Title: Angiosarcoma in a young girl with congenital lymphedema

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Conflict of interest

None.

Abstract

We herein report the case of a 3-year-old girl with atypical congenital right upper limb lymphedema who developed an angiosarcoma. Only a few cases have been reported following congenital form of lymphedema and only 4 in such a young child. We also summarize all cases of angiosarcoma associated with congenital lymphedema reported in the literature.

Keywords

angiosarcoma, congenital, lymphangiosarcoma, lymphedema, sirolimus, Stewart-Treves syndrome

Introduction

Stewart-Treves syndrome is a cutaneous secondary angiosarcoma occurring in a context of chronic lymphedema. Most commonly, it occurs after mastectomy or radiotherapy for breast cancer. More than 400 cases of Stewart-Treves syndrome have been reported but only 4 cases in association with congenital form of lymphedema before the age of 16 years. The first case was reported in 1918 by Kettle.[1,2]

The disease usually occurs after several years of evolution of chronic lymphedema with a mean interval of 9-11 years. The clinical presentation is heterogeneous, and the diagnosis is delayed from 2 months to over 3 years.[1,2] The survival rate is low, and treatment options are limited.

We report herein the case of a 3-year-old girl with congenital atypical primary upper limb lymphedema associated with chylothorax, who developed diffuse and treatment-resistant angiosarcoma with fatal outcome.

Case report

A 7-month-old girl was referred to the Center for Vascular Anomalies for the management of an atypical congenital lymphedema of the right upper extremity associated with bilateral chylothorax. Doppler ultrasound ruled out compression of the deep venous system or associated venous anomaly. Magnetic resonance imaging showed infiltration of the subcutaneous tissue of the right upper limb with- out muscular or bony involvement. Lymphoscintigraphy confirmed the diagnosis of lymphedema.

No family history of lymphedema, chylothorax, or pleural effusion was present. She was otherwise healthy. Genetic analyses were performed trying to identify predisposing factors or etiology. An almost triploid genome with multiple chromosomal anomalies was detected in the cutaneous biopsy. A comprehensive cancer panel was employed, but no mutation was detected. Diagnostic testing for *VEGFR3* and FOXC2 was normal, and no mutation was identified using a larger lymphedema gene panel with targeted next-generation sequencing.

Local treatment with pressotherapy, lymphatic drainage, and multilayer bandages allowed adequate management of the upper limb lymphedema with good volume reduction and softening of the arm. Thoracic drain and low-fat diet were effective to treat acute chylothorax,

but did not prevent its recurrence. Therefore, at the age of 2 years, treatment with sirolimus was initiated at a dose of 0.8 mg/m2/d, with good response regarding pleural effusions.

Three months after having started sirolimus, she developed a papuloerythematous eruption on the right upper limb. A new com- pressive glove had been used, suggesting an allergic contact dermatitis. Despite initial treatment with topical corticosteroids for 1 week, the skin lesions extended with appearance of red papules on the forearm and the palm (Figure 1). A skin biopsy was performed due to the suspicion of an angiosarcoma. Sirolimus treatment was dis- continued.

Histopathologic examination showed an ill-defined dermal tumor characterized by proliferation of undifferentiated cells with a large, irregular, atypical nucleus. The dermal connective tissue was infil- trated and dissected by this cell population, which extended throughout the dermis and the subcutis. Several mitoses were observed. At immunohistochemistry, these cells expressed ERG, D2- 40, and CD31, but not CD34 (Figure 2 a,b).

A PET-CT scan showed thoracic and abdominal extension and suspicious inguinal nodes.

Amputation of the upper limb was not deemed indicated because of dissemination of the tumor into the thorax. Chemotherapy, consisting of a combination of doxorubicin and ifosfamide, was initiated. After three cycles the tumor continued to progress. Second-line chemotherapy consisting of vinblastine and methotrexate was subsequently initiated but did not halt tumor progression. The girl died 8 weeks after diagnosis from respiratory distress.

Discussion and conclusion

Angiosarcoma is a rare and highly aggressive neoplasm, which arises from endothelium of lymphatic or blood vessels. Lymphangiosarcoma or Stewart-Treves syndrome is an angiosarcoma associated with acquired or congenital chronic lymphatic obstruction.[1,2]

All ages combined only 24 cases have been described in association with congenital lymphedema (Tables 1 and 2). The mean age of onset was 33 years (range 2-85 years) and occurrence is predominantly in females (15/24). Presentation in childhood is very rare, with only 4 reported cases in patients younger than 16 years. Our patient is the fifth case (Table 2). All 5 are girls.

