Ital J Gender-Specific Med 2022; 8(1): 10-17

Iron deficiency anemia and thrombosis in young women: a report of 9 cases

Alessia Castellino[1], Elena Migliore[2], Chiara Brignone[2], Mariella Grasso[1], Remo Melchio[2], Margherita Bonferroni[1], Giobatta Cavallero[2]

[1]Department of Hematology, AO Santa Croce e Carle, Cuneo, Italy; [2]Department of Internal Medicine, AO Santa Croce e Carle, Cuneo, Italy

Received 29 December 2020; accepted 14 June 2021

Summary. *Introduction.* Iron deficiency anemia is more frequent in women of reproductive age than in men of the same age, and it is sometimes considered an irrelevant hematological condition. In literature, both arterial and venous thrombotic events associated with iron deficiency anemia have been reported in pediatric age and in young adults, more often in females. A pathophysiological role of erythrocytes in the onset of thrombosis is recognized in both genetic and acquired anemia. *Methods*. We report our experience with 9 young women in whom acute thrombosis, mostly venous, was associated with preexisting chronic iron deficiency anemia. *Results.* The contribution to the onset of thrombotic complications of both the hematological effects induced by iron deficiency and the individual pro-thrombotic factors was collected and analyzed. It can be hypothesized that a potential interaction between iron deficiency anemia and minor individual prothrombotic risk factors – both genetic and acquired – may increase the thrombotic risk for the first event and for any relapse. *Discussion.* According to our experience, an effective management of iron deficiency anemia, in addition to improving the quality of life of patients, could represent a preventive measure to reduce the individual thrombotic risk in young women, when exposed to physiological thrombophilic conditions, such as pregnancy, puerperium or oral contraceptives use and if genetic or acquired prothrombotic factors coexist with anemia.

Keywords. Iron deficiency anemia, anemia, thrombosis, thrombophilia, young women.

Introduction and objectives

Thrombosis is a multifactorial disease. The main predisposing factors were described by the Virchow triad: stasis, activation of blood coagulation and vein damage. Thrombosis develops from the interaction of both genetic and acquired factors. Coagulation activation is mainly responsible for venous thrombosis, while endothelium damage and blood stasis are more involved in the arterial one. In young women, many factors – such as estroprogestinic therapy, pregnancy or puerperium – represent acquired transient risk factors for thrombosis.

Iron deficiency anemia (IDA) – the most widespread single cause of anemia – is more frequent in women of reproductive age than in men of the same age, and it is frequently asymptomatic and often underdiagnosed and untreated.[1]

The adverse effects of IDA are reported in pregnancy (risk of preterm labour, low birth weight), in children (susceptibility to infection) and adults (reduced physical activity, fatigue, reduced work performance).[2]

IDA is not generally considered a common cause of thrombosis; however, an association has been described with ischemic stroke, venous thromboembolism (VTE) and cerebral venous sinus thrombosis (CVST) in both young adults and pediatric cases.[3]

Although the physiopathological mechanisms correlating anemia and thrombosis are still to be demonstrated, this relationship underlines that iron deficiency prevention and a prompt treatment of anemia could produce additional benefits on women's health, and help reduce a cumulative thrombotic risk.

In this study, we report the cases of 9 young women who experienced an acute thrombotic event – arterial or venous – and who were all diagnosed with IDA, with the aim to better assess the relationship between IDA and acute thrombosis.

Materials and methods

This retrospective monocenter analysis, conducted at the Santa Croce and Carle Hospital of Cuneo, Italy, include a series of 9 cases of acute thrombosis, both venous and arterial, occurring in young (between 16 and 50 years old) female patients affected by pre-existing chronic iron deficiency anemia, recorded from January 1995 and January 2020.

Demographic, clinical and lab data were collected through a review of the medical records.

