Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 10 August 2022 doi:10.20944/preprints202208.0190.v1

Review

Neurovascular Manifestations of Iron-Deficient Anemia: Narrative Review and Practical Reflections through A Teaching Case

Marialuisa Zedde[1], Giacomo Portaro[1], Laura Ferri[2], Francesco Cavallieri[1], Manuela Napoli[3], Claudio Moratti[3], Fabrizio Piazza[4], 5 Franco Valzania[1], Rosario Pascarella[3]

[1:] Neurology Unit, Neuromotor and Rehabilitation Department, Azienda USL-IRCCS di Reggio Emilia, Reggio Emilia, Italy; marialuisa.zedde@gmail.com, zedde.marialuisa@ausl.re.it; Cavallieri.francesco@ausl.re.it; portaro.giacomo@ausl-re-it; valzania.franco@ausl.re.it

[2.] Department of Neuroscience, Imaging and Clinical Sciences, University G. d'Annunzio of Chieti-Pescara, Chieti, Italy; lauraferri091@gmail.com

[3.] Neuroradiology Unit, Radiology Department, Azienda USL-IRCCS di Reggio Emilia, Reggio Emilia, Italy; Napoli.manuela@ausl.re.it; moratti.claudio@ausl.re.it; Pascarella.rosario@ausl.re.it

[4.] CAA and AD Translational Research and Biomarkers Laboratory, School of Medicine and Surgery, University of Milano - Bicocca, Via Cadore 48, 20900, Monza, Italy; fabrizio.piazza@unimib.it

Correspondence: marialuisa.zedde@gmail.com; zedde.marialuisa@ausl.re.it

Abstract:

Background:

Anemia is one of the most frequent diseases worldwide, affecting a third of the general population. Anemia in general and in particular, iron-deficient anemia (IDA), has been associated to a higher risk of thrombotic manifestations, including ischemic stroke and cerebral venous thrombosis (CVT), as well as systemic extra cerebral arterial and venous thrombosis. Despite these data, anemia is seldom considered as an etiological factor of stroke.

Methods:

An individual case encompassing all known neurovascular and systemic arterial and venous thrombotic manifestations related to IDA is presented with the focus on clinical reasoning issues in the diagnostic pathways, starting from the neuroradiological signs. The main questions have been identified and addressed in a narrative review of the most relevant data in the literature from a pragmatic and clinical viewpoint.

Results and Discussion:

The presented case concerns a 46 years old man admitted to the Stroke Unit because of acute ischemic stroke with multiple thrombi in large intracranial and extracranial vessels, multifocal ischemic lesions in several arterial territories and the concurrent finding of asymptomatic CVT, pulmonary embolism with lung infarction and aortic thrombosis. An extended diagnostic work-up excluded the main etiologies (arterial dissection, cardiac embolism, genetic and acquired prothrombotic disorders, as cancer and antiphospholipid syndrome), except for a severe IDA, such as to require blood transfusions followed by anticoagulant therapy for the several thrombotic manifestations. Neuroimaging and systemic vascular findings have been analyzed and the main issues proposed by the case in the diagnostic pathway have been identified and discussed in a pragmatic clinical road map reviewing the data provided by the literature.

Conclusions:

IDA is a common but treatable condition that, independently or synergically, may increase the risk of thrombotic events. The diagnostic and therapeutic approach has not yet defined and each case should be individually addressed in a pragmatic clinical road map.

Keywords: iron-deficient anemia; IDA; stroke; cerebral venous thrombosis; brain MRI; aortic thrombosis; pulmonary embolism; embolic pattern;

© 2022 by the author(s). Distributed under a Creative Commons CC BY license.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 10 August 2022 doi:10.20944/preprints202208.0190.v1

1. Background

Acute ischemic stroke with neuroimaging pattern suggesting an embolic source is a not rare occurrence in both young and old patients. Usually, the underlying embolic mechanism is supposed because of the presence of multiple ischemic lesions, usually involving more than one arterial vascular territory, but it is very rare the finding of a thrombus in a large vessel like as "smoking gun" in the diagnostic pathway looking for an etiology of the stroke. It is even rarer to find the simultaneous presence of thrombus in multiple arteries and the association of arterial and venous thrombosis as well as cerebral and extra cerebral thrombosis. The current etiological classifications of ischemic stroke do not include such cases in any category and the diagnostic pathway is not clearly defined, shared and codified. Similarly, the most appropriate therapeutic approach to these situations has not been defined and each case has an individual management. Among the different possible etiologies are included acquired or hereditary prothrombotic conditions, common diseases that have a rare presentation in which stroke is the first manifestation, and not infrequently the diagnostic work-up does not lead to the identification of a certain proof, allowing to collect only a series of faint clues.
The aim of this narrative review is to address the main diagnostic issues raised by a unique clinical case of a patient presenting with cryptogenic embolic stroke.

2. Methods

An individual teaching case was selected among patients admitted to a hospital-based Stroke Unit, fulfilling the attribution of multiple thrombotic events to an IDA as main risk factor. The patient underwent a complete work-up including a neurovascular dedicated approach supported by a detailed neuroimaging study, including Computed Tomography Angiography (CTA) and brain MRI with Magnetic Resonance Angiography (MRA) as well as a whole-body imaging study with Computed Tomography (CT) and Positron Emitting Tomography (PET) and a thorough cardiologic evaluation (including prolonged heart rhythm monitoring and echocardiography). These tests were performed as part of the routine diagnostic pathway of patients with ischemic stroke at our institution.
The diagnostic pathway was guided by issues raised in the clinical neurovascular management of the patient and these steps were identified and analyzed according to a narrative review of the literature on the corresponding topic.

3. Results

A 46-years old man was referred to the Emergency Department (ED) in the afternoon because of unsteadiness, vertigo and nausea, reporting the awareness of the symptoms at awakening, around ten hours before the consultation, with last time seen well 24 hours before. His past medical history was notable for two episodes of head concussion without clinical consequences and brain lesions on CT imaging, the recent finding of increased value of glycated hemoglobin and a long-lasting IDA, erratically treated with iron oral supplementation. The first blood laboratory assessment in ED confirmed the microcytic anemia without other relevant findings (hemoglobin 8.3 g/dl, RBCs 4.26x106/μL, hematocrit 28.6%, MCV 67.3 fL, MCH 19.5 pg, MCHC 28.9 g/dl, platelets 211x1000 μl, fibrinogen 188 mg/dl, D-dimer 2485 ng/ml, regular liver and kidney functions, absence of electrolytic disturbances and normal inflammatory markers). The initial neurological examination was remarkable for impaired alertness (psychomotor slowness, tendency to fall asleep), dysarthria and left limbs ataxia with a global National Institute of Health Stroke Scale (NIHSS) score of 11. The patient underwent an unenhanced brain CT scan, whose findings were significant for multiple subcortical hypodensities in both cerebellar hemispheres and vermis, highly suggestive of subacute ischemic lesions in the territory of bilateral posterior inferior cerebellar artery (PICA) and left superior cerebellar artery (SCA) (figure 1).

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 10 August 2022 doi:10.20944/preprints202208.0190.v1

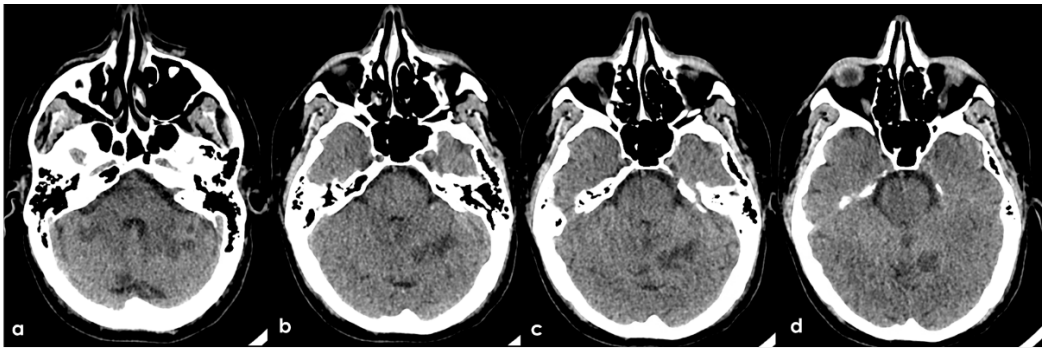

Figure 1. Brain CT performed at the admittance to the ED. From a to d ascending axial CT slices of the posterior cranial fossa, showing bilateral subcortical multiple rounded hypodensities in the cerebellar white matter (a) in PICA territory with left side prevalence (b, c) and a similar hyperintense lesion in the superior part of vermis (b-d) and in the left anterior lobe of the cerebellum, supplied by the superior cerebellar artery (SCA).

