Author's response to reviews

Title: Pheochromocytoma presenting with arterial and intracardiac thrombus in a 47 year old woman: a case report

Authors:

Runhua Hou (runhua_hou@urmc.rochester.edu)
Ann M Leathersich (aleathersich@path.wustl.edu)
Brenda T Ruud (alwaysruud2@hotmail.com)

Version: 2 Date: 1 August 2010

Author's response to reviews: see over
Dear Editor:

Thank you very much for the reviews for our paper “Pheochromocytoma presenting with arterial and intracardiac thrombus in a 47 year old woman: a case report” by Hou et al. We are delighted that the reviewers found the case report interesting and worth reporting. We are pleased to have this opportunity to address the questions and comments raised by the reviewers. We feel that many of the issues raised by the reviewers can be answered by revising text and incorporating references.

We propose to address the comments of reviewers as follows:

Reviewer # 1:

Comments to authors: I think this is an incidental finding. Arterial thrombosis is not directly related with pheochromocytoma; MTHFR heterozygous mutation, contractive pill in thrombosis may play major role in the patient.

We agree with the reviewer that there is no direct proof that pheochromocytoma contributed to the development of thrombosis in this patient and this could be an incidental finding. We rewrote the discussion and conclusion sections of the manuscript to emphasize this point.
Despite that we are unable to prove that arterial thrombosis is directly induced by pheochromocytoma, based on literature search we feel that MTHFR heterozygous mutation and oral contraceptive pills are less likely to be major players in the development of thrombosis in this patient. Oral contraceptives are associated with a 2 to 6 fold increased relative risk of developing venous thromboembolic events [15]. Atherosclerotic events such as stroke and myocardial infarction are also increased in those who use oral contraceptives [16, 17]. However, to the best of our knowledge there has been no report of patients on oral contraceptives developing a ventricular thrombus without myocardial infarction. In addition, the risk of thrombosis induced by oral contraceptives is highest in the first year of use [16, 17] and the risk decreases with duration of use [18]. Therefore, oral contraceptives are less likely the major cause of our patient’s ventricular and arterial thrombus considering she has arterial but not venous thrombosis and thrombosis occurred after a number of years of oral contraceptive pill use. The association of hyperhomocysteinemia, a possible result of MTHFR mutation, with arterial vascular diseases or venous thrombosis is controversial [19-22]. The MTHFR defect, when combined with additional thrombophilic risk factors, is likely to increase the risk of venous thrombosis, especially for a patient with a homozygous mutation. The effect is uncertain when no additional risk factors are present and when the homocysteine level is only mildly elevated (<30 umol/L) [21]. As far as we know, no studies have reported the association of a ventricular thrombus with MTHFR mutation. Furthermore, the mildly abnormal homocysteine level (14 umol/L) obtained on this patient was not a fasting value therefore it is not very useful considering homocysteine level could be affected by dietary protein intake. Thus, the heterozygous mutation for MTHFR our patient has is unlikely to contribute
significantly to her arterial and ventricular thrombosis. Although there is no direct proof that pheochromocytoma caused thrombosis in this patient, it probably contributed significantly to this process based on the aforementioned reasons. MTHFR heterozygous mutation and oral contraceptives may have contributed to this process but the likelihood is low.

Reviewer # 2:

Comments to authors: very well-written manuscript of an interesting case.

We would like to thank Dr. Chin for his review of article and we are glad to hear that he thinks this case report is persuasive and authentic. We are delighted to know that he thinks this is a well written interesting case.

Editor:

1): Please rewrite the follow paragraph: “Although we could not completely eliminate the contribution of thrombocytosis, MTHFR heterozygous mutation, contraceptive pill in thrombosis in this patient, pheochromobytoma likely played a major role in this process.”

Rewritten. Please see text below and also see expanded discussion part in the manuscript.
Although there is no direct proof that pheochromocytoma caused thrombosis in this patient, it probably contributed significantly to this process based on the aforementioned reasons. MTHFR heterozygous mutation and oral contraceptives may have contributed to this process but the likelihood is low. Appropriate anti-coagulation is essential for patients with pheochromocytoma and thrombosis to prevent devastating outcomes.

2) Please rewrite the following paragraph: “We report a rare case of pheochromocytoma presenting with intracardiac and left axillary arterial thrombus. It is likely that pheochromocytoma played a significant role in thrombosis. Further studies on the underlying mechanism of the association of pheochromocytoma and arterial thrombosis are needed for better understanding of its pathogenesis. Diagnosis of pheochromocytoma can be challenging and early referral to centers experienced in this disease can improve patient care outcome.”

Paragraph rewritten. Please see below.

We report a case of pheochromocytoma uniquely presenting with left ventricular and left axillary artery thrombus. This case highlights the complexity of managing patient with pheochromocytoma and presents the possible association of pheochromocytoma with arterial thrombosis. Knowledge of this association and the potential for embolic events will educate clinicians to be more vigilant about the pro-thrombosis state in patients with pheochromocytoma. Anti-coagulation regimen should be employed to avoid devastating
embolic events and therefore reduce morbidity and mortality. This will help to make a difference in the management of patients with pheochromocytoma.

