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Medical Hypothesis

Patent foramen ovale as a preferential mechanism for increasing the likelihood of brain tumor metastasis

Gianluca Rigatelli[1], Andrea Rossi[2], Fabio Dell'Avvocata[1], Paolo Cardaioli[1]

[1]Adult Congenital Heart Disease Management Program, Cardiovascular Diagnosis and Endoluminal Interventions Unit, Rovigo General Hospital, Rovigo, Italy; [2]Department of Cardiology, Verona University School of Medicine and Surgery, Verona, Italy

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Abstract: Metastases are the most common tumors of the central nervous system which may lie dormant behind the brain blood- barrier sheltering from chemiotherapeutic drugs, and whose presence usually indicates a poor prognosis. Development of brain metastases includes the intravasation of the cancer cells through the tumor blood vessels, their circulation within the venous system, passing through the pulmonary filter thus reaching the systemic circulation. Patent foramen ovale (PFO) is a natural communication between the right and left atrium with a prevalence of about 25% in the general population. It may predispose to a right-to-left shunt by-passing the pulmonary filter. Recent literature suggests that the presence of a permanent shunt, large shunt, atrial septal aneurysm and/or venous valve remnants, all increase the risk of paradoxical embolism in PFO patients. The hypothesis that cancer cells may reach the brain circulation through a significant PFO, might open up new fields in brain metastases pathophysiology and prevention.

Keywords: Paradoxical embolism, cancer, metastasis, patent foramen ovale

Introduction

Metastases are the most common tumors of the central nervous system [1] and their frequency appears to increase in time, although the exact incidence in still unknown because diagnosis is lacking in neurologically asymptomatic cancer patients. Lung cancer accounts for 48% of all brain metastases, breast cancer for 15% and melanoma and colon cancer for 5-9%, whereas other less common sites such as ovarian, bladder, prostate, esophageal and sarcomas in generalaccount for 0.5-3.3% [2]. Few studies have addressed the incidence of clinically significant brain metastases: the Mastricht Cancer Registry observed an 8.5%, incidence [3] over a 5-year period which is substantially lower than around 9% found at autopsy [4].

Brain metastases may lie dormant behind the blood-brain barrier, protected from chemiotherapeutic drugs, suggesting that the brain may increasingly become the first and only site of relapse. About 25% of patients who die from cancer have central nervous system metastases at autopsy, 15% of which are in the brain. The median survival for patients who develop brain metastases is measured in months [5].

Patent foramen ovale (PFO) is a common finding in the general population with a prevalence of about 25% [6]. It is mostly a benign condition and its incidental finding in asymptomatic patients requires no specific therapy. On the other hand, PFO is the main cause of right-to left cardiac shunts followed by pulmonary arteriovenous fistulas, and is potentially a risk factor for paradoxical embolism. Classical clinical presentations of patent foramen ovale include cryptogenic stroke, decompression syndrome, orthodeoxia-platypnea syndrome and peripheral embolism [7-8] as well as more controversially, migraine with aura in a small proportion of patients [9]. Recently and with increasing frequency, paradoxically septic embolism through a PFO has been correlated with brain abscesses

and transcatheter PFO closure has been suggested as prevention for recurrent brain abscesses [10-11].

Hypothesis

Pathogenesis of brain metastases is a multistage process which implies that in order to become a metastasis, cancer cells that are genetically suitable for metastasis must undergo a complex series of steps. Each step is fraught with hazards for the cancer cell, so that is not surprising that probably only 0.01% of cancer cells that reach the bloodstream ever become a metastasis [12]. Only a few molecular mechanisms which mediate each step have been completely defined. For normal cells in the primary organ to metastasize, they must undergo genetic transformation of the cancer cell, uncontrolled proliferation of the tumor, angiogenesis which occurs when the tumor grows beyond 1-2 mm, and finally the invasion of the tumor into the host tissue. Then the transportation process takes place, with intravasation of the cancer cells through the tumor blood vessels which have a less complete wall than normal vessels, thus allowing cancer cells to enter the vessel lumen more easily. The cancer cells reach the venous circulation through either capillaries or lymph channels. The tumor cell may gain access to the right side of the heart via the venous circulation and commonly leaves the heart via the pulmonary artery to reach the lung capillary bed where it may form a metastasis or pass through the capillary bed and reach the left atrium and enter the systemic circulation to seed the brain, usually at the grey-white matter junction [13]. In an attempt to explain why some tumors such as breast cancer, melanoma and lung cancer frequently metastasize the brain and others do not, it has been suggested that genetic changes in some types of cancer cells allow them to find the biochemical environment of the brain particularly favorable. Finally, the cancer cells must cross into the brain parenchyma to form metastases, since the blood-brain barrier is no hindrance to tumor cell extravasation.

