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Elevated D-dimer Level is Diagnostic for Venous Malformations

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Abstract

Objective—Differential diagnosis of vascular malformations can be problematic even in specialized interdisciplinary centers. Localized Intravascular Coagulopathy, characterized by elevated D-dimer levels, has been observed in about 40% of patients with venous malformations. We evaluated if this is specific for them, and thus useful for differential diagnosis.

Design—Prospective convenience sample accrued from 2 interdisciplinary sites in Brussels, Belgium and Caen, France.

Participants—The study population comprised 280 patients with clinical data, Doppler ultrasound (for 251 patients) and coagulation parameters.

Main outcome measure—Measurement of D-dimer levels.

Results—A venous malformation was diagnosed in 69,6% (n=195/280) of patients, and 83 of them had elevated D-dimer levels; the sensitivity of D-dimer dosage was 42.6% [95%CI: 35.6%–49.5%]. Among the 85 patients without venous malformation, D-dimer levels were elevated only in 3 patients; the specificity of the dosage was 96.5% [95%CI: 92.5%–100%].

Conclusions—Elevated D-dimer level is highly specific for venous malformations (pure, combined or syndromic), and therefore, this easy and cheap biomarker test should become part of the clinical evaluation of vascular anomalies. It can detect hidden venous malformations and help differentiate glomuvenous malformation (normal D-dimer levels) from other multifocal venous lesions. Elevated D-dimer level also differentiates a venous malformation from a lymphatic malformation. Moreover, slow-flow Klippel-Trenaunay syndrome (capillaro-lymphatico-*venous* malformation with limb hypertrophy) can be distinguished from fast-flow Parkes Weber syndrome (capillary malformation with underlying multiple microfistulas and limb hypertrophy). For these reasons, D-dimer level measurement is a useful complementary tool for diagnosing vascular anomalies in everyday practice.

Keywords

diagnostic accuracy; sensitivity; specificity; venous anomaly; D-dimer level; localized intravascular coagulopathy (LIC); vascular malformation; venous malformation; arterio-venous malformation; lymphatic malformation; Klippel-Trenaunay syndrome; Maffucci syndrome; Parks Weber syndrome; CM-AVM

Differential diagnosis of vascular malformations can be problematic even in specialized interdisciplinary centers for vascular anomalies, as these lesions can mimic each other and some malignant tumors[1, 2]. The diagnosis is firstly based on clinical history (presence at birth, growth during life, triggers such as puberty or trauma, and family history) and examination. Important clinical clues are color (variations of pink, red, blue and purple), aspect (flat, raised, homogeneous, patchy, hyperkeratotic and ulcerated), localization, size, distribution (uni- or multifocal), palpation (hard, firm, compressible, and presence of a thrill), temperature (warm or normal), painfulness (spontaneous or provoking factors) and auscultation (bruit). On the basis of these data, an experienced physician can make the diagnosis for most patients[3, 4].

The rheological subdivision into fast and slow-flow lesions is best confirmed by Doppler ultrasound (DU)[5, 6]. In experienced radiological hands, DU can help distinguish the affected vessel type within slow-flow malformations, e.g. venous versus lymphatic. The extensiveness of the lesion on the underlying tissue is visualized by Magnetic Resonance Imaging (MRI), which is mainly used for evaluation of therapeutic options, but can help in diagnosis[7, 8]. Arteriography, an invasive examination, is rarely needed for diagnosis, but mandatory before treatment of a fast-flow lesion. Conventional radiography detects adjacent skeletal anomalies and overgrowth. Biopsy should be performed whenever diagnosis remains doubtful. Conclusive genetic tests already exist for some rare inherited forms. Biological tests are not available.

In a recent prospective study, Localized Intravascular Coagulopathy (LIC), characterized by elevated D-dimers, was observed in 42 % of patients with venous malformations[9]. As this activation of coagulation is probably due to blood stagnation in the enlarged venous channels [9], Enjolras(new #17), and current 17, we evaluated if elevated D-dimer levels were specific for venous malformation, and hence a biomarker helpful for diagnosis.

