

Characterization of a distinct syndrome that associates complex truncal overgrowth, vascular, and acral anomalies: a descriptive study of 18 cases of CLOVES syndrome

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Overgrowth syndromes with complex vascular anomalies pose a challenge for diagnosis and management. The purpose of this descriptive study is to present a cohort of patients with congenital lipomatous overgrowth, vascular malformations, and epidermal nevi syndrome, a distinct clinical phenotype characterized by a complex truncal-lipomatous mass, vascular, acral, and other anomalies. This cohort was ascertained following review of patient data entered into the Vascular Anomalies Center database of the Children's Hospital, Boston over a period of 7 years. Clinical data, imaging findings, and the photographic archive were reviewed. The search identified 18 unrelated patients with a distinct phenotype. Variable portions of the truncal masses observed in these patients were composed of a lymphatic malformation. Capillary malformations and high-flow lesions were commonly encountered. The lipomatous mass infiltrated the adjacent anatomic spaces and was associated with capillary, lymphatic, venous, and arteriovenous vascular malformations. Paraspinal-intraspinal extension was associated with morbid sequelae. Acral deformities included large, wide feet and hands, macrodactyly, and a wide sandal gap. Scoliosis and other musculoskeletal, neurologic, renal, and cutaneous malformations were also encountered. The uniform and

highly characteristic features of the truncal lipomatous mass, in combination with vascular, acral, and other anomalies, provide evidence of a distinct nosologic and clinical entity. Morbid sequelae of the truncal involvement in this condition can be deforming and disabling; hence, merit prompt diagnosis and multidisciplinary care are necessary. *Clin Dysmorphol* 00:000–000 © 2008 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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Introduction

Overgrowth syndromes with complex vascular anomalies (OSCVAs) frequently pose considerable diagnostic, nosologic, and management challenges, even for experienced clinicians. Despite accumulated clinical experience and the establishment of diagnostic criteria for some of these syndromes, misdiagnosis, and nosologic inaccuracies are common in clinical practice and in cases presented in the literature (Cohen, 1999; Hand and Frieden, 2002; Cohen, *et al.*, 2003; Turner *et al.*, 2004).

OSCVAs are a heterogeneous group of disorders characterized, as the name implies, by a combination of abnormal tissue overgrowth and variable dysmorphic development of one or more vascular lineages (capillary, lymphatic, venous, and/or arterial). Evaluation of patients with OSCVAs by an experienced multidisciplinary team facilitates diagnosis of specific clinical entities within the OSCVA group. At times, a significant overlap in clinical features, however, can create confusion, delay

diagnosis, or result in misdiagnosis, and inappropriate treatment. The purpose of this retrospective study is to define a new entity among these syndromes primarily by using clinical criteria to distinguish it from other OSCVAs.

We define and present the clinical features of a distinct clinical syndrome that combines truncal lipomatous mass with vascular, acral, and other anomalies. This study was performed simultaneously but independently from a recently published report on a cohort of seven patients with a similar phenotype comprising progressive, complex, and mixed truncal vascular malformations and adipose tissue, scoliosis, and other skeletal anomalies (Sapp *et al.*, 2007). The authors named this condition congenital lipomatous overgrowth, vascular malformations, and epidermal nevi (CLOVE syndrome). We propose expansion of the name CLOVE to CLOVES to emphasize the association with scoliosis and skeletal and spinal anomalies.

