

Published: October 31, 2022

Citation: Pérez-Malagón C. D., Díaz-Romo A., et al., 2022. Treatment and Long-term outcome of acute cerebral infarction in a patient with high CA125 and endometriosis, Medical Research Archives, [online] 10(10).

<https://doi.org/10.18103/mra.v10i10.3306>

Copyright: © 2022 European Society of Medicine. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

DOI:

<https://doi.org/10.18103/mra.v10i10.3306>

ISSN: 2375-1924

RESEARCH ARTICLE

Treatment and Long-term Outcome of Acute Cerebral Infarction in a Patient with High CA125 and Endometriosis

Carlos David Pérez-Malagón¹, Angélica Díaz-Romo¹, Fernanda Michelle Balderas-Martín del Campo¹, Dulce María Bonifacio-Delgadillo², *Juan Manuel Marquez-Romero³

¹Universidad Autónoma de Aguascalientes Centro de Ciencias de la Salud, Medicina Aguascalientes, Aguascalientes, MX

²ISSSTE, 3. Departamento de Terapia Endovascular Neurológica. Centro Médico Nacional 20 de Noviembre. México City, México City, MX

³Instituto Mexicano del Seguro Social. HGZ 2. OOAD Aguascalientes, Aguascalientes, MX

*scint1st@gmail.com

Summary: This report describes a novel association between stroke and endometriosis in a patient with extremely high serum levels of CA-125.

ABSTRACT

Background: Cancer antigen 125 is a cell surface glycoprotein present in elevated serum levels with certain types of cancer, especially non-mucinous epithelial ovarian cancers. Still, such elevations can also be seen in benign gynecologic conditions such as severe adenomyosis, uterine myomas, and advanced endometriosis. Recently, high serum levels of cancer antigen 125 have also been associated with an increased risk of stroke.

Case: This report describes the case of a 48 years-old woman that presented a novel association between ischemic stroke and endometriosis in a patient with extremely high serum levels of cancer antigen 125 and illustrates the long-term management strategy utilized for secondary prevention of ischemic stroke.

Conclusion: The role of the cancer antigen 125 level on the pathogenesis of ischemic stroke is yet to be determined. High serum cancer antigen 125 can be seen in ischemic stroke in women of reproductive age. Cancer antigen 125 levels might have some implications on the election of the long-term secondary prevention of IS.

Teaching Points:

- Elevated serum levels of CA-125 are associated with an increased risk of stroke.
- Raised serum levels of CA-125 can be seen in benign gynecologic conditions.
- The finding of high CA-125 might have some implications on the election of the long-term management strategy for the secondary prevention of ischemic stroke.

Introduction

Cancer antigen (CA) 125 is a membrane-bound cell surface glycoprotein that, when found in serum, is utilized as a marker to monitor patients with ovarian epithelial neoplasms. Still, it can also be expressed by normal cells such as those lining the endometrium, fallopian tubes, pleura, peritoneum, and pericardium.¹ At a molecular weight of >200 kDa, it is considered a high molecular weight protein. A CA-125 serum value of 35 U/mL is considered abnormal, with values over 480 U/mL considered extremely high.² CA-125 is markedly elevated in both gynecologic and non-gynecologic cancers. Recently, elevated serum levels of CA-125 have been associated with an increased risk of stroke in cancer patients.³ Additionally, raised serum levels of CA-125 can also be seen in benign gynecologic conditions such as severe adenomyosis, uterine myomas, and advanced endometriosis.⁴ Adenomyosis with elevated CA-125 levels has also been considered a risk factor for women's ischemic stroke (IS).⁵ Also, increased CA-125 has been associated with the advanced stages of endometriosis⁶ and ruptured endometriomas.⁷ Although the mechanism of CA-125 elevation in patients with ruptured endometriomas is not understood, a proposed hypothesis implicates the diffusion of the endometrioma fluid into the blood circulation. The cyst fluid contains high quantities of tumor biomarkers, including CA-125 and CA19-9,⁸ but the high molecular weight of the CA-125 protein coupled with the thick wall of endometriotic cysts may prevent it from crossing into the systemic circulation. Therefore, the rupture of

the endometrioma would allow contact between the CA-125-rich fluid and the peritoneum, causing the elevation of the serum levels.⁹

This report describes a novel association between stroke and ruptured endometrioma in a patient with extremely high serum levels of CA-125. We also describe the long-term management strategy utilized for the secondary prevention of IS, discuss the possible role of CA-125 in evaluating the etiology of IS, and discuss the rationale for selecting anti-thrombotic therapy.

