Elevated D-dimer Level in the Differential Diagnosis of Venous Malformations

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Objective: To evaluate if elevated D-dimer level is specific for venous malformations (VMs) and thus useful for differential diagnosis, which can be problematic even in specialized interdisciplinary centers. Localized intravascular coagulopathy, characterized by elevated D-dimer levels, has been observed in approximately 40% of patients with VMs.

Design: Prospective convenience sample accrued from 2 interdisciplinary sites.

Setting: Two interdisciplinary centers for vascular anomalies in Brussels, Belgium, and Caen, France

Participants: The study population comprised 280 patients with clinical data, Doppler ultrasonograms (for 251 patients), and coagulation parameter measurements.

Main Outcome Measure: Measurement of D-dimer levels.

Results: A VM was diagnosed in 195 of 280 patients (69.6%), and 83 of them had elevated D-dimer levels; the sensitivity of D-dimer dosage was 42.6% (95% confidence interval, 35.6%-49.5%). Among the 85 patients without VM, D-dimer levels were elevated only in 3 patients; the specificity of the dosage was 96.5% (95% confidence interval, 92.5%-100%).

Conclusions: Elevated D-dimer level is highly specific for VMs (pure, combined, or syndromic), and therefore this easy and inexpensive biomarker test should become part of the clinical evaluation of vascular anomalies. It can detect hidden VMs and help differentiate glomuvenous malformation (normal D-dimer levels) from other multifocal venous lesions. Elevated D-dimer level also differentiates a VM from a lymphatic malformation. Moreover, slow-flow Klippel-Trenaunay syndrome (capillary-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.

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DIFFERENTIAL DIAGNOSIS

Differential diagnosis of vascular malformations can be problematic even in specialized interdisciplinary centers for vascular anomalies because these lesions can mimic each other and some malignant tumors. The diagnosis is first 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 (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.

The subdivision into fast- and slow-flow lesions is best confirmed by Doppler ultrasonography (DU). In experienced radiological hands, DU can help distinguish the affected vessel type within slow-flow malformations (eg, venous vs 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. Arteriography, an invasive examination, is rarely needed for diagnosis but is mandatory before treating a fast-flow lesion. Conventional radiography detects adjacent skeletal anomalies and overgrowth. A biopsy should be per-
formed whenever diagnosis remains doubtful. Conclusive genetic tests already exist for some rare inherited forms.

In a recent prospective study, localized intravascular coagulopathy (LIC), characterized by elevated D-dimer level, was observed in 42% of patients with venous malformations (VMs). Because this activation of coagulation is probably due to blood stagnation in the enlarged venous channels, we evaluated if elevated D-dimer levels were specific for VM and hence a helpful biomarker for diagnosis.

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, and Université de Caen, Caen. All participants signed an informed consent form.

**METHODS**

A total of 280 patients with cutaneous, subcutaneous, and mucosal vascular anomalies were evaluated and enrolled in the study (by L.M.B. [Brussels] and A.D. [Caen]). Both centers used the biological classification proposed by Mulliken and Glowacki and adopted by the International Society for the Study of Vascular Anomalies (ISSVA). Clinically and with DU, 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:

- **Clinical criteria:** age, sex, color, unilateral or bilateral location, and size of lesions ($\leq 10$ or $> 10$ cm$^2$) and corresponding percentages ($0.25$, $0.5$, $0.75$, and $1$%) within the affected anatomical unit (AU) (head, neck, chest, abdominal-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 $> 1$ region).

- **Doppler ultrasonography** was performed for 251 patients with color Doppler equipment: Aloka Alpha 10 machine (Aloka Inc, Tokyo, Japan) with 4- to 13-MHz linear transducer (Caen) and Philips Medical System iU22 machine (Koninklijke Philips Electronics NV, Best, the Netherlands) with 2 linear transducers 5 to 17 MHz and 5 to 12 MHz (Brussels). Color DU 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 assessed with pulsed DU. The same well-trained sonologists (P.C. and F.H. in Brussels and M.-T.B. in Caen) belonging to the interdisciplinary centers measured the vascular resistance index, the flow type, and the presence of a nidus, arteriovenous fistula, and dilated veins. Doppler ultrasonography was performed in all lesions, except on small, pure mucosal VMs.