Baseline clinical characteristics – including age, family history of thrombosis, use of oral contraceptive, smoking habit, weight, days of menstrual flow and site of thrombosis – were assessed. Lab data – including hemoglobin (Hb), red blood cell distribution width (RDW), mean corpuscular volume (MCV), platelets, leucocyte and monocyte count and blood group – was recorded, if available. A thrombophilia screening assessment was performed in all cases, including: lupus

anticoagulant (LAC), anticardiolipin antibodies (aCL) IgG (reference value GPL <11 U/ml) and IgM (MPL reference value <30 U/ml), anti-beta2glicoprotein1 antibodies (anti-β2GL1) IgG (reference value IgG <3.5 U/ml) and IgM (reference value <9 U/ml); antithrombin activity (AT, reference value 80-120%), coagulant protein C activity (PC, reference value 60-140%), coagulant protein S activity (PS, reference value 50-120%); factor V Leiden (FVL), prothrombin polymorphism G20210A (FII), homocysteine level (reference value 5-15 in the fasting state), check of paroxysmal nocturnal hemoglobinuria clones (PNH). To obtain AT, PC and PS activity values, a functional assay was performed, while PNH clones were identified through flow cytometric assay.

The laboratory diagnosis of IDA was defined as hypochromic microcytic anemia (hemoglobin <12 g per liter, MCV <80 fl) and low serum ferritin level (<30 µg per liter). The causes of IDA were also assessed.

The diagnosis of thrombosis was made by imaging assessment (brain magnetic resonance imaging, MRI, or computerized tomography, CT scan, ultrasound).

A descriptive analysis of all the cases included was conducted.

Results

From 1995 to 2020, 9 patients were assessed in our hospital for acute thrombotic events, and were included in the present analysis. Mean age was 36.7 years, while median age was 35 years (range 16-50). None of them reported a personal and/or family history of thrombosis, nor recent triggering events (such as major surgery, trauma, hospitalization). Baseline clinical and hematological features and thrombophilic screening are summarized in Tables 1, 2 and 3.

The acute thrombotic events recorded were: venous thrombosis in 7/9 (78%) cases [5/9 (56%) CVST, 1/9 (11%) lower extremity, 1/9 (11%) vena cava], ischemic stroke in 1/9 (11%) cases and aortic mural thrombus in 1/9 (11%).

The concomitant prothrombotic factors assessed included: smoking (2 patients), heterozygous prothrombin G20210A (1 patient), non-0 blood group (5 patients), oral contraceptive treatment (4 patients), thrombocytosis (3 patients), mild iper-homocysteine serum level (2 patients, both with low folic acid serum level). All patients presented at least one concomitant prothrombotic risk factor: 2 had 2, 4 had 3 and 1 patient had 4 concomitant risk factors. These characteristics are summarized in Table 4.

Also, it can be noted that all patients presented RDW higher than 14.4% and a monocyte count greater than 0.120 x 10^9/l. All women of reproductive age had reported the presence of anemia in their past medical history. A laboratory diagnosis of IDA was made in all 9 cases upon the onset of the acute thrombotic event. It should be noted that case 6 showed two consecutive hospitalizations for recurrence of thrombosis. The patient developed two different ischemic events (one cerebral arterial thrombosis, diagnosed through imaging, and one finger ischemia, diagnosed upon a clinical evaluation) at the age of 44 and 49, respectively. Both ischemic events were found to be associated to severe IDA with reactive thrombocytosis. In both events, for patient case 9, a cardiac source of emboli, other traditional cardiovascular risk factors, genetic thrombophilia and clinical atherosclerosis were ruled out as the cause of thrombosis.

Case 9 showed ferritin 39 µg per liter after urgent surgery, and the diagnosis of IDA was confirmed by a positive past medical history and corrected with iron supplementation.

The causes of IDA were: malabsorption in 3/9 (33%) patients (one case of gastrectomy, one celiac disease and one helicobacter pylori infection), heavy menstrual bleeding in 3/9 (33%) and nutritional deficiency in the others.

The diagnosis of CVST and ischemic stroke was confirmed by computerized tomography and magnetic resonance imaging, Doppler ultrasonography and a computerized tomography of the abdomen confirmed the thrombosis of lower extremity veins, vena cava and aorta (Table 4).

All women received LMWH and warfarin for their venous thrombosis; the ischemic stroke was treated with low-dose aspirin and therapeutic platelet apheresis and the aorta thrombosis with low-dose aspirin and anticoagulants. In all cases, IDA and thrombocytosis were resolved with iron supplementation (Table 5).