Recently literature has stressed the role of circulating tumor cells (CTCs), which are cells of still unknown composition that can be identified in transit within the blood stream. Although rare (one per billion normal blood cells in the circulation of patients with advanced cancer) they are thought to be viable metastatic precursors capable of initiating a clonal metastatic lesion [14].

PFO is a natural communication between the right and left atrium: right-to-left shunt allows embolization through a PFO. This is a well-known phenomenon in the presence of pulmonary artery hypertension or other diseases which causes right cardiac chamber failure or stiffness or raised right atrial pressure (right ventricle myocardial infarction, for example) [15], but can also occur in the absence of such conditions, i.e. when a net pressure gradient favouring right-to-left shunt does not exist, as shown by resonance magnetic blood flow and echocardiography studies [16]. It is evident that there is a certain disproportion between the high incidence of PFO in the general population and the low risk of paradoxical embolism as shown in older studies [17-18].

The exact risk of cerebral ischemic events due to paradoxical embolism is still matter of debate and is still little understood because of methodological inconsistencies in designing past studies. Old studies enrolled patients regardless of shunt severity induced with Valsalva manouvre, the presence of a permanent shunt (shunt during normal breath), concurrent large atrial septal aneurysm or the presence of Eustachian valve or Chiari network, and in all cases they were designed for a follow-up period < 5 years. Recent literature suggests that the presence of a permanent shunt, a large Valsalva induced shunt, a large atrial septal aneurysm and venous valves remnants all increase the risk of paradoxical shunt and should be taken into account when designing trials to study the incidence of paradoxical embolism, and the efficacy of medical or interventional therapies [19-20]. It is conceivable that the same criteria would apply to paradoxical cancer cell embolism; patients with such high risk interatrial septum and right atrium anatomical and functional features would probably be at an increased risk of CTC embolism and thus potentially at an increased risk of developing brain metastases compared to patients with no or insignificant PFO.

Historically, tumor embolus passage through a PFO had already been suggested as a cause of stroke in cancer patients, when a solid tumor directly invades a large vein. Similarly, but with different effects, CTC paradoxical embolism might be a potential mechanism of brain metas-