Therefore, an arch-to-vertex CT-angiography (CTA) was performed and it revealed:
a) a rounded hypodense lesion partially adherent to the aortic arch wall and partially floating within the lumen of the aortic arch, in the segment between the origin of the left common carotid artery (CCA) and the left subclavian artery (SA);
b) a similar smaller hypodense rounded structure partially adherent to the posterior wall of the brachiocephalic artery (BCA);
c) a progressive reduction of intensity of contrast filling of the right vertebral artery (VA) starting from the V2-V3 transition, leading to a complete occlusion in the V4 segment;
d) a lack of contrast filling of the right lateral dural venous system involving transverse sinus (TS) and sigmoid sinus (SS) and also reaching the jugular bulb and the proximal extracranial segment of the right internal jugular vein (IJV).
The intraluminal arterial hypodensities described in a and b (figure 2) are suggestive for intraarterial partially floating thrombi with V4 VA occlusion (c) (figure 3), with a presumed mechanism of artery-to artery embolism. Conversely the filling defect on the intracranial venous compartment (right TS, SS and IJV) (d) (figure 4) is highly suggestive of cerebral venous thrombosis (CVT).

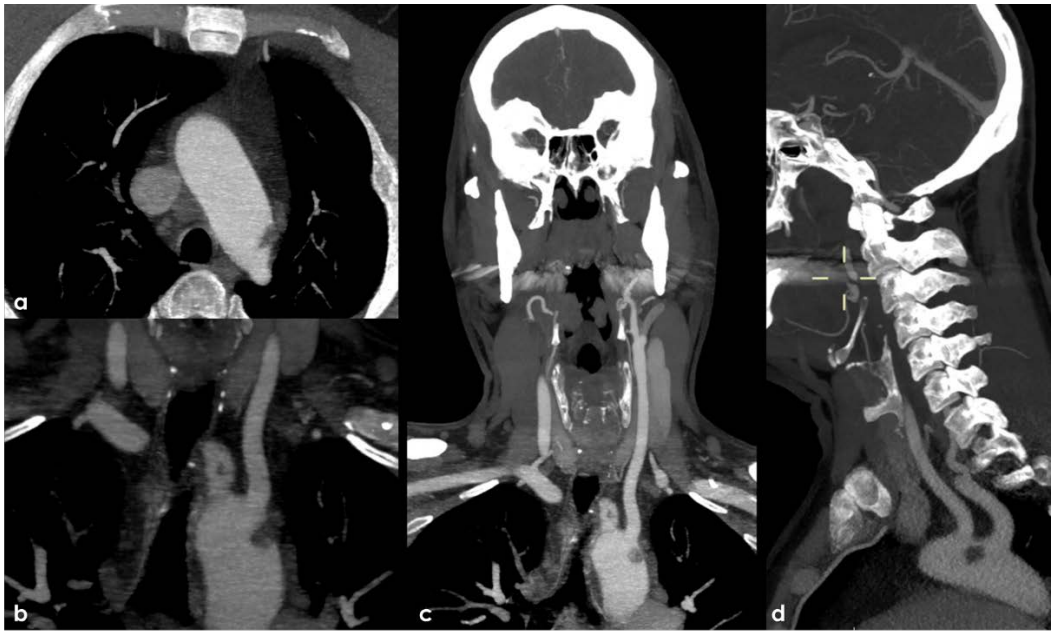

Figure 2. Arch-to-vertex CTA. The main findings are illustrated in the pictures from a to d:

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 10 August 2022 doi:10.20944/preprints202208.0190.v1

a) Axial source slice at the aortic arch level with an irregularly rounded hypodense lesion adherent to the posterior-superior wall of the aorta and partially floating into the lumen
b) Maximum Intensity Projection (MIP) reconstruction on a coronal plane at the level of the hypodensity seen in a and showing the spatial relationship with the left CCA origin (magnificated picture). A similar smaller rounded hypodensity, apparently floating into the BCA lumen is also evident
c) The same MIP coronal plane as in b with a minor magnification, allowing to better appreciate the final potential locations of artery-to-artery embolism from the above signaled thrombotic formations
d) MIP reconstruction in a sagittal plane showing the site of the aortic arch thrombus between left CCA and left SA.

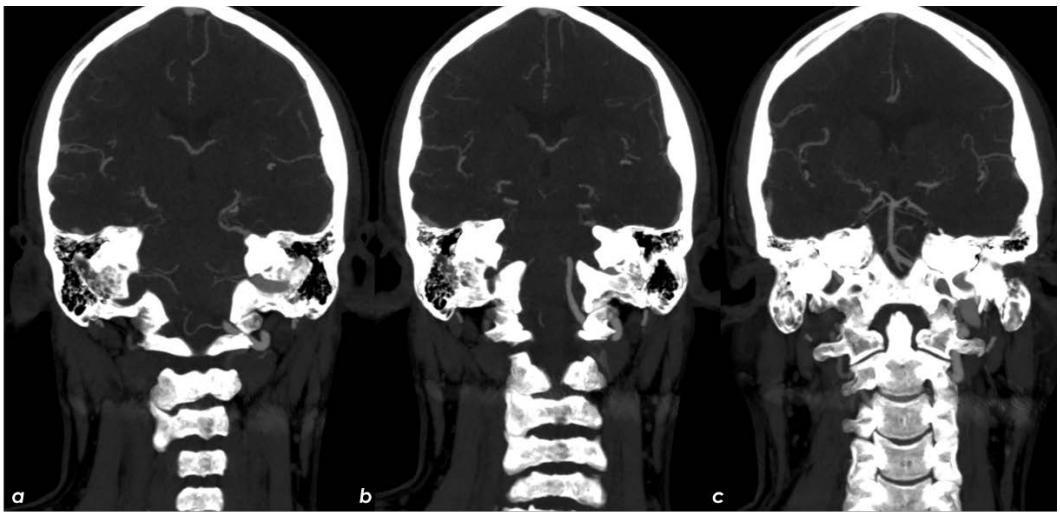

Figure 3. Arch-to-vertex CTA with MIP reconstructions in the coronal plane. The lack of contrast filling of the right distal V3 (a) and V4 (b) VA is evident in comparison to the left VA starting from the dural ring with retrograde filling of the pre-junctional segment (c).

