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Characterization of Thrombosis in Patients with Proteus Syndrome

Kim M. Keppler-Noreuil[1], **Jay N. Lozier**[2], **Julie C. Sapp**[1], and **Leslie G. Biesecker**[1]

Medical Genomics and Metabolic Genetics Branch, National Human Genome Research Institute, National Institutes of Health, Bethesda, MD

[2]Department of Laboratory Medicine, Warren Magnuson Clinical Center, National Institutes of Health, Bethesda, MD

Abstract

Patients with overgrowth and complex vascular malformation syndromes, including Proteus syndrome have an increased risk of thromboembolism. Proteus syndrome is a mosaic, progressive overgrowth disorder involving vasculature, skin, and skeleton, and caused by a somatic activating mutation in *AKT1*. We conducted a comprehensive review of the medical histories and hematologic evaluations of 57 patients with Proteus syndrome to identify potential risk factors for thrombosis. We found that six of ten patients, who were deceased, died secondary to deep venous thrombosis and/or pulmonary embolism. Of the remaining 47 living patients, six had thromboembolic events that all occurred postoperatively and in an affected limb. Eleven of 21 patients had an abnormal hypercoagulable panel including Factor V Leiden heterozygotes, antithrombin III deficiency, positive lupus anticoagulant, or Protein C or S deficiencies. We observed that eight of 17 patients had an abnormal D-dimer level >0.5 mcg/dl, but deep venous thromboses occurred in only four of those with D-dimer >1.0 mcg/dl. We conclude that the predisposition to thrombosis is likely to be multifaceted with risk factors including vascular malformations, immobility, surgery, additional prothrombotic factors, and possible pathophysiologic effects of the somatic *AKT1* mutation on platelet function or the vascular endothelium. The D-dimer test is useful as a screen for thromboembolism, although the screening threshold may need to be adjusted for patients with this disorder. We propose developing a registry to collect d-dimer and outcome data to facilitate adjustment of the D-dimer threshold for Proteus syndrome and related disorders, including PIK3CA-Related Overgrowth Spectrum.

Keywords

Proteus syndrome; Thrombosis; Deep vein thrombosis (DVT); Pulmonary embolism (PE)

INTRODUCTION

Proteus syndrome is a highly variable disorder with asymmetric and disproportionate overgrowth, connective tissue nevi, epidermal nevi, dysregulated adipose tissue, and vascular

Corresponding Author: Kim M. Keppler-Noreuil, MD, Medical Genomics and Metabolic Genetics Branch, Clinical Genomics Section, 49 Convent Drive Room 4A68, Bethesda, MD 20892, Tel: 301-275-7985, kim.keppler-noreuil@nih.gov.

malformations [Figure 1] [Biesecker et al., 1999; Biesecker et al., 2006] caused by a somatic activating mutation in *AKT1* [Lindhurst et al., 2011]. Patients with Proteus syndrome have an increased risk for deep vein thrombosis (DVT) and pulmonary embolism (PE) [Figure 2] [Skovby et al., 1993; Eberhard, 1994; Slavotinek et al., 2000; Staub et al., 2006]. Other disorders with vascular malformations, including Klippel-Trenaunay syndrome (KTS) and CLOVES syndrome, which are both in the spectrum of PIK3CA-Related Overgrowth Spectrum (PROS), also have an increased risk for DVT and PE [Mulak et al., 1995; Huiras et al., 2005; Douma et al., 2012; Sapp et al., 2007; Alomari et al., 2010; Keppler-Noreuil et al., 2015], although the magnitude of DVT/PE risk may not be the same in Proteus syndrome and PROS. PIK3CA-Related Overgrowth Spectrum has phenotypic overlap with Proteus syndrome, but is caused by somatic mutations in *PIK3CA*, which is in the same signaling pathway as *AKT1* [Kurek et al., 2012; Lindhurst et al., 2012; Keppler-Noreuil et al., 2014]. Furthermore, there are multiple reports of patients with isolated congenital vascular malformations not associated with an underlying syndrome that have increased risk of DVT and PE [Enjolras et al, 1997; Mason et al, 2001; Mazoyer et al, 2002; Merli, 2005; Dompmartin et al, 2008; Mazoyer et al., 2008; Oduber et al, 2009]. However, in all these conditions, the underlying mechanism for increased risk of thromboembolism remains unknown. To better understand the natural history of DVT and PE and potential causative factors, we set out to evaluate the largest cohort of patients with Proteus syndrome for these complications. We present the clinical findings in 57 individuals with Proteus syndrome, including relevant history, physical examination, radiologic, and laboratory results of the hematologic evaluations. The purposes of this study were to identify potential risk factors for thrombosis in Proteus syndrome, which would form the basis for future etiologic investigations of DVT and PE.

