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Introduction

Cryptogenic stroke in the young is becoming an increasingly important phenomenon. Despite the well-known established risk factors a thorough search for conditions posing a risk of embolic events is of utmost importance in this setting; nonetheless, some cases exist in which, despite an accurate diagnostic workout, no evidence about the presence of predisposing conditions can be found.

Abnormal blood shunting between the pulmonary and systemic circulation (left-to-right shunting, LRS) has been long debated as a condition which can be associated to an increased risk of stroke or TIA. In many centers, systematic search of LRS is performed in patients with cryptogenic stroke according to TOAST criteria. The presence of LRS can be obviously ascertained in elderly stroke/TIA patients as well, but its causative role in such patients should be confronted with the presence of other risk factors - e.g., hypertension, dyslipidemia, diabetes, overweight - the burden of which is probably greater. Existing literature about the association of LRS and TIA/stroke gives controversial information, although a general accord exists about the pathogenetic role of this condition in otherwise healthy people with acute cerebrovascular events. Searching for LRS, on the other part, requires additional examinations with related costs as well a strong suspicion for it to exist, in order to justify the performing of costly and invasive procedures. Besides the problems related to diagnosis, current evidences in terms of best treatment of this condition are inconclusive. The percutaneous closure of a patent foramen ovale (PFO), the most frequent anomaly associated to RLS, is nowadays a procedure commonly performed in many cardiovascular interventional units, but its efficacy has to be compared to best medical therapy (antiaggregation). The problem therefore arises when confronted to the presence of PFO and the decision about which should be the best option.

In this paper we report two cases of acute cerebrovascular events in young people in whom unusual findings, finally found to be consistent with LRS, brought to repair of the anatomic abnormality.

Case histories

Case 1. A 46-year old woman was admitted to the hospital ward following acute presentation of paresthesias and transient weakness of the left arm. Two years earlier she underwent (left) quadrantectomy for breast adenocarcinoma, with regular follow-up since then and no evidence of disease progression. She was treated with triptorelin (GnRH analogue). Her past clinical history was otherwise unremarkable. No history of hypertension, smoke, significant alcohol intake, head or neck trauma, vascular disorder, connective tissue disease, diabetes mellitus or other endocrine disorders was present. Brain CT scan and angio-CT were normal. A brain MRI scan showed a minute T2-hyperintense lesion without diffusivity restriction consistent with a small non recent lacunar infarct in the right hemisphere. Laboratory examinations including blood cell count, platelet count, hepatic and kidney function tests, TSH, homocysteine, blood lipids were within normal range. A transthoracic echocardiogram yielded normal results. Contrast-enhanced transcranial Doppler was performed by injection of a mixture of saline solution:air 9:1 in an antecubital vein in basal conditions and 7 sec after performing Valsalva's maneuver. The appearance of HITS in the right middle cerebral artery was monitored by a 2-MHz ultrasonic probe placed above a suitable bone window in the homolateral temporal aspect of head. In the case HITS were recorded, the entity of the shunt was evaluated arbitrarily based on the number of HITS detected (small, 1-3 HITS; moderate, 3-10 HITS, large, 10+ HITS) according to existing literature. A search for embolic foci in the lower limb veins was negative. CE-TCD evidenced the appearance of a few small microembolic signals suggestive of LRS. A transesophageal echocardiogram, however, failed to confirm LRS demonstrating a normal atrial septum. It was decided, in accordance with the patient, to perform a cardiac catheterization which evidenced the presence of a RLS secondary to a persistent foramen ovale. The patient was then referred to transcatheter closure of PFO by means of Gore 25-mm septal occluder. The procedure was uneventful and allowed the complete closure of PFO. The patient was then treated for 6 months with dual antiplatelet therapy (aspirin plus clopidogrel), after which the drugs were withdrawn. No further events were recorded at follow-up.