Discussion

Women of reproductive age showed a higher risk of venous thromboembolism (VTE) and CVST than men of similar age, due to their intake of oral contraceptives and to pregnancy.[4,5] By contrast, young women are at a lower risk of cardiovascular diseases than males.

Both venous and arterial thrombosis should be considered as multifactorial diseases because, although they share some thrombotic risks factors, they have a different pathophysiology.[6,7]

The role of erythrocytes in thrombosis is emphasized in various diseases.[8] In fact, clinical and epidemiological studies have associated both quantitative and qualitative erythrocyte abnormalities with both arterial and venous thrombotic events.[9] Many reports have highlighted a correlation between an elevated hematocrit

Table 1. Baseline clinical characteristics

Patient	Age (years)	Thrombosis Family history	Oral contraceptive	Smoking habit	Menstrual flow day/ month	Weight (kg)	Site of thrombosis
Case 1	30	Negative	Ethinylestradiol/ dienogest	-		49	CVS
Case 2	49	Negative	Ethinylestradiol/ gestodene	-	3-4	87	CVS
Case 3	28	Negative	Ethinylestradiol/ drospirenone	+	4-5	62	CVS
Case 4	34	Negative	-	-	7	66	Lower extremity veins
Case 5	16	Negative	-	-	7	55	CVS
Case 6	44	Negative	-	-	5-6	45	Cerebral artery
Case 7	45	Negative	Ethinylestradiol/ gestodene	-	2-4	75	CVS
Case 8	35	Negative	-	-	8	NA	Inferior vena cava
Case 9	50	Negative	-	+	3-7	77	Aorta

CVS: cerebral venous sinus; -: non-use; +: use.

Table 2. Baseline hematological characteristics

Patients	Hb g/dl	RBC M/µl	Ferritin µg/l	RDW %	MCV fl	Platelet count x 10^9/l	Leucocyte count x 10^9/l	Monocyte count x 10^9/l
Case 1	10.8	2.99	13.3	19.2	64	182,000	8.80	0.730 (8.3%)
Case 2	8.7	2.11	10.3	21.1	62	386,000	5.43	0.540 (9.9%)
Case 3	11.1	3.01	4.3	17.2	77	298,000	9.86	0.168 (1.7%)
Case 4	8.4	1.95	4	17.4	68	529,000	10.63	0.393 (3.7%)
Case 5	9.3	2.80	7	19.3	62.6	252,000	7.12	0.299 (4.2%)
Case 6	6.1	1.05	4	32.5	64.9	1,072,000	11.70	0.713 (6.1%)
Case 7	7.4	1.79	3.2	20.1	60.7	621,000	8.99	1.042 (11.6%)
Case 8	10.3	2.45	3.4	16.3	79	270,000	5.02	0.331 (6.6%)
Case 9	10.3	2.57	3.9	24.5	79	335,000	11.01	0.910 (8.3%)

Hb: hemoglobin (reference value 12-16 g/dl). RBC: red blood cell count (reference value 3.8-5.4 M/µl), RDW: red blood cell distribution width, (reference value <14.8); MCV: mean corpuscular volume (reference value 80-97 fl); ferritin (reference value 10-291 µg/l); platelet count (reference value 130-424 x 10^9/l), leucocyte count (reference value 4.0- 10.8 x 10^9/l), monocyte count [reference value 0.1-1.0 x 10^9/l (2-10%)].

