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Menorrhagia, Tranexamic Acid and False Negative D-Dimer in Patients with Venous Thromboembolism Case Report and Systematic Literature Review

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Authors' contributions

This work was carried out in collaboration between all authors. All authors contributed to case management. Authors GL and LM designed the case study, performed the systematic literature review and wrote the first draft of the manuscript. All the authors read and approved the final manuscript.

Case Study

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ABSTRACT

A 56 years-old woman came to our attention for abrupt onset of shortness of breath. Pulmonary embolism was firstly ruled out due to negative D-Dimer and unlikely probability. On second day, the patient presented with heavy menorrhagia and treated with tranexamic acid (TA). She informed that similar episode happened some months ago, so she had been treated with cycles of TA, discontinued the last time few days before the hospital admission. After three days from oral intake of TA, the patient suffered from abrupt painful left calf without any cardiac or respiratory sign. Urgent legs ultrasonography showed distal deep vein thrombosis and this time a new D-Dimer assay showed a mild positivity. The patient underwent to computer tomography pulmonary angiography which revealed bilateral segmental pulmonary embolism. Other three case reports referred to patients with acute venous thromboembolism after taking TA for menorrhagia emerged

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from systematic review of literature. Two of them presented with false negative D-Dimer. In another one D-Dimer assay was positive but performed after cardiopulmonary resuscitation.
TA could link with venous thromboembolism both influencing D-Dimer value, proving false negativity, and increasing the thrombotic risk in young-adult females suffering from menorrhagia. These possibilities should be taken into account in this population.

Keywords: Menorrhagia; tranexamic acid; deep vein thrombosis; pulmonary embolism; D-Dimer; diagnosis; clinical probability; Wells score.

1. BACKGROUND

Low or intermediate clinical probability (PTP) based on validated scores, such as revised Wells and Geneva scores, associated to negative D-Dimer assay are now considered the gold standard for ruling out venous thromboembolism (VTE) without the need of diagnosis confirmation by using more invasive tools such as computer tomography pulmonary angiography (CTPA), pulmonary angiography or lung scan [1-3]. Sensitivity, specificity and negative predictive value of the combination of negative high sensitive D-Dimer/low PTP for ruling out VTE are respectively 98.7% (95% CI: 96.2-99.6%), 57.4% (55.1-59-7%), 99.7% (99.1-99.9%) when used revised Wells score and 100% (95% CI: 99.4-100%), 40.8% (38.9-42.7%), 100% (99.6-100%) when used Geneva score [4].

D-dimer is generated from the fibrinolytic system by the action of coagulation factor XIIIa (plasmin) which degrades the cross-linked fibrin polymers who make the fibrin clot [5]. Therefore D-Dimer levels increase every time the coagulative cascade is activated and it represents an indirect marker of venous thromboembolism (VTE), despite non specific [5]. Diagnostic accuracy of D-Dimer in the setting of VTE is reduced in many clinical conditions such as advanced age, infectious or inflammatory diseases, chronic obstructive pulmonary diseases, pregnancy, cancer, anticoagulant therapy and others [5]. In anticoagulated patients, D-Dimer values are reduced compared to non anticoagulated patients, reducing the negative predictive value [6].

Tranexamic acid (TA) is a synthetic lysine derivative with anti-fibrinolytic properties used with the aim of stabilizing the fibrin clot in bleedings associated with hyperfibrinolysis [7,8]. It reversibly and competitively prevents the binding between plasminogen to fibrin blocking the lysine-binding sites, thereby inhibiting the conversion of plasminogen to plasmin and finally inhibiting the fibrin clot dissolution. At higher doses, TA directly inhibits the plasmin. TA is well adsorbed when orally administered. Volume distribution is around 0.4L/Kg after multiple doses intake, maximum peak concentration is around 2.5 hours, half-life is two hours and elimination is renal for 95%. Most elimination takes place during the first eight hours from oral intake [7,8].

TA is considered an effective choice for the treatment of females suffering from menorrhagia and this one is considered one of the leading indication for its use [8]. Clinical studies have in fact demonstrated that TA administered at dosage of 2-3g daily in females with menorrhagia reduces bleeding of around 40% compared to placebo or other non surgical strategies [9].

Whether TA administered for menstrual disorders is linked with VTE and how remains unclear. We describe the case of an adult female treated with TA for heavy menorrhagia receiving a delayed diagnosis of pulmonary embolism (PE) due to false negative D-Dimer associated to low PTP.