Case 2. A 46-year old woman was admitted to the hospital ward following acute presentation of paresthesias and transient weakness of the left arm. Two years earlier she underwent (left) quadrantectomy for breast adenocarcinoma, with regular follow-up since then and no evidence of disease progression. She was treated with triptorelin (GnRH analogue). Her past clinical history was otherwise unremarkable. No history of hypertension, smoke, significant alcohol intake, head or neck trauma, vascular disorder, connective tissue disease, diabetes mellitus or other endocrine disorders was present. Brain CT scan and angio-CT were normal. A brain MRI scan showed a minute T2-hyperintense lesion without diffusivity restriction consistent with a small non recent lacunar infarct in the right hemisphere. Laboratory examinations including blood cell count, platelet count, hepatic and kidney function tests, TSH, homocysteine, blood lipids were within normal range. A transthoracic echocardiogram yielded normal results. Contrast-enhanced transcranial Doppler was performed by injection of a mixture of saline solution:air 9:1 in an antecubital vein in basal conditions and 7 sec after performing Valsalva's maneuver. The appearance of HITS in the right middle cerebral artery was monitored by a 2-MHz ultrasonic probe placed above a suitable bone window in the homolateral temporal aspect of head. In the case HITS were recorded, the entity of the shunt was evaluated arbitrarily based on the number of HITS detected (small, 1-3 HITS; moderate, 3-10 HITS, large, 10+ HITS) according to existing literature. A search for embolic foci in the lower limb veins was negative. CE-TCD evidenced the appearance of a few small microembolic signals suggestive of LRS. A transesophageal echocardiogram, however, failed to confirm LRS demonstrating a normal atrial septum. It was decided, in accordance with the patient, to perform a cardiac catheterization which evidenced the presence of a RLS secondary to a persistent foramen ovale. The patient was then referred to transcatheter closure of PFO by means of Gore 25-mm septal occluder. The procedure was uneventful and allowed the complete closure of PFO. The patient was then treated for 6 months with dual antiplatelet therapy (aspirin plus clopidogrel), after which the drugs were withdrawn. No further events were recorded at follow-up.

Discussion and Conclusions

PFO is a relatively common finding in general population and often remains asymptomatic for the entire life span; however, its observation in people with acute cerebrovascular events and no evidence of other risk factors raises the question of a possible pathogenetic role.

Several studies have investigated the effects of PFO closure compared to medical therapy in patients with cryptogenic stroke or TIA, and the overall results, although inconclusive as concerns the comparative efficacy, seem to indicate that PFO closure allows, in effect, to remove a potential embolic source. More debatable is the case in which, despite evidence of LRS in patients with cryptogenic stroke or TIA, the source of the shunt cannot be easily found with conventional tests. The question arises whether a further search can be rewarding given the uncertainty about the need to close a PFO in terms of secondary prevention. The reasons at the basis of a "cryptogenic" LRS are different. The most common setting is related to anatomic variants (most commonly, persistence of valve of Eustachius) which are an obstacle for microbubbles to be directed towards the atrial septum and make the passage of the same inconsistent when coming from the superior vena cava.

Several studies have investigated the pathogenetic role of PFO in cryptogenic stroke, its definition being quite unclear. It is reasonable to reserve such definition to acute cerebrovascular events occurring in people who do not present the common (diabetes, hypertension, obesity, smoke) or other uncommon but well-established (connective tissue disorders, coagulopathies, cancer, hormonal therapy) vascular risk factors. Age is to be taken into account since it represents per se a risk factor. Epidemiological surveys indicate that 95 percent of strokes occur after age 45. A trend towards a greater incidence of stroke in people aged below 45 has been observed in some studies, and the hypothesis has been raised that such an increase can be related to the higher burden of risk factors such as obesity or drug abuse. Stroke in otherwise healthy people should be considered as exceedingly uncommon, so that the precise weight of condition which pose a risk in such instance should be properly considered.

Based on literature and also by the experience from our center, the finding of positive CE-TCD is highly predictive of RLS and implies the need for a thorough search even when conventional studies, i.e., TEE, fail to demonstrate the presence of a PFO. It should be taken into account that, besides PFO, other conditions can be responsible for RLS, the most common of which is pulmonary AVM. Irrespective of the source of RLS, it has to be evaluated, as said before, the relative benefit of reparative treatment compared to medical therapy. An "argument" which could support the endovascular treatment is that, in a young patient and provided other risk factors have been ruled out, it is possible to spare for-life pharmacological antiaggregation. Since few data exist about the long-term efficacy of procedural approach it will be necessary to proceed to extended follow-up in order to collect such kind of information.