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**Table 1. Clinical Parameters and D-dimer Levels According to Vascular Anomaly**

<table>
<thead>
<tr>
<th>Vascular Anomaly</th>
<th>Total No.</th>
<th>Unilateral</th>
<th>Localization</th>
<th>Size $&gt;10$ cm$^2$</th>
<th>D-dimers $\geq 0.5$ µg/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pure slow flow malformations</td>
<td>225</td>
<td>191 (84.9)</td>
<td>78 (34.7)</td>
<td>65 (28.0)</td>
<td>64 (28.4)</td>
</tr>
<tr>
<td>Venous malformations</td>
<td>172</td>
<td>143 (83.1)</td>
<td>143 (83.1)</td>
<td>65 (37.8)</td>
<td>12 (7.0)</td>
</tr>
<tr>
<td>Unifocal or multifocal</td>
<td>154</td>
<td>137 (89.0)</td>
<td>62 (40.3)</td>
<td>41 (26.6)</td>
<td>11 (7.1)</td>
</tr>
<tr>
<td>Blue rubber bleb nevus syndrome</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>GVMs$^a$</td>
<td>16</td>
<td>6 (37.5)</td>
<td>3 (18.8)</td>
<td>3 (18.8)</td>
<td>1 (6.3)</td>
</tr>
<tr>
<td>CMs</td>
<td>33</td>
<td>31 (93.9)</td>
<td>7 (21.7)</td>
<td>12 (36.4)</td>
<td>3 (9.1)</td>
</tr>
<tr>
<td>CM, unifocal</td>
<td>22</td>
<td>20 (90.9)</td>
<td>7 (31.8)</td>
<td>8 (36.4)</td>
<td>1 (4.6)</td>
</tr>
<tr>
<td>CM with tissue hypertrophy</td>
<td>4</td>
<td>4 (100)</td>
<td>0</td>
<td>1 (25.0)</td>
<td>1 (25.0)</td>
</tr>
<tr>
<td>CM with venous dilatation</td>
<td>7</td>
<td>7 (100)</td>
<td>0</td>
<td>3 (42.9)</td>
<td>1 (14.3)</td>
</tr>
<tr>
<td>Lymphatic anomalies</td>
<td>20</td>
<td>17 (85.0)</td>
<td>6 (30.0)</td>
<td>7 (35.0)</td>
<td>5 (25.0)</td>
</tr>
<tr>
<td>Lymphatic malformation</td>
<td>18</td>
<td>16 (88.9)</td>
<td>6 (32.3)</td>
<td>5 (27.8)</td>
<td>5 (27.8)</td>
</tr>
<tr>
<td>Lymphoedema</td>
<td>2</td>
<td>1 (50.0)</td>
<td>0</td>
<td>2 (100)</td>
<td>0</td>
</tr>
<tr>
<td>Combined slow-flow malformations</td>
<td>14</td>
<td>14 (100)</td>
<td>1 (7.0)</td>
<td>6 (42.9)</td>
<td>2 (14.3)</td>
</tr>
<tr>
<td>Capillaryvenous malformation</td>
<td>7</td>
<td>7 (100)</td>
<td>1 (14.3)</td>
<td>4 (57.1)</td>
<td>0</td>
</tr>
<tr>
<td>Capillaro-lymphatico-venous malformation</td>
<td>6</td>
<td>6 (100)</td>
<td>0</td>
<td>2 (33.3)</td>
<td>2 (33.3)</td>
</tr>
<tr>
<td>CM with multifocal venous malformations</td>
<td>1</td>
<td>1 (100)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Syndromic malformations</td>
<td>15</td>
<td>12 (80)</td>
<td>0</td>
<td>10 (66.7)</td>
<td>0</td>
</tr>
<tr>
<td>KTS$^a$</td>
<td>11</td>
<td>8 (72.7)</td>
<td>0</td>
<td>7 (63.6)</td>
<td>0</td>
</tr>
<tr>
<td>Maffucci syndrome$^a$</td>
<td>4</td>
<td>4 (100)</td>
<td>0</td>
<td>3 (75.0)</td>
<td>0</td>
</tr>
<tr>
<td>Fast-flow malformations</td>
<td>26</td>
<td>20 (76.9)</td>
<td>10 (38.5)</td>
<td>4 (15.4)</td>
<td>2 (7.7)</td>
</tr>
<tr>
<td>Arteriovenous malformation</td>
<td>20</td>
<td>15 (75.0)</td>
<td>9 (45.0)</td>
<td>2 (10.5)</td>
<td>2 (10.5)</td>
</tr>
<tr>
<td>CM-AVM$^d$</td>
<td>3</td>
<td>2 (66.7)</td>
<td>1 (33.3)</td>
<td>1 (33.3)</td>
<td>0</td>
</tr>
<tr>
<td>PW syndrome$^a$</td>
<td>3</td>
<td>3 (100)</td>
<td>0</td>
<td>3 (100)</td>
<td>0</td>
</tr>
</tbody>
</table>