2. Case Report

A 56 years old caucasian non-smoker woman came to the Emergency Department of our Hospital for abrupt onset of moderate-severe dyspnoea complaint from two days.

Her history revealed obesity (BMI 38Kg/mq), family history for VTE (85 years old father with recent diagnosis of PE due to deep vein thrombosis), blood arterial hypertension treated with beta-blockers, major depressive disorder treated with serotonine re-uptake inhibitors (SSRI). Past history of asthma, chronic obstructive pulmonary disease and interstitial lung diseases was mentioned. Three years before the present hospitalization, she began presenting recurrent menorrhagia, so she underwent two diagnostic/therapeutic endometrial curettages for endometrial hypertrophy.

7 months before the actual respiratory symptoms, a new episode of heavy menorrhagia happened again, so she began taking TA cyclically (1000mg three times daily for one week every month). The last TA intake was reported around ten days before shortness of breath presentation to the Emergency Department access. Here, physical examination revealed wheezing, tachycardia (120bpm), tachypnea (34 respiratory acts for minute), labial cyanosis, face and chest skin erythema, no signs suggestive of lower limbs deep vein thrombosis, no jugular venous distention. Blood arterial pressure values were 110/60 mmHg (usual values 130/85 mmHg). The 12-leads electrocardiogram showed sinus rhythm, heart rate 110 beats for minute, no abnormalities in PR, QRS and ST segments. The arterial blood gas examination showed hypoxemia (paO2 57.8mmHg), hypocarbia (paCO2 29.6 mmHg), respiratory alkalosis (pH=7.46), normal bicarbonates (HCO3=22mmol/L). Chest X-ray was completely normal. Blood examinations showed negative immune-turbidimetric D-dimer assay (158 ng/mL, cut-off for positivity > 230ng/mL, HemosIL, Instrumentation Laboratory, IL, Milan, Italy) and normal level of brain natriuretic peptide, troponin I and C-reactive protein. PE was initially ruled out because of the association between unlikely probability at Wells' score (1.5) and negative D-dimer. A trans-thoracic echocardiogram was performed, but it showed no abnormality.

The patient recovered in the Internal Medicine ward of our Hospital with diagnosis of "asthma attack" and treated with steroids and short acting bronchodilators. Pharmacological VTE prevention was not performed due to the low risk according to Padua Prediction Score (score 2 based on respiratory failure and obesity, cut-off for thromboprophylaxis being 4) [10].

On day 2, severe menorrhagia started again, so the gynecologist prescribed TA (1000mg per os tid) and scheduled a hysteroscopy. On day 3, the physical examination started getting better until day 4, on which wheezing disappeared. On day 5, the patient started complaining sudden left calf pain without respiratory symptoms. This time D-dimer resulted mildly positive (456ng/mL, normal value < 230ng/mL). Legs ultrasonography showed left distal deep vein thrombosis. The computer tomography pulmonary angiography showed bilateral segmental pulmonary embolism (Fig. 1).

After that, anticoagulation with Fondaparinux (7.5mg once daily) overlapped with warfarin was started. The patient was discharged from hospital five days later.