Lymphatic malformations are due to dysgenesis of the lymphatic network. According to the ISSVA (International Society for the Study of Vascular Anomalies) classification, primary

lymphedema is a subtype of lymphatic malformation. Familial primary congenital lymphedema is called Nonne-Milroy disease. Chylous effusions can be associated. Lymphedema praecox begins at puberty.[3] Our patient was presented with atypical primary congenital lymphedema associated with bilateral chylous pleural effusion. Thus, there could be an associated central conducting lymphatic anomaly. Over 20 genes are known to be associated with various types of primary lymphedema.[4] None of the known genes for lymphedema were abnormal. However, in the biopsy of the angiosarcoma, genome instability and several chromosomal anomalies often seen in sarcomas were observed.

Offori et al[1] in 1993 reviewed 15 cases of angiosarcoma associated with congenital lymphedema. Tabareau-Delalande et al[2] identified 4 additional cases in 2013. We subsequently identified another 5 cases (Table1).[5-9] Angiosarcoma associated with congenital chronic lymphedema affects the extremities, except for one case located in the genital area (Table 1). The four children with this dis- ease were girls with involvement of the extremities, as our case (Table 2). It most frequently (n = 12/24) presents as firm, palpable red to blue papules or nodules (Tables 1 and 2). Clinical signs are similar in children (Table 2). Other clinical signs such as ecchymosis (1 case), ulcerations (8 cases), or blisters (2 cases) have also been observed. Indeed, the clinical presentation of angiosarcoma is extremely variable, which frequently results in delayed diagnosis. Time to diagnosis ranges from 3 weeks to 3 years.

Histological analysis usually shows endothelial tumor cells with mitotic changes dissecting dermal collagen. Immunohistochemistry with the positive panel of markers, such as factor VIII, CD31, CD34, and ERG, may confirm the diagnosis. ERG and CD31 are sensitive markers for endothelial cells and vascular tumors. Other antibodies are more specific markers for lymphatic origin, that is, podoplanin (D2-40), lymphatic vessel endothelial receptor-1 (LYVE-1), prospero homeobox protein 1, and vascular endothelial growth factor receptor 3 (VEGFR-3).[2]

The mainstay of treatment for angiosarcoma is surgical resection. Among the 24 cases reported in the literature, more than 2 of 3 of the patients underwent amputation of the affected limb. Early amputation is the only treatment shown to prolong survival; however, long-term survival is rare.[10] Only 5 patients received adjuvant chemotherapy and 6 others adjuvant radiotherapy (Table 1). Chemotherapy that has been reported in the treatment of

angiosarcoma includes 5-fluorouracil, methotrexate, vincristine, actinomycin D, cyclophosphamide, doxorubicin, dacarbazine, bleomycin, or a combination of these drugs.[2] Shon et al[9] treated a patient with ifosfamide, doxorubicin, and paclitaxel after surgery, which seemed to prolong survival by a few months. However, 13 of the 24 patients described in the literature died rapidly despite treatment, as did our case. Among the 11 patients who were alive at the time of publication, 3 have recurred. Patient age does not seem to be correlated with poor prognosis.

Among the known five reported pediatric cases of angiosarcoma, only our patient received chemotherapy alone, because the tumor was inoperable. All other cases underwent surgery. Two patients survived the follow-up, which was short. Our patient died despite a short delay in diagnosis, which does not seem to influence survival (Table 2).

Locoregional chemotherapies (isolated limb perfusion, limb infusion, and electrochemotherapy) have been used to treat multifocal cutaneous tumors, but only in adult patients who developed angiosarcoma in the context of a chronic acquired lymphedema after mastectomy.[12]

Other systemic adjuvant therapies such as nab-paclitaxel, bevacizumab, and pazopanib have been used as adjuvant treatment for cutaneous angiosarcoma.[13] Experience of their use in children, as well as their efficacy or availability for pediatric patients, is limited. They were not used to treat this patient.