Table 3. Thrombophilia screening

Patients	LAC	aCL U/ml	Anti-β 2GL1 U/ml	AT %	PC %	PS %	Homo	FVL	F II G20210A	Blood group	JAK 2	Anti-transglu-taminase ABs	PNH clone
Case 1	Positive	Negative	IgG 4.9^	121	195	89	8.9	Absent	Absent	0 Rh^+	NA	NA	NA
Case 2	Negative	Negative	Negative	NA	113	63	12.2	Absent	Absent	A Rh^+	Absent	Negative	Negative
Case 3	Negative	Negative	Negative	117	136	64	9.59	Absent	NA	B Rh^+	NA	NA	NA
Case 4	Negative	Negative	Negative	87	104	79	11.4	Absent	Absent	A Rh^+	NA	Negative	NA
Case 5	Negative	32 MPL	Negative	97	67	55	7.47	Absent	Heterozygous	NA	Absent	Negative	Negative
Case 6	Negative	Negative	NA	111	71	56	27.27*	Absent	Absent	A Rh^+	NA	NA	Negative
Case 7	Negative	29 GPL#	Negative	81	80	35§	7.7	Absent	Absent	0 Rh^+	Negative	Positive	Negative
Case 8	Negative	Negative	Negative	NA	134	75	11.1	Absent	Absent	0 Rh^+	Absent	Negative	Negative
Case 9	Negative	Negative	IgG 20	128	NA	NA	29**	Absent	Absent	B Rh^-	Negative	Negative	Negative

LAC: lupus anticoagulant; aCL: anticardiolipin antibodies IgG (reference value GPL <11 U/ml), IgM (MPL reference value <30 U/ml); anti-β2GL1: anti-beta2glicoprotein1 antibodies (reference value IgG <3,5 U/ml); IgM (reference value <9 U/ml); AT: antithrombin activity (reference value 80-120%); PC: protein C activity (reference value 60-140%); PS: protein S activity (reference value 50-120%); FVL: factor V Leiden; FII: prothrombin polymorphism G20210A; homo: homocysteinemia (reference value 5-15 in the fasting state); NA: not available; PNH: paroxysmal nocturnal hemoglobinuria.
*with decrease serum concentration of vitamin B12 and folate; **with decrease serum concentration of vitamin B12; §during acute thrombotic event; °first determination; #second determination 15 GPL U/ml; ^second determination IgG 8,3 U/ml.

Table 4. Combined prothrombotic factors in our cohort

Patient	RDW >16%	Thrombocytosis >450x10^9/l	Genetic thrombophilia	Non-0 blood group	Oral contraceptive	Smoking habit
Case 1	√	-	-	-	√	-
Case 2	√	-	-	√	√	-
Case 3	√	-	-	√	√	√
Case 4	√	√	-	√	-	-
Case 5	√	-	√	NA	-	-
Case 6	√	√	-	√	-	-
Case 7	√	√	-	-	√	-
Case 8	√	-	-	-	-	-
Case 9	√	-	-	√	-	√

NA: not assessed.

Table 5. Hematological characteristics: baseline values compared to values after 3 months of iron supplementation

Patients	Hb g/dl		RBC M/µl		Ferritin µg/l		RDW %		MCV fl		Platelet count x 10^9/l		Leucocyte count x 10^9/l		Monocyte count x 10^9/l	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
Case 1	10.8	13.8	2.90	4.55	13.3	35.2	19.2	16.5	64	75	182	169	8.80	8.30	0.730 (8.3%)	0.207 (2.5%)
Case 2	8.7	15.1	2.11	4.88	10.3	81.2	21.1	13.6	62	74	386	186	5.43	5.78	0.540 (9.9%)	0.462 (8.0%)
Case 3	11.1	14.2	3.01	4.67	4.3	32.1	17.2	12.6	77	86	298	270	9.86	8.40	0.168 (1.7%)	0.126 (1.5%)
Case 4	8.4	14.7	1.95	4.22	4	46.3	17.4	12.2	68	79	529	323	10.63	4.99	0.393 (3.7%)	0.409 (8.2%)
Case 5	9.3	14.6	2.80	4.58	7	23.8	19.3	12.4	62.6	94	252	223	7.12	3.99	0.299 (4.2%)	0.340 (8.5%)
Case 6	6.1	14.1	1.05	4.95	4	96	32.5	13.3	64.9	87	107	166	11.70	4.40	0.713 (6.1%)	0.540 (12.3%)
Case 7	7.4	13.9	1.79	4.73	3.2	68.6	20.1	13.8	60.7	88	621	290	8.99	6.63	1.042 (11.6%)	0.620 (9.4%)
Case 8	10.3	13.8	2.45	4.66	3.4	23	16.3	12.2	79	85	270	220	5.02	7.02	0.331 (6.6%)	0.505 (7.2%)
Case 9	10.3	12.1	2.57	4.75	3.9	46	24.5	16.8	79	83	335	361	11.01	7.11	0.910 (8.3%)	0.530 (7.4%)