METHODS

Fifty-seven patients with Proteus syndrome were evaluated at the National Institutes of Health between 1997 and 2012, as part of a natural history study approved by the National Human Genome Research Institute (NHGRI) IRB (study # 04-HG-0132). Written informed consent from participants or their guardians was obtained. All met clinical diagnostic criteria for Proteus syndrome [Biesecker et al., 1999; Biesecker, 2006]. Fifty-two of the 57 patients had the somatic activating mutation, c.49G>A, p.Glu17Lys in *AKT1* confirmed from the affected tissue samples (data not shown). For the ten of the 57 patients who were deceased, the cause of death was recorded. Of the remaining 47 patients with Proteus syndrome, their medical records were reviewed for relevant findings, medical course, history of superficial and deep venous thromboembolic events, use of anticoagulants, comorbidity, and whether they had a hematology consultation including D-dimer levels, coagulation testing, and pertinent radiologic studies e.g., Doppler ultrasounds of the extremities and CT scan of the chest. Components of the hypercoagulable studies included: PT, PTT, antithrombin III activity, Factor V Leiden mutation, fibrinogen, lupus anticoagulant, Protein C and S activities, prothrombin mutation, c.*97G>A, (G20210A) in *F2*, thrombin time, and homocysteine. The D-dimer assay used at the NIH is the STA Liatest (Diagnostica *Stago*, *Parsippany, NJ*), which has been validated for screening in the general population with a threshold of 0.5 mcg/ml [Aguilar et al., 2002; Kulstad et al., 2004; Rathbun et al., 2004].

RESULTS

Of 57 individuals with Proteus syndrome, six of ten deceased individuals had DVT and bilateral PE as the confirmed cause of death. Review of the 47 living patients, ages two to 66 years, showed six of them had non-fatal thromboembolism. All occurred postoperatively, and the DVT was in an affected limb. One patient had recurrent thromboembolic events. The clinical scenarios in these six patients were as follows: 1) A female, age 14 years with left leg DVT (left popliteal vein with extension to the greater saphenous vein, which was still present at this writing). Her examination showed asymmetric overgrowth of her legs, left more than right, and superficial varicosities. 2) A female, age 40 years with right leg DVT, whose examination showed asymmetric overgrowth of her legs (right more than left). 3) A male, age 18 years, who had four separate episodes of DVTs in the right leg, and after the first event in the upper right leg, he had bilateral PE, which improved after anticoagulation therapy for 6 months. However, 8 months later, he had a DVT in the overgrown right leg. 4) A male, age 16 years with right leg overgrowth, who had right saphenous vein DVT and bilateral PE. 5) A male, age 21 years with left leg overgrowth and prominent varicosities in both legs, who had left popliteal vein DVT; ten years later at 31 years, he was diagnosed with PE and has been treated with warfarin without recurrence. 6) A male, age 16 years with left leg asymmetric overgrowth and left buttock thrombophlebitis, who had left upper thigh femoral vein DVT.