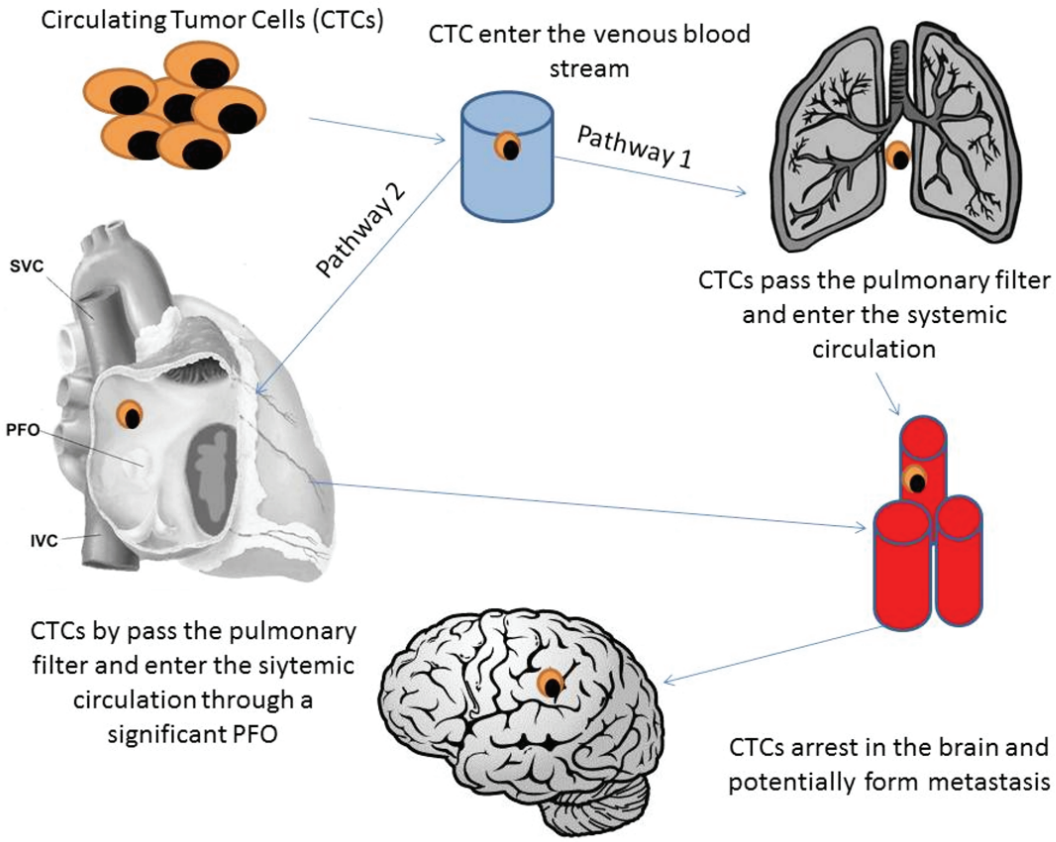

Figure 1. Schematic illustration of the proposed hypothesis: The circulating tumor cells (CTCs) may reach the brain circulation along two concurrent pathways. Pathway 1 includes the possibility for CTCs to pass the pulmonary filter and reach the systemic circulation through the pulmonary capillaries. CTCs may reach the systemic circulation by-passing the pulmonary filter thanks to the right-to-left shunt in significant PFO (Pathway 2).

tasis spreading in patients otherwise at high risk of paradoxical embolism. The paradoxical embolism of infective agents has been already suggested in the pathophysiology of brain abscesses, thus, it is conceivable that a small amount of CTCs may recurrently embolize from the venous site to the systemic site of circulation, by-passing the pulmonary filter through a significant PFO, thus increasing the probability of brain metastases (**Figure 1**).

Proposal of investigation

The proposed hypothesis would not be simple to test because of the different propension of different tumors to give rise to brain metastases and the association of multiple factors needed to make a PFO at a high risk of paradoxical embolism. Moreover, an important ethical issue may be raised as regards the need for new instrumental investigations in patients with a poor prognosis who are probably at the end of their lives: non-invasive and as far as possible soft diagnostic tools should be considered, such as transthoracic echocardiography and Transcranial Doppler ultrasound rather than transesophageal, and magnetic resonance imaging. Hypothetically, a preliminary study should involve patients affected by those solid cancers with certain brain metastases i.e. lung, colon, melanoma, ovarian, bladder, prostate, and esophageal cancers. Patients should be screened for asymptomatic silent brain metastases with magnetic resonance imaging. Moreover all patients should undergo transcranial Doppler to detect any right-to-left shunt: any potential shunt should be graded as small, moderate and severe under Valsalva manouvre or permanent

shunt according to existing literature. In the case of large or permanent shunts, patients should undergo transthoracic echocardiography with a bubble test in order to diagnose the site of right-to-left shunt (pulmonary or interatrial septal), to evaluate the presence of atrial septal aneurysm (ASA), and Eustachian valve or Chiari network (EV/CN). Correlations between the incidence of brain metastases and a high risk PFO profile might suggest that significant PFO may pose an increased risk of brain metastases. In such cases, a study to assess the incidence of high risk profile PFO and potential development of brain metastases in cancer patients with no diagnosed brain metastasis could be designed with at least 5 years follow-up. All these requirements and drawbacks obviously make this kind of study difficult to be performed at least in the short time.

Conclusion

The proposed hypothesis would open up a new field in brain metastasis pathophysiology and treatment: prophylactic closure of significant PFO in some cancer patients to prevent brain metastases might offer a chance to improve survival rates in patients with early stage solid tumors. Intriguingly, although it is as at least as difficult to assess as the real risk of stroke in patients with PFO, this hypothesis would be more preferable to test for, because of the different clinical setting. Prevention of brain metastasis in cancer patients is undoubtedly more appealing, due to the severity of the underlying disease, than prevention of stroke in otherwise healthy people. Moreover, a real confirmation of this hypothesis would be also indirectly give an answer to the much debated field of stroke prevention in PFO patients.

Address correspondence to: Dr. Gianluca Rigatelli, Adult Congenital Heart Disease Interventions, Cardiovascular Diagnosis and Endoluminal Interventions, Rovigo General Hospital, Viale Tre Martiri, 45100, Rovigo, Italy Fax: +390425394513; E-mail: jackyheart71@yahoo.it

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