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Clinical course of pediatric large vascular anomalies located in the extremities

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What is already known on this topic?

- *The most common vascular anomalies located in the extremities are vascular malformations and hemangiomas.*
- *Vascular lesions, especially on the extremities, can be confused with the malignant diseases of childhood.*
- *The treatment decision differs according to the etiology and location of the lesion and the severity of the symptoms.*

What this study adds on this topic?

- *The diagnosis and presentation of vascular malformations are complex in children.*
- *Vascular lesions located in the extremities can be confused with fibrosarcoma or angiosarcoma, which are malignant diseases of childhood, and histopathological examination might be required in suspicious cases. As authors' own experience, two children who were previously considered and followed up as vascular malformation were diagnosed with sarcoma after biopsy, and amputation was avoided in one child.*
- *The correct diagnosis of a vascular lesion is critical for timely and appropriate interventions and to inform families of affected children accurately.*

ABSTRACT

Objective: Difficulties encountered in the diagnosis and treatment of vascular anomalies located in the extremities of the children. The most common vascular lesions are hemangiomas and venous malformations. The complex malformations, such as, Klippel-Trenaunay Syndrome are much less commonly encountered lesions. Treatment of vascular malformations are variable based on the etiology of the lesion and clinical presentation. In this study, we aimed to share our experience on the clinical features of vascular lesions in the extremities of the children.

Material and Methods: The demographic, clinical and prognostic features of 330 children with vascular anomalies followed at IUC, Cerrahpasa Medical Faculty, Department of Pediatric Hematology and Oncology were retrospectively reviewed. Fifty-one patients with lesions >5 cm in diameter were included into the study. The diagnosis, age, sex, history of prematurity, lesion type and location, imaging and biopsy findings, complications, details of treatment, and follow-up were evaluated.

Results: Twenty-nine (57%) of patients were female and 22 (43%) were male. The female to male ratio was 1.3:1. The median age at admission was 15 months (10 days-180 months). Eight patients (16%) had a history of premature birth. Thirty-one patients (61%) had lesions since birth, eight lesions (8%) appeared in the first month of life and 6 (12%) occurred after 1 year of age. Sixteen of the patients (31%) had hemangioma, 11 (22%) had lymphangioma, 19 (37%) had venous malformation and 5 (10%) were diagnosed as Klippel Trenaunay Syndrome. The lesions were in the upper extremity in 21 patients (41%), in the lower extremity in 27 patients (53%), and both lower and upper extremities were affected in 3 patients (6%). Of all patients, six had intramuscular and two had intraarticular lesions. The diagnosis was made on clinical grounds in most of the cases. In 22 children Magnetic Resonance Imaging was performed for differential diagnosis and to demonstrate the infrastructure of the lesion and the extent of local infiltration. Histopathologic examination by biopsy was done in four patients. Complications developed in 19 patients as follows: Disseminated intravascular coagulation in 6, bleeding in 4, thrombosis in 3, and soft tissue infection in 6. Twenty-one patients were not given any treatment. Medical treatments were propranolol in 14 patients, sirolimus in 4 patients, propranolol and sirolimus in 5 patients. Intralesional bleomycin injection was performed in 3 children.

Conclusion: The diagnosis, classification and treatment of extremity located vascular malformations in children are complex. Treatment strategy should be defined as in accordance with a combination of the type of the vascular malformation, the age of the patient and the clinical picture.

Keywords: Children, extremity, hemangioma, vascular malformation

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Introduction

The occurrence and course of vascular anomalies in children vary according to the type of lesion. Diagnosis and treatment of vascular anomalies located in the extremity region may be problematic. The most common vascular anomalies located in the extremities are hemangiomas and venous malformations Complex vascular malformations, such as Klippel-Trenaunay Syndrome (KTS), are also grouped in vascular lesions located in the extremities.

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Hemangiomas are the most common benign vascular tumors in childhood (1). It can be congenital or can occur in the infantile period. The diagnosis of superficial hemangiomas made clinically, but magnetic resonance imaging (MRI) or biopsy may be required in the differential diagnosis of intramuscular and intraarticular lesions (2). Vascular malformations are caused by impaired vascular morphogenesis. They are mostly congenital but also noticeable in later ages. Vascular malformations are evaluated in two groups as high-flow (arteriovenous) and low-flow (capillary, venous, lymphatic) lesions. Low-flow vascular malformations are the most common (seven-fold more common) subtype (3). Magnetic resonance angiography is a useful method in the diagnosis of these lesions (4). Klippel-Trenaunay Syndrome is a congenital complex vascular anomaly with lymphatic, venous components and soft-tissue hypertrophy. It is classically located in the extremity and accompanied by bone and soft tissue hypertrophy (5). Computed tomography (CT) or MRI could be performed in its differential diagnosis.