Hb: hemoglobin (reference value 12-16 g/dl); RBC: red blood cell count (reference value 3.8-5.4 M/µl), RDW: red blood cell distribution width (reference value <14.8); MCV: mean corpuscular volume (reference value 80-97 fl); ferritin (reference value 10-291 µg/l); platelet count (reference value 130-424 x 10^9/l), leucocyte count (reference value 4.0- 10.8 x 10^9/l), monocyte count [reference value 0.1-1.0 x 10^9/l (2-10 %)].

and thrombosis. Also, in some anemic conditions, both acquired and genetic, such as paroxysmal nocturnal hemoglobinuria or sickle cell disease, a change in the properties of erythrocytes contribute to a tendency towards thrombotic complications. A similar predisposition to thrombosis has been observed also in hemolytic anemia, suggesting a pathogenetic role of the erythrocyte anomalies.[9]

Thrombosis in otherwise healthy children – a population with a low incidence of thrombosis and atherosclerosis, when extensive study excluded any thrombophilic condition – suggested that IDA may also contribute to thrombosis.[10]

IDA, a common disorder characterized by microcytic anemia and low ferritin serum levels, is not considered among the common risks factor for venous thrombosis;[5] however, it has been associated with VTE,[11] CVST and ischemic stroke, both in young adults and in pediatric patients, with a predominance in females.[3]

The mechanism at the basis of thrombosis in these cases remains unknown, and is yet to be investigated. To explain the correlation between IDA and thrombosis, many hypotheses have been formulated: frequently secondary thrombocytosis is referred as a significant risk factor; others could be endothelial dysfunction secondary to anemic hypoxia, an abnormal adherence of erythrocytes to the endothelium, an abnormal platelets activation and function, an alteration of blood rheology.[3]

The association between thrombosis and IDA was observed in the female sex alone, without excluding a contribution by the endogenous sex hormone in the thrombosis mechanism. As it has recently been reported, endogenous female sex hormones could play a relevant role in increasing the VTE risk,[12] while their possible contribution to cardiovascular diseases remains uncertain.

Reactive thrombocytosis (RT) may be provoked by IDA. The risk of venous thrombotic complications with RT is generally low, but not irrelevant in critically ill patients – such as those admitted in intensive care units – and in subjects who underwent splenectomy or major trauma.[13] Some case reports suggested that in this setting RT caused by iron deficiency may play a role in thrombosis.[3] In our patients, RT was not observed in all cases (only 3/9 – 33% – patients), and probably additional factors contributed to the onset of thrombosis.

An increased RDW, a measure of the variation in the erythrocyte size, is a marker of iron deficiency, and is also observed in vitamin deficiency anemia and other inflammatory conditions.

We found higher RDW values in all the cases reported, without any other known comorbidity which could explain this value, except for IDA. Moreover, a normalization of RDW values was observed after therapeutic iron supplementation.

RDW is positively correlated with venous thromboembolism[14,15] and cardiovascular diseases,[16] however, it's still unclear whether this association indicates a causal role of erythrocytes in thrombosis, or if it represents just an epiphenomena of underlying predisposing condition to thrombosis. In VTE it was hypothesized that a great heterogeneity in cell size could increase blood viscosity and impair blood flow, leading to increased blood stasis, one of main risk for venous thrombosis.[14] This suggestion is in accordance with a higher prevalence of venous thrombosis in the cases reported.

Another possible mechanism could be explained by the role of the hematocrit in the modification of clot formation and lysis. Reduction in the hematocrit has been reported to affect the traditional thromboelastography parameters. Patients with sideropenic anemia were shown to have significantly increased levels of maximum clot firmness compared to non-anemic controls, mimicking a sort of 'hypercoagulable profile'[17] that could play a role in the development of thrombosis.