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 10 August 2022 doi:10.20944/preprints202208.0190.v1

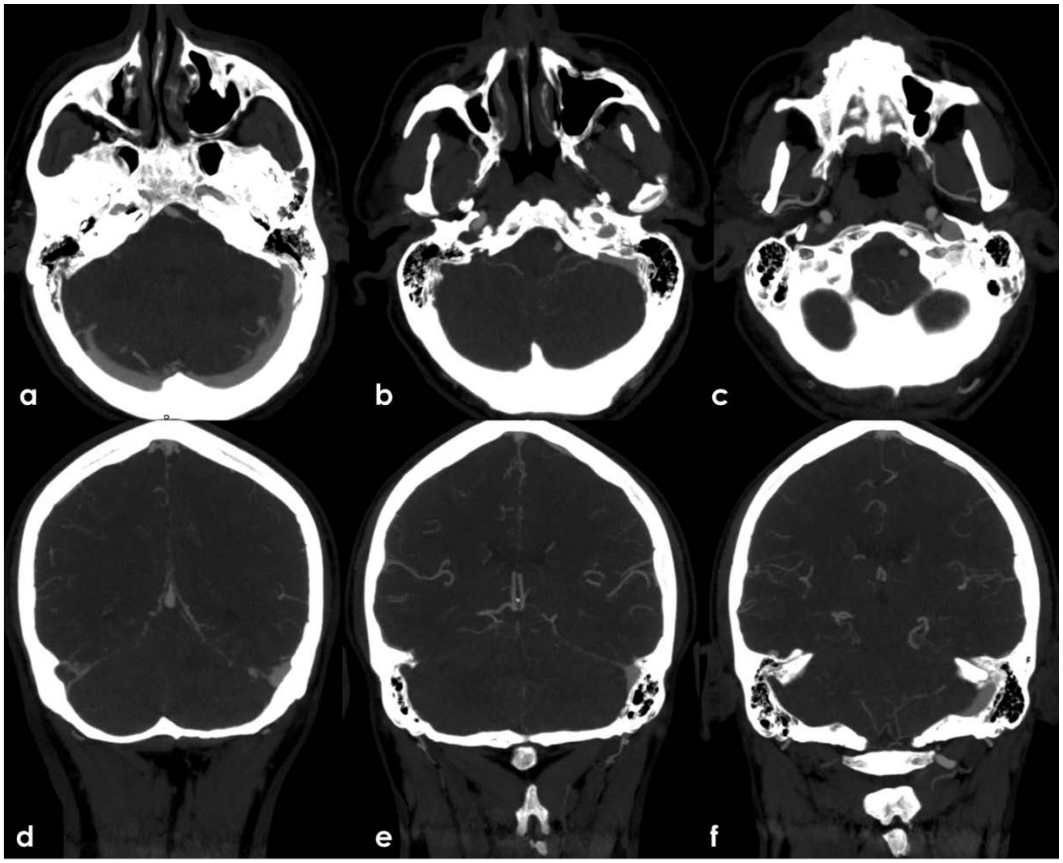

Figure 4. Arch-to-vertex CTA with MIP reconstructions. The lack of contrast filling of the right TS (from its middle segment), SS and IJV in comparison with the regularly contrast filled contralateral segments is showed in axial cranio-caudal slices (a-c) and in coronal posterior-to-anterior slices (d-f).

The patient was evaluated for intravenous or endovascular revascularization but acute treatment was not performed because of the multiple subacute ischemic lesions already evident in the brain CT at admission. Therefore, the patient was admitted to the Stroke Unit for acute stroke care and further investigations and started single antiplatelet treatment and low-molecular weighted heparin at a prophylactic dose. At the admission, the patient shown a stepwise neurological worsening and the final clinical examination at 12 hours from the admission was remarkable for a right facio-brachial hemiplegia, cerebellar dysarthria, dysphagia, inconstant limitation on left lateral gaze without nystagmus and a left cerebellar syndrome. A brain MRI was performed at about 15 hours from the admission, confirming the presence of multiple subacute ischemic areas, located in the left parasagittal vermis and in the medial-superior region of both cerebellar hemispheres, and outlining other subacute infarctions involving the right frontal and parietal lobe (mainly in cortical locations) and the left paramedian medullary region (figure 4). Moreover, MR angiography (MRA) highlighted the lack of visualization of the right V4 VA ant the corresponding PICA, as well as the CVT involving the right TS, SS and IJV. The number and distribution of the subacute ischemic lesions in several vascular territories is coherent with the location of thrombi in large arteries as showed by CTA, i.e. right VA, BCA with potential involvement of the ipsilateral ICA and VA territories, and in the aortic arch near the origin of the left SA.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 10 August 2022 doi:10.20944/preprints202208.0190.v1

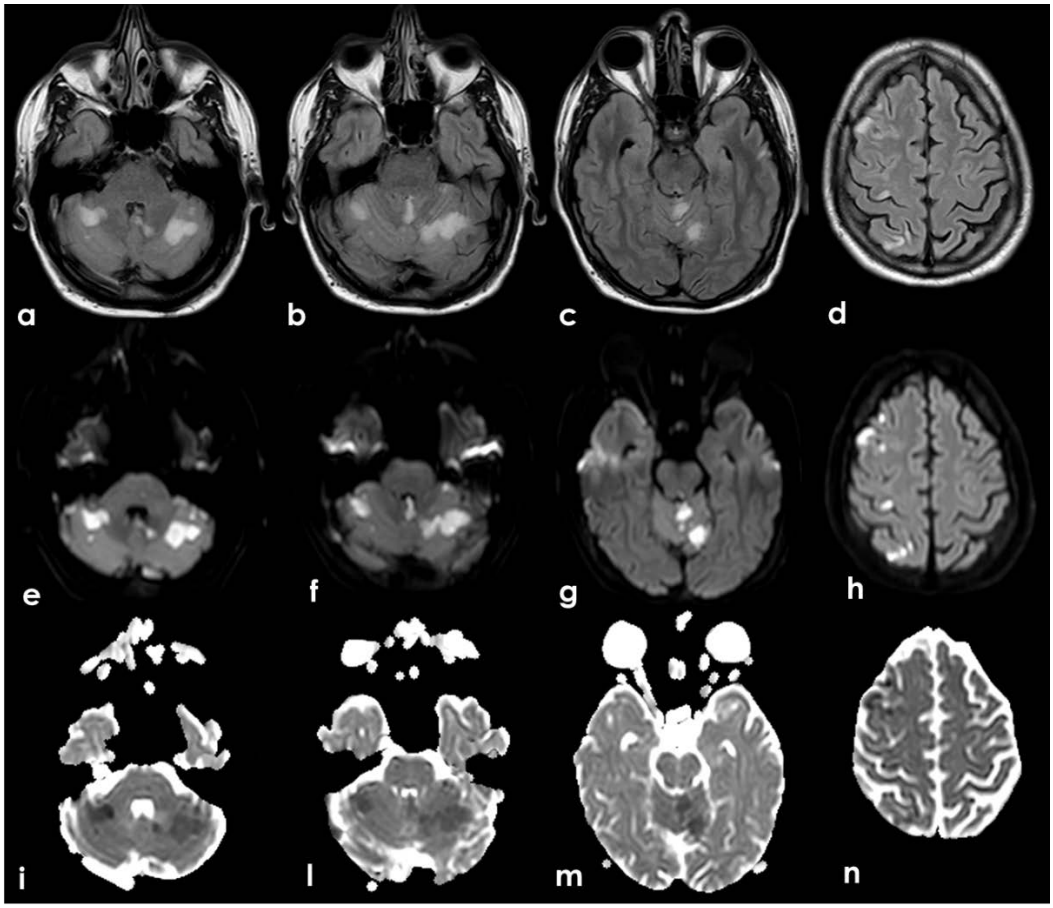

Figure 5. Brain MRI. Axial Fluid Attenuated Inversion recovery sequences (a-d) and the corresponding Diffusion Weighted Imaging (DWI) (e-h) and Apparent Diffusion Coefficient (ADC) images showing multiple recent ischemic lesions in cerebellar hemispheric white matter and vermis and in frontal and parietal right cortex with involvement of the cortical-subcortical junction. All the areas of signal change are hyperintense on FLAIR and DWI sequences and hypointense on ADC and these features are coherent with the ischemic nature and the subacute timing.

Further examinations were performed trying to identify other prothrombotic factors and to clarify the etiology of the clinical picture. The extended laboratory investigations included normal total (360.6) and unsaturated iron-binding Capacity (283.6), transferrin saturation (21.3%), serum ferritin (39 ng/ml), serum iron (77 μg/dl) and transferrin (284 mg/dl). Fecal occult blood test was negative, nocturnal paroxysmal hemoglobinuria, hemolytic anemia were excluded, and the analysis of hemoglobin subgroups resulted within a normal profile. Antibodies anti-double stranded DNA, anti-mitochondrial (AMA), anti-smooth muscle (ASMA), anti-nuclear (ANA), anti-phospholipid, anti-deamidated gliadin peptide and anti-transglutaminase were within the normal range; the main onco-markers (AFP, CEA, CYRA, NSE, PSA) did not express any significant pathological increase. Antithrombin levels were within normal range, search for mutation of Factor V-R506Q was negative; a heterozygote genotype was identified for MTHFR-C677T and an insignificant increase of homocysteine values were found. Transthoracic and Transesophageal echocardiography as well as 24-hours ECG monitoring were unremarkable. Conversely, a thoracic-abdominal CT scan highlighted thromboembolisms involving also the sub-segmental branches of both pulmonary inferior lobes and an 8 mm free thrombus adherent to a crescent-shaped atheroma of aorto-iliac junction and floating within the lumen (figure 6).