Several forms of immunotherapy have been tried in the past: recombinant IL2 and more recently the PD-1 inhibitor pembrolizumab, which was successful in a recent case report.[13]

Sirolimus is an immunosuppressive drug most frequently used for kidney transplant recipients. It inhibits the “mammalian target of rapamycin” (mTOR), which gives rise to antiangiogenic and antiproliferative properties. It is used to treat several types of cancers, particularly renal cell carcinoma and Kaposi sarcoma. Sirolimus is emerging as a potential treatment for lymphatic, venous, and combined malformations and chronic recurrent chylothorax that is resistant to conventional treatment.[14] Our patient responded well to sirolimus in terms of resolution of chylothorax.

As an immunosuppressive agent, sirolimus treatment is associated with an increased risk of infection, malignant skin tumors, and lymphoma. Sarcoma as adverse effect of sirolimus has

never been reported.[15] Whether sirolimus treatment at such a small dosage and for such a short duration could have accelerated the occurrence of angiosarcoma in our patient remains unresolved.

In conclusion, angiosarcoma is a rare but often fatal complication of congenital lymphedema. It should be suspected when cutaneous lesions start to develop on a lymphedemic limb or area. Surgical resection remains the treatment of choice whenever possible. Chemotherapy and radiation therapy have not proved their efficacy. Without possible complete surgical resection, most patients die within 5-8 months after diagnosis.

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Table 1 Cases of angiosarcoma associated with congenital lymphedema reported in literature for patients older than 16 y (modified from Offori et al, 1993, Tabareau-Delalande et al, 2013)

	Author references	Age	Sex	Tumour site	Clinical appearance	Interval in diagnosis	Lymphedema congenital	Treatment for lymphoedema	Treatment for angiosarcoma	Outcome
1	Kettle et al[a] (1918)	44	F	RLL	Blue-red lesion	Not stated	Lymphoedema praecox	Silk drains	Amputation	Alive at 3 y
2	Liszauer et al[a] (1957)	28	M	RLL	Ulcerated lesion	4 mo	+	No stated	Local excision	Died at 11 mo
3	Scott et al[a] (1960)	50	F	LUL	Papillomatous nodules	>7 mo	Lymphoedema praecox	No stated	Local excision, amputation, chemotherapy (nitrogen mustard) radiotherapy	Died at 37 mo
4	Taswell et al[a] (1962)	17	M	LUL	Ulcerated lesion	Not stated	+	No stated	Disarticulation at shoulder	Died at 24 mo
5	Vandaele et al[5] (1963)	50	F	RUL	Red-blue bleeding nodule	3 wk	+	Surgery and sclerotherapy	Excision	Recurrence 10 mo after surgery
6	Finlay-jones et al[a] (1970)	34	M	LLL	Ulcerated blue tumor	Not stated	+	Radiation therapy	Excision, radiation therapy and chemotherapy	Died at 31 mo

7	Merrick et al[a] (1971)	52	M	LUL	Swelling Blue nodules	6 mo	+	Surgery	Wide local excision, amputation, radiotherapy and chemotherapy	Died at 40 mo
8	Mackenzie et al[a] (1971)	64	M	RLL	Nodules Ulcerations	2 mo	+	No stated	Hindquarter amputation and radiotherapy	Alive at 24 mo, then unknown
9	Dubin et al[a] (1974)	29	F	LUL	Ulcerated lesion	3 y	Lymphoedema praecox	No stated	Disarticulation	Died at 45 mo
10	Laskas et al[a] (1975)	85	F	RUL	Purple papules and blisters/ulcerations	10 mo	+	No stated	Mid-arm amputation Incomplete excision of tumor	Died at 14 mo
11	Banathy et al[a] (1977)	50	F	LUL	Purple nodules	Not stated	+	No stated	Mid-humeral amputation	Died at 26mo
12	Sordillo et al[a] (1981)	23	F	LUL	No stated	Not stated	+	No stated	Amputation	Alive at 19 y
13	Wendt et al[6] (1988)	59	M	LLL	Solitary tumor	Some months	+	No stated	Amputation at the thigh	Alive at 1 y
14	Broström et al[a] (1989)	19	F	RUL	Infected lesion	4 mo	Milroy disease	No stated	Amputation of the upper arm	Died at 1 y

