclerotherapy Compression bandaging
5	F	18	Port wine stain Dilated veins Itchiness	Left lower limb	Left lateral marginal vein	Sclerotherapy Compression Bandaging
6	F	15	Pain Port wine stain Itchiness Swelling	Left lower limb	Left lateral marginal vein	RFA Sclerotherapy
7	M	40	Prominent dilated veins Port wine stain Increased limb girth	Right lower limb	Right lateral marginal vein Varicose veins involving short saphenous vein	Sclerotherapy

*F- Female; M-Male; RFA- Radiofrequency ablation.

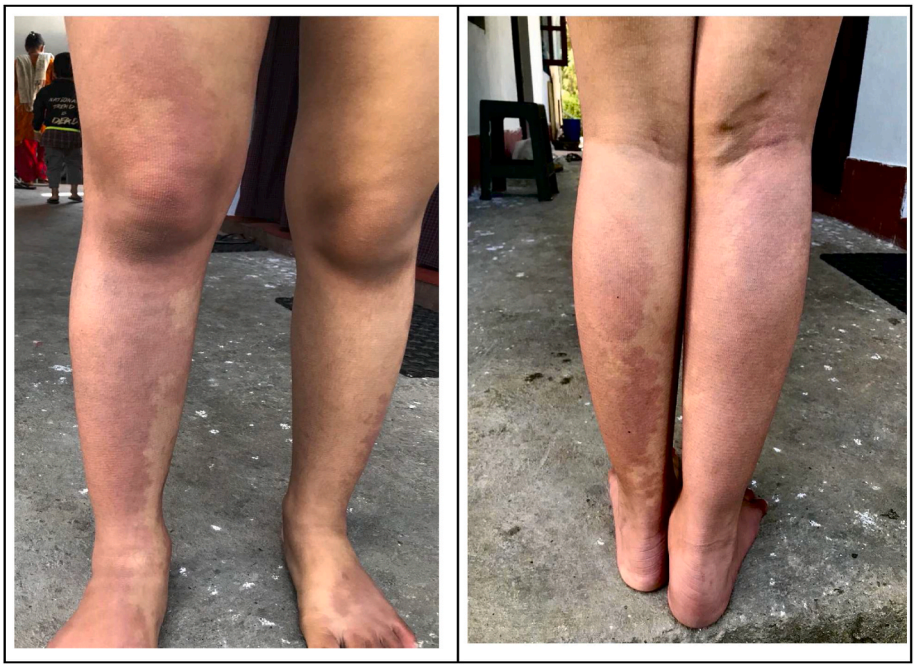

Fig. 1. Port-wine stain in the bilateral lower limb with soft tissue swelling in the right lower limb a) anterior view, b) posterior view.

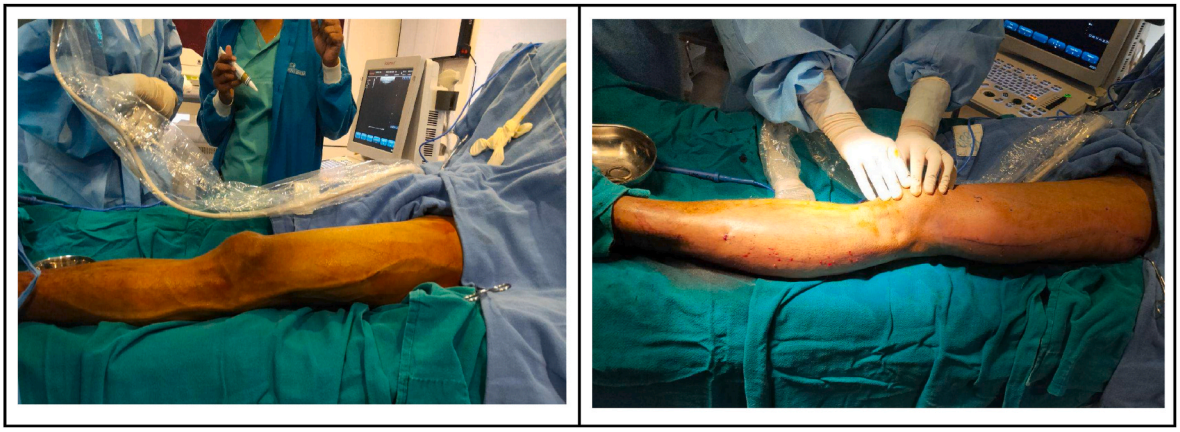

Fig. 2. a) Pre radiofrequency ablation picture of lateral marginal vein of Servelle b) Post radiofrequency ablation showing decreased prominence of the vein.