METHODS

We conducted a prospective study from January 2006 to March 2008 in 2 interdisciplinary centers for vascular anomalies (Brussels, Belgium and Caen, France). This study was approved by the ethics committees of Université catholique de Louvain, Brussels, Belgium and Université de Caen, France. All participants signed an informed consent form.

PATIENTS

A total of 280 patients with cutaneous, subcutaneous and mucosal vascular anomalies were evaluated and enrolled to the study by LMB (Brussels) and AD (Caen). Both centers used the biological classification proposed by Mulliken and Glowacki and adopted by ISSVA (International Society for the Study of Vascular Anomalies)[10]. Clinically and with Doppler ultrasound, all the vascular malformations were subdivided into pure slow-flow, combined slow-flow, syndromic and fast-flow malformations (Table 1).

The following data points were recorded prospectively from the clinical and radiological evaluations:

1. Clinical criteria: age, sex, color, unilateral or bilateral location and size of lesions: < or > 10cm^2 and corresponding percentages (0.25, 0.5, 0.75, 1) within the affected anatomical unit (AU: head, neck, chest, abdomino-pelvic region, left and right arms, forearms, hands, thighs, and legs and feet) grouped secondarily into 4 anatomic regions (AR: head and neck, limbs, trunk, and more than one region).
2. Doppler Ultrasound (DU) was performed for 251 patients with Color Doppler equipment: Aloka Alpha 10 machine (Tokyo, Japan) with 4–13 Mhz linear transducer (Caen) and Philips Medical System iU22 machine (Best Netherlands) with 2 linear transducers L 5–17 Mhz and L 5–12 Mhz (Brussels). Color Doppler

US was performed using a restricted field and by scanning the entire lesion. The area of higher vascularization identified by color flow was selected and Doppler shifts were ascertained with pulsed Doppler. The same well-trained sonologists (PhC and FH in Brussels, MTB in Caen) belonging to the interdisciplinary centers measured the vascular resistance index, the flow type, and the presence of a nidus, AV fistula and dilated veins. Doppler Ultrasound was performed in all lesions, except on small, pure mucosal venous malformations due to typical clinical presentation (n = 6), or when diagnosis was already confirmed by histopathologic examination (n=19), or genetic analysis (n=4) (1 CM-AVM and 3 GVM).

3. Magnetic Resonance Imaging (MRI) with T1 and T2-weighted, and fat saturated sequences were performed for 186 patients for therapeutic evaluation. Conventional radiography was used to evaluate syndromic malformations or associated overgrowth in 18 patients. Arteriography was done for 12 patients for therapeutic evaluation of their fast-flow lesion.

PROCEDURES

At the initial examination and at every follow-up every 2–3 months for 1–2 years, blood was drawn from a peripheral vein not involved by the vascular malformation for coagulation tests, outside a symptomatic inflammatory event. Platelets (reference range 150×10^9/l – 400×10^9/l) were counted in an EDTA sample using an automated instrument (Sysmex XE-2100 Roche Diagnostics, Basel, Switzerland). Fibrinogen level (reference range 200–450mg/dl, Fibriquick, bioMérieux) were measured in a tube containing 0.129M of trisodium citrate and determined using a coagulation device (MDA 2 bioMérieux). Plasma D-dimers (reference range <0,500µg/ml) were determined using enzyme-linked immunosorbent assay (VIDAS® D-Dimer New DD2 bioMérieux).

STATISTICAL ANALYSIS

Based on an expected specificity of D-dimers in the diagnosis of VM of 90% and a frequency of VM of 60% within patients in specialized interdisciplinary centers, we estimated that a total number of 220 patients would be needed to limit the size of 95% confidence interval to a value of 0.10 (less than 10 percentile unit difference)[11, 12]. The statistical analysis was performed using SAS software (version 9). Factors associated with high D-dimer levels were analyzed in a univariate analysis using the chi^2 test for categorical variables and the non-parametric Kruskal-Wallis test for quantitative variables. A logistic regression model was built for variables significantly associated with positive D-dimer levels with a threshold of 0.20 in univariate analysis. $P<0.05$ was considered as significant in all the statistical analyses.