Of the 47 patients, 23 had a NIH hematology consult and 21/47 (44%) had an evaluation for clinical laboratory testing associated with thrombosis. Eleven of the 21 (52%) patients had heterogeneous abnormalities on the hypercoagulable panel, including two with Factor V Leiden heterozygous variants, one with mild Factor 12 deficiency, one with mildly low Anti-thrombin III (ATIII) activities, and Protein C and S deficiencies, one with partial Anti-thrombin III deficiency, one with low Protein C and Protein S activities, one with borderline Lupus anticoagulant and normal aPTT, three with positive Lupus anticoagulant, and one with prolonged PT, which suggested a vitamin K deficiency. One patient with the mildly low ATIII, and protein C and S deficiencies had a DVT. A second patient with low protein C and S activities had three superficial venous clots in the lower extremity. There were two of three patients who had positive lupus anticoagulant; two of these had DVTs, one with thrombophlebitis and the other with a PE. Among the 11 patients with abnormalities on the hypercoagulable panel, four had thromboembolic event, which was not significantly different ($p = 0.0902$).

Of the 17 patients who had D-dimer levels, eight had an abnormal level [Figure 3]. Three with elevated levels (0.69, 0.6, 0.7 μg/ml) had no evidence of DVT/PE, on the basis of a normal Doppler ultrasound of the legs and CT scan of the chest (ages 6, 42, and 32 years, respectively). Five individuals had levels >1 mcg/ml (1.14, 2.09, 2.17, 2.64, 3.19 mcg/ml), four had positive findings of DVT and/or PE, and one had recurrent superficial thrombi. Six individuals with median age 16.5 years were diagnosed with DVT (two also had PE) after surgery (of the spine in one and of affected limb in four); one was recurrent. Two of these individuals did not have D-dimer levels [Table 1]. Seven patients had other venous abnormalities. These venous abnormalities were: enlarged portal venous malformation,

phlebitis and extensive varicosities, phleboliths, underdevelopment of the deep venous system in the leg, and superficial venous thromboses.

DISCUSSION

This retrospective cohort study confirms the conclusions of earlier case reports of an increased risk for DVT and/or PE in individuals with Proteus syndrome [Skovby et al., 1993; Eberhard et al., 1994; Slavotinek et al., 2000; Staub et al., 2006]. These reports included six individuals with Proteus syndrome, who developed pulmonary or portal thromboembolism, two postoperatively, all with ages <27 years, and all but one fatal. It has been suggested that the vascular malformations are the primary risk factor for thromboembolism in patients with Proteus syndrome [Slavotinek et al., 2000], but other risk factors have not been investigated. In this review of the clinical, radiological, and laboratory evaluations of a large cohort of patients with Proteus syndrome, we found that six of ten deaths (60%) were the result of a DVT and bilateral PE at a young age (median age of 17 years), and amongst living patients, that six of 47 (16%) had DVTs, with three of the six having co-occurrence of PE, and another 7 of 47 (15%) had evidence of thrombophlebitis and other venous malformations. We also know that among the ten deceased patients that DVT and PE occurred in several patients, some perioperative, and some associated with acute illnesses. This younger age and frequency of superficial venous thromboses, DVT, and PE in patients with Proteus syndrome is striking. Amongst the 47 currently living patients, the recognized DVT/PE events occurred postoperatively in an affected (overgrown) limb. In addition, venous varicosities were visible on examination in half of these patients. We found that the occurrence of thrombosis in patients with Proteus syndrome was not primarily attributable to an increase in any one of the well-known prothrombotic conditions such as factor V Leiden, prothrombin mutation, c.*97G>A, (G20210A) in *F2*, deficiency of antithrombin III, protein C, or protein S, that typically increase the rate of thrombin production and fibrin clot generation. While we recognize that a study of this size is limited in power, the high frequency of DVT and PE in Proteus syndrome argues against these being major factors, because they are relatively uncommon. Therefore, our findings point to other potential mechanisms for thromboembolism in Proteus syndrome. We speculate that the biology of Proteus syndrome may have adverse effects on hemostasis by other mechanisms, such as endothelial abnormalities or platelet dysfunction, beyond the well-recognized effects of stasis associated with vascular malformations. Indeed, this strikingly high rate of DVT and PE in patients with Proteus syndrome lead us to speculate that this disorder may have a level of risk that is out of proportion to the vascular malformations and may be attributable to specific vascular and/or platelet dysfunction caused by the *AKT1* p.E17K mutation.