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 10 August 2022 doi:10.20944/preprints202208.0190.v1

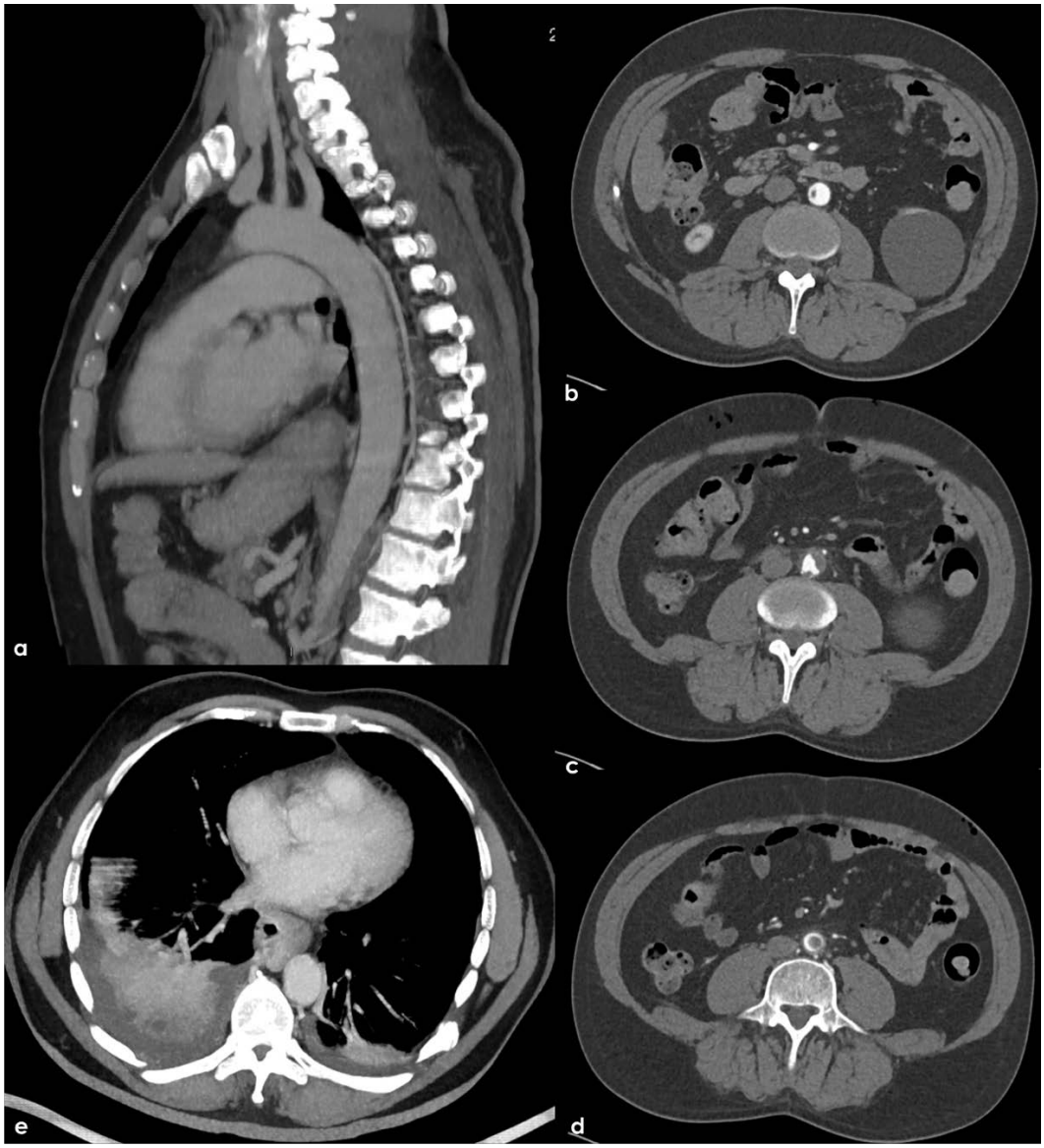

Figure 6. Thorax and Abdomen CTA with Maximum Intensity Projection (MIP) reconstructions. In a, a sagittal plane view of the left half of the aortic arch and descending aorta demonstrated the disappearance of the thrombotic hypodensities previously seen (figure 2) Consecutive axial slices of the pre-terminal segment of the abdominal aorta (fb-d, rom cranial to caudal tip) shown a hypodense structure arising from a crescent-shaped structure in the aortic wall with atheromatous features and partially floating into the aortic lumen. The occlusion of sub-segmental branches of the pulmonary artery on both sides with a lung infarction on the right side is illustrated in e.

At 30 days from the symptoms' onset, the neurological condition remained stable. A follow-up brain MRI highlighted a regular evolution of the ischemic lesions and confirmed the persistent occlusion of the right V4 VA. Moreover, the brain MRI shown as unchanged the white matter hyperintensities in the external capsula and centrum semiovale (Figure 7) together with few subcortical punctate cavitating lesions in the posterior thalamus on both sides and a left temporal hyperintense lesion in the cortical location. All these lesions are quite suggestive of vascular ischemic nature.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 10 August 2022 doi:10.20944/preprints202208.0190.v1