RESULTS

Within the 280 patients, 184 were females and 96 were males with a mean age of 26.8 years (SD=16.18) and a medium age of 23 years (Table 1). The medium size of the vascular malformation was 1.04 AU (SD 1.48) with a median size of 0.50 AU. Sixty-one percent

(n=171/280) were >10cm^2. The lesions in the 280 patients were localized in the following anatomical regions: head and neck (n=89), limbs (n=83), trunk (n=25) and in more than one region (n=83). Eighty-five percent of them were unilateral (n=237/280). Slow-flow vascular malformations were present in 239 patients (85,7%): 172 venous lesions (154 VM, 16 GVM, 2 BRBN), 33 capillary lesions (22 CM, 7 CMVD, 4 CM with tissue hypertrophy), 20 lymphatic anomalies (18 LM, 2 lymphoedema) and 14 combined slow-flow lesions (7 CVM, 6 CLM, 1 CM+VM). Fifteen patients had a syndromic malformation (11 KT and 4 Maffucci syndrome). Fast-flow lesions were present in 26 patients (20 AVM, 3 CM-AVM and 3 Parkes Weber syndrome) (Table 1).

Eighty-six patients with vascular malformations (30.7%) had repeatedly elevated D-dimers (> 0.500µg/ml) (Table 1 and Table 2). The frequency of elevated D-dimers decreased according to the diagnosis:

- Syndromic malformations: 8/15 patients (53.3%), all with KT (8/11). All 8 had large, deep venous lesions. Among the 3 remaining KT patients, one had extensive venous anomalies, but was under oral vitamin K antagonist to prevent deep venous thrombosis and pulmonary embolism; the other two patients had limited, superficial venous lesions, but important lymphatic ones with frequent infections of the limb. All 4 patients with Maffucci syndrome had normal D-dimer levels.
- Combined malformations: 6/14 patients (42.85%); 1/1 CM+VM, 5/7 with CVM, and 0/6 CLM.
- Venous malformations: 69/172 patients (40.1%); 5/5 with multifocal sporadic VM, 2/2 with BRBN, 62/149 with a solitary VM, and 0/16 with GVM.
- Capillary malformations: 2/33 patients with CM (6.06%); 2/22 with unifocal CM. One had repeatedly D-dimer levels very close to normal range (0.504µg/ml) and the second had elevated D-dimers (2.289µg/ml) associated with various pathologies, such as hereditary thrombophilic defect (G 20210A prothrombin gene mutation) and colic diverticulosis. All patients with CMVD (n=7) or CM with tissue hypertrophy (n=4) had normal D-dimer levels.
- Fast-flow malformations: 1/26 patient (3.84%); 1/20 AVM. He had a chronically ulcerated scrotal lesion with repeatedly a borderline D-dimer level at 0.501 µg/ml. All patients with CM-AVM (n=3) or Parkes Weber syndrome (n=3) had normal D-dimer levels.
- Lymphatic anomalies: 0/20. No patient with LM (n=18) or lymphedema (n=2) had elevated D–dimer levels.

Among the patients with elevated D-dimers (n=86), 83 had malformations with a venous component: KT (n=8/11), CM+VM (n=1/1), CVM (n=5/7) and VM (n=69/172) (Table 2). Thus, the sensitivity of D-dimer dosage to detect a venous anomaly was 43.5% [95%CI : 36.4–50.5].

Among the 85 patients with lesions without a venous component, D-dimer levels were elevated only in 3 patients (2 with unifocal CM and 1 with AVM). They all had an explicable

reason. The specificity of the dosage was 96.5% [95%CI: 92.5%–100%]. In the multivariate analysis, the results confirmed that the size of the venous malformation and the presence of palpable phleboliths were statistically associated with elevated D-dimers, as previously reported [9]. This was underscored by higher mean/median D-dimer levels observed for lesions involving more than one anatomic region (Table 2).

