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Overgrowth syndromes with complex vascular anomalies

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ABSTRACT

Management of overgrowth syndromes with complex vascular anomalies is challenging. Careful analysis of the various clinical features by an interdisciplinary team of physicians experienced in this field is paramount to proper diagnostic and therapeutic approaches. In this article, we focus on the spectrum of the clinical presentation and the management strategies of the most common overgrowth syndromes with complex vascular anomalies.

Introduction

Proper diagnosis of complex and syndromic vascular anomalies can be challenging mostly because of the overlapping clinical appearance and their relative rarity. The vascular component of these syndromes is typically associated with other soft tissue (such as adipose and fibro-adipose tissue) and skeletal overgrowth and anomalies. The etiology of resulting symptoms, primarily pain and functional impairment, is also multifactorial and can be difficult to characterize and manage.[1,2]

Careful analysis of the clinical features and the use of proper nosology are essential for the management of these disorders. Treatment of vascular anomalies and syndromes requires an interdisciplinary team of physicians with experience in overgrowth and vascular anomalies. This article reviews the wide spectrum of clinical presentation and management strategies of the most frequently encountered overgrowth syndromes with complex vascular anomalies at specialized vascular anomalies centers.

Classification of overgrowth syndromes with complex vascular anomalies

Overgrowth syndromes with complex vascular anomalies encompass a myriad of very heterogeneous group of disorders, many of which present with similar clinical features. In addition, these conditions are predisposed by diverse etiologies, many of which have not been deciphered yet. Accordingly, classification and analysis of these disorders based on a common denominator is particularly challenging and can be rather arbitrary.

Recent major advances in the genetics of various overgrowth syndromes and vascular anomalies have refined our understanding and classification of the phenotypic spectrum of these conditions. Nevertheless, while the phenotypic discrimination of these disorders plays a pivotal role in the diagnosis and management, entirely different phenotypes can be caused by similar genetic defects. The reverse is true: different genotypes may manifest similar trait.

Klippel–Trenaunay syndrome (KTS), CLOVES, and fibro-adipose vascular anomaly (FAVA) represent different phenotypic manifestations of somatic mosaic PIK3CA mutations. Bannayan–Riley–Ruvalcaba syndrome and Cowden syndrome result from mutations in the PTEN gene and are collectively referred to as PTEN Hamartoma Tumor Syndrome (PTHS).[3,4] Mutations in the RASA1 gene cause capillary malformation–arteriovenous malformation (CM-AVM) and Parkes Weber syndrome.[5] The genetics of vascular anomalies are discussed in detail elsewhere in this article.

Klippel–Trenaunay Syndrome (KTS)

Klippel–Trenaunay syndrome (KTS) (OMIM # 149000) represents the prototype of complex overgrowth syndromes associated with vascular anomalies. KTS comprises capillary, lymphatic, and venous malformations of the limb with overgrowth and affects the lower extremity in the vast majority of patients.[6] Soft tissue overgrowth is predominantly fatty and located primarily in the extrafascial/subcutaneous compartment. Osseous overgrowth of