The treatment of vascular anomalies differs according to the etiology, location of the lesion and the severity of the symptoms. While hemangiomas can regress spontaneously and could be followed without treatment, vascular malformations and KTS generally do not regress. Medical treatment is usually the first choice in treatment of hemangiomas, while surgical interventions could be used in addition to medical treatment for other vascular malformations and KTS.

In this study, we aimed to share the clinical features and outcomes of large vascular lesions located in the extremity region of children.

Material and Methods

The study was conducted according to the Helsinki Declaration principles and Cerrahpasa Medical Faculty ethics committee approval was obtained with the number 53720 on 13/04/2020. In this study, the medical records of 330 children with extremity-located vascular malformations diagnosed and treated at IUC, Cerrahpasa Medical Faculty, Department of Pediatric Hematology and Oncology, between Jan 2000- Jan 2020 were reviewed. Fifty-one patients were included in the study. One patient was diagnosed with fibrosarcoma and excluded. Patients with a superficial, small-sized (<5 cm) hemangioma in the extremity region were also excluded. The age at diagnosis, gender, prematurity, type and location of the lesion, imaging and biopsy findings, complications, treatment, and follow-up were examined.

The diagnosis of vascular anomalies located in the extremities was made clinically. Superficial red-pink lesions that did not create a mass appearance were defined as hemangiomas. Blue-purple lesions with a mass appearance were interpreted mainly as venous vascular malformations. Lesions that cause hypertrophy in the affected extremity were evaluated as KTS. Superficial Doppler ultrasound or MRI was used for imaging in lesions that could not be clinically discriminated as hemangioma or venous malformation. Doppler imaging was performed in the case of a suspected thrombosis. A biopsy was indicated from the lesion if the lesion creates a mass appearance with a solid component and malignancy could not be excluded by imaging. The treatment and management of the patients were based on the specific diagnosis. In our clinic, propranolol is the most commonly preferred drug in the treatment of hemangiomas. Sirolimus (Rapamycin) and surgical interventions were mostly preferred in the treatment of venous and/or lymphatic malformations. For KTS, treatment was mainly directed based on the complications.

Results

The primary diagnosis of 51 patients included in the study were as follows: hemangioma in 16 (31%), lymphangioma in 11 (22%), children with venous malformation in 19 (37%), KTS in 5 (10%) (Table 1).

Table 1. Characteristics and findings of patients with vascular lesions located in the extremity region

	Number of patients (n), median (range)	Percent (%),
Total patients	51	
Female:Male	29:22 (1.3:1)	
Admission Age (month)	15	
(10 days-180 months)		
Hemangioma	16	(%31)
Superficial	5	
Intramuscular	9	
Intraarticular	2	
Lymphangioma	11	(%22)
Upper extremity	3	
Lower extremity	8	
Vascular malformation	19	(%37)
Upper extremity	7	
Lower extremity	12	
KTS	5	(%10)
Upper extremity	2	
Lower extremity	1	
Upper+Lower extremity	2	
Imaging (MRI)	22	(%43)
Hemangioma	9	
Vascular malformation	7	
Lymphangioma	7	
Biopsy	4	(%8)
Hemangioma	2	
Angioma	2	
Complication	19	(%37)
DIC	6	
Infection	6	
Thrombosis	3	
Bleeding	4	
Treatment		
Follow-up without treatment	21	(%41)
Propranolol	14	
Sirolimus	3	
Propranolol+Sirolimus	2	
Other medical treatments (steroid, IFN, vincristine, warfarin)	3	
Medical+Intralesional treatment	7	
Excision	1	

DIC: disseminated intravascular coagulation; IFN: interferon; KTS: Klippel-Trenaunay syndrome; MRI: magnetic resonance imaging