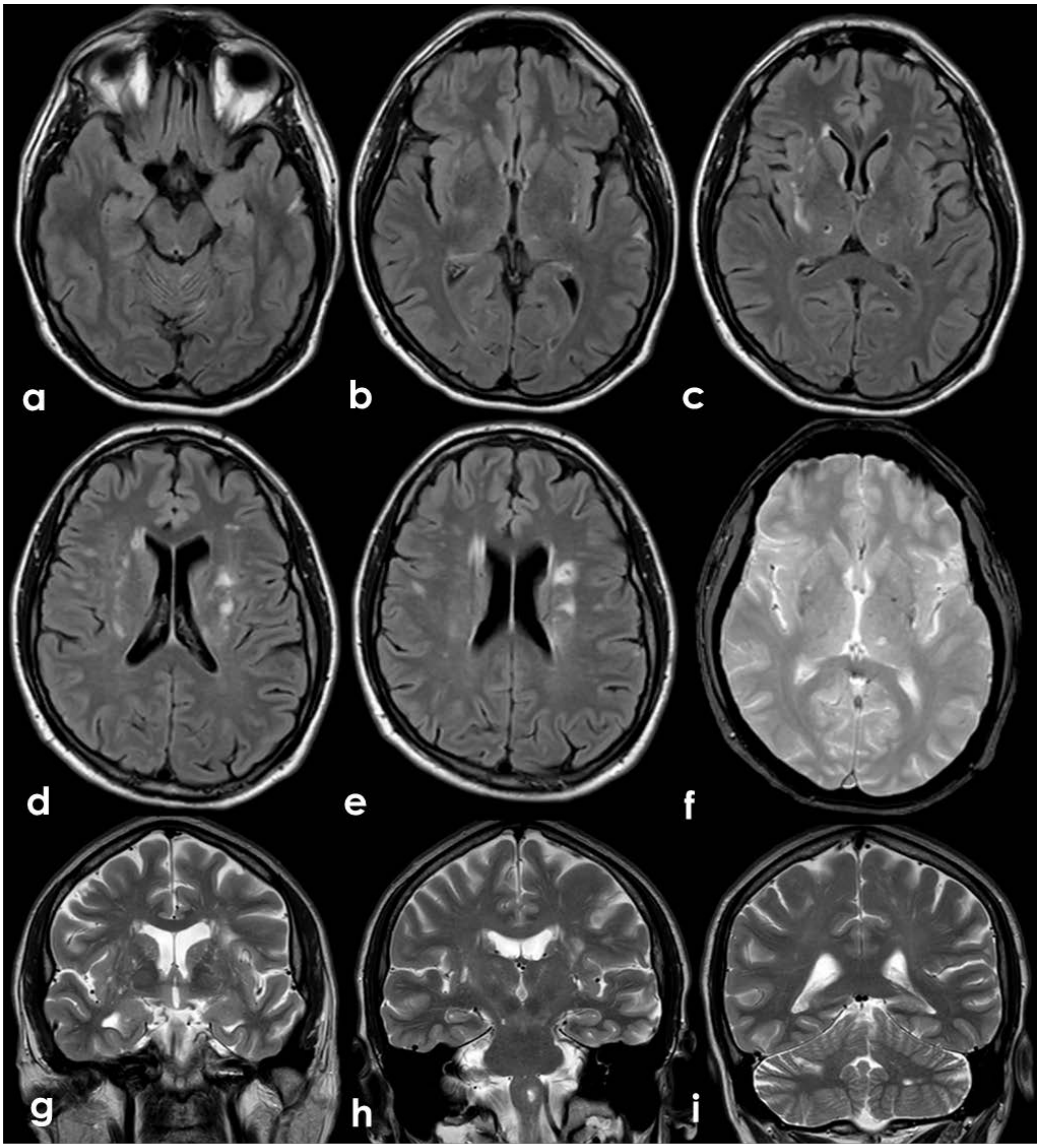

Figure 7. Brain MRI performed after 4 weeks from the admission. Axial FLAIR images (a-e) showing multiple white matter hyperintensities in the deep and subcortical location, (ie. centrum semiovale, external capsula) and few cavitating lesions in the posterior thalamus on both sides (b, c). In a and b also a focal cortical hyperintense lesion in the left temporal lobe is identifies. Gradient Echo (GRE) sequences show a single deep small and rounded hypointense area (microbleed) and T2-weighted sequence images in coronal plane (g-i) show several enlarged perivascular spaces, mainly in basal ganglia on both sides.

Conversely, the right TS, SS and IJV CVT resolved in the follow-up MRA (figure 8), suggesting a recent timing of the intraluminal thrombus, although it was most likely an incidental finding, and the partially floating thrombus in the abdominal aorta also disappeared in the follow-up CTA (figure 8).

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 10 August 2022 doi:10.20944/preprints202208.0190.v1

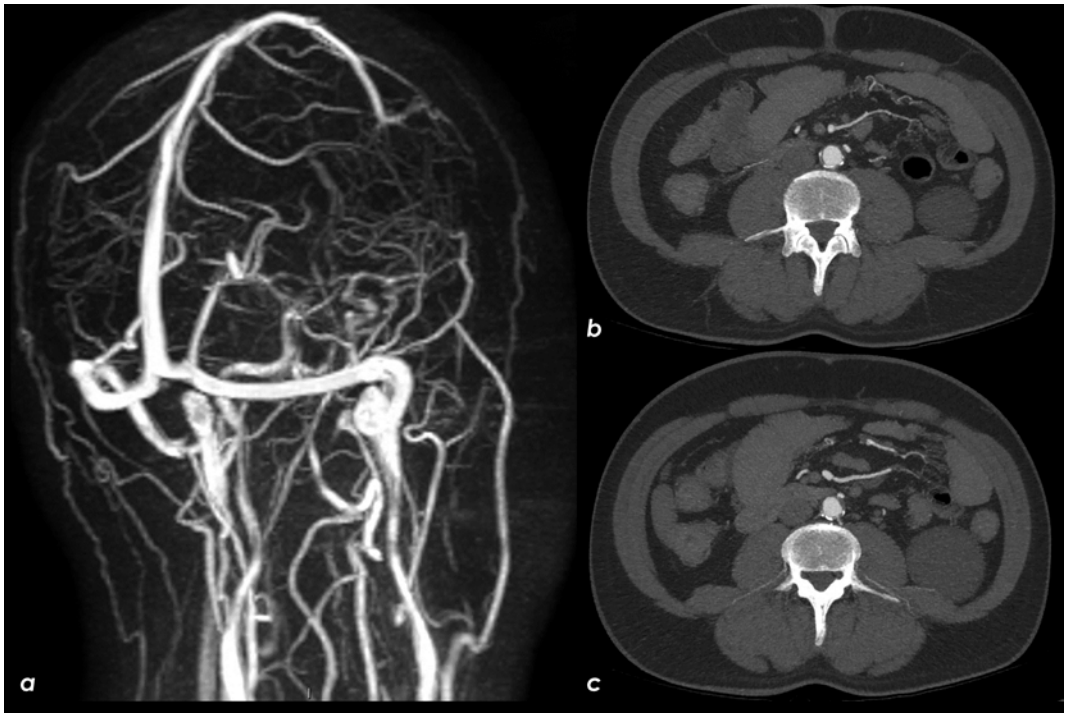

Figure 8. Brain MRI and abdominal CTA in follow-up. The right lateral dural venous system was patent in the MRA (a, time of flight reconstruction). Aortic CTA shown the disappearance of the floating hypodense structure previously seen and adherent to a crescent-shaped atheroma (b and c, axial MIP reconstructions).

Finally, a whole-body G18-FDG PET did not show abnormal metabolic activities except for both basal pulmonary areas and for the gastro-duodenal region. The former one was explained by the pleural effusion secondary to pulmonary embolism, while the latter was explored with endoscopic and histologic studies, that did not reveal abnormalities.
During the hospital staying, the neurological condition was steady. A transfusion with two units of packed red blood cells was performed, followed by iron intravenous infusion and vitamin replacement, obtaining the stabilization of hemoglobin values. An anticoagulant treatment with Low Molecular Weight Heparin (LMWH) was started on the second day and insulin therapy was set up.
Even though a large panel of investigations was performed, we were not able to identify other genetic or acquired prothrombotic factors but IDA, neither a cause of bleeding that could explain the microcytic anemia. In consideration of the multi-district thrombosis, involving also the pulmonary district, after the hospital discharge oral anticoagulation with rivaroxaban 20 mg was started for VTE treatment. 12-months follow-up did not raise any other etiology.

4. Discussion

This clinical case raises several questions both in the diagnostic steps and in the therapeutic choices and has almost unique characteristics, grouping in a single individual simultaneous thrombotic manifestation in several districts. The initial diagnostic approach was focused on the symptoms, which led the patient to the ED, expression of subacute ischemic stroke. In the characterization of this event with advanced neuroimaging techniques, right from the ED access, the complexity of the clinical picture and the simultaneous presence of occluding thrombotic formations at the level of the large arteries supplying the brain and the cerebral venous system became evident. While arterial thrombosis was symptomatic and its acute timing became evident because of the presence of recent cerebral ischemia with multiple lesions, CVT was an incidental and asymptomatic finding and, as such, undated. Only later did the resolution of CVT with anticoagulation support

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 10 August 2022 doi:10.20944/preprints202208.0190.v1

his recent temporality. Already at this point, even with a history of chronic IDA, the causal hypotheses for simultaneous arterial and venous thrombosis were substantially limited to genetic or acquired prothrombotic conditions. The former ones would have had a lower probability in relation the simultaneity of thrombotic findings and the absence of a previous history of thrombotic events, even minor ones. The simultaneous involvement of the venous and arterial district virtually excluded major cardioembolic sources as atrial fibrillation (AF) and a paradoxical embolism mechanism would not be able to take account of the etiology of venous thrombi. The presented patient does not have a defect of the interatrial septum and a two weeks lasting heart monitoring did not identifies atrial fibrillation.