Patients and methods

This study was reviewed and approved by the Children's Hospital Boston Committee on Clinical Investigation. The clinical and photographic archives of the Vascular Anomalies Center contain data on more than 7000 patients affected by vascular malformations and tumors from June 1999 till now. The database was searched for entries on patients with truncal overgrowth associated with vascular anomalies using the keywords overgrowth, trunk/truncal, lymphaticovenous, spinal arteriovenous, lipomatosis, lipoma, truncal Klippel-Trenaunay Syndrome (KTS), and the common abbreviations of these terms. In addition, the photographic archive was reviewed for truncal and overgrowth disorders. The medical records, imaging studies, and photographs of these patients were reviewed. Data collected on these patients were categorized according to: patients' demographics; perinatal history; family history; truncal mass (location and extension, size, treatment history); vascular anomalies (type, location, and association with mass, treatment); acral anomalies; cutaneous; musculoskeletal, and other findings. Findings generated from available imaging studies [mainly MRI and computed tomography (CT) scans] were described and photographs were analyzed. Information on cutaneous signs (such as lymphatic vesicles and capillary malformations) was extracted from the clinical notes and photographs. Deeply seated lesions (such as retroperitoneal lymphatic malformations and extension of the lipomatous masses) were evaluated by imaging studies (MRI, CT, and ultrasound). Patients with classic clinical findings of known overgrowth syndromes [e.g. KTS, Parkes Weber syndrome, Proteus syndrome (PS), Bannayan-Riley-Ruvalcaba syndrome (BRRS), etc.] were excluded from this retrospective study but patients who were given the diagnosis of atypical form of these syndromes were included based on the consensus of the multidisciplinary vascular anomalies team.

Results

The distinct phenotype described in this study was identified in 18 sporadic patients, of which eight were male and 10 were female. The cohort was ethnically diverse with 15 Caucasian, two Asian (Chinese, Vietnamese) and one black patient. Patients ranged in age from one month to 26 years. Similarly affected individuals in the patients' families were not found. The mode of delivery was normal vaginal delivery in three, cesarean section in three and undocumented in the remaining 12 patients. In one case, pregnancy was complicated by preeclampsia and gestational weight gain of 30 pounds.

To analyze the collected data, clinical findings were divided into four major categories: overgrowth, vascular, acral, and others. This simplified approach also allows a systematic comparison of these findings with other

Table 1 Summary of the most prominent features in CLOVES syndrome and comparison with features observed by Sapp *et al.*

System involved	Feature	No. of patients affected (n=18)	No. of patients Sapp <i>et al.</i> (n=7)
General	Family history	0	0
	Asymmetric disease	18	7
	Hemihypertrophy	1	NK
	Lipomatous mass	18	6
Musculoskeletal	Leg length discrepancy	6	NK
	Chondromalacia patellae	1	0
	Dislocated knees	1	1
	Scoliosis	6	6
Hands and feet	Wide hands and feet	9	7
	Furrowed sole ^a	2	3
	Wide sandal gap	6	NK
	Macroductyly	8	5
	Talipes	2	NK
Neurological	Windswept hand	2	NK
	Postoperative CVA	2	NK
	Neural tube defect	3	1
	Tethered cord	2	1
	Spasticity/paresis	3	NK
Vascular	Low-flow malformations	18	7
	Perispinal high flow malformations	5	NK
	Venous thrombosis/embolism	2	1
Cutaneous	Linear epidermal nevus	2	4
	Multiple small nevi	2	NK
Renal	Renal agenesis/hypoplasia	5	1

^aNot cerebriiform connective tissue nevus.