Several reports[14] found that a higher peripheral blood monocyte count, even within the reference range, is associated with venous thrombosis in a dose-response manner, and that a low monocyte count (below 0.120 $x10^9$/l) is associated with a lower risk of venous thrombosis. Interestingly, all the 9 cases we reported showed a blood monocyte count higher than 0.120 x 10^9/l, with some (case 1, 6, 7 and 9) presenting an elevated monocyte count also in absolute terms (monocyte count higher than 0.700 x 10^9/l). This observation could find some explanations: first, monocytes are known to express tissue factor and represent about 30% of the leukocytes in a venous thrombus after 48 hours of flow restriction. Also, they are the type of leukocyte that predominantly contribute to tissue factor-driven coagulation, and are the most important leukocytes involved in the modulation of venous thrombus resolution. Moreover, they have also been found to play a role in arterial thrombosis: in atherosclerosis, monocytes are the central drivers of vascular inflammation, and play a role in atherogenesis.[14]

Smoke, oral contraceptive, non-0 blood group, genetic thrombophilia and hyperhomocysteinemia are other known risk factors for arterial and venous thrombosis, and were observed also in our cohort. Moreover, the risk is even higher when it has been acquired and the genetic risk factors are combined.[18]

In our cases, 8 out of 9 patients indicated to have at least one of the reported risk factors associated with IDA upon the onset of their first event (Table 4): 1 patient with mild genetic thrombophilia, 1 with oral contraceptive, 1 with oral contraceptive + smoking + non-0 blood group, 1 with OC + non-0 blood group, 1 with thrombocytosis, 1 with thrombocytosis + non-0 group, 1 with thrombocytosis + non-0 group + mild hyperhomocysteinemia, 1 with smoking + non-0 blood group + mild hyperhomocysteinemia; this suggests a potential interaction between the qualitative and quantitative changes in red blood cells related to iron deficiency and minor prothrombotic factors in defining the final risk of thrombosis for each patient.

The majority of anemic patients developed CVST (5/9, 56%). The consequence and symptomatology of a thrombus in the cerebral vein circulation are well described,[18] but it is still not clear what could be the reason of this unusual thrombosis site.

Most of the risk factors for CVST coincide with those of VTE, and anemia was reported in the list of possible risk factors.[19] A stronger association was observed between CVST and microcytic[20] and severe anemia,[21] without specifying the cause of anemia, although iron deficiency was suggested. In this setting of thrombosis, the diagnosis and correction of iron deficiency would be a preventive measure, and a goal to be achieved, together with a correct anticoagulation.

The clinical presentation of case 6, found in two hospitalizations, underlined that IDA may contribute not only to thrombotic complications, but also to the recurrence of thrombosis. After excluding a cardiac source of the emboli and with no traditional cardiovascular risk factors, nor genetic thrombophilia, nor clinical atherosclerosis, the patient developed two different ischemic events (one arterial cerebral thrombosis and one finger ischemia) at the age of 44 and 49, both associated with severe IDA with RT. RT and anemia were effectively reversed with iron supplementation, ruling out a chronic myeloprolipherative disorder. This case showed a marked thrombocytosis in association with non-0 blood group and mild hyperhomocysteinemia, secondary to vitamin B12 and folate deficiency, which could have contributed to arterial complications. It is still unclear whether a mild hyperhomocysteinemia could be considered as a biological marker or a pathogenetic agent of thrombosis; however it should always be corrected with vitamin supplementation.

Case 1 showed bilateral arthritis after 4 months from CVST, and a diagnosis of systemic lupus erythematosus was made through laboratory investigation. In this patient, the main prothrombotic factors were: certainly, the autoimmune disorder, clinically unknown at the time of the onset of thrombosis, and the oral contraceptive. However, the coexisting iron deficiency, later re-

versed through iron supplementation, should be evaluated before prescribing oral contraceptives, with the aim of removing anemia as a preventable cause of CVST.

Case 9 complained of acute limb ischemia due to the embolization of a primary aortic mural thrombus. Past medical history revealed IDA and smoking habit, without other traditional cardiovascular risk factors. The patient manifested microcytic anemia upon hospitalization and, after urgent thrombectomy, we observed a ferritin level of 39, a platelet count in the normal range, mild hyperhomocysteinemia with B12 vitamin deficiency, anti-beta2glicoprotein1 antibodies positive (first determination), non-0 blood group. In this patient, multiple mild risk factors, in combination with iron deficiency, may be involved in the systemic hypercoagulability responsible for the arterial event, even in the absence of atherosclerosis.