The D-dimer is a widely used and sensitive screening test for venous thrombosis [Wells et al., 2003; Lees et al., 2011; Molugu et al., 2013]. D-dimer is a circulating fibrin degradation product that forms when a thrombus is degraded by thrombin, coagulation factor XIIIa and fibrinolysin [Molugu et al., 2013; Wells, 2004; Wedlund and Voslar, 2014]. The D-dimer levels reflect endogenous fibrinolysis, which may be used as a marker of DVT [Lees et al., 2011]. In this study, of the eight of 17 individuals with Proteus syndrome who had D-dimer levels, four of eight (50%) with levels >1 mcg/dl had thrombotic events. In contrast, none of three patients with a level between 0.5 and 1.0 had a DVT or PE detectable by imaging. If

we assume that the individuals with a D-dimer level of <0.5 mcg/ml did not have a DVT or PE, this yields a sensitivity of 100% and a PPV of 37% (4/11). This compares favorably with the performance of the D-dimer test as a DVT/PE screen in the general population with suspected DVT, which has a PPV of ~20–30% and a sensitivity of ~96% (we assume here that all of the patients reported here with a D-dimer <0.5 mcg/ml did not have DVT or PE) [Nelson et al., 2009; Pulivarthi and Gurram, 2014]. We conclude that the D-dimer test is useful in patients with Proteus syndrome and should be used liberally. What is less clear is whether the screening threshold used in this context should be the same as it is for the general population (which is 0.5 mcg/ml for the STA Liatest D-dimer assay).

Adjustments to the D-dimer threshold for screening based on age have been proposed, tested and validated in prospective clinical trials that utilized the STA Liatest D-dimer assay among others, and found to decrease the proportion of patients tested who required further diagnostic evaluation without loss of sensitivity (Age-Adjusted D-Dimer Cutoff Levels to Rule Out Pulmonary Embolism - The ADJUST-PE Study) [Righini et al., 2014]. A strategy of adjusting the threshold for D-dimer screening for DVT in patients with Proteus syndrome, based on the observed increase in D-dimer levels in those without DVT should be considered. Notably, most patients with Proteus syndrome with DVT in our cohort have had their events at early ages, well before adjustments to the D-dimer threshold for DVT are made (typically age 50). Patients who are positive for DVT or PE on imaging should be undergo acute anticoagulation according to the standard American College of Chest Physicians guidelines (Antithrombotic Therapy for VTE Disease: CHEST Guideline and Expert Panel Report) [Kearon et al., 2016].

Thromboembolism has also been reported in patients with PROS, which subsumes the previous phenotypic descriptors of CLOVES syndrome KTS [Alomari et al. 2010; Keppler-Noreuil et al., 2014; Mirzaa et al., 2013], and other phenotypes. Oishi and Ezaki [2010] described three preadolescent patients with the clinical diagnosis of KTS who had large upper extremity venous malformations and developed DVT; two had documented PE, one of which was fatal. The specific pathogenesis for thromboembolism in PROS is also unknown, although the presence of vascular malformations as a risk factor is assumed, as for Proteus syndrome, and these disorders are both caused by somatic mutations in the PI3K-AKT signaling pathway. The p110α catalytic subunit of PI3K is essential for endothelial cell migration and angiogenesis, and sustained endothelial activation of AKT1 has been shown to induce the formation of structurally and functionally abnormal blood vessels [Graupera et al., 2008; Phung et al., 2006]. In addition, RAS activation in endothelial cells resulted in abnormal vascular morphogenesis, which is regulated by PI3K signaling [Bajaj et al., 2010]. There are also many reports of other patients with congenital vascular malformations not associated with an underlying syndrome who have increased prevalence of thromboembolism [Enjolras et al, 1997; Mason et al, 2001; Mazoyer et al, 2002; Merli, 2005; Dompmartin et al, 2008; Oduber et al, 2009]. Of course, it is possible that many of these reports of patients with presumed non-syndromic vascular malformations may in fact have an undiagnosed or subclinical form of Proteus syndroem or PROS. It is therefore possible that the risk of DVT and PE is substantially attributable to dysfunction of the AKT/PI3K pathway.