COMMENTS

In this prospective study, we measured D-dimer levels among patients with vascular malformations seen in 2 interdisciplinary centers for vascular anomalies (Table 1). Among them, a coagulation abnormality was frequent (n=86/280, 30.7%). This was almost exclusively due to venous anomalies with a high specificity (96.5%, [95%CI: 92.5%–100%]): the patients had pure venous malformation (VM), capillarovenous malformation (CVM), diffuse CM with multifocal VM (CM+VM), or Klippel-Trenaunay syndrome (KT). The test had a low sensitivity (43.5% [95%CI: 36.4%–50.5%]) as expected, because only 42% of venous malformations had repeatedly elevated D-dimer levels in our previous study[9].

All patients with multifocal venous malformations (5 with sporadic multifocal VM and 2 with BRBN) had very high D-dimer levels (≥5.649μg/ml). In one of the BRBN patients, the high D-dimers were associated with low fibrinogen level (95mg/dl), similar to two reported BRBN patients, who had acute or chronic disseminated intravascular coagulopathy[13, 14]. We suggested earlier that the high D-dimer levels could be due to the combined lesional volume in multifocal VM patients[9]. Interestingly, hereditary multifocal VM (VMCM) is not always associated with elevated D-dimer levels[15]. This might be due to etiology. Thus, the identified somatic Tie2 mutations in 50% of sporadic VMs may play a role[16].

Most of the CVM patients (n=5/7) had elevated D-dimer levels. All these lesions had an important venous component, and they were located in the limbs, two of which with a truncal extension. These extensive lesions had D-dimer levels over 1μg/ml reinforcing the observation that severe LIC is associated with large lesions that often affect an extremity[9, 17, 18]. In contrast, the venous component of the 2 CVM patients with normal D-dimer levels (n=2/7) was not important: one had a small CM (<10cm^2) of the left thigh associated with a small VM, which was surgically removed, and the other one had a large CM of the left lower limb associated with a superficial and limited venous malformation.

Klippel-Trenaunay patients (capillaro-lymphatico-venous malformation with limb hypertrophy) with deep, extensive venous malformations had elevated D-dimer levels (n=8/11). This underscores the specificity of D-dimer levels for venous malformations, an important criterion for KT diagnosis[19–21]. This also helps differentiate fast-flow Parkes Weber syndrome, with or without a RASA1 mutation, from the Klippel-Trenaunay syndrome, a frequent diagnostic dilemma.

Among all the vascular anomaly patients, only three without a venous component had elevated D-dimer levels. Two of them had D-dimers only slightly above the normal limit (0.501μg/ml and 0.504μg/ml, respectively). One of them had an ulcerated AVM of the

scrotum, and the other one a CM with a venous ulcer on the ankle. The latter was also using oral hormonal contraceptives. Venous insufficiency regardless of accompanying ulceration, mildly enhances D-dimer levels[22, 23]. Moreover, slight elevation of D-dimer levels occurs in patients taking hormonal contraceptives, with mean level increasing from 0.172μg/ml to 0.351μg/ml, which is still within the normal limits (< 0.5μg/ml)[24–26]. The third patient had a CM and very high D-dimer levels (2.200μg/ml) associated with hereditary thrombotic defect and an inflammatory bowel disease. These two disorders are known to lead to increase in D-dimer levels[27, 28].

One of our patients was initially diagnosed with an extensive patchy capillary malformation of the body. However, D-dimer levels were very high (3.589 μg/ml) and she had unexplained pain. Subsequent Doppler ultrasound and MRI detected multiple deep venous malformations. This illustrates how D-dimer level measurement can help in clinical examination. (Figure 1)

All other patients had normal D-dimer levels. They had glomuvenous, lymphatic, capillary or fast-flow malformations, or Maffucci syndrome. For GVMs, this had been noted by Boon and co-workers[29]. The lack of coagulation abnormality in GVM may be due to the more cellular architecture and therefore less compressible texture of these lesions. GVMs are also more superficially located, probably accounting for the absence of coagulation abnormality even in extensive plaque-like GVM[30]. As differential diagnosis between multifocal VM and GVM may be difficult, D-dimer level measurement is an interesting novel biological tool. All the 20 LM and 6 CLM patients had normal D-dimer levels too, when measured outside an infectious period. This seems logic as lymphatic stagnation should not generate fibrin thrombi. Similarly, all except three pure capillary malformations and fast-flow lesions had normal D-dimer levels, likely due to the absence of blood stagnation. The three with elevated D-dimer levels, had explicable reasons. D-dimer levels were also normal for all 4 Maffucci patients. They had spindle cell hemangioendotheliomas, specific slow-flow histopathological lesions[31, 32].