of the ankle for a year. Doppler ultrasonography revealed venous malformation along with tortuous veins in the lateral part of the thigh and calf communicating with deep veins. Following imaging findings, four sclerotherapy sessions were done, along with advice on compression bandaging. On routine follow up, her symptoms had drastically resolved.

2.6. Case 6

A fifteen-year-old female presented with a history of persistently increasing pain in the left foot region for four years, aggravated by the limb's movement. It was associated with painless itchy skin discolouration along with swelling and the presence of prominent tortuous veins in the same limb for one and a half years. On clinical examination, a dilated tortuous vein was present on the posterolateral aspect of the calf region with purplish skin discolouration. Conservative management with the use of compressive stocking was done. Doppler ultrasonography showed a left-sided abnormal vein connected to deep veins by multiple perforators (Fig. 4), MRI of the left lower limb also revealed venous and lymphatic anomaly along with hypertrophy of bony cortex. The findings were consistent with the presence of lateral marginal veins. Radiofrequency ablation (RFA) of the vein was done, following which sclerotherapy was performed twice in the venous and lymphatic part at one-week intervals. On a recent follow-up, her symptoms have improved.

2.7. Case 7

A forty-year-old male presented with progressive prominent dilated veins and skin discolouration in the right lower limb since childhood. For the last five years, he noticed an increase in girth of the right lower limb compared to the left lower limb. The prominent veins were more in the lateral and posterior parts of the leg (Fig. 5). Doppler ultrasonography was suggestive of varicose veins involving lateral marginal vein of Servelle and short saphenous vein with extensive perforators in the calf. The patient had undergone a surgical procedure (phlebectomy) two times in another centre. In our centre, the patient received two sessions of sclerotherapy with some resolution in venous prominence.

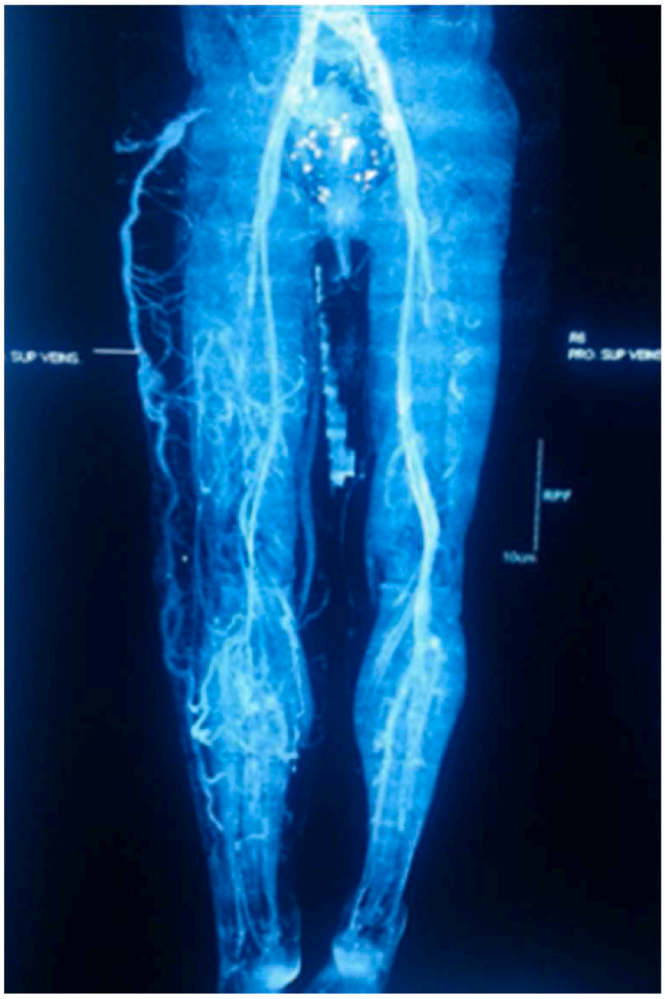

Fig. 3. CT venogram showing right-sided Persistent embryonic lateral marginal Vein of Servelle.