The findings of these three cases have clinical implications, such as: if not resolved, IDA may represent a risk for the recurrence of thrombosis; in anemic patients, a careful prescription of oral contraceptives should be considered, and an effort to correct behaviour risks, such as smoking, together with the iron deficiency status, may help reduce the personal thrombotic risk. Our study has certain limitations: it is a retrospective collection of 9 cases, which – over a long time frame – came to our attention due to the onset of an acute thrombotic event. Then were found the patients to be all affected by chronic sideropenic anemia: thus, we cannot calculate the incidence of thrombotic events in all the populations of IDA patients. In addition, we collected only the cases hospitalized for major thrombotic events; therefore, minor cases of thrombosis in the young and healthy IDA population, managed in an outpatient setting, could be much more frequent than we observed. Although our analysis included only 9 patients, we have to consider that the prevalence of IDA and of acute thrombosis among healthy woman in Italy remained unchanged in the past decades. However, a suggested relationship between IDA and thrombosis remains to be prospectively investigated and confirmed on a larger number of patients. Another limitation is that, in order to analyze the associated thrombophilic risk factors, common thrombophilia tests were considered (PC, PS, AT, FVL, prothrombin G20210A mutation, homocysteine, antiphospholipid antibodies presence), and some of these factors were missing. In detail, in case 9 the assays for PS ad PC for concomitant anticoagulation were missing, although it is unlikely that a natural coagulation inhibitor deficiency may have a role in arterial thrombosis. In case 6, the anti-β2 GP1 antibody was missing because it was not available at time of diagnosis, and the patient has been well until now, without any antithrombotic treatment; in addition, case 3 refused any other laboratory investigation. Finally, the assays for JAK2, PNH clone and anti-transglutaminase antibody were not performed in all patients; however, the clinical follow-up and a complete response to oral iron supplementation likely exclude the presence of these subclinical diseases.

In conclusion, IDA should always be considered and ruled out in young female patients with acute thrombotic complications, and it should always be treated with adequate iron supplementation. Additionally, IDA patients should be aggressively monitored and managed for underlying bleeding or malabsorption, in order to reduce the risk of chronic anemia and the subsequent risk of thrombotic events and their possible recurrences.

Key messages

With the limitations of our retrospective analysis and incomplete assessment of thrombophilia, we can make some considerations.

- IDA detected in a young woman always deserves consideration, since it can easily be resolved through oral iron supplementation, and should not be underestimated as a common benign disorder.
- The association between IDA and both venous and arterial thrombosis suggests that iron deficiency may play a different role in determining thrombosis in different statuses.
- Keeping in mind the clinical association with arterial and venous thrombosis, the correction of anemia may decrease the individual potential thrombotic risk and prevent the recurrence of events, especially when patients are exposed to sex-specific common transient thrombotic factors, such as oral contraception, pregnancy/puerperium and assisted reproductive techniques, or when a clinical evaluation shows a personal or family history of thrombosis, smoking or potential factors for iron deficiency.
- IDA is a preventable and solvable condition, which has never been overlooked, because in particular women and in particular situations it may be associated with an increased risk of adverse outcomes.
- In asymptomatic anemic women, the prescription of combined estrogen-progestin hormonal contraceptives should be avoided until a complete diagnostic evolution and the resolution of iron deficiency have been achieved.
- Future epidemiology analyses, the investigation of iron metabolism and the erythrocytes' role in the pathogenesis of thrombosis could help us understand the clinical association between IDA and thrombotic events.