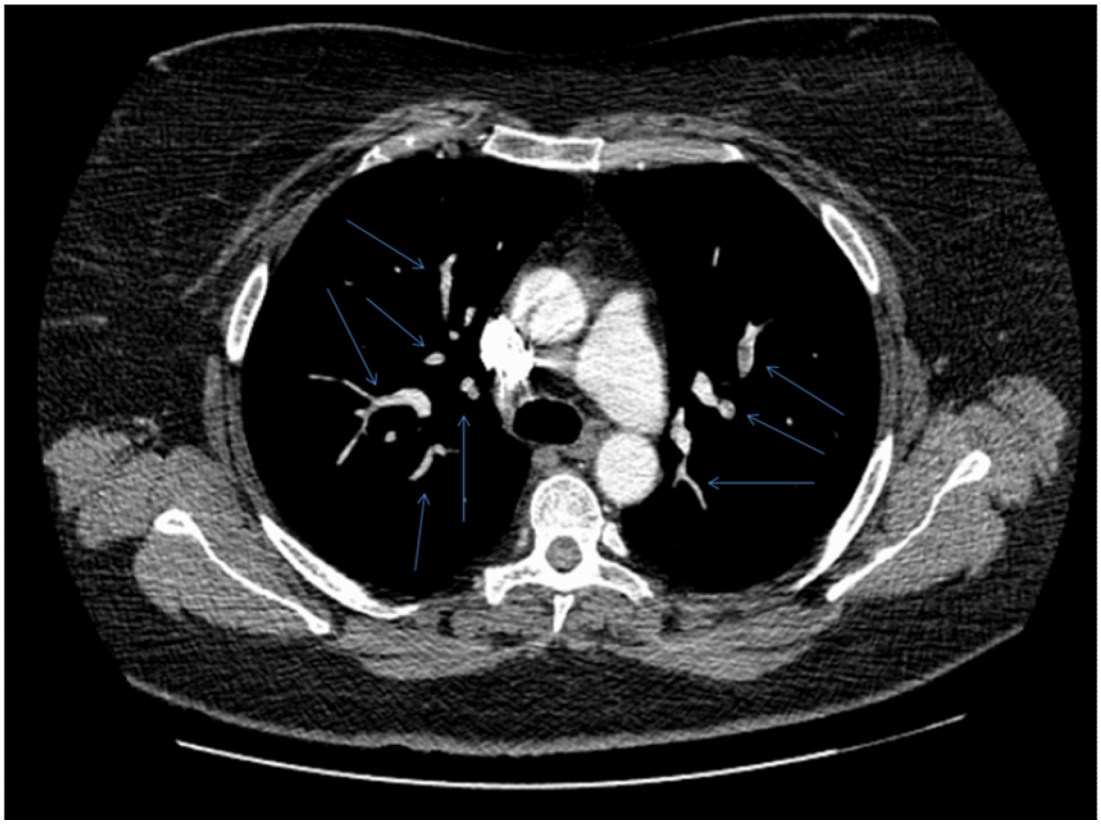

Fig. 1. Bilateral segmental pulmonary embolism

3. DISCUSSION

Our case report highlights and focus on two main points: i) The potential delayed diagnosis of VTE in women taking TA for heavy menstrual bleedings due to false negativity of D-Dimer due to the action of TA on blocking the fibrin degradation ii) The pro-thrombotic role of TA.

As abovementioned, TA is an anti-fibrinolytic agent which inhibits the fibrin degradation [7]. Therefore, it's not surprisingly that inhibition of fibrinolysis by TA could reflect in reduced plasma D-Dimer concentration and potential false negativity. In the present case report the first D-Dimer assay (negative) proved a delay in diagnosis of PE due to the association with unlikely PTP. The next onset of painful left calf brought to reconsider the diagnosis of VTE. It should be remarked that the patient had shown a dramatic improvement in respiratory symptoms compared to the severity of respiratory distress on hospital arrival and this improved clinical course masked the diagnosis of PE and sustained the uncorrected diagnosis of asthmatic crisis until the sudden onset of painful calf. After the onset of calf pain, the second measurement of D-Dimer levels revealed only mildly positivity. These values were the lowest in our personal case series of PE from 2008 to 2012 in patients with pulmonary embolism and D-Dimer measured, also in patients with low risk/non massive PE

according to European Society of Cardiology (ESC), such as our patient (Table 1) [11]. Our hypothesis is that the negative D-Dimer at first examination, could be explained with the chronic use of TA used by the patient for her menorrhagia, despite the fact that it was discontinued some days before.

Table 1. D-Dimer levels in our Institution from 2008 to 2012 in patients with pulmonary embolism presenting with unlikely probability by using Wells score

Patients number	**84**
Sex	41 males/43 females
Mean age ± SD (range)	76.72±11.75 years (35-98)
D-Dimer levels mean ± SD (range) 100% of patients	3415±1783ng/mL (range 483-7895)
D-Dimer levels in high risk/massive PE mean ± SD (range) 16 % of patients	3764±1572ng/mL (1458-5530)
D-Dimer levels in intermediate risk/sub-massive PE mean ± SD (range) 52% of patients	3688±1623ng/mL (483-6382)
D-Dimer levels in low risk/non massive PE mean ± SD (range) 32% of patients	2862±2021ng/mL 551-7895)
Cut-off D-Dimer 230 ng/mL	

Legend: high risk/massive PE=patients presenting with shock or haemodinamic instability; intermediate risk/sub-massive PE= patients presenting echocardiographic right heart dysfunction and/or biomarkers of right heart dysfunction or myocardial damage increased; low risk/non massive PE= patients without echocardiographic or biomarkers signs of right heart dysfunction or myocardial damage