Case

A 48 years-old woman presented to the emergency room for the onset of abdominal pain and vomiting; the physical examination revealed tenderness localized at the superior quadrants, hypoactive bowel sounds, and normal abdominal palpation. Laboratory results are shown in Table 1. Other laboratory results were unremarkable. The abdominal ultrasound scan study revealed a moderate quantity of free abdominal fluid and the presence of a right-sided ovoid mixed anechoic and homogeneously echogenic para-adnexal mass. Abdomen and Pelvis CT scan with contrast confirmed the presence of a complex right para-adnexal mass that measured 94 by 57 by 56 mm and showed irregular nodular enhancement. The patient underwent exploratory laparotomy that showed hemoperitoneum and a presumptive diagnosis of fimbrial endometrioma. The immediate postoperative period was uneventful.

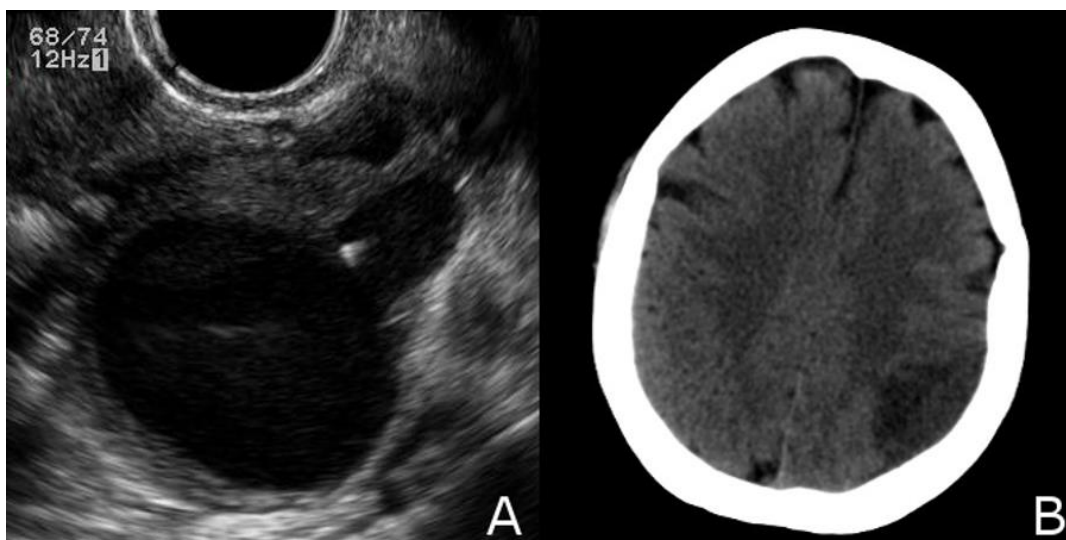
Nevertheless, approximately 30 hours after de surgical procedure, the patient developed hypertension (155/92) and intelligible speech. Attending physicians in the gynecology ward requested a neurology consultation. The evaluation was performed approximately 90 minutes after the onset of symptoms, the patient presented with receptive aphasia and right-sided hypoalgesia (NIHSS score 7). A brain CT scan showed no abnormal findings. Intravenous tPA was withheld due to the presence of three relative contraindications: mild or improving stroke symptoms, recent

major surgery, and recent gastrointestinal or genitourinary hemorrhage. Neurological deficit improved to mild transcortical sensory aphasia (NIHSS score 3) within 3 hours after the onset of symptoms. The patient was put on low-molecular-weight heparin 24 hours after the onset of symptoms. The brain CT scan obtained the second day after the stroke demonstrated a left subcortical infarct in the middle cerebral artery's superficial territory (Figure 1).

Table 1. Laboratory test results

Lactate Dehydrogenase	602 IU/L
β-subunit of hCG gonadotropin	0.10 mIU/L
Alpha-fetoprotein	1.28 ng/mL
CA125	861.8 IU/mL
Hemoglobin	11.3g/dL
White blood cells count	8.10 × 10 ³ /mL
Platelets	231,000

Figure 1.