15	Offori et al[1] (1993)	43	F	LLL	Blue/purple nodules	2 mo	Milroy disease	No stated	High thigh amputation and sampling of lymph nodes	Alive 9 mo after surgery
16	Janse et al[7] (1995)	19	M	RLL	Not stated	Not stated	+	No stated	Chemotherapy (adriamycin) and surgery	Died 23 mo after onset of treatment
17	Cerri et al[b] (1998)	42	F	Pubic region	Ecchymotic plaque	Not stated	+	No stated	Hemipelvectomy and local radiation therapy	Perineal recurrence and metastases 1y after treatment
18	Hulme et al[8] (2007)	64	M	LUL	Pink/blue nodules and blisters	>3 mo	+	No stated	Forequarter amputation Radiotherapy after recurrence	Recurrence 1 y after surgery, then unknown
19	Shon et al[9] (2012)	18	M	RLL	Red-blue papules and nodules	Not stated	+	Compression garments	Below-the-knee amputation and chemotherapy (doxorubicin, ifosfamide and paclitaxel)	Alive at 3.5 y

20	Tabareau-Delalande et al[2] (2013)	21	F	Right groin	Purple/reddish infiltrated and ulcerated mass	10 mo	+	Lymphatic drainage	Surgery	Died at 3 mo

LLL: Left lower limb; RLL: Right lower limb; LUL: Left upper limb; RUL: Right upper limb; wk: weeks; mo: months; y: years.

[a]Cited by Offori et al (1993).

[b]Cited by Tabareau-Delalande et al (2013).

Table 2 Cases of angiosarcoma associated with congenital lymphedema reported in literature for patients younger than 16 y

	Author references	Age	Sex	Tumour site	Clinical appearance	Interval in diagnosis	Lymphedema congenital	Treatment for lymphoedema	Treatment for angiosarcoma	Outcome
1	Bunch et al[1] (1969)	13	F	UL	No stated	Not stated	Congenital lymphangioma with lymphedema	No stated	Interscapular amputation/	Died at 1 y
2	Broström et al[1] (1989)	10	F	LLL	Blue/red nodules	8 mo	Milroy disease	No stated	Hip disarticulation	Alive at 10 mo
3	Bernardi et al[10] (2009)	4	F	LLL	Ulcerated lesion/blue nodules	1 y	+	No stated	Local excision	Alive at 14 mo
4	Deyrup et al[11] (2011)	2	F	Foot	No stated	Not stated	+	No stated	Local excision	Died at 1 y
5	Present case (2016)	3	F	RUL	Erythematous eruption with red papules and nodules	2 mo	+	Sirolimus and compression therapies	Chemotherapy	Died at 2 mo

LLL: Left lower limb; RLL: Right lower limb; LUL: Left upper limb; RUL: Right upper limb; wk: weeks; mo: months; y: years.

Figures legend

Figure 1: Angiosarcoma, with red-blue macules and papules on the right forearm.

Figure 2: Histological analysis: A-D, Hematoxylin-eosin 5×, 10×, 20×, 40×. Tumor composed by atypical cells tapening anastomosing vascular structures or forming mass. Immunohistochemistry: E-H, Hematoxylin-eosin 20×. Tumor cells express ERG, CD31, and D2-40, negative for CD34.

Figures

Figure 1.

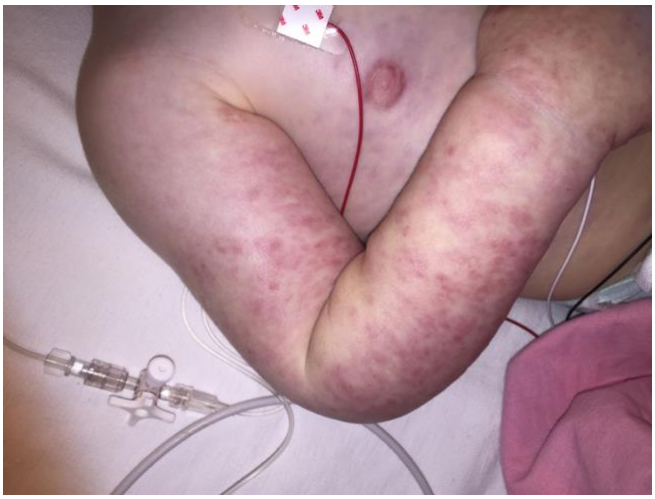

Figure 2.