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Authors

Levin-Epstein, R
Kumar, P
Rusheen, J
et al.

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RESEARCH ARTICLE

Investigation of patent foramen ovale as a mechanism for brain metastasis in patients without prior lung involvement

R. Levin-Epstein[1] · P. Kumar[2] · J. Rusheen[3] · R. G. Fleming[2] · Z. McWatters[4] · W. Kim[5] · T. B. Kaprealian[1] · B. West[6] · J. M. Tobis[2]

Abstract

Purpose The mechanisms of brain metastasis are incompletely understood. Circulating tumor cells travel to the right heart and through the pulmonary circulation, where they may become lung metastases, and can circulate further to the left heart and brain. In patients who develop brain metastases without lung involvement, we hypothesized that cancer cells may travel directly from the right atrium to left atrium via a patent foramen ovale (PFO), akin to paradoxical embolism. If the prevalence of PFO is greater in these individuals compared to the general population (20–30%), PFO may play a role in brain metastasis, and prophylactic closure may provide benefit. Accordingly, we investigated the prevalence of PFO in patients with brain metastases without prior lung involvement.

Methods We prospectively identified patients with brain metastases from a non-lung primary cancer with no preceding or concurrent lung involvement. Nine eligible participants underwent a transcranial Doppler study with intravenous agitated saline to assess for PFO.

Results Among nine participants, primary cancers were breast ($n = 6$), upper gastrointestinal ($n = 2$), and thyroid ($n = 1$). A positive bubble study was identified in 2/9 (22.2%) participants: one female with breast cancer and one male with duodenal adenocarcinoma. No participants developed lung metastases on subsequent chest imaging.

Conclusion In this prospective pilot study, we found a similar prevalence of PFO in patients who developed brain metastases without preceding lung involvement compared to estimates for the general population. Through a larger study is needed, the development of brain metastases in these individuals may primarily reflect tumor-specific biological factors diecting metastasis organotropism.

Keywords Brain metastasis · Brain metastases · Patent foramen ovale · PFO · Metastatic cancer · Organotropism

✉ R. Levin-Epstein
RLevinepstein@mednet.ucla.edu

1 Department of Radiation Oncology, University of California, Los Angeles, 200 UCLA Medical Plaza, Suite B265, Los Angeles, CA 90095, USA

2 Department of Medicine/Interventional Cardiology, University of California, Los Angeles, Los Angeles, CA, USA

3 David Geffen School of Medicine at the University of California, Los Angeles, Los Angeles, CA, USA

4 Sidney Kimmel Medical College at the Thomas Jefferson University, Philadelphia, PA, USA

5 Department of Neurosurgery, University of California, Los Angeles, Los Angeles, CA, USA

6 Department of Cardiology, University of California, San Diego, San Diego, CA, USA

Introduction

Brain metastases affect approximately 8–28% of patients with cancer and are associated with substantial morbidity and mortality [1–4]. Individuals with brain metastases have a median survival of only 7 months after diagnosis, though survival rates vary with patient factors [5]. While systemic extracranial disease is a common cause of mortality, death from neurologic complications of brain metastases occurs in 14–52% of affected individuals [6–8].

The most common primary tumors that metastasize to the brain are lung (41–56% of brain metastases), breast (13–30% of brain metastases), melanoma (6–11% of brain metastases), renal cell carcinoma (3–6% of brain metastases), and colorectal cancer (3–8% of brain metastases) [9, 10]. Among

all cancers, lung cancer has the highest frequency of brain metastasis (20–28%) [2, 4, 9, 10].

Hematogenous dissemination is the primary route of metastatic spread to the brain [11]. Much of the exploration regarding mechanisms of metastatic spread, including penetration of the blood–brain barrier and proliferation in the brain, have focused on "seed and soil" factors, reflecting tumor molecular factors and the ability to modify the surrounding microenvironment [11].

Circulatory patterns of blood flow also play a large role in metastatic patterns, including hematogenous spread to the brain [12]. Venous blood draining systemic tumors returns to the right heart, which subsequently pumps it into the pulmonary circulation, where cells may be filtered by the pulmonary capillaries and potentially manifest as lung metastases. From the lungs, blood returns to the left heart and into the systemic arterial circulation, including the arterial circulation to the brain [12]. Given the greatest proclivity for primary lung cancers to metastasize to the brain [2, 9, 10], a plausible advantage promoting brain metastasis is the established pulmonary tumor population, which can be drained by the pulmonary veins to the left heart and into the arterial cerebral circulation. Concordantly, the presence of lung metastases has been associated with an increased risk of subsequent brain metastasis [13, 14].