In general, the three primary clinical factors associated with thrombosis risk include those comprising Virchow's triad: 1) vessel wall damage due to inflammation or trauma; 2) changes in blood flow or volume due to immobility, ischemia, or other conditions; and 3) hypercoagulable factors present in the blood, including inherited and acquired coagulation disorders [Merli et al., 2005]. Many patients with large venous malformations have had serologic evidence of coagulopathy (decreased fibrinogen, elevated D-dimer, elevated prothrombin times and normal to low platelet counts [Oduber et al., 2009]. In several studies, the severity of the coagulopathy correlated with the extent of the malformation [Enjolras et al., 1997; Mason et al., 2001; Mazoyer et al., 2002]. Of course, the Virchow's triad model of pathogenesis was proposed long before the molecular delineation of the causes of vascular malformations. It is now recognized that mosaicism is not as rare as previously supposed [Biesecker and Spinner, 2013] and that many vascular malformations are caused by mosaic mutations of the AKT/PI3K pathway. We hypothesize that the outsize risk of DVT/PE in patients with Proteus syndrome, the elevated risk in patients with PROS, coupled with a speculation that many apparently non-syndromic vascular malformations are also due to mosaic mutations in this pathway, all point to AKT/PI3K pathway being a fourth major underlying factor of susceptibility to DVT and PE.

We conclude that patients with Proteus syndrome have a striking predisposition to DVT and PE and that liberal use of the D-dimer test as a screen for these complications is useful, as it can identify patients, including young children, who can benefit from anticoagulation. While most DVT and PE in patients with Proteus syndrome developed perioperatively, others did not, and clinicians must maintain a high index of suspicion, especially since DVT and PE are rare in children who do not have Proteus syndrome. We suggest that D-dimer is a useful screen for the presence of a DVT in patients with Proteus syndrome when the level is above 0.5 mcg/dl (for the STA Liatest D-dimer assay). To better understand the diagnosis, management, etiology, genetic mechanisms, and natural history of thromboembolism in Proteus syndrome and related disorders, including PROS, we plan to undertake several efforts. First, we will establish a registry to collect data on D-dimer screening and subsequent evaluations for all patients with Proteus syndrome or PROS. We also plan to conduct a prospective evaluation of clinical, radiological and laboratory studies, and contribute to development of therapeutic approaches for these disorders. Using these approaches, we are optimistic that we can lower the morbidity and mortality of Proteus syndrome and PROS.