By performing a systematic review of literature published on MEDLINE from 1966 to 2014 May 31 by searching the PubMed databases for “tranexamic acid” matched with “pulmonary embolism”, “deep vein thrombosis”, “D-Dimer” by using the Boolean “AND” in title, abstracts or text, we found three case reports of VTE referred to young-adult females with menorrhagia and treated with TA and undergone to D-Dimer assay [12-14]. Fig. 2 summarizes the searching process. Two of them seem completely similar with our case report findings, showing, in fact, false negative D-Dimer and delayed diagnosis of VTE due to it, whereas the last one of Gybel-Brask et al showed positive D-Dimer but performed after around eight hours from cardiopulmonary resuscitation in a female with massive PE rapidly evolving in cardiac arrest [14]. Any consistent clinical study was found. Table 2 summarizes main findings of the four case reports.

Experimental studies demonstrate that the anti-fibrinolytic agents reduce the products deriving from fibrin degradation in the case of thrombosis, such as D-Dimer and much interestingly one experimental study in provoked PE in dogs demonstrate that the effect of anti-fibrinolytic agents on fibrin degradation inhibition could prolong for some days after drug discontinuation [15-17]. This evidence could explain why our patients, such as the case report of Salam et al. [12], presented with negative D-Dimer despite TA had been discontinued some days before the laboratory assay.

Moreover, our case report focused on the pro-thrombotic role of TA favouring the thrombotic apposition by fibrinolysis inhibition [18,19]. This could explain why our patient suffered for abrupt onset of painful left calf after three days from the new oral administration of TA. TA could in fact have proved the extension of already present deep vein thrombosis which was migrated to pulmonary arteries some days before, when the patient had presented the abrupt onset of dyspnoea.

Table 2. Summary of literature case reports describing false negative D-Dimer in patients taking tranexamic acid for menstrual disorders

Reference	Journal	D-Dimer type and manufactory	D-Dimer cut-off value for positivity	D-Dimer levels at hospital presentation	Brief case description	TA indication and dosage	Last TA intake	Wells score	VTE	Time from D-Dimer assay and diagnosis
Salam A et al. [12]	BMJ case reports 2013	Immunoturbidimetric, quantitative, HemosIL DD HS assay, Instrumentation Laboratory, Milan, Italy	≥ 230 ng/mL	15 ng/mL	47-years old Afro-Caribbean woman with shortness of breath and dizziness from one week prior to hospital arrival	1000 mg three times a day for 3-4 days during menstrual period for menorrhagia in uterine fibroid	7 day prior to hospital arrival	1,5 PE score	Isolated PE	Not reported, but patient initially recovered in gynecologic ward and undergone to next re-evaluation for respiratory symptoms persistence
Mihalache RM et al. [13]	CATH 2012	Immunoturbidimetric, quantitative NycoCard, Axis-Shield, Dundee, Scotland and Immunoturbidimetric, quantitative Instrumentation Laboratory, Milan, Italy	> 320 ng/mL > 300 ng/mL	240 ng/mL 280 ng/mL	38-years old woman with painful left calf and minimal pitting edema (ethnicity not reported)	500 mg four times a day for menorrhagia to cover menstrual period	Painful left calf occurred at 6th day during TA treatment	2 DVT score	Isolated DVT	2 days
Gybel-Brask M et al. [14]	Ugeskr Laeger 2013	Immunoturbidimetric, quantitative HemosIL D-dimer HS, Instrumentation Laboratory, Milan, Italy	>500 ng/mL	D-dimer 6900 ng/mL after 6-8 hours from cardiopulmonary resuscitation	30-years old woman presenting with rapidly increasing shortness of breath, hyperventilation and cardiogen shock evolving in cardiac arrest underwent to cardiopulmonary resuscitation	1000 m g three times daily for menorrhagia	Not known (not evidence of discontinuation in medical records during the last visit in gynecology clinic)	>4 PE score	Isolated PE	Hyperacute, rapidly progressing case
Lorenzini G et al.	Case report described in this journal	Immunoturbidimetric, quantitative HemosIL DD HS assay, Instrumentation Laboratory, Milan, Italy	≥ 230 ng/mL	158 ng/mL	56-years old Caucasian woman with abrupt onset of shortness of breath	1000 mg three times a day for 10 days a month for menorrhagia in uterine hypertrophy	10 days prior to hospital arrival (around one week from symptoms onset)	1,5 PE score	PE with distal DVT	5 days