Abbreviations: CM, capillary malformation; CM-AVM, capillary malformation–arteriovenous malformation; GVMs, glomuvenous malformations; KTS, Klippel-Trenaunay syndrome; PW, Parkes Weber.

SI conversion factor: To convert D-dimers to nanomoles per liter, multiply by 5.476.

$^a$Histopathological diagnosis and/or glomulin mutation present.

$^b$Capillaro-lymphatico-venous malformation with limb hypertrophy.

$c$Multiple enchondromas associated with spindle cell hemangioendothelioma.

$d$RASA1 mutation present.

$^e$Capillary malformation with underlying multiple microfistulas and limb hypertrophy.
owing to typical clinical presentation (n=6) or when diagnosis was already confirmed by histopathologic examination (n=19) or genetic analysis (n=4) (1 capillary malformation–arteriovenous malformation [CM-AVM] and 3 glomuvenous malformations [GVMs]).

- Magnetic resonance imaging (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 performed for 12 patients for therapeutic evaluation of their fast-flow lesion.

PROCEDURES

At the initial examination and at follow-up examinations every 2 to 3 months for 1 to 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, 150–400 x 10^9/L, [to convert to x10^9/L, multiply by 1.0]) were counted in an EDTA sample using an automated instrument (Sysmex XE-2100; Roche Diagnostics, Basel, Switzerland). Fibrinogen levels (reference range, 200–450 mg/dL, [to convert to micromoles per liter, multiply by 0.0294]) were measured (Fibriquick; bioMérieux, Lyon, France) in a tube containing 0.129M trisodium citrate and determined with a coagulation device (MDA 2; bioMérieux). Plasma D-dimers (reference range, <0.500 µg/mL, [to convert to nanomoles per liter, multiply by 5.476]) were determined by enzyme-linked immunosorbent assay (VIDAS D-Dimer New DD2; bioMérieux).

STATISTICAL ANALYSIS

On the basis of 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 the 95% confidence interval (CI) to a value of 0.10 (less than a 10% percentage point difference).11,12 The statistical analysis was performed using SAS software (version 9; SAS Institute Inc, Cary, North Carolina). Factors associated with high D-dimer levels were analyzed in a univariate analysis, with the chi^2 test for categorical variables and the nonparametric Kruskal-Wallis test for quantitative variables. A logistic regression model was built for variables significantly associated with positive D-dimer levels with a P value threshold of .20 in univariate analysis. P < .05 was considered significant in all the statistical analyses.

RESULTS

Of the 280 patients, 184 were female and 96 were male, with a mean (SD) age of 26.8 (16.2) years and a median age of 23 years (Table 1). The median (SD) size of the vascular malformation was 1.04 (1.48) AU, with a median size of 0.50 AU. Of the 280 vascular malformations, 171 (61%) were larger than 10 cm^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 1 region (n=83); 85% were unilateral (n=237 of 280). Slow-flow vascular malformations were present in 239 patients (85.7%): 172 venous lesions (154 VMs, 16 GVMs, and 2 cases of blue rubber bleb nevus [BRBN]) syndrome, 33 capillary lesions (22 CMs, 7 capillary malformation with venous dilatation, and 4 CMs with tissue hypertrophy), 20 lymphatic anomalies (18 lymphatic malformations and 2 lymphoedemas), and 14 combined slow-flow lesions (7 capillaryovenous malformations [CVMs], 6 CLMs, and 1 CM + VM). Fifteen patients had a syndromic malformation (11 with Klippel-Trenaunay syndrome [KTS] and 4 with Maffucci syndrome). Fast-flow lesions were present in 26 patients (20 AVMs, 3 CM-AVM, and 3 cases of Parkes Weber syndrome) (Table 1).