Of the 16 patients diagnosed with hemangioma, 9 (56%) were female and 7 (44%) were male. Lesions of 6 patients (37%) were present since birth, appeared in the first month of life in 2 (12%) and after the age of 1 in 4 of them (25%). All lesions occurred after the age of one were intramuscular. The median age at presentation was 14 months (10 days-180 months). Five patients (31%) had a history of premature birth. Lesions were located on the upper extremity in 10 (62%) of the patients, and on the lower extremity in 6 (38%). Four of these were intramuscular and one was intraarticular lesions. Magnetic resonance im-

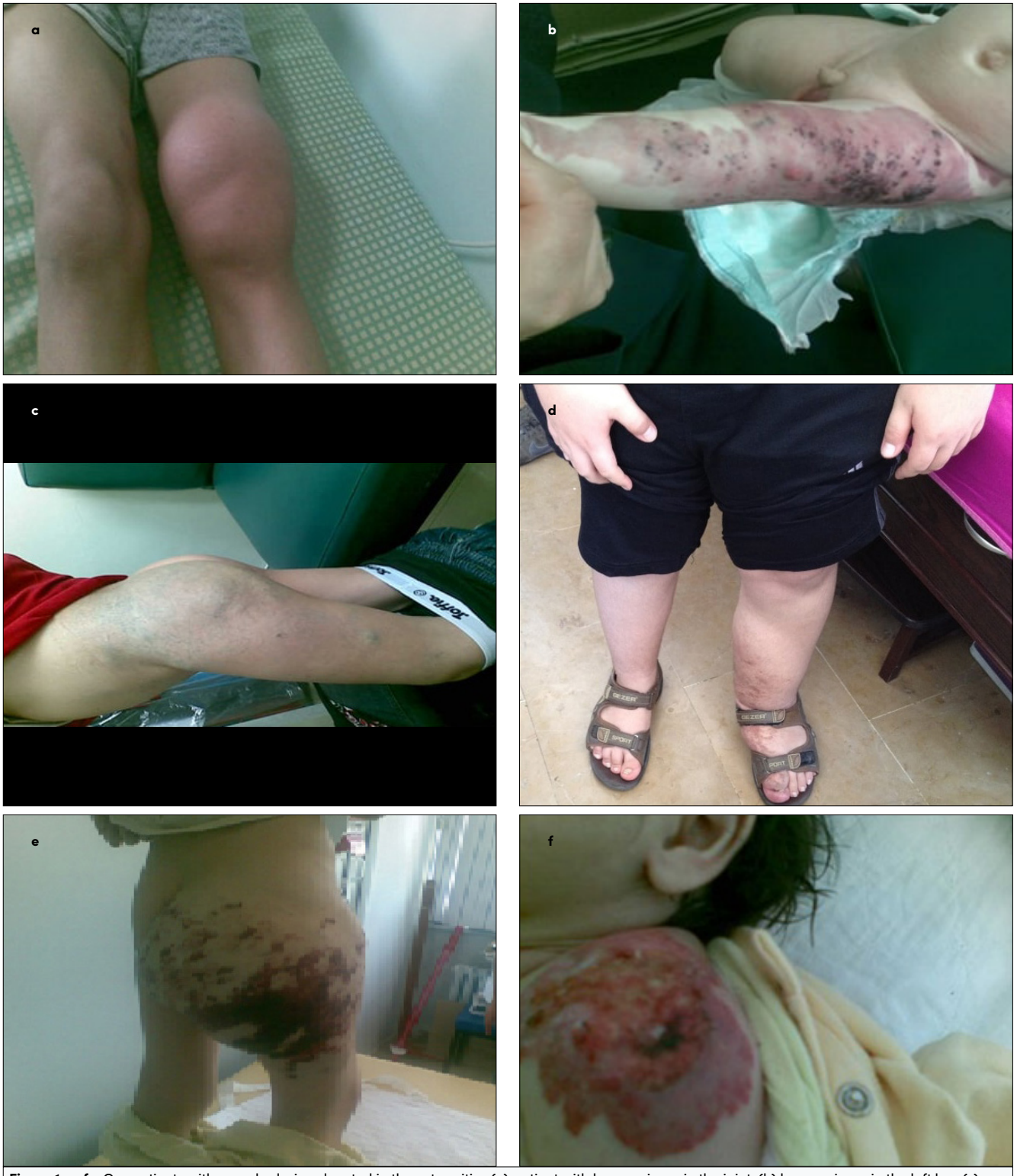

Figure 1. a-f. . Our patients with vascular lesions located in the extremities (a) patient with hemangioma in the joint, (b) hemangioma in the left leg, (c) vascular malformation in the right leg, (d) Klippel-Trenaunay syndrome in the left leg, (e) vascular malformation in the right hip, (f) hemangioma complicated by ulceration in the right shoulder