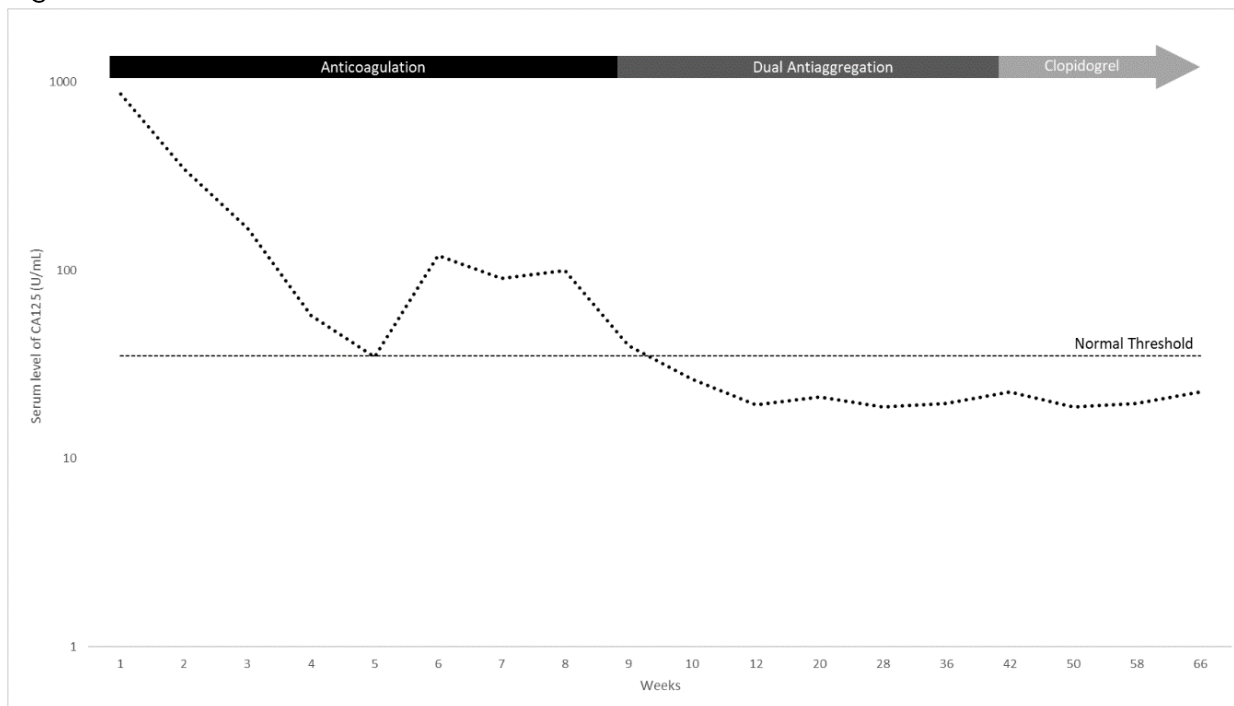
Panel A. Abdominal ultrasound scan study shows free abdominal fluid and a right-sided ovoid mixed anechoic and homogeneously echogenic para-adnexal mass. Panel B. Brain CT scan obtained 48 hours after stroke shows a left subcortical infarct in the superficial territory of the middle cerebral artery.

The patient was discharged from the hospital with a modified Rankin scale (mRs) score of 2 and a prescription for LMWH (enoxaparin 1mg/kg SC q12hr). Histologic examination following adnexectomy revealed a ruptured endometrioma without trace of malignancy. A complete stroke work-up, including transthoracic echocardiography, 24-hour Holter monitoring, and carotid ultrasound, were otherwise unremarkable. Hypercoagulable condition evaluations also deemed negative results; these included antiphospholipid antibody syndrome, factor V Leiden mutation,

prothrombin gene mutation, protein C, protein S, and antithrombin III deficiency.

CA-125 serum levels persisted elevated (Figure 2) LMWH was maintained on weekly follow-up visits until CA-125 levels reached normal levels. The patient was then switched to acetylsalicylic acid and clopidogrel for six months and then clopidogrel alone. At a 1-year follow-up visit, functional status was mRs 1 with no recurrent thromboembolic events (including recurrent stroke) or endometriosis symptoms.

Figure 2.



CA125 serum levels during the follow-up period and matched management strategy for the secondary prevention of ischemic stroke.

Discussion

We report a novel association between IS and endometriosis in the context of elevated serum levels of CA-125. Cerebral infarction

occurred during the early postoperative period from exploratory laparotomy that yielded the diagnosis of advanced endometrioma. Previous reports have

successfully linked CA-125 to IS due to the mucinous nature of the CA-125 molecule.² Although extremely high serum levels of CA-125 have been observed in endometriosis, specifically with endometrioma,⁴ there are no previous IS reports in such patients.