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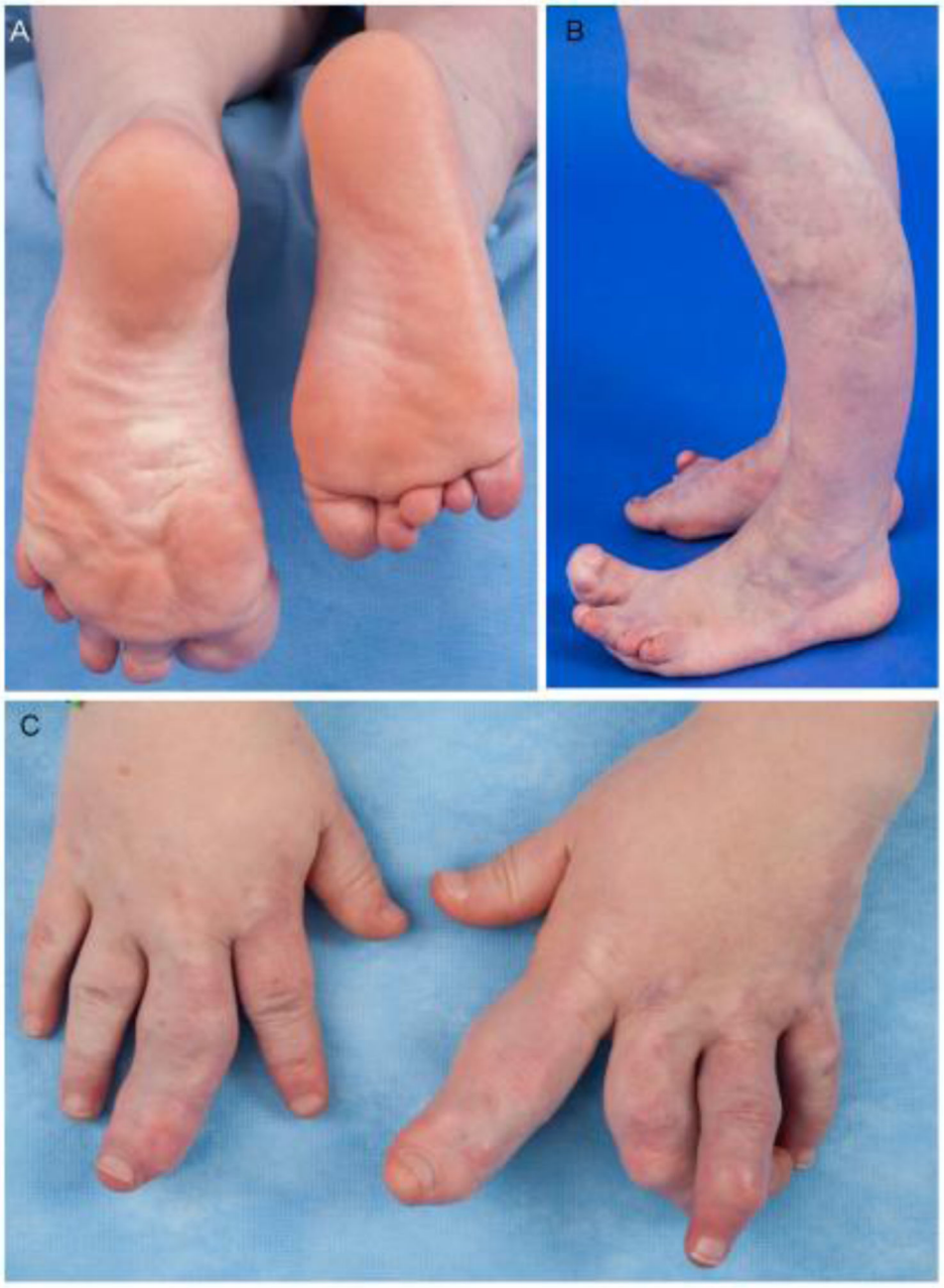

Figure 1.

6.5-year-old boy with Proteus syndrome, (A) developing cerebriform connective tissue nevus of the left foot, and bony overgrowth of bilateral feet and toes, (B) venous malformations with bony overgrowth of legs and feet, (C) bony overgrowth and distortion of the fingers, and capillary malformations of the fingers and hands.