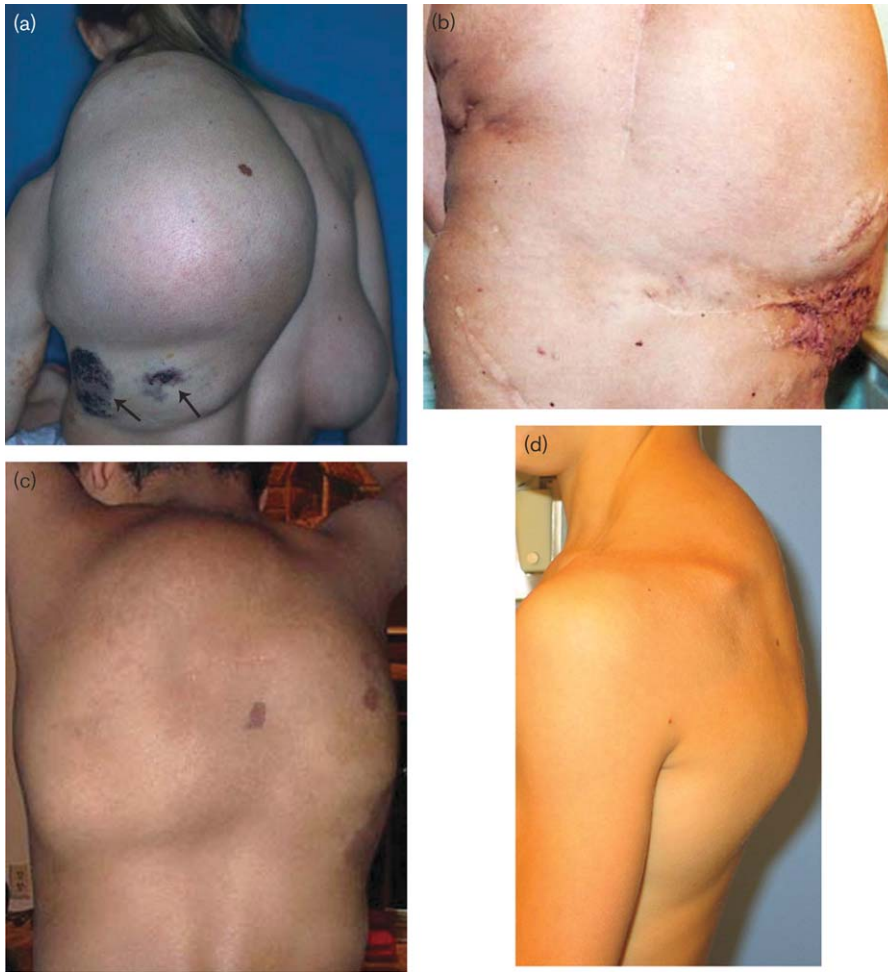
CVA, complex vascular anomalies; NK, not known.

related syndromes. The clinical features of our 18 patients are summarized in Table 1 where they are compared with the findings in the seven patients reported by Sapp *et al.* (2007).

Truncal lipomatous mass

In all 18 patients studied, a large truncal lipomatous mass of variable size was noted at birth. A port-wine stain partially involving the skin overlying the mass was noted in all patients from whom the preoperative assessment was available. The mass was identified prenatally in three patients. In all patients, the masses involved the trunk, most commonly affecting the posterolateral back/flank area (14 patients) the back midline in two patients or the upper back-cervical area (two patients) (Figs 1 and 2). Variable extension to adjacent anatomic areas was seen including the contralateral side across the midline, the abdominal wall, and groin anteriorly, and the gluteal area inferiorly (Fig. 3). In 15 patients the mass was predominantly unilateral and in three bilateral. The lipomatous masses showed an infiltration into adjacent areas such as the retroperitoneal, mediastinal, pleural, and epidural spaces and paraspinal muscles. Eight patients had paraspinal-intraspinous extension. MRI and CT scans showed that the truncal masses were predominantly composed of lipomatous tissue and variable lymphatic and vascular components. Surgical excision of the lipomatous masses was undertaken in 15 patients. Follow-up of eight of these patients showed that all of

Fig. 1



Truncal masses in congenital lipomatous overgrowth, vascular malformations, and epidermal nevi syndrome. (a) Very large tumor involving the left side of the back. A smaller tumor is seen on the contralateral side. The overlying port wine stains (arrows) are seen on the inferior aspect of large lesion with some dark areas representing lymphatic vesicles. (b) Postoperative dark lymphatic vesicles studding the surgical scars. The patient has a history of surgical resection and recurrence of a right truncal mass. (c) Large midline truncal thoracic mass. (d) Cervicothoracic lesion.

them experienced recurrence of the excised mass. Six patients were reported to have pain related to the mass.