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

- Syndromic malformations (n=15): 8 patients (53.3%), all with KTS (n=8 of 11), had elevated D-dimer levels. All 8 had large, deep venous lesions. Among the 3 remaining patients with KT syndrome, 1 had extensive venous anomalies but was receiving therapy with an oral vitamin K antagonist to prevent deep venous thrombosis and pulmonary embolism; the other 2 patients had limited, superficial venous lesions associated with an important lymphatic malformation with frequent infections of the limb. All 4 patients with Maffucci syndrome had normal D-dimer levels.

- Combined malformations (n=14): 6 patients (42.8%) had elevated D-dimer levels—1 of 1 patient with CM + VM, 5 of 7 patients with CVMs, and 0 of 6 patients with CLMs.

- Venous malformations (n=172): 69 patients (40.1%) had elevated D-dimer levels; 5 of 5 patients with multi-
focal sporadic VMs, 2 of 2 patients with BRBNs, 62 of 149 patients with solitary VMs, and 0 of 16 patients with GVMs.

- Capillary malformations (n=33): 2 patients (6.1%) had elevated D-dimer levels; 2 of 22 with unifocal CMs. One had D-dimer levels very close to the reference range (0.504 µg/mL) on repeated measurements, and the other had an elevated D-dimer level (2.289 µg/mL) associated with various pathologic conditions, such as hereditary thrombophilic defect (G20210A prothrombin gene mutation) and colic diverticulosis. All patients with CMVDs (n=7) or CMs with tissue hypertrophy (n=4) had normal D-dimer levels.
- Fast-flow malformations (n=26): 1 patient (3.8%) had an elevated D-dimer level; 1 of 20 AVMs. 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 of 20. No patient with LM (n=18) or lymphedema (n=2) had elevated D-dimer levels.

Among the patients with elevated D-dimer levels (n=86), 83 had malformations with a venous component: KTS (n=8 of 11), CM+VM (n=1 of 1), CVM (5 of 7), and VM (n=69 of 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 dosages was 96.5% (95% CI, 92.5%-100%). In the multivariate analysis, the results confirmed that the size of the VM and the presence of palpable phleboliths were statistically significantly associated with elevated D-dimer levels, as previously reported. This was underscored by higher mean and median D-dimer levels observed for lesions involving more than 1 anatomic region (Table 2).

**COMMENT**

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 (86 of 280 patients [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 VM, CVM, diffuse CM with multifocal VM (CM+VM), or KTS. The test had a low sensitivity (43.5% [95% CI, 36.4%-50.5%]) as expected because only 42% of VMs had repeatedly elevated D-dimer levels in our previous study.

All patients with multifocal VMs (3 with sporadic multifocal VMs and 2 with BRBN syndrome) had very high D-dimer levels (≥5.649 µg/mL). In one of the patients with BRBN syndrome, the high D-dimer level was associated with a low fibrinogen level (95 mg/dL), similar to 2 reported patients with BRBN syndrome, who had acute or chronic disseminated intravascular coagulopathy. We had previously suggested that the high D-dimer levels could be due to the combined lesional volume in patients with multifocal VMs. Interestingly, hereditary multifocal VM (VM+CM) is not always associated with elevated D-dimer levels. This might be owing to the cause. Thus, the identified somatic Tie-2 mutations in 50% of sporadic VMs may play a role.