3). It is probably that pheochromocytoma played a significant role in thrombosis, but also can be occurred only coincidentally. Please discuss it clearly... How this case makes a difference to clinical practice and please adds information about its diagnostic or clinical value because we still didn’t have a proof between association of pheochromocytoma and arterial thrombosis.

We agree with the editor that it is probably that pheochromocytoma played a significant role in thrombosis but also can be occurred only coincidentally. Despite that we are unable to prove that arterial thrombosis is directly induced by pheochromocytoma, based on literature search we feel that MTHFR heterozygous mutation and oral contraceptive pills are less likely to be major players in the development of thrombosis in this patient. Oral contraceptives are associated with a 2 to 6 fold increased relative risk of developing venous thromboembolic events [15]. Atherosclerotic events such as stroke and myocardial infarction are also increased in those who use oral contraceptives [16, 17]. However, to the best of our knowledge there has been no report of patients on oral contraceptives developing a ventricular thrombus without myocardial infarction. In addition, the risk of thrombosis induced by oral contraceptives is highest in the first year of use [16, 17] and the risk decreases with duration of use [18]. Therefore, oral contraceptives are less likely the major cause of our patient’s ventricular and arterial thrombus considering she has arterial but not venous thrombosis and thrombosis occurred after a number
years of oral contraceptive pill use. The association of hyperhomocysteinemia, a possible result of MTHFR mutation, with arterial vascular diseases or venous thrombosis is controversial [19-22]. The MTHFR defect, when combined with additional thrombophilic risk factors, is likely to increase the risk of venous thrombosis, especially for a patient with a homozygous mutation. The effect is uncertain when no additional risk factors are present and when the homocysteine level is only mildly elevated (<30 umol/L) [21]. As far as we know, no studies have reported the association of a ventricular thrombus with MTHFR mutation. Furthermore, the mildly abnormal homocysteine level (14 umol/L) obtained on this patient was not a fasting value therefore it is not very useful considering homocysteine level could be affected by dietary protein intake. Thus, the heterozygous mutation for MTHFR our patient has is unlikely to contribute significantly to her arterial and ventricular thrombosis. Therefore, MTHFR heterozygous mutation and oral contraceptive pills are unlikely the major cause of the arterial thrombosis in this patient. Although there is no direct proof that pheochromocytoma caused thrombosis in this patient, it probably contributed significantly to this process based on the aforementioned reasons.

We feel that the clinical value of this case lies in increasing the awareness of the potential association of pheochromocytoma and ventricular and arterial thrombosis. Given that prior reported cases and this case all have embolic events leading to severe morbidity, knowledge of this association will educate clinicians to be more vigilant about hypercoagulable state in patients with pheochromocytoma. The most recent published case report (reference 8, added to
discussion part) showed a patient with pheochromocytoma and cardiac thrombus developed systemic embolization leading to kidney infarction, lower extremity infarction requiring bilateral below the knee amputation as a result of delayed anti-coagulation. Therefore, anti-coagulation regimen should be employed promptly to prevent similar devastating embolic events. This case also highlights the complexity of managing patient with pheochromocytoma and suggests a multi-disciplinary approach to this disease. We hope our case will help to make a difference in the management of patients with pheochromocytoma.

4) Please rearrange all references, without any exception, as reference styles and then check again.

All added references were checked for format to conform to journal’s requirement.

4): In order to increase clarity for all readers of the journal please add more legends to figure 2 A and b.

All figure legends rewritten.

Figure 1. $^{123}$I-metaiodobenzylguanidide ($^{123}$I-MIBG) scan showing intensive uptake in the adrenal mass but no uptake in the lung. $^{123}$I-MIBG scan was obtained to determine whether the
left adrenal mass and right lung mass are pheochromocytoma. Shown are the frontal and back views of the total body scan at 72 hours. Significantly increased uptake is seen in the left adrenal lesion. No uptake was found in the lung. Physiological uptake is seen in the salivary glands, heart and liver. $^{123}I$-MIBG is renally excreted and is visible in the bladder.

Figure 2. A. High power (400x) view of the resected adrenal tumor. The resected adrenal pheochromocytoma shows chromaffin cells with a classic nested and trabecular architecture. Other characteristic morphologic features include nuclear enlargement and hyperchromasia with cytoplasm that is both oncocytic (pink and granular) in some cells and basophilic (blue) in others. B. Intra-vascular invasion of tumor (400X). Pheochromocytoma cells seen within a blood vessel. Vascular invasion is not a reliable indication of a malignant pheochromocytoma. Only metastatic disease to regional lymph nodes or distant sites (ribs, spine, liver and lung most common) will define this tumor as a malignant lesion.

We hope that you will agree with these changes and reconsider our revised manuscript for publication in the JMCR. We are happy to discuss with you further if there are any other questions.

Thank you. We look forward to hearing from you soon.
Sincerely yours,

Runhua Hou