Vascular malformations

Low-flow (lymphatic, venous, and capillary) and high-flow (arteriovenous) vascular malformations were documented in 15 patients. Lymphatic malformations and vesicles were seen within the truncal masses, with variable extension into the retroperitoneum and mediastinum (Fig. 4). Of the 11 patients for whom data was available, capillary malformations (port-wine stain) were confirmed in nine. Venous malformations were seen in the form of phlebectasia in three and prominent superficial veins coursing over and/or around the truncal lesions in six patients. Arteriovenous malformations were reported in five patients, developing within and around the lipomatous masses in the paraspinous region.

Acral and musculoskeletal deformities

Musculoskeletal anomalies most commonly involved the extremities, particularly the feet and the hands. The most commonly encountered findings were wide triangular feet or large hands (nine patients); macrodactyly, typically involving the third toe or third finger (eight patients); and a widened sandal gap (six patients) (Fig. 5). Findings were mainly limited to upper extremities in three patients.

Scoliosis was documented in six patients. Posterior scalloping of the lumbar vertebral bodies was reported in one patient; widening of the neural foramina was noted in another patient. Three patients had spina bifida, two of them with a tethered cord. A rib anomaly was present in one patient. Chest wall deformities were common. Specifically, pectus excavatum was reported in three

Fig. 2



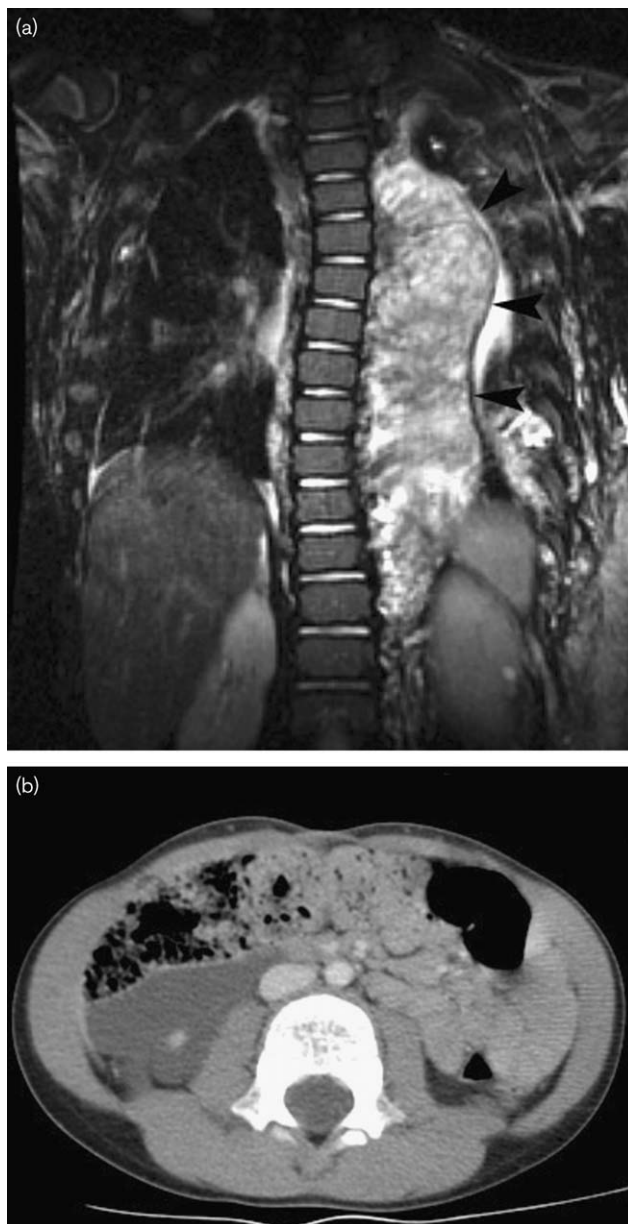
Computed tomography scan through a left back/flank lesion. The lipomatous mass is replacing the paraspinal muscle extending to the lateral abdominal wall. Extension into the left retroperitoneal area (arrow). The left kidney is missing. Note that the thecal sac is displaced contralaterally with large blood vessels in the epidural space and fat insinuating into the left neural foramina.