As a general construct, the presence of multiple cerebral ischemic lesions with a main embolic pattern and without an identifiable known etiology leads to the consideration of the embolic stroke of undetermined source (ESUS) [1] concept. From its proposal, mainly as tool to select patients for trials of antithrombotic treatment, it underwent many refinements with recent reappraisal in a more complex and subcategorized form [2]. A recent well-structured criticism of the ESUS concept as proposed until now has been published [3], starting from the too optimistic assumption that the majority of ESUS were thromboembolic and therefore probably treatable with anticoagulants. Another point is that the proposed minimum diagnostic pathway to define a stroke as ESUS is not be able to answer to the multiplicity of etiological phenotypes included into the main neuroimaging pattern of ESUS. Moreover, several concurrent etiologies may be simultaneously present in an individual patient with stroke.

In the diagnostic work-up of cryptogenic embolism, the co-occurrence of venous and arterial thrombi in cerebral circulation was suggestive for two main diagnostic hypotheses, i.e. antiphospholipid antibodies syndrome (APS) and cancer associated stroke (CAS). APS is a disease classically associated to many thrombotic manifestations in arterial and venous districts [4-6], but it has been excluded by the normal findings of the autoimmunity blood tests. Moreover, neuroimaging features of APS-associated stroke are not completely congruent with the presented case. Indeed, an interesting study [7] comparing APS-associated stroke and AF-associated stroke starting from cerebral cryptogenic embolism and in particular multi-territory lesions, shown that the first one has mild neuroimaging features (small lesion prevalence, smaller infarct volume, and absence of relevant artery occlusion).

CAS was a meaningful diagnostic hypothesis and several issues may raise it in the context of the diagnostic work-up of cryptogenic embolism [8]. Indeed, in clinical neurovascular practice the main acquired cause of cerebral and systemic coagulopathy is cancer. Stroke has been reported as the first manifestation of an occult malignancy in up to 3% of patients [9,10]. Approximately, up to 20% % of the patients with cryptogenic stroke have an underlying unknown malignancy [11] and stroke as a complication of known cancer increases the morbidity and mortality. The burden of cerebrovascular diseases in cancer patients is not negligible, because it is the second most common neurological manifestation following metastases [12] with a 6-months incidence of 3.0% vs compared with 1.6% in control patients (HR: 1.9; 95% CI: 1.8 to 2.0) [13]. Among patients with cryptogenic cerebral embolism, CAS with a first diagnosis of previously unknown cancer is about 20% and the main features are higher D-dimer levels (over 20 times higher than those without cancer are) and a stroke pattern on neuroimaging with multiple lesions in multiple vascular territories [14]. These features, proposed again and confirmed in other larger studies, have been proposed as useful clinical clues to select patients to screening for hidden malignancy. The first issue, i.e. the neuroimaging pattern of stroke with multiple acute cerebral infarcts on DWI-MRI, has been proposed as highly specific of CAS [15]. This neuroimaging finding has been so much emphasized as MRI marker of CAS that it produced a dedicated sign, the Three Territory Sign (TTS), proposed as highly specific marker and 6 times more frequently observed in CAS than AF-related ischemic stroke and in patients with TTS is suggested the screening for an underlying malignancy [16].

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 10 August 2022 doi:10.20944/preprints202208.0190.v1

Moreover, a multiple scattered lesion pattern, often reported in CAS, was associated to higher D-dimer values [17-19]. These findings support the link between infarction in multiple vascular territories and cancer-associated hypercoagulation as the underlying stroke mechanism.

Unfortunately, these clues have some limitations. In particular, because stroke itself is frequently associated to an increased D-dimer, its value alone is not sufficient for this purpose. D-dimer is a more general marker of an activated coagulation system and the presence of thrombi and ischemic lesions in the presented case is usually associated to the finding of increased D-dimer values independently from the cause of the thrombosis. Another surrogate marker of the pro-thrombotic role of cancer is the detection of High-Intensity Transient Signals (HITS), also known as microembolic signals, on Transcranial Doppler (TCD) [20], but in the present case, the need of this detection as diagnostic clue is largely overcome by the identification of thrombotic structures in several large vessels. The finding of multiple large thrombi in large vessels, both arteries and veins, in the presented case deserves a dedicated consideration as potential clue for a hidden malignancy, being hypercoagulability the most relevant mechanism of CAS [21] and known in its more catastrophic appearance as Trousseau syndrome. It has been associated to the occurrence of multiple territories ischemic stroke [22]. It has been demonstrated in an interesting study [23] that patients with CAS with embolic pattern have an elevated risk of associated venous thromboembolism (VTE) and arterial thromboembolism with a negative impact on the 1-year's prognosis. In this study, VTE has been considered also as deep vein thrombosis in legs and pulmonary embolism, but other unusual location of venous thrombosis have not been assessed. Moreover, recurrent venous and arterial thromboembolic events are often associated in patients with active cancer, despite anticoagulation [24].

If the diagnostic pathway of the presented case was analyzed according to the advanced diagnostic protocol (figure 9) proposed in cryptogenic embolism [8], the results would be unsatisfactory and a univocal characterization would not be reached (figure 10).

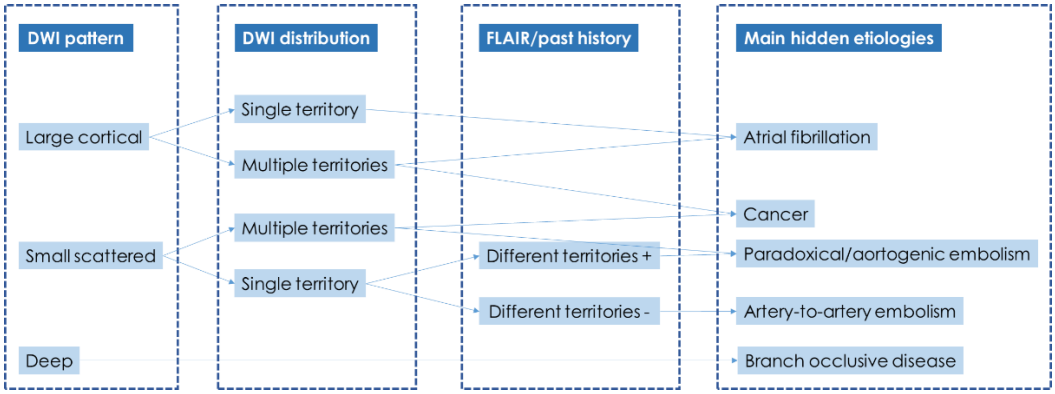

Figure 9. DWI/FLAIR MRI findings as tool for hypothesize the main hidden etiologic categories in cryptogenic embolism (simplified and adapted from Bang OY [16]. The categorization is based on the step-by-step analysis of

- DWI infarct pattern: embolic versus deep and large versus small scattered
- DWI infarct distribution: ≥1 vascular territory involved
- Past stroke on history or fluid-attenuated inversion recovery (FLAIR) image: the same side versus different territory.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 10 August 2022 doi:10.20944/preprints202208.0190.v1

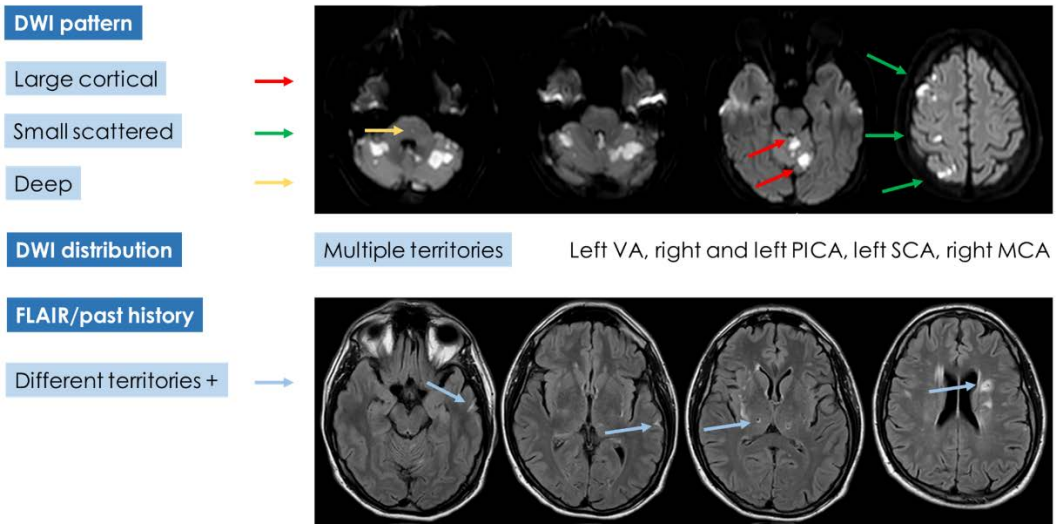

Figure 10. Application of the categorization prosed in the figure 9 to the presented case.