Legend: BMJ=British Medical Journal; CATH=Clinical and Applied Thrombosis and Hemostasis; TA=tranexamic acid; VTE=venous thromboembolism; DVT=deep vein thrombosis; PE=pulmonary embolism

This could be plausible also analysing the second measurement of D-Dimer in our patient. The mild positivity observed at this moment could reflect the postulate DVT enlargement, confirming the literature evidence showing that D-Dimer values are linearly correlated with VTE extension and severity [20]. However, the pro-trombotic burden of TA in women suffering from menorrhagia is yet unclear. Despite literature reports on many cases of VTE associated to the use of TA for menorrhagia, in a large study on this female population, TA seems not to significantly increase the VTE risk (OR 3,20, 95% CI: 0.65-15.78) [21]. On the other hand a meta-analysis showed that cumulative VTE event rate was 1.9% (95% CI: 1.1-2.9%) in 3225 patients treated with TA. However only 11.4% of patients (370) were treated with TA for menorrhagia and VTE event rate was not extrapolated for this subgroup of patients [22].

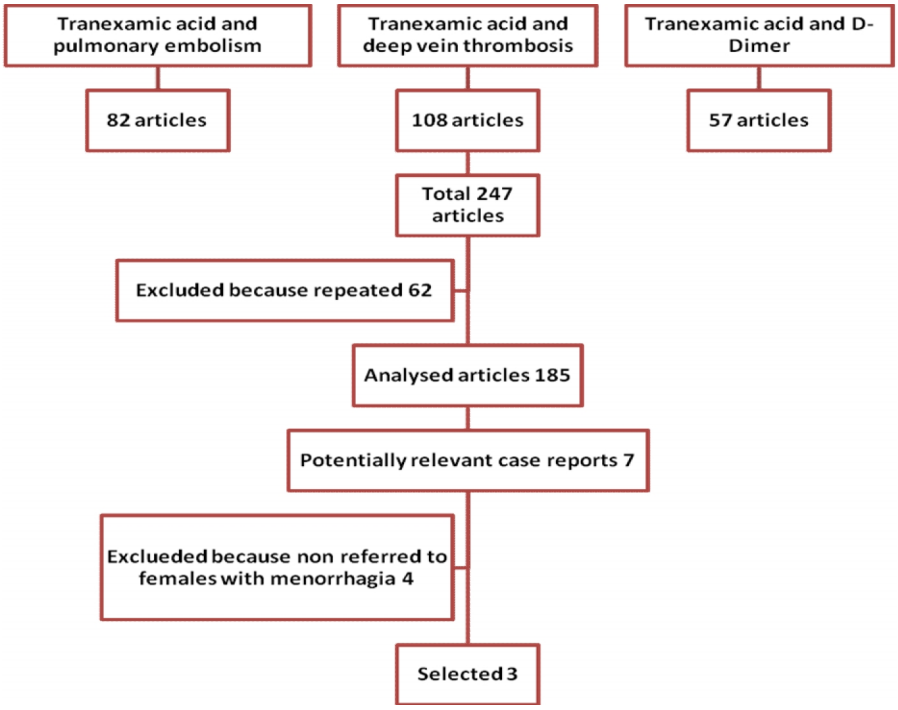

Fig. 2. Pub-Med searching process

4. CONCLUSION

In conclusion, the use of TA in young-adult females with menorrhagia, should be always investigated in the presence of symptoms of VTE and occurrence of negative D-Dimer/low PTP with the aim of avoiding diagnostic bias and under-treat a potentially life-threatening disease.

Key messages

- Tranexamic acid is a recommended treatment for menorrhagia.
- Tranexamic acid acts on coagulative cascade by blocking the fibrinolysis system.
- Tranexamic acid could have prothrombotic properties.

- D-Dimer could be falsely negative in patients taking tranexamic acid due to fibrinolysis block.
- Diagnosis of pulmonary embolism could be falsely ruled out in patients taking tranexamic acid for menorrhagia.
- Negative D-Dimer associated low pre-test probability does not permit to rule out the diagnosis of pulmonary embolism in patient taking tranexamic acid.

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CONSENT

Not applicable.

ETHICAL APPROVAL

Not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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