Klippel-Trenaunay syndrome

Timothy H Clayton, Alan D Irvine

Klippel-Trenaunay syndrome (KTS) is a rare congenital disorder of blood and lymphatic vessels that is characterised by a combined vascular malformation of the capillaries, veins and lymphatics, congenital abnormalities, and associated limb hypertrophy. This review provides an overview of the disease with emphasis on the management and underlying aetiology of the syndrome. Management of this condition is largely conservative and requires a multidisciplinary approach. In the majority of cases a conservative approach is indicated with compression as the mainstay of conservative management. Laser can be used to treat port wine stains. Serious complications can occur and regular surveillance is necessary.

Key words

Klippel-Trenaunay syndrome
Cellulitis
Lymphoedema
Congenital and vascular malformation

Klippel-Trenaunay syndrome (KTS) is a rare congenital disorder of blood and lymphatic vessels that is characterised by a combined vascular malformation of the capillaries, veins, and lymphatics, congenital venous abnormalities, and associated limb hypertrophy (*Figure 1*). It is also referred to as Angio-osteohypertrophy syndrome.

A variety of blood and lymphatic vascular malformations are observed, including capillary malformations/port wine stains (PWS), lymphangiomas, lymphoedema and very occasionally arteriovenous malformation (AVM) (Viljoen et al, 1987). Often these malformations are co-associated and KTS is best classified as a complex-combined slow flow vascular malformation (Hand and Frieden, 2002). The condition should be distinguished from Parkes Weber syndrome, where the vascular stain is associated with limb overgrowth and significant arteriovenous shunting of the involved limb (Mattassi, 1993).

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Aetiology

The exact cause of KTS is unknown, although a number of theories have been suggested. Early reports suggested that KTS occurs due to deep vein abnormalities resulting in obstruction to the venous blood flow, venous hypertension, dilatation of blood vessels and limb hypertrophy (Vissers et al, 2003). Baskerville et al (1985) contend that a mesodermal defect during embryogenesis causes maintenance of microscopic arteriovenous communications resulting in KTS (Baskerville et al, 1985). Although KTS is in most cases sporadic, familial cases have been reported (Aelvoet et al, 1992). Para dominant inheritance of a single gene defect may explain the development of KTS, as well as the occurrence of both familial and sporadic cases. This theory was proposed by Happle (1993), who noted that the lesions of KTS were arranged in a mosaic pattern (Happle, 1993). Heterozygotes

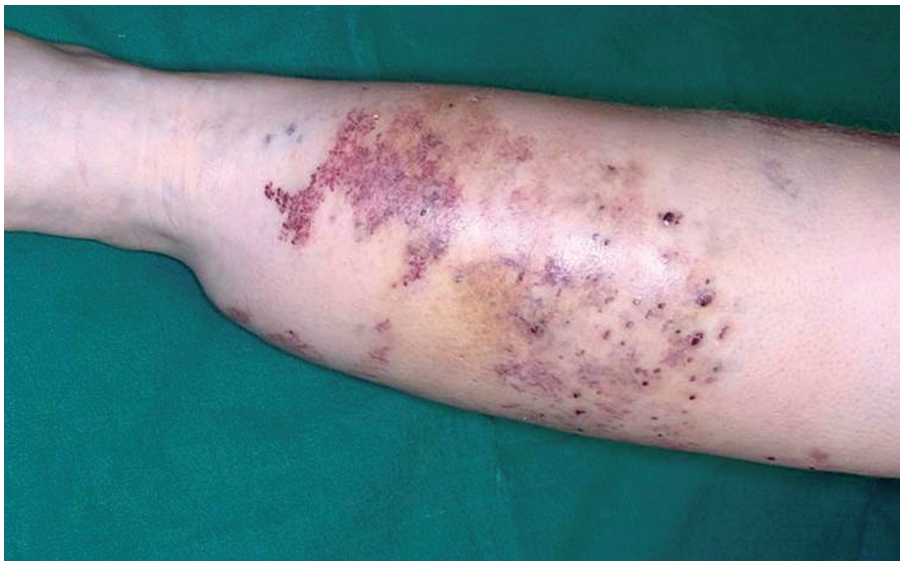

Figure 1. Typical lower limb appearance of KTS.