References

1. Camaschella C. Iron-deficiency anemia. N Engl J Med. 2015;372(19):1832-43.
2. Zimmermann MB, Hurrell RF. Nutritional iron deficiency. Lancet. 2007;370(9586):511-20.
3. Keung Y-K, Owen J. Iron deficiency and thrombosis: literature review. Clin Appl Thromb Hemost. 2004;10(4):387-91.
4. Middeldorp S. Thrombosis in women: what are the knowledge gaps in 2013? J Thromb Haemost. 2013;11(Suppl 1):180-91.
5. Lijfering WM, Rosendaal FR, Cannegieter SC. Risk factors for venous thrombosis-current understanding from an epidemiological point of view. Br J Haematol. 2010; 149(6):824-33.
6. Wolberg AS, Rosendaal FR, Weitz JI, Jaffer IH, Agnelli G, Baglin T et al. Venous thrombosis. Nat Rev Dis Primers. 2015;1:15006.
7. Aird WC. Vascular bed-specific thrombosis. J Thromb Haemost. 2007;5(Suppl 1):283-91.
8. Weisel JW, Litvinov RI. Red blood cells: the forgotten player in hemostasis and thrombosis. J Thromb Haemost. 2019;17(2):271-82.
9. Byrnes JR, Wolberg AS. Red blood cells in trombosis. Blood. 2017;130(16):1795-9.
10. Maguire JL, de Veber G, Parkin PC. Association between iron-deficiency anemia and stroke in young children. Pediatrics. 2007;120(5):1053-7.
11. Hung SH, Lin HC, Chung SD. Association between venous thromboembolism and iron-deficiency anemia: a population-based study. Blood Coagul Fibrinolysis. 2015;26(4):368-72.
12. Sheres LJJ, van Hylckama Vlieg A, Bellieux BEPB, Fauser BCJM, Rosendaal FR, Middeldorp S et al. Endogenous sex hormones and risk of venous thromboembolism in young women. J Thromb Haemost. 2019;17(8):1297-304.
13. Ho KM, Yip CB, Duff O. Reactive thrombocytosis and risk of subsequent venous thromboembolism: a cohort study. J Thromb Haemost. 2012;10(9):1768-74.
14. Rezende SM, Lijfering WM, Rosendaal FR, Cannegieter SC. Hematologic variables and venous thrombosis: red cell distribution width and blood monocyte count are associated with an increased risk. Haematologica. 2014; 99(1):194-200.
15. Cay N, Unal O, Kartal MG, Ozdemir M, Tola M. Increased level of red blood cell distribution width is associated with deep venous thrombosis. Blood Coagul Fibrinolysis. 2013;24(7):727-31.
16. Danese E, Lippi G, Montagnana M. Red blood cell distribution width and cardiovascular diseases. J Thorac Dis. 2015;7(10):402-11.
17. Spiezia L, Radu C, Marchioro P, Bertini D, Rossetto V, Castelli M et al. Peculiar whole blood rotation thromboelastometry (Rotem) profile in 40 sideropenic anemia patients. Thromb Haemost. 2008;100(6):1106-10.
18. Martinelli I, De Stefano V, Mannucci PM. Inherited risk factors for venous thromboembolism. Nat Rev Cardiol. 2014;11(3):140-56.
19. Capecchi M, Abbattista M, Martinelli I. Cerebral venous sinus thrombosis. J Thromb Haemost. 2018;16(10):1918-31.
20. Coutinho JM, Zuurbier SM, Gaartman AE, Dikstaal AA, Stam J, Middeldorp S et al. Association between anemia and cerebral venous thrombosis: case-control study. Stroke.2015;46(10):2735-40.
21. Stolz E, Valdueza JM, Grebe M, Schlachetzki F, Schmitt E, Madlener K et al. Anemia as a risk factor for cerebral venous thrombosis? An old hypothesis revisited. Result of a prospective study. J Neurol. 2007;254(6):729-34.

Author contribution statement: CGB designed the study, collected clinical data and wrote the manuscript; CA wrote the manuscript; ME, BC, GM, MR and BM reviewed and approved the manuscript.

Conflict of interest statement: all Authors declare that they have no competing interests.

Ethics approval: the study was conducted in accordance with the ethical standards of the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent: all the patients offered written informed consent to reproduce and publish their data.

Correspondence to:
Alessia Castellino
Divisione di Ematologia
AO Santa Croce e Carle di Cuneo
Via Michele Coppino 26
12100 Cuneo, Italy
email castellino.ale@ospedale.cuneo.it