Endometriosis has previously been identified as a risk factor for IS in a population-based cohort study (adjusted hazard ratio 1.19 [95% CI 1.04-1.36]); Okoth et al.¹⁰ theorize that some explanations for this elevated risk include: the systemic inflammatory nature of endometriosis, its arrhythmogenic potential, and its association with high levels of atherogenic low-density lipoproteins (LDL). They also implicate vascular and cardiac myocyte dysfunction due to prolonged exposure to reactive oxygen species from oxidative stress as an additional arrhythmogenic mechanism leading to IS, but they did not include the possibility of a hypercoagulable state related to CA-125.

The role of CA-125 as a tumor marker for mucin-producing gynecological cancer is well known,¹¹ especially in ovarian cancer.¹² Before 2021, there were only some case reports linking this mucin molecule with cancer-associated hypercoagulation. All inpatients with mucin-producing tumors.^{13, 14} In that year, Maezono-Kandori et al.,¹⁵ reported the first study associating CA125 with stroke due to cancer-associated hypercoagulation; their results showed that CA125 was independently associated with hypercoagulation with an adjusted odds ratio of 5.59 ([95% confidence interval]: 1.33-

26.41). However, none of the 77 IS patients had a gynecologic malignancy.

The closest published association between IS and non-malignant gynecologic conditions accompanied by elevated CA-125 is with adenomyosis; Abdelazim et al. reported the case of a 46-year-old woman with adenomyosis uterus and CA-125 serum levels of 1658 IU/ml which rapidly decreased to normal range one week after surgery.¹⁶ Still, the patient did not present IS. In a report similar to the present case, Yamashiro et al. described the case of a 42-year-old woman with adenomyosis who developed IS. Her CA-125 level was 1750 U/mL, and the complete study revealed malignancy.¹⁷

Although there appears to be a strong association between endometriosis and adenomyosis, they are far from equal entities; endometriosis usually affects women during the reproductive period of life with pelvic pain, bleeding disorders, and infertility.¹⁸ However, many remain symptom-free or display only minor discomfort, thus remaining undiagnosed, as in the present case. In contrast, adenomyosis manifests more commonly with primary dysmenorrhea, menorrhagia, and dyspareunia.¹⁹ Thus, we are confident in affirming that the present case is the first report of a patient with endometriosis, IS associated with high serum levels of CA-125. Given the high prevalence of endometriosis (201.3 per 10000 population in 2017),¹⁰ the possibility of an asymptomatic course and its association with high levels of CA-125 is worth asking if CA-125 has a place

in the diagnostic work-up of IS in women of reproductive age.

Regarding management, the critical aspect of the present case was determining IS's etiology to choose the patient's long-term secondary prevention for IS. For us, the presence of anemia, recent surgery, and the extremely high serum levels of CA-125 were determining factors that swung the election of secondary prevention from anti-aggregation to anticoagulation with heparinoids during the suspected hypercoagulable state produced by the high concentration of mucinous CA-125 in the patient's blood. Nonetheless, due to the speculative nature of the proposed mechanisms, it was still necessary to exclude alternative etiologies of IS through an appropriate diagnostic work-up. Once the diagnostic work-up was complete, and the high CA-125 serum levels were the only abnormality remaining, we considered the use of anticoagulants, which had previously been applied in a patient with IS and adenomyosis with high CA-125 who incidentally was receiving aspirin as part of adenomyosis treatment.²⁰

Nevertheless, the election between anticoagulation and anti-aggregation was not as straightforward as we would like it to be, and no guidelines were available to support the choice. In a study of patients with confirmed strokes from cancer-related hypercoagulable states, the choice of anti-thrombotic therapy type did not affect the risk of recurrent thromboembolism and death. Still, the authors theorize that patients may have been preferentially treated with

anticoagulation (mostly low-molecular-weight heparins).²¹ Subcutaneous unfractionated heparin has been the drug of choice for cancer-mediated venous thromboembolism. However, recently direct oral anticoagulants have arisen as a potential alternative for patients with cancer-associated IS.²² Still, evidence to support the ideal scheme for secondary prevention of thromboembolism regarding the long-term efficacy and safety for patients with cancer and IS is lacking, as is for sporadic occurrences as the case portrayed in the present manuscript.