In patients who develop brain metastases in the absence of prior lung involvement, it is unknown whether these metastatic cancer cells take an alternate route, bypassing the lungs, to gain entry to the cerebral circulation. Though this pathway has been minimally explored in oncology [15], it is well described in the cardiovascular literature as a mechanism for cryptogenic stroke [16–18]. A patent foramen ovale (PFO) is a communication between the right and left atria of the heart (Fig. 1), which persists after birth in approximately 20–30% of the general population and is frequently asymptomatic [19–21]. PFO has been implicated as a cause of cryptogenic stroke, and PFO closure reduces the risk of subsequent stroke [22–24].

If PFO acts as a conduit for metastatic spread to the brain, prophylactic PFO closure could potentially prevent significant morbidity and mortality in patients with advanced cancer. We conducted a prospective single-center pilot study to evaluate whether the presence of PFO is associated with the development of brain metastases in patients with metastatic cancer from a non-lung primary malignancy and no preceding lung involvement.

Patients and methods

We prospectively identified patients with brain metastases seen in a single-center radiation oncology department from March 2018 to January 2020. Eligible patients had a solid
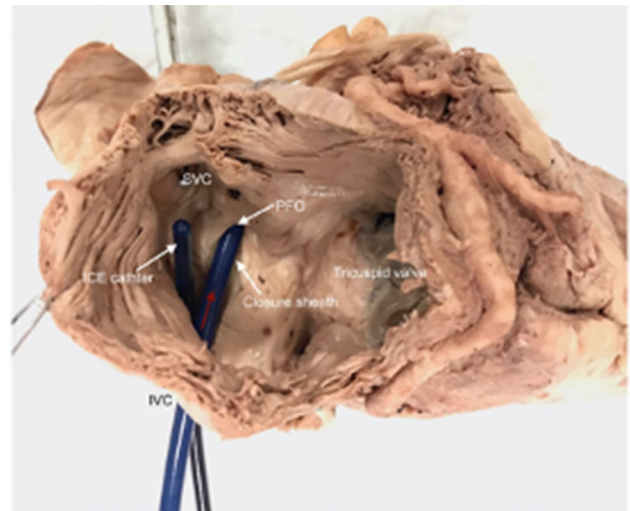

Fig. 1 View into the right atrium showing a closure device traversing a patent foramen ovale (PFO). *ICE* intracardiac echocardiography; *SVC* superior vena cava; *PFO* patent foramen ovale; *IVC* inferior vena cava

non-lung primary malignancy and no prior or concurrent metastatic spread to the lungs at the time of first brain metastasis diagnosis. Exclusion criteria consisted of leptomeningeal disease at time of brain metastasis diagnosis, hematologic (non-solid) primary malignancy, insufficient prior chest imaging to evaluate for lung metastases, or the presence of indeterminate pulmonary nodules. To reduce the risk of including patients with subclinical lung metastases at the time of brain metastasis diagnosis, patients were screened for the development of lung metastases on their next chest computed tomography (CT) subsequent to the diagnosis of brain metastases.

Participants were assessed for a PFO with a transcranial Doppler (TCD) (Terumo Medical Corporation, Tokyo, Japan) study [25]. The study consisted of two phases: the first phase involved the patient performing a Valsalva maneuver and the second phase, which was only done if the first phase was positive, was done with the patient at rest. The Valsalva maneuver was performed with the patient blowing air into a tube, which was connected to a manometer, to generate and maintain a pressure of 40 mm Hg for ≥ 10 s. An agitated saline mixture, consisting of 8.5 mL of normal saline, 1 mL of blood, and 0.5 mL of air, was administered intravenously into an antecubital vein, and the number of bubbles seen in the bilateral middle cerebral arteries over one minute was recorded. The Spencer Logarithmic Scale criteria were used to detect and grade the results: no bubbles (grade 0), 1–10 bubbles (grade 1), 11–30 bubbles (grade 2), 31–100 bubbles (grade 3), 101–300 bubbles (grade 4), and ≥ 300 bubbles (grade 5) [26]. Based on prior cardiac catheterization studies, a Spencer grade ≥ 3 indicates a

positive study, consistent with a PFO [26]. A positive TCD study is the most sensitive noninvasive method to detect a PFO. Although a TCD does not directly visualize the PFO, it demonstrates the presence of a right-to-left shunt. A pulmonary arteriovenous fistula can also produce a positive TCD study, but this only accounts for 1% of cases; the remaining 99% are due to a PFO [25].

This prospective study was approved by our Institutional Review Board. Informed consent was obtained from all participants. All work was conducted in accordance with the Declaration of Helsinki for experiments involving human subjects.

Table 2 Transcranial Doppler (TCD) results

Patient	Primary histology	TCD grade at Valsalva	TCD result
1	Breast	3	Positive
2	Breast	0	Negative
3	Breast	0	Negative
4	Breast	0	Negative
5	Breast	0	Negative
6	Breast	0	Negative
7	Duodenal adenocarcinoma	3	Positive
8	Esophageal adenocarcinoma	0	Negative
9	Papillary thyroid cancer	0	Negative

Results

Seventeen patients who met eligibility criteria were accrued to the study. Eight patients discontinued participation prior to undergoing TCD due to symptomatic disease progression, decline in overall health status, or logistical barriers. Ultimately, nine eligible participants underwent PFO assessment.