Fig. 3



Lipomatous mass extending inferiorly into the gluteal area.

Fig. 4



(a) The lymphatic component depicted in a coronal T2-WI MRI of left truncal masses (arrowheads). Both macrocystic and microcystic types are seen. (b) Enhanced computed tomography of the abdomen showing a nonenhancing low-attenuation right retroperitoneal lesion, typical of lymphatic malformations.

patients. Two patients were found to have abnormal vertebral bodies. Developmental dysplasia of the hip was present in four cases.

Neurological status

Eight patients were described as having some degree of neurological impairment. One patient sustained a post-operative stroke because of pulmonary embolism and

Fig. 5



Acral and musculoskeletal findings in congenital lipomatous overgrowth, vascular malformations, and epidermal nevi syndrome. (a) Wide triangular feet with widened first interdigital space. (b) Macroductyly of the third fingers with windswept deformity. (c) Furrowed sole. (d) Wide foot with third-toe macroductyly.

cardiac arrest. The cause of stroke in a second patient was not clear. Data on intellectual development was documented in six patients; all were normal. Additional renal, cutaneous, and hematological abnormalities are listed in Table 1.

Discussion

The clinical overlap that exists between different OSCVAs can create confusion and disagreement regarding the diagnosis (Biesecker *et al.*, 1999; Turner *et al.*, 2004; Biesecker, 2006). Of the several known OSCVAs, PS (OMIM 176920), KTS (OMIM 149000), BRRS (OMIM 153480), and hemihyperplasia-multiple lipomata (HML) syndrome are among the most frequently characterized and reported in the literature.

The pattern of abnormalities affecting the patients in this cohort clearly suggests a different syndrome with distinct truncal involvement and a strikingly significant vascular component. The clinical and radiological findings for the affected individuals show a phenotype with a predilection for specific anatomical areas and commonly shared complications.

The main features of this syndrome are truncal lipomatous mass, vascular malformations, and acral/musculoskeletal anomalies. The key constant feature was a truncal lipomatous mass of variable size. The truncal lipomatous masses associated with this phenotype display recalcitrant behavior that is in some ways similar to malignant tumors such as postresection recurrence, hypervascularity, and infiltrative growth. Involvement of the adjacent spinal column was a prominent feature in our patients presenting with direct extension of the mass into the epidural space resulting in compression of the cord, thecal sac, and nerve roots, high-flow malformations, scoliosis, vertebral anomalies, and neural tube defects.

Recently, Sapp *et al.* (2007) described a newly recognized phenotype of complex, mixed primarily truncal vascular malformations, dysregulated adipose tissue, and osseous abnormalities in seven patients. The authors named this as CLOVE syndrome.

The 18 patients reported here were analyzed simultaneously and independently at our vascular anomalies center. Both groups have demonstrated a progressive

course of the syndrome and occurrence has been sporadic with mosaicism suggested as mechanism. We have showed additional findings, such as the morbid paraspinous high-flow lesions and phlebectasia.

Although the acronym CLOVE used by Sapp *et al.* (2007) encompasses most of the common findings in this phenotype, we propose the acronym CLOVES syndrome to emphasize the association of this syndrome with major skeletal/scoliosis, and spinal abnormalities.