for a defective gene would be phenotypically normal, but the defective allele could be transmitted throughout many generations. Thus, KTS would only occur if a somatic mutation (often referred to as a 'second hit' after Knudson's original hypothesis) (Knudson, 1971; Devilee et al, 2001) occurred during embryogenesis that resulted in a loss of heterozygosity, leading to a clonal population of cells that were homozygous or hemizygous for the KTS mutation (Happle, 1993).

A balanced 5:11 translocation (an equal exchange of material between two chromosomes with no genetic information added or lost) has been associated with KTS (Whelan et al, 1995). Further studies have identified that some patients with KTS have over expression of an important angiogenic factor located in chromosome 5q13.3 (Tian et al, 2004), although this has yet to be replicated and may not be a true association (Barker et al, 2006).

Clinical features

The cutaneous vascular malformation in KTS is usually apparent at birth and may increase in size over the first few years. It commonly extends onto adjacent truncal skin and is usually extensive, although some areas of skin may be spared even on the affected limb. It may be distributed in a confluent geographic pattern, or more randomly on the affected limb and adjacent trunk (*Figure 2*). The presence of a geographic vascular stain is a predictor of the risk of both associated lymphatic malformation and complications in patients with KTS, including sepsis from cellulitis and phlebitis (Maari and Frieden, 2004).

Geographic stains are commonly found on the lateral aspect of the thigh, knee, and lower leg. The associated limb hypertrophy may not be initially apparent and is due to a number of factors including lymphatic obstruction with associated lymphoedema, dilatation of veins, increase in soft tissue, and bone hypertrophy.

In 1991, a large review of 144 patients with KTS reported that 137 patients (95.1%) had a cutaneous vascular malformation, 134 (93.1%) had soft tissue or bony hypertrophy and in most patients (71.5%) the disease involved one lower extremity (Gloviczki et al, 1991). The hypertrophy may preferentially involve the digits. This leads to leg length discrepancy and an unsteady gait. Involvement of both the upper and lower extremities may occur in 10–15% of cases and is usually ipsilateral.

Patients also commonly have lymphatic abnormalities with associated lymphoedema and susceptibility to infection and cellulitis, which may manifest as fever and recurrent painful swelling with sterile blood cultures.

Venous varicosities become prominent in adolescence and can produce deep venous stasis, which, in turn, can produce pain, bleeding, thrombophlebitis, ulceration and pulmonary emboli (Gloviczki et al, 1991). Patients also commonly have lymphatic abnormalities with associated lymphoedema and susceptibility to infection and cellulitis, which may manifest as fever and recurrent painful swelling with sterile blood cultures. The vascular malformation in KTS is typically low flow which causes some trapping of platelets with mild-to-moderate depression of the platelet count. When an AVM is present as in PWS, congestive heart failure may result from high output.

Management

A multidisciplinary approach (dermatologists, paediatricians, nurses, physiotherapists, radiologists, counsellors, occupational therapists and orthotic technicians) to the management of KTS is essential, involving regular clinical and radiological assessment of the affected limbs. Patients with significant limb length discrepancies may require serial radiographic studies for measurement of limb length. Patients are evaluated using a non-invasive imaging strategy including color duplex ultrasonography, magnetic resonance imaging (MRI), lymphoscintigraphy, and plain radiographs. The treatment of KTS is in the main conservative and focuses on controlling symptoms and treating associated complications such as cellulitis (Berry et al, 1998).

