Hong Kong College of Physicians
Case report for Interim Assessment
Specialty Board of Advanced Internal Medicine (AIM)

For AIM Training, case reports should be submitted in the prescribed format together with the application form for Interim Assessment at least EIGHT Weeks before the date of Interim Assessment

Name of candidate (print and sign):
Hospital and Unit: Specialty:
Name of supervisor (print and sign):
Date(s) and place (hospital) of patient encounter: 1/10/20
Date of report submission: 8/3/21

Case report

Note: Failure to follow the prescribed format (including the number of words) results in a FAILURE mark (score between 0 and 4) for the Case Report.

Title: Should A Hole in The Heart Be Closed?

Case history:

Our patient was an 87-year-old gentleman with lacunar infarct in 2007, from which he fully recovered. However the etiology of stroke was uncertain. He never smoked and did not have diabetes mellitus, hypertension or hyperlipidaemia. Holter monitoring did not reveal any arrhythmia nor did an echocardiogram in 2009 reveal any abnormality. He had been taking prophylactic aspirin since then.

He was brought to the hospital for loss of consciousness after coughing at home. No seizure or preceding symptom e.g. chest pain was reported. He regained consciousness within one minute. The paramedic found him hypoxic with the pulse oximetry showing the oxygen saturation (SpO_2) 80% only. He was given 100% oxygen via mask. At the emergency department, he was fully conscious and able to communicate normally. He expressed no symptoms despite SpO_2 being 70-80%. Physical exam revealed no pyrexia and normal haemodynamics. There was central cyanosis and mild tachypnoea, but the cardiopulmonary & neurology systems were otherwise unremarkable. Chest radiography and electrocardiogram were unremarkable. Arterial blood gas analysis confirmed hypoxaemia with the partial pressure of oxygen (P_aO_2) being 4.9kPa (reference interval: 11-14.4), partial pressure of carbon dioxide (P_aCO_2) 4.5kPa (reference interval: 4.7-6.4) and pH7.49.

It was compatible with type 1 respiratory failure with hyperventilation. Computer tomography (CT) of pulmonary angiogram revealed no pulmonary embolism. Intensive care unit (ICU) was consulted however patient refused intubation or ICU admission.

He was transferred to the medical ward for further management. Regardless of the concentration of supplementary oxygen provided, ranging from room air to 100% oxygen, there was no difference in SpO_2 or P_aO_2. Therefore a right-to-left shunt was suspected. Within 2 hours after admission, his SpO_2 spontaneously increased to 100%. He remained asymptomatic until the next morning, when he desaturated again. The SpO_2 increased from 71% to 86-91% when the bed inclination changed from 90° to supine. Bedside trans-thoracic echocardiogram with agitated saline demonstrated microbubbles in the left atrium within 3 heartbeats, while the patient was at rest without assuming any maneuver. The diagnosis of a patent foramen ovale (PFO) with a right-to-left shunt (RLS) was confirmed by trans-oesophageal echocardiogram (TEE). No atrial septal aneurysm (ASA), pericardial effusion or pulmonary hypertension was identified. Prophylactic enoxaparin was initiated.

PFO closure was tentatively planned if patient agreed for peri-procedural ICU support but the patient developed acute right hemiplegia on the next day. CT of brain with angiogram confirmed a distal left middle cerebral artery occlusion, without intra- or extra-cranial large vessel stenosis. Tissue plasminogen activator was given within 2 hours and beyond 12 hours of the last dose of enoxaparin. There was no lower limb deep vein thrombosis clinically. Blood test revealed no diabetes or hyperlipidaemia. There was partial neurological recovery and repeated brain scan showed established cortical infarct. Unfortunately the patient developed torrential haemorrhoidal bleeding 2 days later. His general condition deteriorated and finally succumbed to hospital-acquired pneumonia.