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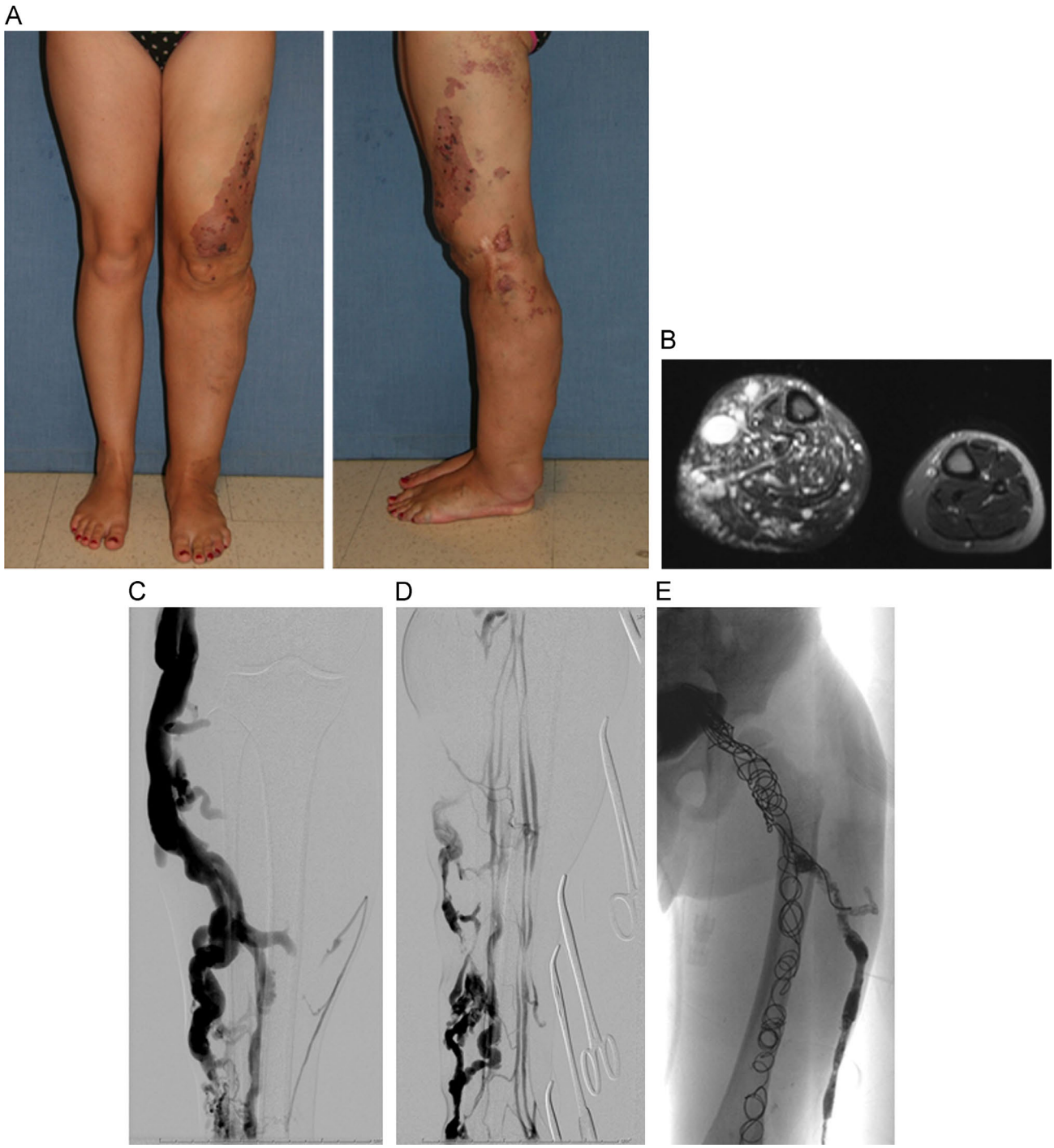

Fig. 1. (A) Klippel-Trenaunay syndrome of the left lower extremity. Note the capillary stain and lymphatic vesicles mainly located on the lateral aspect of the overgrown limb. (B) Axial T2-weighted MRI image showing extrafascial as well as intrafascial fatty overgrowth in right lower extremity. Note the dilated marginal vein. Diversion venography of the right leg before (C) and after (D) the application of multiple tight tourniquets. Initially, only the marginal venous system was opacified but not the deep veins though they were patent (D). (E) Embolization of the marginal venous system. The right internal iliac and sciatic veins were embolized with fibered pushable coils while the marginal vein proper was embolized with glue. (Color version of figure is available online.)

the extremity typically follows the soft tissue. KTS characteristically lacks high-flow components. The affected limb shows no signs of hyperdynamic flow with normal temperature.

The capillary malformation (CM, port-wine stain) occurs on the lateral side of the extremity, mainly the thigh and upper aspect of the calf (Figure 1A). Lymphatic vesicles commonly erupt through the CM and may cause bleeding, leakage of lymph or bleeding. Lymphatic malformations of the macrocystic, microcystic, or combined types are commonly present and are responsible for recurrent episodes of infections and pain. The marginal venous system is the hallmark of venous malformations in KTS. The marginal venous system coexists and competes with a smaller deep venous system, which can be underdeveloped.[7] These incompetent persistent embryologic networks of veins typically originate in the dorsal aspect of the foot and ascend in the lateral aspect of the calf and thigh (Figure 1B). The system often continues in the thigh as the sciatic vein terminating into the deep iliac vein. The marginal venous system typically demonstrates stagnant flow