Patient characteristics for the participants who underwent TCD are displayed in Table 1. Among the nine participants, primary cancers were breast cancer (six participants), esophageal adenocarcinoma (one participant), duodenal adenocarcinoma (one participant), and papillary thyroid carcinoma (one participant). In the eight participants who never completed PFO assessment, primary cancers were renal cell carcinoma (one patient), esophageal adenocarcinoma (one patient), gastric adenocarcinoma (one patient), ovarian carcinoma (one patient), breast carcinoma (two patients), and melanoma (two patients).

TCD results are presented in Table 2. A positive TCD study was identified in 2/9 (22.2%) participants. One individual was a female with breast cancer who had no preceding extracranial metastases, and the other individual was a male with duodenal adenocarcinoma whose only prior metastatic disease was distant lymphadenopathy, which was

in remission at brain metastasis diagnosis. No participants developed lung metastases on their subsequent chest CT.

Discussion

In this prospective single-center pilot study investigating the prevalence of PFO in patients with brain metastases without preceding lung involvement, 22.2% of participants had a positive TCD study, a frequency that is similar to the estimated prevalence of PFO in the general population [19–21]. This result argues against the hypothesis that a right-to-left shunt through a PFO provides a pathway for tumor cells to metastasize to the brain. For the hypothesis to be supported, we would expect the prevalence of PFO in our study population to be 40–90% based on studies of PFO in other conditions [27, 28].

The role of PFO in the development of brain metastases has been previously hypothesized by Rigatelli and colleagues, who described the concept of a "paradoxical cancer cell embolism" of circulating tumor cells through a PFO [15]. To the best of our knowledge, the present study is the first to prospectively test this theory.

Patients with metastatic breast cancer comprised the majority of the study population, although individuals with

Table 1 Patient characteristics

Patient	Patient sex	Age	Primary histology	Preceding metastatic disease sites
1	F	81	Breast	None
2	F	51	Breast	None
3	F	56	Breast	Bone
4	F	63	Breast	Bone, liver
5	F	51	Breast	Adrenal, lymphadenopathy
6	F	58	Breast	Bone
7	M	69	Duodenal adenocarcinoma	Lymphadenopathy
8	M	78	Esophageal adenocarcinoma	Lymphadenopathy
9	F	43	Papillary thyroid cancer	Lymphadenopathy

a greater diversity of primary cancers were eligible for the study but did not undergo TCD testing. The high prevalence of metastatic breast cancer in this study may reflect its prevalence as the most common malignancy that metastasizes to the brain apart from lung cancer [9, 10], but may also reflect its more favorable natural history (i.e., participants with breast cancer that metastasized to the brain were more physically able to participate in an elective study) [5].

Organotropism and the organ microenvironment play a large role in the development of systemic and intracranial metastases [11, 12, 29]. Ultimately, these may be the dominant drivers of brain metastases even in the absence of lung metastases, consistent with our study findings that there was an absence of increased frequency of right-to-left circulatory shunts in this population. Tumor biomarkers and molecular alterations are extensively described as important factors in brain metastasis development, such as epidermal growth factor receptor (EGFR) mutations and anaplastic lymphoma kinase (ALK) rearrangements in lung cancer [30, 31], BRAF and NRAS gene mutations in melanoma [32], and triple-negative and human epidermal growth factor 2 (HER2)-overexpressing breast cancers [13, 33]. In an eloquent example of metastatic breast cancer cell tropism, Klotz and colleagues implanted human metastatic breast cancer cells that had metastasized to the brain into a mouse xenograft and observed that the cells again developed into brain metastases [34].

The main limitation of our study was the small sample size. A challenge in study accrual was the morbidity associated with the natural history of brain metastases and metastatic disease; potential participants meeting eligibility criteria were frequently not optimal candidates due to poor health status, and several individuals who were initially accrued to the study discontinued participation before undergoing TCD testing due to clinical deterioration. This finding in itself underscores the importance of continuing to search for methods to prevent or at least mitigate the risk of developing brain metastases. An additional limitation is the inability to unequivocally rule out the presence of subclinical lung metastases that were never radiographically visible.

Conclusions

In summary, we investigated the prevalence of PFO with right-to-left systemic shunting in a population of patients with metastatic cancers who developed brain metastases in the absence of preceding or concurrent lung involvement. We did not find a greater PFO frequency compared to the observed prevalence in the general population, though the study population size was limited. Given the significant morbidity associated with the development of brain metastases,

continued investigation to examine potential targets to reduce the risk of developing brain metastases is essential.

Compliance with ethical standards

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