In conclusion, D-dimer test is a useful tool for diagnosing a venous component of a vascular malformation. In our interdisciplinary centers, slow-flow malformations (n=225, 83.4%), and especially venous malformations (VMs) (n=172, 61.4%) account for the majority of consultations. When D-dimer levels are elevated in a vascular anomaly patient with no other associated pathology, a venous malformation is present in 96.5% of patients. However, when D-dimer levels are normal, a small VM cannot be ruled out. D-dimer level can help evaluate and thus diagnose the presence of a venous component in combined and syndromic malformations. This is especially interesting for KT. Furthermore, fast and slow-flow lesions may be more easily separated. Finally, this tool helps in differentiating GVMs from other multifocal venous lesions. Thus, this easy and cheap biomarker test is useful and highly specific for VMs, and should be used as a routine test in clinical evaluation of vascular anomaly patients. *However, it does not replace any imaging needed for evaluation of management.*

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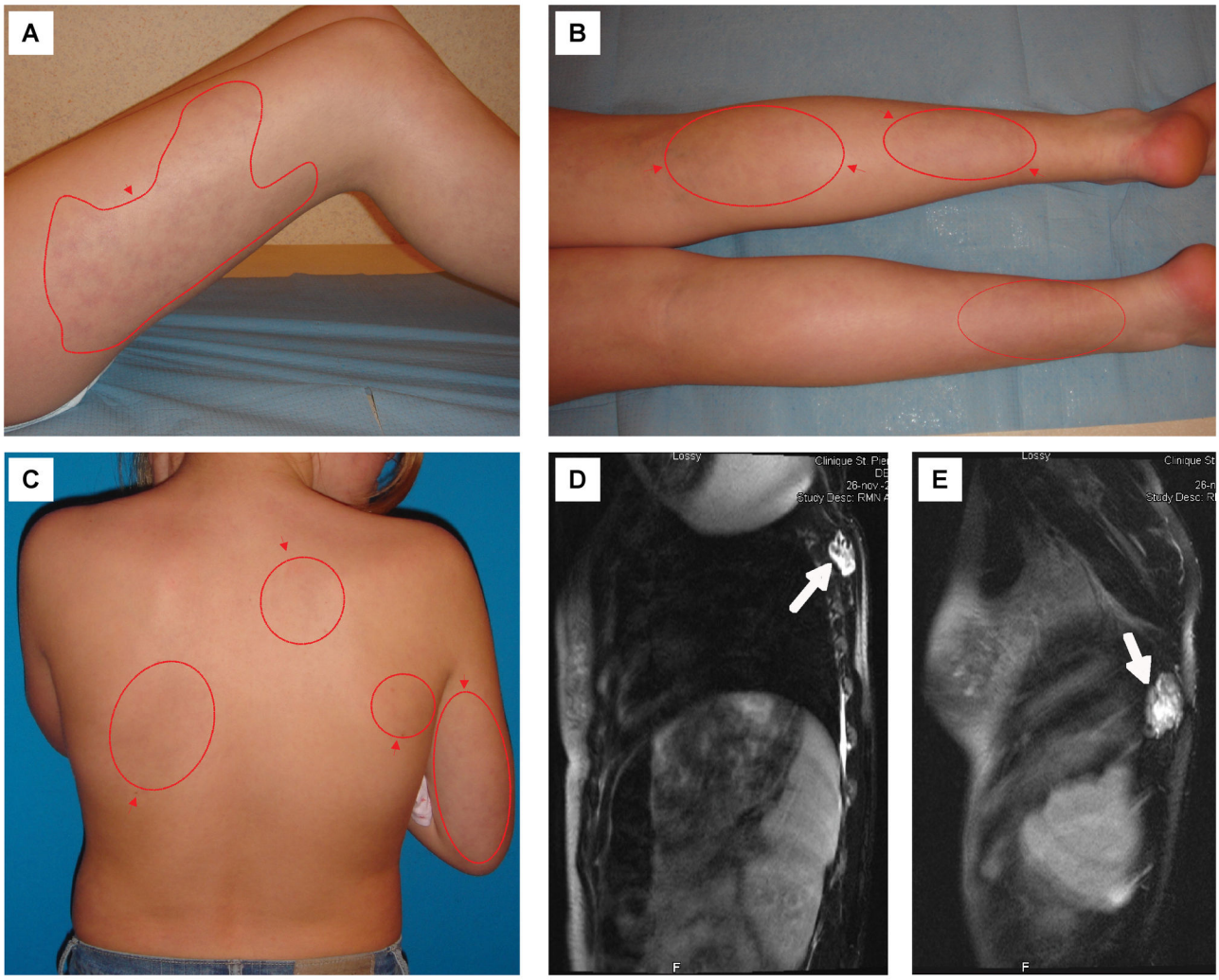