3. Discussion

Klippel-Trenaunay Syndrome (KTS) is a rare overgrowth syndrome with veno-capillary malformation with or without lymphatic involvement [6]. Numerous case studies have been reported, to date, but there is no literature revealing the true incidence and prevalence of this disease [7].

The exact aetiology of KTS remains indistinct [7] and has been attributed to many theories linking it to various genetic defects. These include GNAQ or GNA11 activating mutations [8], overexpression of the angiogenic factor AGGF1 (Previously known as VG5Q) [9,10] and a de novo supernumerary ring chromosome 18 [11]. Recent clinical and molecular genetic studies highlight that KTS belongs to the PIK3CA-related overgrowth spectrum (PROS), which occurs due to a somatic gain of function mutation in the PIK3CA gene [3,12]. Though distinct, these clinical entities with overlapping phenotypic features belonging to PROS should be differentiated properly for ascertaining proper treatment and ensuring personalized healthcare delivery [3].

Cutaneous vascular stain (typical port-wine stain), the persistence of embryonic vein forming varicosities, limb hypertrophy with or without cystic lymphatic malformation causing lymphedema, represent the key clinical features [2,13]. The cutaneous discolouration is present since birth and usually affects unilateral lower limbs; rarely, affecting the bilateral lower extremities, upper extremities, trunk and visceral organs [2,14]. These stains can have geographic patterns with sharp demarcation or patchy patterns with less distinct margins [2]. Additionally, the presence of a geographic vascular stain indicates an increased risk of underlying lymphatic malformation and developing complications like cellulitis and phlebitis [2]. According to Jacob et al., the diagnosis of this disease is based on the presence of two out of these three features, including–capillary malformation, soft tissue or bony overgrowth and venous malformation [15].

Like capillary malformation, venous disorders are usually present since birth [2]. They remain obscure until the person begins to walk [2]. These involve the persistence of embryonic avalvular venous structures, primarily the lateral marginal vein of Servelle and sciatic vein; sometimes involving the deep venous system [2,7]. The lymphatic malformation can present as lymphatic hyperplasia, hypoplasia or aplasia; not always occurring concurrently with other typical features of KTS [13]. The venous and lymphatic malformation, both are attributed to the increasing limb overgrowth along with soft tissue/bony hypertrophy [2,13]. When left untreated, the patient can develop varied complications like–severe haemorrhage, thromboembolic disorders, recurrent bouts of infection and skin ulceration [2,7,13]. In our study, the cutaneous vascular stain and dilated tortuous vein was present in all seven patients. These symptoms affected only the lower limb in all the cases; left lower limb in four patients, two in the right limb and bilaterally in one. The major reason for the presentation of almost all the patients was pain in the extremities, additionally, two of the patients reported itchiness in