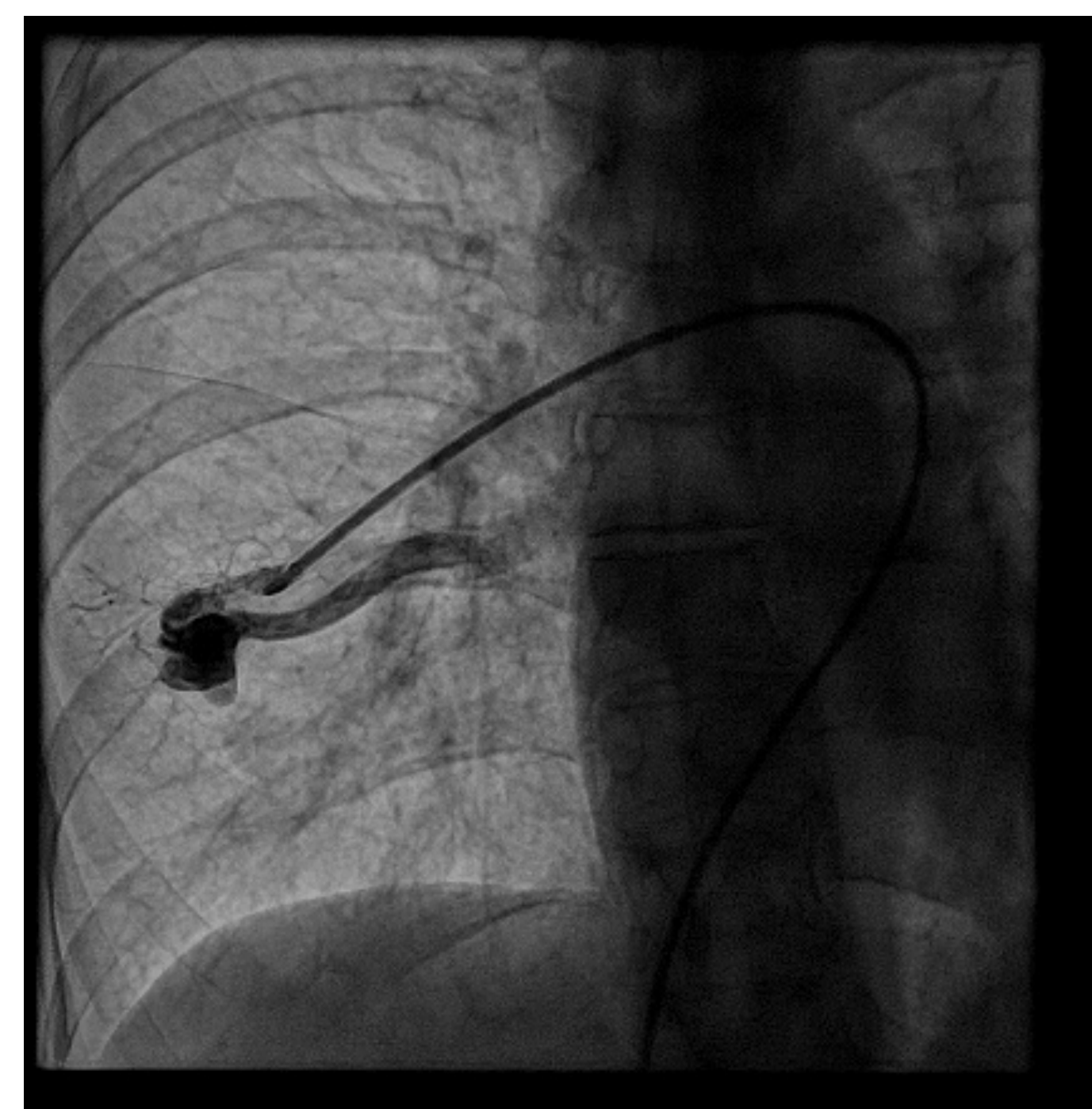


Figure 1. Right pulmonary artery catheterism showing AVM (Case 2).