Compression garments are indicated for chronic venous insufficiency, lymphoedema, recurrent cellulitis, and recurrent bleeding from capillary or venous malformations of the extremity. The compression

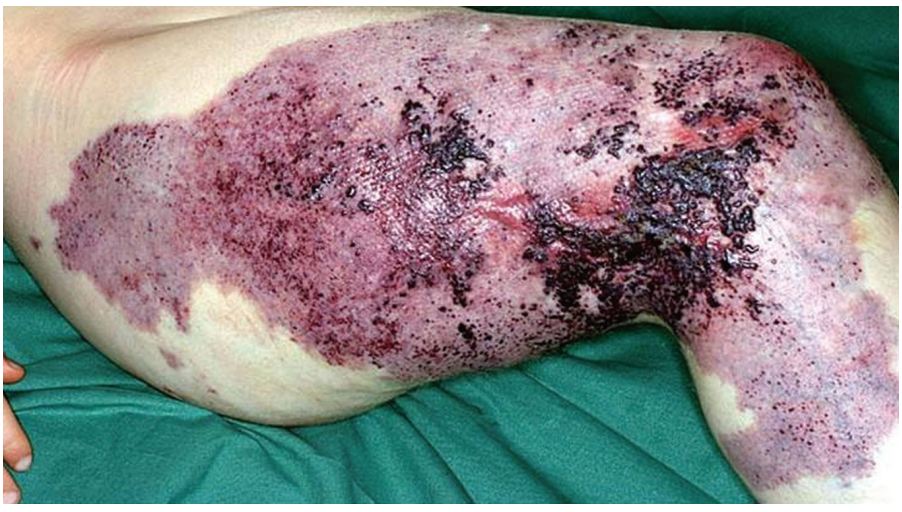

Figure 2. Geographic pattern of vascular malformation in KTS.

garment may also protect the limb from trauma. It is essential that the garment is accurately fitted and regularly reviewed. Early compression therapy in these authors's clinical experience appears to prevent or ameliorate later complications, but further work is required to establish a convincing evidence base for these interventions. Intermittent pneumatic compression (IPC) devices may reduce limb size and control varicosities. However, in some patients with absent or hypo plastic deep venous systems, elastic compression may increase venous stasis and result in discomfort.

Surgical treatment for the vascular malformation in KTS is rarely needed and it continues to be controversial, as it can be complicated by infection, lymph seepage and skin necrosis (Gloviczki et al, 1991). Detailed evaluation and anatomic mapping of the venous system of the limb is mandatory before surgery and complete resection of varicose veins will not halt bony hypertrophy. Capillary malformations may be treated with the pulsed-dye laser, but results are less satisfactory than for non-complex or isolated facial and truncal port wine stains. Lymphatic haemorrhagic blebs are difficult to eradicate and may require treatment with surgical excision or destructive laser techniques.

Recurrent attacks of thrombophlebitis and cellulitis are treated medically with anti-inflammatory agents and antibiotics. Anticoagulant medication may be necessary to prevent and treat deep venous thrombosis, especially in those with massive slow flow vascular malformations (Mazereeuw-Hautier et al, 2007).

In conclusion, KTS is a rare congenital vascular disorder associated with disturbed growth of bone and soft tissue. Patients with this condition require regular long-term follow up by a multidisciplinary team. They should be evaluated for recurrent complications such as cellulitis and superficial thrombophlebitis. Laser treatment may improve the cosmetic appearance of the vascular stain. Lymphoedema of the affected limb is commonly found and should be managed with suitable compression garments, which will require regular alterations throughout childhood. JL

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Key points

- Klippel-Trenaunay syndrome (KTS) is a rare congenital disorder of blood and lymphatic vessels that is characterised by a combined vascular malformation of the capillaries, veins, and lymphatics, congenital venous abnormalities, and associated limb hypertrophy.
- The cutaneous vascular malformation in KTS is usually apparent at birth and may increase in size over the first few years.
- A multidisciplinary approach (dermatologists, paediatricians, nurses, physiotherapists, radiologists, counsellors, occupational therapists and orthotic technicians) to the management of KTS is essential, involving regular clinical and radiological assessment of the affected limbs.
- Lymphoedema of the affected limb is commonly found and should be managed with suitable compression garments, which will require regular alterations throughout childhood. .

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