aging performed in seven of the patients including 4 children with intramuscular lesions. A tru-cut biopsy taken from two of the intramuscular lesions and were reported as hemangioma. One patient was excluded from the study because the MRI was compatible with hemangioma, but the histopathological examination was revealed the diagnosis of fibrosarcoma. Four patients had ulceration and bleeding on the lesion. The median duration of follow-up was 10 months (2-132 months). Eight (50%) of the patients received no specific therapy. Lesions regressed in 4 of these and remained stable in other 2 children. Five patients received propranolol alone, one patient propranolol and steroid, and one patient received propranolol and intralesional alcohol treatment. While the lesion regressed in these seven patients, there was no regression in the lesion in one patient with an intramuscular lesion who was given propranolol and sirolimus treatment.

Of the 30 patients diagnosed with venous malformation and lymphangioma, 17 (56%) were female and 13 (44%) were male. Lesions of 20 patients (66%) were present since birth, in two of them (6%) appeared in the first month of life, and in 4 of them (13%) after 1 year of age. The median age of diagnosis at presentation was 21.5 months (20 days - 180 months). Three patients (10%) had a history of premature birth. Lesions were located on the upper extremity in 11 (37%) of the patients, and on the lower extremity in 19 (63%). 2 of these were intramuscular and 1 was intraarticular lesions. Doppler ultrasonography was performed in 2 patients, MRI in 13, MR angiography in one, CT in one patient, and angiography in one patient with a suspicion of thrombosis. Two patients diagnosed with lymphangioma by ultrasonography. Seven of the patients were evaluated as lymphatic, two as venous, five as arteriovenous malformation with MRI. A biopsy was taken because the lesions of two patients had solid mass appearance and differential diagnosis could not be made by imaging. Biopsies were reported to be compatible with angioma. A total of 13 patients developed complications: DIC developed in 4 of the patients with venous malformation, thrombosis in two, and ulceration in two. In patients with lymphangioma DVT (deep venous thrombosis) (1), bleeding (1), DIC (2), and lymphangitis (1) were the major complications. The median duration for follow-up was 9 months (1-48). Nine of the patients were followed up without treatment. In one of them, the lesion was spontaneously regressed, the others remained stable. Eight patients received propranolol therapy alone, five had a significant regression in the lesion. Three patients received sirolimus alone with a regression in two. Six patients needed more than one medical treatment. There were cases in which steroid, interferon, and vincristine treatments were added in 6 patients unresponsive to propranolol and sirolimus. Surgical interventions were performed to 4 out of 6 patients who received multi-drug therapy. Excision, bleomycin injection, and embolization were performed surgically. In 5 of these patients, the lesions were significantly regressed. Propranolol, steroid, sirolimus, laser, and embolization treatments were applied to a patient with lymphangioma through 6 years, and partial recovery was observed.

Three of 5 patients with KTS were female and 2 were male. The lesion of all patients was present since birth. The median age at diagnosis at presentation was 11 months (20 days-180 months). Lesions were located on the upper extremity in two of the patients, on the lower extremity in one and at both lower and upper extremities in two patients. Propranolol treatment was given to only one of the patients for 6 months, the others were followed up without treatment. No change in the lesion observed including the patient given propranolol.

Discussion

Hemangiomas are the most common benign tumors in childhood. It is seen in 5% of healthy infants. They are benign lesions and while 36% are detected from birth, 75% becomes visible at the end of the first month. Its etiology is unknown and more common in girls and prematures (1). Of our 16 patients diagnosed with hemangioma, 9 (56%) were female, 5 (31%) were premature. While the lesions of six patients (37%) were present since birth, 75% of them were lesions that occurred under 1 year of age. Lesions that emerged after the age of one were intramuscular.