Most of the patients with CVMs (n=5 of 7) had elevated D-dimer levels. All of these lesions had an important venous component and were located in the limbs, 2 of which had a truncal extension. These extensive lesions had D-dimer levels above 1 µg/mL, reinforcing the observation that severe LIC is associated with large lesions that often affect an extremity. In contrast, the venous component in the lesions of the 2 patients with CVMs with normal D-dimer levels (n=2 of 7) was not important: one had a small CM (≈10 cm²) of the left thigh associated with a small VM, which was surgically removed, and the other had a large CM of the left lower limb associated with a superficial and limited VM.

Patients with KTS (capillaro-lymphatico-venous malformation with limb hypertrophy) with deep, extensive VMs had elevated D-dimer levels (n=1 of 11). This underscores the specificity of D-dimer levels for VMs, an important criterion for the diagnosis of KTS. This also helps differentiate fast-flow Parkes Weber syndrome, with or without a RASA1 mutation, from the KTS, a frequent diagnostic dilemma.

Among all the patients with vascular anomalies, only 3 without a venous component had elevated D-dimer levels. Two of them had D-dimer levels only slightly above the normal limit (0.501 µg/mL and 0.504 µg/mL). Of the 2, one had an ulcerated AVM of the scrotum and the other had a CM with a venous ulcer on the ankle. The latter patient was also using oral hormonal contraceptives. Venous insufficiency, regardless of accompanying ulceration, mildly enhances D-dimer levels. Moreover, a slight elevation of D-dimer levels occurs in patients taking hormonal contraceptives, with the mean level increasing from 0.172 µg/mL to 0.351 µg/mL, which is still within the normal limits (<0.5 µg/mL). The third patient had a CM and very high D-dimer levels (2.200 µg/mL) associated with hereditary thrombotic defect and an inflammatory bowel disease. These 2 disorders are known to lead to an increase in D-dimer levels.

One of our patients was initially diagnosed as having 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 DU and MRI detected multiple deep VMs. This illustrates how D-dimer level measurement can help in clinical examination.

All other patients had normal D-dimer levels. They had glomuvenous, lymphatic, capillary, or fast-flow malformations or Maffucci syndrome. For GVMs, Boon and coworkers had noted normal D-dimer levels. The lack of coagulation abnormality in GVM may be due to the more cellular architecture and therefore less compressible texture of these lesions. Glomuvenous malformations are also more superficially located, probably accounting for the absence of coagulation abnormality even in extensive plaquelike GVM. Because differential diagnosis between multifocal VM and GVM may be diffi-
cult, D-dimer level measurement is an interesting novel biological tool. All the 20 patients with LMs and the 6 patients with CLMs had normal D-dimer levels also, when measured outside an infectious period. This seems logical because lymphatic stagnation should not generate fibrin thrombi. Similarly, all except 3 pure CMs and fast-flow lesions had normal D-dimer levels, likely due to the absence of blood stagnation. The 3 with elevated D-dimer levels had explicable reasons. D-dimer levels were also normal for all 4 patients with Maffucci syndrome. They had spindle cell hemangioendotheliomas, specific slow-flow histopathological lesions.31,32

In conclusion, the 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 VMs (n=172 [61.4%]) account for the majority of consultations. In patients with vascular anomalies, with elevated D-dimer levels and no other associated pathologic condition, VMs are present in 96.5%. 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 KTS. 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 inexpensive biomarker test is useful and highly specific for VMs, and should be used as a routine test in the clinical evaluation of patients with vascular anomalies. However, it does not replace any imaging needed for evaluation and management.

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Author Contributions: Dr Boon had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Dompmartin, Vikkula, and Boon. Acquisition of data: Dompmartin, Ballieux, Thibon, Lequerrec, Barrellier, Labbé, and Boon. Analysis and interpretation of data: Dompmartin, Hermans, Clapuyt, Hammer, Vikkula, and Boon. Drafting of the manuscript: Dompmartin, Ballieux, Vikkula, and Boon. Critical revision of the manuscript for important intellectual content: Dompmartin, Thibon, Lequerrec, Hermans, Clapuyt, Barrellier, Hammer, Labbé, Vikkula, and Boon. Statistical analysis: Dompmartin and Thibon. Obtained funding: Vikkula. Study supervision: Dompmartin, Vikkula, and Boon.

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REFERENCES