Indeed, the neuroimaging pattern of the patient does not fulfill a single category but it combines features belonging to the three DWI patterns and leaves open the possibility of multiple etiologies, except branch occlusive disease. The multiplicity of lesions (with embolic pattern and in small vessels territory) and the recent and past timing of the findings is hard to lead back to a single category.

The presented case has been extensively investigated looking for a hidden malignancy but all studies were negative on this regard both in the acute phase and in the 12-months follow-up. Other, even rare, recognized causes of stroke and thrombosis have been searched and excluded. At this point IDA was considered with more attention, focusing on the described mechanisms linking IDA and thrombosis and on the literature data.

Anemia is one of the most frequent diseases worldwide and, although the great differences due to age, sex and geographical distribution make difficult to assess the real incidence, it roughly affects a third of the general population [27]. Among all the causes, IDA is considered the most frequent and poor dietary intake, blood loss, reduced iron absorption or chronic diseases [28] can sustain it. Identification of the underlying causes and iron supplementation represent the mainstay of the management. In the last years, several studies raised the association between anemia, especially IDA, and an increased thrombotic risk. Indeed, anemia has emerged as risk factor for cerebrovascular diseases and many evidences demonstrated how the recognition and treatment of underlying anemia might improve the outcome in patients with acute stroke, although its role as an independent risk factor is still controversial [28]. In this regard, few years ago, Maguire and coll. [29] outlined how, in a population of children without previous relevant diseases, IDA was more frequent in patients who developed stroke than in controls. They also acknowledged IDA as a consistent vascular risk factor, given that it affected around half of the children presenting with stroke without other possible etiologic factors. Moreover, they also stated that CVT were even more frequent than ischemic stroke, in children with IDA. In adult patients, the early reports of arterial thrombosis associated with IDA were anecdotal. Yakushiji [30] described two cases of ischemic stroke from embolic sources in female patients with aortic floating thrombi without an atheromatous ground and with IDA as main risk factor. Earlier, Akins and coll. [31] collected three cases of patients with transient focal neurological symptoms or ischemic stroke associated with carotid artery thrombosis. They had in common the absence of any of the classical prothrombotic risk factors and the finding of IDA, also complicated by thrombocytosis. On the other hand, the venous district may also suffer from the consequences produced by anemia. Indeed, in the same way as in children, IDA has been accounted among the risk factors for CVT.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 10 August 2022 doi:10.20944/preprints202208.0190.v1

A recent case-control study [32] confirmed a higher prevalence of CVT in patients with anemia, especially in microcytic forms, and outlined an inverse correlation between the value of hemoglobin and the risk of developing thrombosis in the venous compartment. In particular, the association of IDE with reactive thrombocytosis has been considered as the main responsible of the hypercoagulable state underlying the increased risk of VTE as component of Virchow's triad. In a population-based case-control study in an Asian population [33] the association between IDA and VTE was statistically significant (3.41 vs. 2.06%, respectively, $P < 0.001$) and the odds ratio (OR) of previous IDA for subjects with a VTE was 1.43 [95% confidence interval (CI): 1.10-1.87] compared with the controls. The mechanisms of the association between IDA and increased thrombotic risk, both arterial and venous, however, are not fully clarified and the simultaneous finding of multiple arterial and venous thrombotic events in the same individual has been reported only in an anecdotal way and often evokes etiologies different from anemia in the differential diagnostic pathway. Moreover, the prothrombotic role of IDA therefore appears to be considerably underestimated in neurovascular clinical practice and the diagnostic and therapeutic pathways of these patients have yet to be defined, raising still unanswered questions.

The association between IDA and thrombotic risk is furtherly increased by thrombocytosis. To this regard, the development of an elevated platelets count, probably due to the hyperactivity of erythropoietin in anemic state, has been considered one of the potential thrombotic mechanisms [34]. Indeed, some studies described a higher number of thrombotic events in IDA associated with thrombocytosis than in patients with a normal platelets count [32]. Analyzing other cases of stroke associated with IDA, other hypotheses have been postulated about their connection. First of all, the reduction in hemoglobin levels may produce a decrease in oxygen-concentration in the blood flow and the brain territories could be the most affected by this change [33,34]. Moreover, a possible endothelial dysfunction has been taken into account, considering that it may be the result of a hyperkinetic condition of the blood flow as well as the steady inflammatory state, both produced by persistent anemia [28]. All these factors, together with a possible dysfunction of erythrocyte kinetic abilities, may increase the risk of infarction in watershed territories [28].

A further consideration relating to this and other attempts at phenotyping of cryptogenic embolism, both before and after the introduction of the ESUS concept, is that none of these includes the finding of large thrombi in large vessels as a distinctive element nor the coexistence of arterial and venous thrombosis or the simultaneous presence of cerebral and systemic thrombosis. In some of these classifications, the cerebral and systemic ischemic lesions of which a multiple thrombotic genesis is hypothesized are considered, but the identification of thrombotic formations in the vessels is not among the classifiable items. Interestingly, also the more detailed subtyping proposed by the critics of ESUS concept [27] included as a separate category cancer associated coagulopathy but not specifically anemia as known prothrombotic factor.

To our knowledge, there are no previous case descriptions of simultaneous arterial and venous thrombosis in patients with IDA as isolated prothrombotic factors. However, if the prothrombotic power of anemia has been widely accepted, how and if it may independently be responsible of arterial and/or venous thrombosis has not been completely clarified. Nevertheless, our case confirm how IDA might be considered, de facto, a strong prothrombotic factor and it is able to produce a multi-district systemic thrombosis in a young patient without other relevant medical conditions. Thus, it should be important to point the attention on a treatable disease, as IDA, and its strict association with a life-threatening condition, as cerebral and systemic thrombosis. Moreover, if we consider that vascular events may be related to hardly-modifiable risk factors, anemia falls into the category of treatable conditions ant its correction may affect the outcome of many patients. A key issue might be that, despite or due to its high incidence in general population, anemia could be underdiagnosed. Furthermore, a poor compliance to long-term iron replace-

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 10 August 2022 doi:10.20944/preprints202208.0190.v1

ment could influence the success of the therapy, as happened to our patient. Surely, raising the awareness on the importance of an earlier identification of anemia and its causes might be a critical target, although it was not been demonstrated that treating anemia reduces the risk of thrombotic events.

5. Conclusions

This unique clinical case raised the attention on a common but treatable condition that, independently or synergically, may increase the risk of thrombotic events in all body districts and across all ages. IDA should be considered as a cause of ischemic stroke, mainly if associated with the evidence of thrombotic occlusion of large vessels and with systemic and venous thrombosis.

Author Contributions: Conceptualization, M.Z., F.V. and R.P.; methodology, F.P.; investigation, M.N., C.M. and R.P.; data curation, G.P., F.C.; writing—original draft preparation, G.P., M.Z. and R.P.; writing—review and editing, M.Z. and R.P. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Informed Consent Statement: the patients have given written consent for their personal and clinical details along with any identifying images to be published in this study.