Discussion and literature review

PFO and Stroke

PFO is present in at least 25% of the general population based on TEE study (1). Most of them are asymptomatic and never require follow-up or management. One of the most recognizable manifestations is paradoxical embolism-related cryptogenic stroke, which is defined as stroke without identifiable cardioembolic source or large vessel disease and not compatible with small vessel disease or lacunar infarct (2). Based on this definition, our patient's lacunar infarct back in 2007 may be more likely related to small vessel disease than to paradoxical embolism. It is important to realize that the finding of PFO in a stroke patient, especially elderly, does not necessarily indicate the etiology, i.e. the PFO could just be an incidental finding since it is so common.

The association between cryptogenic stroke and PFO was first postulated from the observation that PFO is more prevalent, up to 38%, in subjects with cryptogenic stroke (3). In a 2007 prospective case-control study, PFO was present in 44% of cryptogenic stroke patients <55-year-old, and in 28% (similar to general population) ≥55-year-old (4). In both age groups, the prevalence of PFO was significantly higher in patients with cryptogenic stroke than those with other stroke etiologies, and multivariate analysis also showed PFO was an independent risk factor for cryptogenic stroke even in the older age group (4). Summarised from different studies, age <55, the absence of conventional cardiovascular risk factors, size of PFO, spontaneous RLS and the presence of atrial septal aneurysm are some factors to suggest a higher etiological association between PFO and stroke (5).

Risk of Paradoxical Embolism (RoPE) score was devised from meta-analysis to estimate the attributability of PFO to a cryptogenic stroke (5). The scoring system includes 6 factors namely the history of hypertension, diabetes, stroke or transient ischaemic attack (TIA), smoking, cortical infarct on imaging and age. A higher RoPE score (ranging from 0 to 10) predicts higher etiological link between PFO and stroke, and a lower risk of recurrent stroke. Our patient scored 4 points from RoPE score, which translated to a low likelihood of 38% that the stroke was related to PFO and a 12% 2-year risk of recurrent stroke.

It is agreeable that an incidental finding of PFO does not necessitate any treatment or primary prophylaxis for stroke. However, given that our patient had a history of stroke of uncertain etiology back in 2007, frequent spontaneous RLS and was immobile on bed since admission, it was reasonable to start prophylactic

anticoagulation to prevent venothrombosis and paradoxical embolism. Unfortunately ischaemic stroke still occurred and it would pose a challenging question on the optimal modality of secondary prophylaxis, if our patient survived.

The author of RoPE score emphasized that the score alone should not be used to decide PFO closure as a secondary stroke prophylaxis. Stroke with higher PFO-attributable fraction is associated with lower stroke recurrence risk than stroke of other etiology (5). Among stroke patients with high PFO-attributable fraction, the presence of ASA and small shunt are associated with higher recurrent stroke risk but the size of PFO is not (6). Although the RoPE score of our patient was not high, the fact that the second stroke in his life happened under the prophylaxis of aspirin & enoxaparin, and that he had frequent spontaneous RLS would suggest paradoxical embolism as a likely stroke etiology, i.e. the RoPE score might have underestimated the PFO-attributable fraction for our patient.

In the 2020 recommendations by the American Academy of Neurology, PFO closure as secondary stroke prophylaxis is considered only for patients aged <60 without alternative causes of stroke (7). If the patient or the physician decides not for PFO closure, either antiplatelet or anticoagulant can be considered with comparable outcome. It is worth noting the atrial fibrillation risk of 0.33% per year after PFO closure and many PFO closures are followed by double-antiplatelet therapy for 3 months (7). Patients aged above 60, particularly senile patients such as our patient are generally considered not candidate for PFO closure due to the lack of data, and that alternative stroke etiology is more likely. PFO closure might not offer more prevention than medical therapy alone in this age group.

In our case, PFO closure was initially (before that hyperacute stroke) proposed by the cardiology team for the frequent desaturation due to RLS instead of stroke prophylaxis. If PFO was not to be done, the patient's secondary prophylaxis might be empirical full dose anticoagulation. In retrospective thinking, PFO might be after all indicated for his frequent RLS and that he may not be safe for lifelong anticoagulation due to the haemorrhoidal bleeding risk.