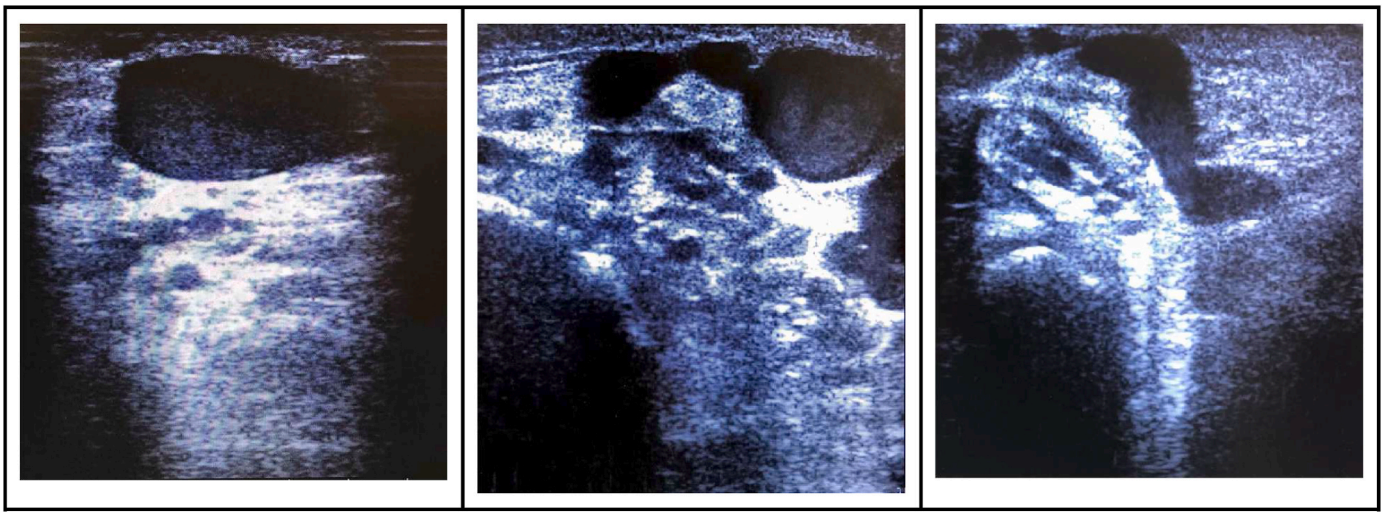

Fig. 4. Doppler Ultrasonography showing persistent embryonic lateral marginal vein of Servelle along with other dilated veins and multiple perforators.

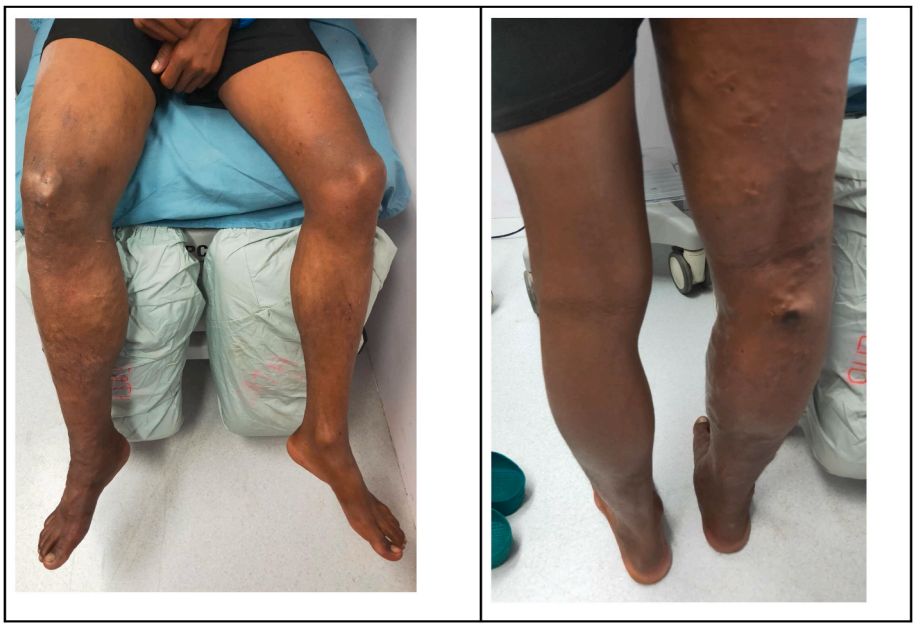

Fig. 5. Lower limb with right-sided skin discolouration, prominent dilated vein and girth discrepancy compared to left limb a) anterior view b) posterior view.

the area of pigmentation.