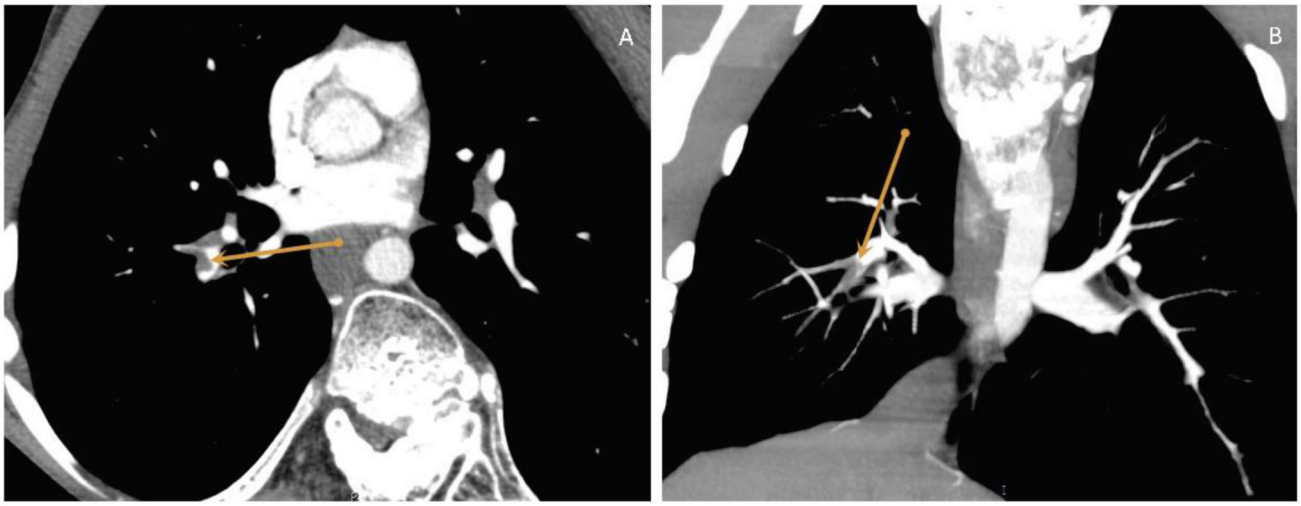

Figure 2.

16-year-old boy with Proteus syndrome, (A) Axial and (B) Coronal, Maximum intensity projection (MIP) contrast enhanced CT scan images of the chest showing an intraluminal filling defect in the descending branch of the right pulmonary artery diagnostic of a pulmonary embolus.