Figure 1.

11-year-old girl with extensive patchy capillary malformation (red contours and arrows, A–C) and multiple deep venous malformations (white arrows) identified with T2-weighted MRI (D–E).

Table 1

Clinical parameters and D-dimer levels according to vascular anomaly.

	Total Number	Unilateral		Localization				Size >10cm^2		D-dimers >0.5µg/ml	
	N	N	%	Head&Neck	Limbs	Trunk	>1region	N	%	N	%
Pure Slow Flow Malformations	225	**191**	**84.9**	**78(34.7%)**	**63(28.0%)**	**20(8.9%)**	**64(28.4)**	**130**	**57.8**	**71**	**31.6**
Venous Malformations	172	143	83.1	143(83.1%)	65(37.8%)	12(7.0%)	51(29.7%)	87	50.6	69	40.1
• *Uni- or multifocal*	*154*	*137*	*89.0*	*62(40.3%)*	*41(26.6%)*	*11(7.1%)*	*40(26.0%)*	*80*	*52.0*	*67*	*43.5*
• *Blue rubber bleb naevus syndrome*	*2*	*0*	*0*	*0(0%)*	*0(0%)*	*0(0%)*	*2(100%)*	*2*	*100*	*2*	*100*
• *Glomuvenous malformation* (1)	*16*	*6*	*37.5*	*3(18.8%)*	*3(18.8%)*	*1(6.3%)*	*9(56.2%)*	*5*	*31.3*	*0*	*0*
Capillary Malformations	33	31	93.9	7(21.7%)	12(36.4%)	3(9.1%)	11(33.3%)	30	90.9	2	6.0
• *Capillary malformation, unifocal*	*22*	*20*	*90.9*	*7(31.8%)*	*8(36.4%)*	*1(4.6%)*	*6(27.3%)*	*20*	*90.9*	*2*	*9.1*
• *Capillary malformation with tissue hypertrophy*	*4*	*4*	*100*	*0(0%)*	*1(25.0%)*	*1(25.0%)*	*2(50.0%)*	*4*	*100*	*0*	*0*
• *Capillary malformation with venous dilatation*	*7*	*7*	*100*	*0(0%)*	*3(42.9%)*	*1(14.3%)*	*3(42.9%)*	*6*	*85.7*	*0*	*0*
Lymphatic Anomalies	20	17	85.0	6(30.0%)	7(35.0%)	5(25.0%)	2(10.0%)	13	65.0	0	0
• *Lymphatic malformation*	*18*	*16*	*88.9*	*6(23.3%)*	*5(27.8%)*	*5(27.8%)*	*2(11.1%)*	*11*	*61.1*	*0*	*0*
• *Lymphoedema*	*2*	*1*	*50.0*	*0(0%)*	*2(100%)*	*0(0%)*	*0(0%)*	*2*	*100*	*0*	*0*
Combined slow-flow Malformations	**14**	**14**	**100**	**1(7.0%)**	**6(42.9%)**	**2(14.3%)**	**5(35.7%)**	**13**	**92.9**	**6**	**42.9**
• *Capillarovenous malformation*	*7*	*7*	*100*	*1(14.3%)*	*4(57.1%)*	*0(0%)*	*2(28.6%)*	*7*	*100*	*5*	*71.4*
• *Capillarolymphatic malformation*	*6*	*6*	*100*	*0(0%)*	*2(33.3%)*	*2(33.3%)*	*2(33.3%)*	*5*	*83.3*	*0*	*0*
• *Capillary malformation with multifocal venous malformations*	*1*	*1*	*100*	*0(0%)*	*0(0%)*	*0(0%)*	*1(100%)*	*1*	*100*	*1*	*100*
Syndromic Malformations	**15**	**12**	**80**	**0(0%)**	**10(66.7%)**	**0(0%)**	**5(33.3%)**	**13**	**86.7**	**8**	**53.33**
• *Klippel-Trenaunay syndrome* (2)	*11*	*8*	*72.7*	*0(0%)*	*7(63.6%)*	*0(0%)*	*4(36.4%)*	*10*	*90.9*	*8*	*72.7*
• *Maffucci syndrome* (3)	*4*	*4*	*100*	*0(0%)*	*3(75.0%)*	*0(0%)*	*1(25.0%)*	*3*	*75.0*	*0*	*0*
Fast Flow Malformations	**26**	**20**	**76.9**	**10(38.5%)**	**4(15.4%)**	**2(7.7%)**	**10(38.5%)**	**15**	**57.7**	**1**	**3.8**
• *Arteriovenous malformation*	*20*	*15*	*75.0*	*9(45.0%)*	*2(10.5%)*	*2(10.5%)*	*7(35.0%)*	*7*	*35.0*	*1*	*5.0*