Owing to its rarity and unclear aetiology, there are no consensus diagnostic criteria and specific laboratory investigations [2]. Diagnosis is mainly clinical, but confirmation requires additional evaluation like D-dimer assay, gene analysis and diagnostic imaging–Doppler ultrasonography, MRI, contrast phlebography, venous duplex scan or venous duplex ultrasonography [14–16]. In our setting, we opted for evaluation by Doppler Ultrasonography, which is both diagnostic and therapeutic for performing minimally invasive surgeries. MRI and CT venogram was reserved in a few cases with complex vascular abnormality.

Management is primarily conservative; there is no permanent cure for the disease [2]. It includes symptomatic non-invasive treatment aimed at improving patients' quality of life [2]. Use of compression garments–elastic or non-elastic stockings in the affected limb are the mainstay in the management [2]. In conjunction, leg elevation, physiotherapy, lifestyle changes, and stringent cleanliness are a must [2,4]. Endovascular therapy is indicated when the conservative treatment of varicosities has failed; however, limited studies have been done to support its role in KTS [4,17]. Other surgical intervention with the involvement of a multidisciplinary team is warranted when varied complications like the presence of patent deep veins, symptomatic varicose veins and vascular compromise are present [2,16]. Complicated venous abnormalities can be treated efficiently with a less invasive approach–RFA and sclerotherapy [18] RFA has also been shown to gain more advantages over open surgical procedures like stripling due to its cost-effectiveness and good postoperative outcome [19].

Literature suggests minimally invasive procedures superior to open surgeries due to unsatisfying post-surgical outcomes associated with many post-surgical complications and includes a combination of stab phlebectomy, vein stripping, and high ligation of persisting embryonic veins subfascial endoscopic perforator surgery [16,17]. Thus, open surgery is now reserved only for patients who are not suitable for minimally invasive procedures [17].

In our report, we adopted a multidisciplinary treatment modality for the management of all the cases (Fig. 6). All patients were managed conservatively by the use of compression garments and a suggestion to follow the exercises suggested by the physiotherapist. We opted for performing minimally invasive procedures–sclerotherapy with or without RFA, in all seven cases, except in one patient who denied going under the knife. Foam sclerotherapy was done targeting the venous malformation, which showed drastic improvement in all the cases. On follow up, all the patients had a significant reduction in their complaints relating to the prominent dilated vein and debilitating pain.

All things considered, Klippel-Trenaunay Syndrome (KTS) can have varied prognoses depending upon the extent of the disease. Thus, its management requires an early diagnosis with individualized treatment, primarily supportive, with the involvement of a multidisciplinary team.

4. Conclusion

Klippel-Trenaunay Syndrome (KTS) requires a multidisciplinary approach for diagnosis and management. Comprehensive management with physiotherapy, sclerotherapy, minimally invasive surgery like radiofrequency ablation, phlebectomy with a regular follow-up is the mainstay of treatment.

Ethical approval

We have obtained written informed consent from the patients for the publication of this case series.

Sources of funding

No funding were received to conduct this research.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Registration of research studies

N/A.