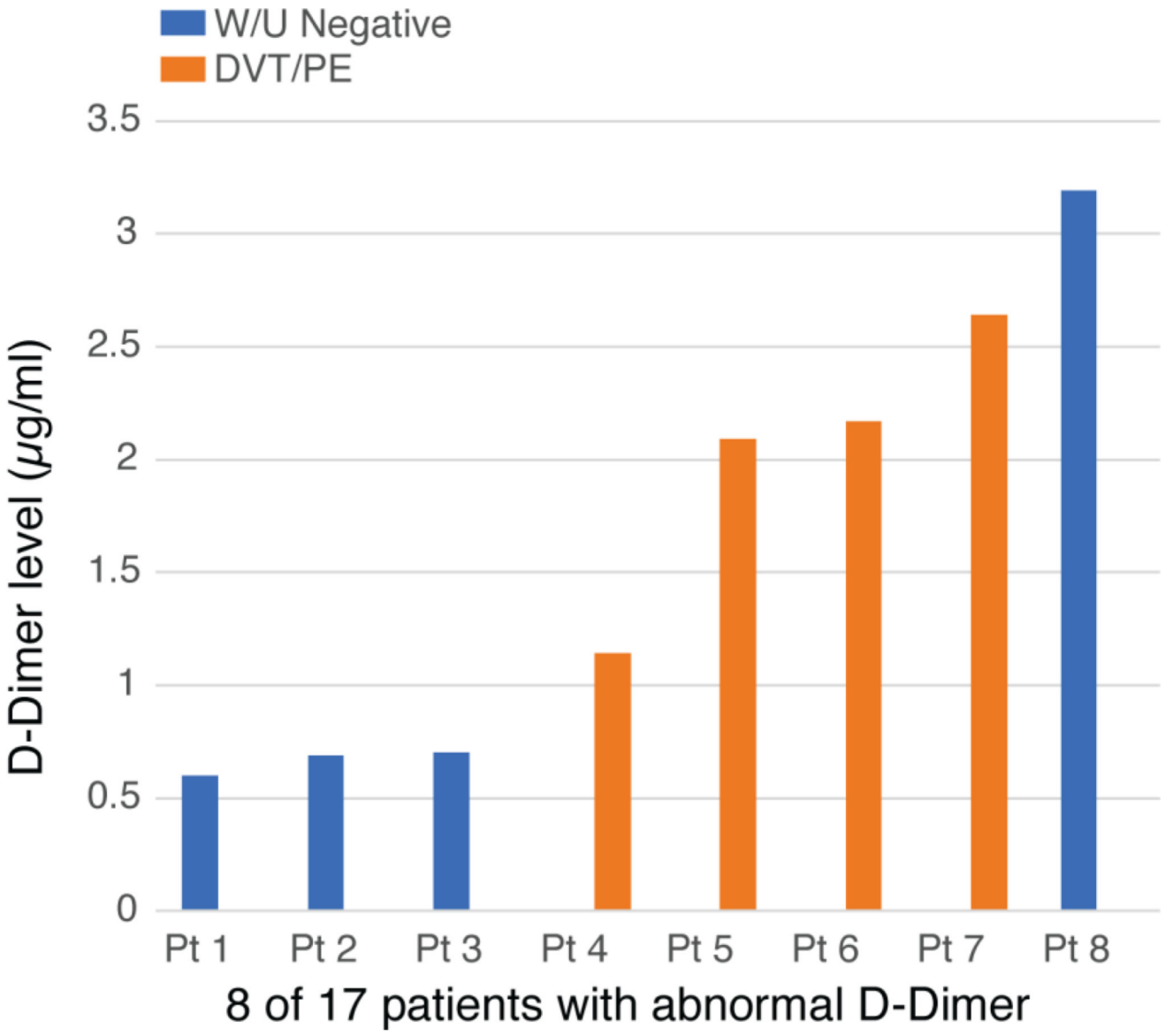

Figure 3.
Abnormal D-dimer levels in 8 of 17 patients with Proteus syndrome, four of which had deep venous thromboembolism and/or pulmonary embolism.

Table I

Clinical findings in the patients with Proteus syndrome having abnormal D-Dimer levels and/or thrombosis

Patient	Age (yrs)	Gender	Affected limb	DVT in affected limb	Pulmonary Embolism	Post-surgery	D-dimer level (μg/ml)	L.A.	Protein C/S Levels	Antithrombin III activity	Prothrombin 20210 Mutation
1	42	F	R Leg	−	−	−	0.60	+	nl/nl	nl	−
2	6	M	L Leg	−	−	−	0.69	−	nl/nl	nl	−
3	32	M	R Leg	−	−	−	0.7	N.D.	N.D.	N.D.	N.D.
4	18	M	R Leg	+	+	+	1.14	N.D.	N.D.	N.D.	+
5	14	F	L Leg	+	−	+	2.09	−	Low/low	Mildly low	−
6	6	F	R Leg	−	+	+	2.17	−	Low/nl	nl	−
7	17	M	R Leg	+	+	+	2.64	N.D.	N.D.	N.D.	N.D.
8	54	M	Bil Legs L>R	_ *	−	−	3.19	−	Low/nl	−	−
9	16	M	L Leg	+	−	+	N.D.	+	N.D.	N.D.	N.D.
10	21	M	L Leg	+	+	+	N.D.	N.D.	N.D.	N.D.	N.D.

−, none; +, present;

*, recurrent superficial thrombi;

abnl, abnormal; Bil, bilateral; DVT, Deep venous thrombosis; L, left; L.A. Lupus Anticoagulant; lat, laterality; N.D., Not done; nl, normal; R, right; yrs, years