<u>PFO and Hypoxaemia</u>

RLS should be suspected in hypoxaemia that does not improve with the fraction of inspired oxygen (F_iO_2). The RLS in PFO is mostly transient and not associated with pulmonary hypertension. The transient RLS can be brought on by coughing or Valsalva maneuver. Patients with frequent spontaneous RLS should still have pulmonary embolism excluded as it can increase the right heart pressure and thus

exacerbate the RLS. Intuitively one may think that the post-tussive syncope in this case can be explained by a transient RLS. However there is no literature describing syncope as a typical symptom of PFO or RLS, thus syncope is not an indication for PFO closure.

It is intriguing that our patient with persistent profound hypoxaemia could still appear relatively comfortable. This phenomenon has also been observed in some patients with COVID-19 infection and has become a topic of debate during the pandemic. The exact pathophysiology of this "happy hypoxaemia" phenomenon is unclear but some of the hypotheses might explain our patient's presentation. The chemoreceptors in the regulatory center of ventilation are far more sensitive to hypercapnia than to hypoxaemia. With an intact respiratory system, hypoxaemia-driven compensatory hyperventilation will lead to hypocapnia and thus limiting the effect of hypoxemic drive on further hyperventilation (8).

Platypnoea-orthodeoxia syndrome (POS) is another uncommon manifestation of PFO (9), which was present in our patient. It refers to the occurrence of dyspnoea or hypoxaemia when the subject assumes an upright posture from lying. The physiological mechanism is unclear but was postulated that assuming an upright posture would increase venous return from the inferior vena cava and deform the atrial septum transiently, leading to more RLS across any right-to-left conduit. Similar to the relationship between stroke and PFO, since PFO is so common, other causes for POS should be sought for including intra-pulmonary shunting/ hepatopulmonary syndrome as in cirrhosis, constrictive pericarditis and pericardial effusion etc (9).

POS is an elective indication for PFO closure based on a French study on 78 elderly patients (mean age of 63 ±11.3) (10). Normalization of oxygen saturation was immediate after procedure and dyspnea score reduced from 2.7 to 1. It is essential to exclude severe pulmonary hypertension before PFO closure.

Tables and figures (where applicable) (no more than two figures)

Nil

Reference (not more than 10)

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2. Saver JL. CLINICAL PRACTICE. Cryptogenic Stroke. N Engl J Med. 2016;374(21):2065-74.

3. Lamy C, Giannesini C, Zuber M, Arquizan C, Meder JF, Trystram D, et al. Clinical and imaging findings in cryptogenic stroke patients with and without patent foramen ovale: the PFO-ASA Study. Atrial Septal Aneurysm. Stroke. 2002;33(3):706-11.

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6. Thaler DE, Ruthazer R, Weimar C, Mas JL, Serena J, Di Angelantonio E, et al. Recurrent stroke predictors differ in medically treated patients with pathogenic vs. other PFOs. Neurology. 2014;83(3):221-6.

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8. Dhont S, Derom E, Van Braeckel E, Depuydt P, Lambrecht BN. The pathophysiology of 'happy' hypoxemia in COVID-19. Respir Res. 2020;21(1):198.

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10. Guerin P, Lambert V, Godart F, Legendre A, Petit J, Bourlon F, et al. Transcatheter closure of patent foramen ovale in patients with platypnea-orthodeoxia: results of a multicentric French registry. Cardiovasc Intervent Radiol. 2005;28(2):164-8.

No of words in Case History and Discussion (excluding references): 1604

(should be between 1000-2000)

Declaration

I hereby declare that the case report submitted represents my own work and adheres to the prescribed format. I have been in clinical contact with the case selected. The case report has not been submitted to any assessment board or publication and it is NOT related to my second specialty(ies), if any. My consent is hereby given to the College to keep a copy of my case report, in written and/or electronic, at the College Secretariat and allow the public to have free access to the work for reference.

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(signature of Trainee)

Endorsed by Supervisor *

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