Guarantor

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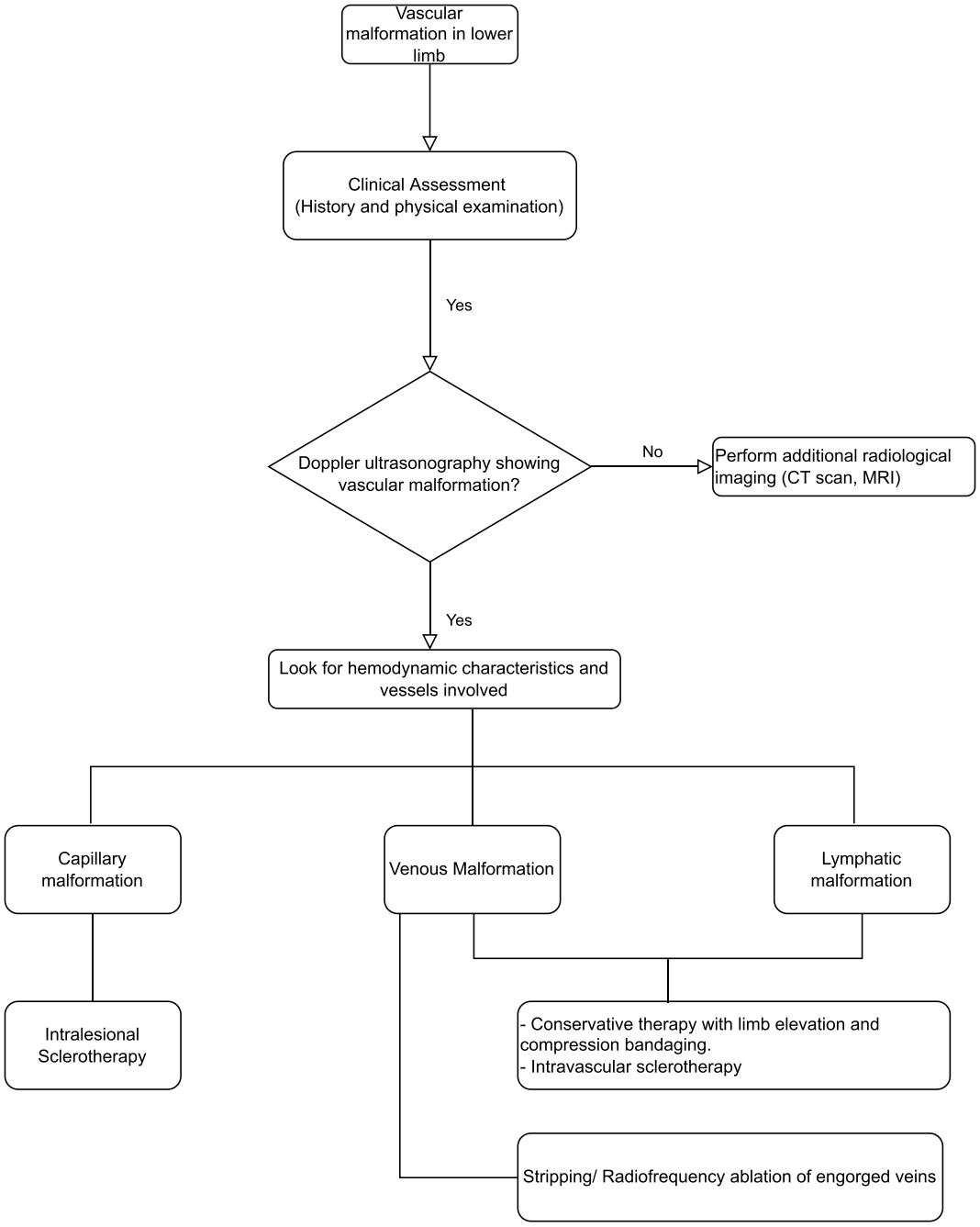

Fig. 6. Flowchart showing management algorithm for treatment of Klippel-Trenaunay Syndrome.

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Patient perspective

After explaining to the patient about the entire project and its benefit for clinicians and patients globally, the patients were extremely happy.

Declaration of competing interest

There are no conflicts of interest.

Ethical approval

N/A.

Please state any sources of funding for your research

None.

Author contribution

Robin Man KarmacharyaSurgical procedure, patient care, manuscript writing, Guarantor, Satish Vaidya-Surgical procedure, Patient care, manuscript writing., Swechha Bhatt -Manuscript writing and editing., Ashish Tamang,-Manuscript writing, Rohit Bhasink Shrestha,–Manuscript writing, Niroj Bhandari,–Manuscript writing, Bijaya Paudel-Manuscript editing, Manish Shah–Manuscript editing, Gaurav -Nepal, Manuscript editing.

Please state any conflicts of interest

None.

Registration of research studies

N/A.

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Consent

Written informed consent was taken from all the participants and none of the identifying characteristics were included in the original article.

International journal of surgery case reports

The following information is required for submission. Please note that failure to respond to these questions/statements will mean your submission will be returned. If you have nothing to declare in any of these categories, then this should be stated.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.amsu.2022.103732.

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