Approximately 15% of hemangiomas are located in the extremities (5). Infantile hemangiomas do not prevent the growth of the extremity it affects and rarely cause functional problems (6). Ulceration is the most common complication of infantile hemangiomas. Ulceration and infection are seen in 15-25% of patients and more frequently in hemangiomas with segmental involvement (7). These lesions can be complicated by bleeding and infection in areas open to trauma (7). Infection due to ulceration and bleeding in the lesion area developed in our 4 patients with superficial hemangioma. The patients were hospitalized and followed up with wound care and antibiotic therapy, and thus the lesions were controlled.

Vascular malformations are proposed to be caused by angiogenic developmental errors. These lesions are usually seen from birth and the lesion does not regress with age. It is rarer than hemangiomas, there is no gender difference, and classified as capillary, venous, arterial, and lymphatic malformation (8,9). These lesions can lead to a localized consumption coagulopathy. This is more common in malformations with a venous component and/or a lymphatic component. If it is a low-flow malformation, it may also be complicated by thrombosis (10,11). Of our 19 patients with vascular malformation, DIC developed in 4, thrombosis in 2, and ulceration in 2. DVT developed in one of our 11 patients with lymphangioma, bleeding in one, DIC in two, and lymphangitis in one.

Klippel-Trenaunay syndrome is a syndrome characterized by bony and soft tissue hypertrophy and vascular malformations causing varicose veins. It mostly involves the lower extremities, but in 10-15% of the cases, both the upper and lower extremities may be affected (12,13). It causes the diameter of the extremity to grow with age and complications such as dermatitis and thrombophlebitis develop (14,15). The walking difficulty was observed due to unilateral growth in the lower extremity in the follow-up of our 5 patients with KTS involvement of the lower extremity.

The diagnosis of vascular lesions and hemangiomas is usually made on clinical findings Doppler ultrasonography is a useful imaging method in differential diagnosis of vascular lesions (16). Magnetic resonance imaging (MRI) is also critical in the diagnosis of deep-seated lesions and to plan surgical intervention (2).

Vascular lesions located in the extremities can be confused with fibrosarcoma or angiosarcoma, which are malignant diseases of childhood. Therefore, a biopsy may be required in suspicious cases. We had cases that were considered as malignancy and referred for amputation and diagnosed as complex vascular malformation upon admission to our center. On the other hand, while MRI was compatible with intramuscular hemangioma in one patient, biopsy resulted in fibrosarcoma.

Most hemangiomas do not require treatment. Various options such as medical treatment, radiotherapy, laser therapy, and surgical intervention are available depending on the size, type, and location of the lesion. The most common treatment indication is cosmetic with an intention to prevent psychosocial sequela (17). Treatment should be directed to lesions that are large, rapidly growing lesions located in the critical parts of the body or in the presence of complications (18). The first-line treatment for capillary malformation is propranolol in clinical practice (19). Corticosteroids (topical, systemic, intralesional), interferon-alpha, and more rarely vincristine and topical imiquimod (Aldara®) might be used other than propranolol (20).

Successful results can be obtained with sirolimus (rapamycin) in the treatment of complicated vascular malformations (21). Sirolimus is used with a dose of 1.2 mg to 3 mg/m^2/day. When using this treatment, patients may develop mouth sores, hypertriglyceridemia, frequent infections, or lymphangitis. The risk of infection is reduced when used with trimethoprim-sulfamethoxazole prophylaxis in young children. In general, the response is generally evident after two months of treatment. The optimal duration of the treatment has not been defined. We used rapamycin for 4 years in one patient with no significant side effects.

In the treatment of vascular anomalies, surgical or interventional approaches such as bleomycin injection into the lesion, excision of the lesion, or embolization in the presence of a single feeding vessel might be used alone or in combination with medical treatment (22,23).

Conclusion

Difficulties may be experienced in the diagnosis and treatment of vascular anomalies located in the extremity region. First, it is necessary to determine the type of lesion to decide to the treatment method accurately. A good differential diagnosis with combination of clinical and radiological features should be made to discriminate vascular malformations from malignancies. Especially lesions with the mass appearance or an intramuscular, intraarticular localization should be evaluated with MRI and biopsy should be taken if diagnosis is suspicious. Making the correct diagnosis is crucial for timely and appropriate treatment.

Ethical Committee Approval: Ethical committee approval was received from the Cerrahpasa Medical Faculty ethics committee with the number 53720 on 13/04/2020.

Informed Consent: Written informed consent was obtained from patients' parents who participated in this study

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