Several features of CLOVES syndrome described in this study differentiate it from PS, a rare hamartomatous condition characterized by asymmetric body overgrowth, connective tissue nevi, epidermal nevi, dysregulated adipose tissue, and vascular anomalies (Cohen, 2005). Hyperostosis, elongated neck, and mental retardation were also reported as important features of PS by Burgio and Wiedemann (1984). Despite established diagnostic guidelines, many patients are erroneously diagnosed with PS (Turner *et al.*, 2004) and from a purely clinical point of view, patients labeled with this syndrome do not necessarily share the same condition (Biesecker, 2006). The cerebriform connective tissue nevus (CCTN) is virtually pathognomonic for PS; no CCTN was seen in any of the 18 CLOVES patients reported; compared with an incidence of 83% in PS (Nguyen *et al.*, 2004). Two patients included in this study demonstrated furrowed soles of the feet, most likely related to fatty deposits. This clinical feature, however, differs from CCTN, which is mainly composed of disorganized collagenous tissue (Viljoen *et al.*, 1988; Biesecker, 2006). Vascular anomalies in PS seem to develop in the first month of life with little tendency to expand or develop into additional lesions (Twede *et al.*, 2005), an expected course in congenitally dysplastic tissue. In contrast, the lipomatous masses characteristic of the CLOVES syndrome, behave more like tumors, and thus, are inclined to enlarge and recur after resection. Lymphatic malformations (15/18) and paraspinous high-flow lesion (5/18) and phlebectasia (3/18) were documented in this study. These do not appear to form part of the spectrum of vascular anomalies in PS (Hoeger *et al.*, 2004).

The cardinal features of KTS include extensive combined malformations comprised of capillary, lymphatic, and venous malformations (CLVM) associated with overgrowth of the affected extremity (Vikkula *et al.*, 2001). Like PS, KTS is a sporadic disorder. It typically affects the lower extremities and occasionally affects the upper extremities or presents bilaterally. Involvement of the trunk, aggressive, and progressive neoplastic behavior of the masses, spinal/paraspinous high-flow lesions, post-operative recurrence, and distinct musculoskeletal deformities are common features of CLOVES syndrome described in this retrospective study and not typically

seen in KTS. The type and distribution of vascular anomalies is also different.

BRRS, caused by germline mutations in the PTEN gene, (Eng, 2003a,b) is an autosomal dominant disorder characterized by macrocephaly, developmental delay, lipomatosis, and speckled penis. It is not associated with the high-flow vascular lesions, which are frequent in CLOVES syndrome. The consistent and characteristic truncal lipomatous mass, acral deformities, and normal intelligence further differentiate CLOVES from BRRS. Only one patient in the currently described cohort was tested for a PTEN mutation with negative results. PTEN mutations were excluded in the patients reported by Sapp *et al.* (2007)

The entity of HML encompasses cases with a distinct combination of hemihyperplasia associated with capillary malformations (Cohen, 2005). The course of the HML is static or mildly progressive (Biesecker *et al.*, 1998). In contrast, CLOVES syndrome is more progressive and infiltrative in nature. Vascular malformations and bilateral involvement of the extremities are not recognized features of HML.

The pathogenesis of CLOVES is still unknown. Happle (Happle, 1987) proposed a concept of autosomal lethal genes capable of surviving only in mosaicism to explain the origin of several rare syndromes. This genetic mechanism might explain the sporadic, variable, and asymmetric phenotypes seen in some overgrowth syndromes including CLOVES.

In a brief retrospective analysis of the published literature, it is clear that some case reports of patients presumed to have PS have features of CLOVES, rather than PS. Atalar *et al.* (2006) reported a case of lymphatic malformations of the trunk with overlying port-wine stains in association with foot anomalies (macroductyly and widened sandal gap) and thought that these findings were a localized form of PS. We, however, believe that these features are more consistent with CLOVES syndrome. Similarly, the case described by Ram and Noor (1993) of a neonate born with truncal overgrowth, large port-wine stains, lymphatic malformation, and foot abnormalities most likely has CLOVES.

Our study was a retrospective analysis of data exclusively retrieved from a vascular anomalies database with referral to clinical notes, imaging studies, and photographs. The task of gathering complete patient records was limited by the numerous clinicians, institutions involved in each case over a long period of time and some of the collected data (e.g. the strong association of the CLOVES syndrome with vascular anomalies and patient's age) might have been influenced by referral bias to our tertiary

pediatric institution. Additional research and longitudinal follow-up are needed to further characterize the spectrum of clinical findings, probable etiology, and natural history of this syndrome. It is imperative, however, to recognize this pattern early in the clinical course, and then predict and address the potential morbidities.

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