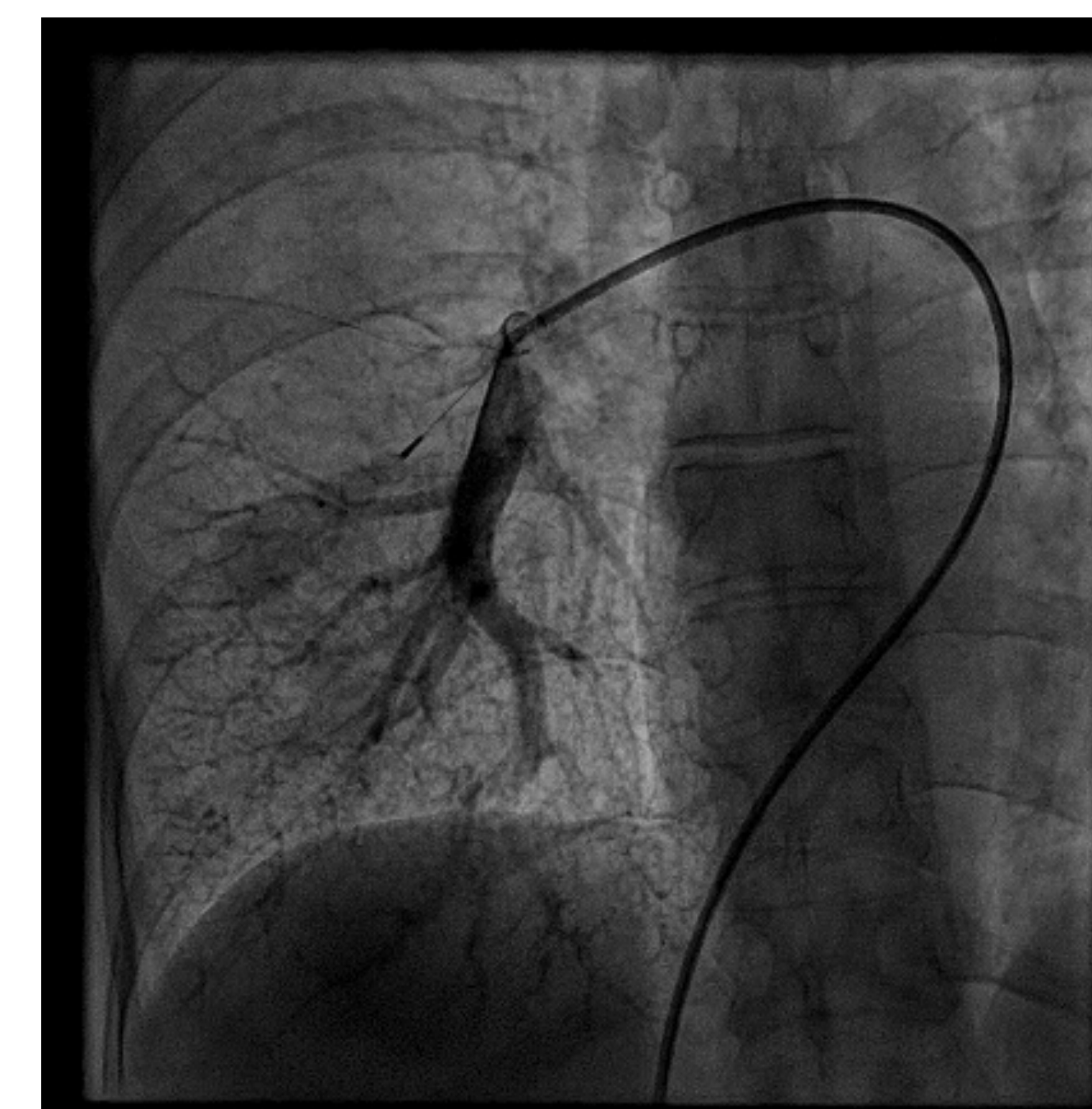


Figure 2. Pulmonary AVM (see Fig 1) excluded after transcatheter occlusion

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