Data Availability Statement: Not applicable

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Hart, R. G. et al. Embolic strokes of undetermined source: the case for a new clinical construct. Lancet Neurol. 2014;13, 429–438. doi: 10.1016/S1474-4422(13)70310-7
2. Diener HC, Easton JD, Hart RG et al, Review and update of the concept of embolic stroke of undetermined source. Nat Rev Neurol. 2022 Aug;18(8):455-465. doi: 10.1038/s41582-022-00663-4
3. Fuentes B, Gutiérrez-Zúñiga R and Díez-Tejedor E (2020) It's Time to Say Goodbye to the ESUS Construct. Front. Neurol. 11:653. doi: 10.3389/fneur.2020.00653
4. Cheng C, Cheng GY, Denas G et al. Arterial thrombosis in antiphospholipid syndrome (APS): Clinical approach and treatment. A systematic review. Blood Rev. 2021 Jul;48:100788. doi: 10.1016/j.blre.2020.100788
5. Radin M, Sciascia S, Erkan D et al. APS ACTION. The adjusted global antiphospholipid syndrome score (aGAPSS) and the risk of recurrent thrombosis: Results from the APS ACTION cohort. Semin Arthritis Rheum. 2019 Dec;49(3):464-468. doi: 10.1016/j.semarthrit.2019.04.009
6. Kearon C, Parpia S, Spencer FA et al. Antiphospholipid antibodies and recurrent thrombosis after a first unprovoked venous thromboembolism. Blood. (2018) 131:2151–60. 10.1182/blood-2017-09-805689
7. Yang W, Kang DW, Kim JM et al. Neuroimaging features of antiphospholipid antibody-related stroke compared with atrial fibrillation-related stroke. Sci Rep. 2022 Jul 8;12(1):11686. doi: 10.1038/s41598-022-16019-3
8. Bang OY, Ovbiagele B, Kim JS. Evaluation of cryptogenic stroke with advanced diagnostic techniques. Stroke. 2014 Apr;45(4):1186-94. doi: 10.1161/STROKEAHA.113.003720
9. Uemura, J., Kimura, K., Sibazaki, K et al. Acute stroke patients have occult malignancy more often than expected. Eur. Neurol. 2010; 64 (3), 140–144. doi: 10.1159/000316764
10. Cocho, D., Gendre, J., Boltes, A. et al. Predictors of occult cancer in acute ischemic stroke patients. J. Stroke Cerebrovasc.Dis. 2015; 24 (6), 1324–1328. doi: 10.1016/j.jstrokecerebrovasdis.2015.02.006
11. Selvik, H.A., Thomassen, L., Logallo, N., Næss, H., 2014. Prior cancer in patients with ischemic stroke: the Bergen NOR-STROKE study. J. Stroke Cerebrovasc. Dis. 23 (5),919–925. doi: 10.1016/j.jstrokecerebrovasdis.2013.07.041
12. Zhang, Y.Y., Chan, D.K.Y., Cordato, D et al. Stroke risk factor, pattern and outcome in patients with cancer. Acta Neurol. Scand. 2006;114 (6), 378–383. doi: 10.1111/j.1600-0404.2006.00709.x
13. Navi BB, Reiner AS, Kamel H et al. Risk of Arterial Thromboembolism in Patients With Cancer. J Am Coll Cardiol. 2017 Aug 22;70(8):926-938. doi: 10.1016/j.jacc.2017.06.047
14. Kim SJ, Park JH, Lee MJ et al. Clues to occult cancer in patients with ischemic stroke. PLoS One. 2012;7:e44959. doi: 10.1371/journal.pone.0044959
15. Schwarzbach, C.J., Fatar, M., Eisele, P. et al. Patterns of acute cerebral infarcts in patients with active malignancy using diffusion-weighted imaging. Cerebrovasc. Dis. 28 (4),411–416. https://doi.org/10.1159/000235629

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 10 August 2022 doi:10.20944/preprints202208.0190.v1

16. Nouh AM, Staff I, Finelli PF. Three Territory Sign: An MRI marker of malignancy-related ischemic stroke (Trousseau syndrome). Neurol Clin Pract. 2019 Apr;9(2):124-128. doi: 10.1212/CPJ.0000000000000603
17. Kim, K., Lee, J.-H. Risk factors and biomarkers of ischemic stroke in Cancer patients. J. Stroke 2014;16 (2), 91-96. doi: 10.5853/jos.2014.16.2.91
18. Kim, S.G., Hong, J.M., Kim, H.Y. et al. Ischemic stroke in cancer patients with and without conventional mechanisms: a multicenter study in Korea. Stroke. 2010;41 (4), 798–801. https://doi.org/10.1161/STROKEAHA.109.571356
19. Shen Y, Li Y, Chen C, Wang W et al. D-dimer and diffusion-weighted imaging pattern as two diagnostic indicators for cancer-related stroke: A case-control study based on the STROBE guidelines. Medicine (Baltimore). 2020 Jan;99(4):e18779. doi: 10.1097/MD.0000000000018779
20. Seok JM, Kim SG, Kim JW et al. Coagulopathy and embolic signal in cancer patients with ischemic stroke. Ann Neurol. 2010;68:213–219. doi: 10.1002/ana.22050
21. Grazioli, S., Paciaroni, M., Agnelli, G. et al. Cancer-associated ischemic stroke: a retrospective multicentre cohort study. Thromb. Res. 2018;165 (March), 33–37. doi: 10.1016/j.thromres.2018.03.011
22. Ling Y, Li Y, Zhang X et al. Clinical features of Trousseau's syndrome with multiple acute ischemic strokes. Neurol Sci. 2022 Apr;43(4):2405-2411. doi: 10.1007/s10072-021-05619-y
23. Ha J, Lee MJ, Kim SJ et al. Prevalence and Impact of Venous and Arterial Thromboembolism in Patients With Embolic Stroke of Undetermined Source With or Without Active Cancer. J Am Heart Assoc. 2019 Nov 5;8(21):e013215. doi: 10.1161/JAHA.119.013215
24. Brenner B, Bikdeli B, Tzoran I et al. Arterial Ischemic Events Are a Major Complication in Cancer Patients with Venous Thromboembolism. Am J Med. 2018 Sep;131(9):1095-1103. doi: 10.1016/j.amjmed.2018.04.037
25. Song AB, Kuter DJ, Al-Samkari H. Characterization of the rate, predictors, and thrombotic complications of thrombocytosis in iron deficiency anemia. Am J Hematol. 2020 Jul 3. doi: 10.1002/ajh.25925
26. Fuentes B, Gutiérrez-Zúñiga R and Díez-Tejedor E (2020) It's Time to Say Goodbye to the ESUS Construct. Front. Neurol. 11:653. doi: 10.3389/fneur.2020.00653
27. Lopez A, Cacoub P, Macdougall IC et al. Lancet. 2016 Feb 27;387(10021):907–16. doi: 10.1016/S0140-6736(15)60865-0
28. Kaiafa G, Savopoulos C, Kanellos I et al. Anemia and stroke: Where do we stand? Acta Neurol Scand. 2017 Jun;135(6):596–602. doi: 10.1111/ane.12657
29. Maguire JL, deVeber G, Parkin PC. Association between iron-deficiency anemia and stroke in young children. Pediatrics. 2007 Nov;120(5):1053–7. doi: 10.1542/peds.2007-0502
30. Yakushiji Y, Terasaki Y, Otsubo R et al. Brain embolism caused by a mobile aortic thrombus with iron deficiency anemia. Cerebrovasc Dis. 2005;20(6):475–8. doi: 10.1159/000089335
31. Akins PT, Glenn S, Nemeth PM et al. Carotid artery thrombus associated with severe iron-deficiency anemia and thrombocytosis. Stroke. 1996 May;27(5):1002–5. doi: 10.1159/000089335
32. Coutinho JM, Zuurbier SM, Gaartman AE et al. Association Between Anemia and Cerebral Venous Thrombosis. Stroke. 2015 Oct 1;46(10):2735–40.6. DOI: 10.1161/STROKEAHA.114.007240
33. Hung SH, Lin HC, Chung SD. Association between venous thromboembolism and iron-deficiency anemia: a population-based study. Blood Coagul Fibrinolysis. 2015 Jun;26(4):368-72. doi: 10.1097/MBC.0000000000000249
34. Chang Y-L, Hung S-H, Ling W et al. Association between ischemic stroke and iron-deficiency anemia: a population-based study. PLoS One. 2013;8(12):e82952. https://doi.org/10.1371/journal.pone.0082952