	Total Number	Unilateral		Localization				Size >10cm^2		D-dimers >0.5µg/ml	
	N	N	%	Head&Neck	Limbs	Trunk	>1region	N	%	N	%
• *Capillary malformation-arteriovenous malformation* (4)	*3*	*2*	*66.7*	*1(33.3%)*	*1(33.3%)*	*0(0%)*	*1(33.3%)*	*3*	*100*	*0*	*0*
• *Parkes Weber syndrome* (5)	*3*	*3*	*100*	*0(0%)*	*3(100%)*	*0(0%)*	*0(0%)*	*3*	*100*	*0*	*0*

(1) GVM: histopathological diagnosis and/or glomulin mutation present

(2) KT:capillaro-lymphatico-venous malformation with limb hypertrophy

(3) Maffucci:multiple enchondromas associated with spindle cell hemangioendothelioma.

(4) CM-AVM: RASA1 mutation present

(5) PW: capillary malformation with underlying multiple microfistulas and limb hypertrophy

Table 2

Mean and Median D-dimer levels per localization

Mean and Median D-dimer levels per localization (of those > 0,5 mg/ml)		D-dimers >0.5µg/ml			
		N	**%**	**mean**	**median**
Malformations with venous component	**Blue rubber bleb naevus syndrome**	**2/2**	**100**	7.824	NA
	Capillary malformation with multifocal venous malformations	**1/1**	**100**	3.598	NA
	Klippel-Trenaunay syndrome	**8/11**	**72.7**	6.021	6.710
	Limbs	*4/7*	*57.1*	5.301	NA
	> 1 region	*4/4*	*100*	6.742	NA
	Capillarovenous malformation	**5/7**	**71.4**	1.600	0.989
	Head & Neck	*1/1*	*100*	0.638	NA
	Limbs	*2/4*	*50*	0.973	NA
	> 1 region	*2/2*	*100*	2.709	NA
	Venous malformation, uni- or multifocal	**67/154**	**43.5**	2.439	1.500
	Head & Neck	*21/62*	*33.9*	1.827	1.000
	Limbs	*17/41*	*41.5*	2.444	1.411
	Trunk	*8/11*	*72.7*	2.735	2.009
	> 1 region	*21/40*	*52.5*	2.934	2.909
Malformations without venous component	**Capillary malformation with venous ulcer**	**1/33**	**3.0**	0.504	NA
	Capillary malformation, thrombophilia & diverticulosis	**1/33**	**3.0**	2.289	NA
	Arteriovenous malformation	**1/20**	**5.0**	0.501	NA

N = D-dimer positive lesions per total in category

NA= median statistically not applicable if <5 patients