Conclusion

In conclusion, this case report shows that high serum CA-125 can be present in women of reproductive age with IS and no traditional risk factors. Although we acknowledge that the role of the CA-125 level on the pathogenesis of IS is yet to be determined, this co-occurrence raises the possibility of a pathogenetic association between this mucinous protein and the occurrence of IS in susceptible individuals, namely women of reproductive age. Given the mucinous nature of the CA-125 protein, we can draw a parallel from the pathology evidence of the presence of intravascular mucin in patients with mucinous cancers resulting in IS. After managing the present case, we firmly believe that the finding of high serum CA-125 in a patient with stroke, regardless of the underlying diagnosis (cancer/benign gynecologic conditions), has some implications not only etiological but also on the election of the long-term management strategy for the secondary prevention of IS.

Corresponding author

Juan Manuel Marquez-Romero
Instituto Mexicano del Seguro Social
HGZ 2. OOAD Aguascalientes
Av. de los Conos 102. Aguascalientes
Aguascalientes, MX 20230
Email: scint1st@gmail.com

Funding Statement

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Acknowledgments:

None

Conflict of Interest Statement

None

References

1. Scholler N, Urban N. CA125 in ovarian cancer. *Biomark Med* 2007;1:513-523.
2. Jovin TG, Boosupalli V, Zivkovic SA, Wechsler LR, Gebel JM. High titers of CA-125 may be associated with recurrent ischemic strokes in patients with cancer. *Neurology* 2005;64:1944-1945.
3. Xie X, Chen L, Zeng J, et al. Clinical features and biological markers of lung cancer-associated stroke. *J Int Med Res* 2016;44:1483-1491.
4. Ghaemmaghami F, Karimi Zarchi M, Hamedi B. High levels of CA125 (over 1,000 IU/ml) in patients with gynecologic disease and no malignant conditions: three cases and literature review. *Arch Gynecol Obstet* 2007;276:559-561.
5. Yin X, Wu J, Song S, Zhang B, Chen Y. Cerebral infarcts associated with adenomyosis: a rare risk factor for stroke in middle-aged women: a case series. *BMC Neurol* 2018;18:213.
6. Shen A, Xu S, Ma Y, et al. Diagnostic value of serum CA125, CA19-9 and CA15-3 in endometriosis: a meta-analysis. *Journal of International Medical Research* 2015;43:599-609.
7. Dai X, Jin C, Hu Y, et al. High CA-125 and CA19-9 levels in spontaneous ruptured ovarian endometriomas. *Clin Chim Acta* 2015;450:362-365.
8. Kristjansdottir B, Partheen K, Fung ET, et al. Ovarian cyst fluid is a rich proteome resource for detection of new tumor biomarkers. *Clin Proteomics* 2012;9:14.
9. Kurata H, Sasaki M, Kase H, Yamamoto Y, Aoki Y, Tanaka K. Elevated serum CA125 and CA19-9 due to the spontaneous rupture of ovarian endometrioma. *Eur J Obstet Gynecol Reprod Biol* 2002;105:75-76.
10. Okoth K, Wang J, Zemedikun D, Thomas GN, Nirantharakumar K, Adderley NJ. Risk of cardiovascular outcomes among women with endometriosis in the United Kingdom: A retrospective matched cohort study. *BJOG* 2021.
11. Korenaga TK, Tewari KS. Gynecologic cancer in pregnancy. *Gynecol Oncol* 2020;157:799-809.
12. Charkhchi P, Cybulski C, Gronwald J, Wong FO, Narod SA, Akbari MR. CA125 and Ovarian Cancer: A Comprehensive Review. *Cancers (Basel)* 2020;12.
13. Okada S, Miyagawa-Hayashino A, Fujinami J, et al. Trousseau's syndrome associated with pulmonary pleomorphic carcinoma exhibiting aggressive features: A case report. *Mol Clin Oncol* 2020;12:36-40.
14. Tachihara M, Nikaido T, Wang X, et al. Four cases of Trousseau's syndrome associated with lung adenocarcinoma. *Intern Med* 2012;51:1099-1102.

15. Maezono-Kandori K, Ohara T, Fujinami J, Makita N, Tanaka E, Mizuno T. Elevated CA125 is Related to Stroke Due to Cancer-Associated Hypercoagulation. *J Stroke Cerebrovasc Dis* 2021;30:106126.
16. Abdelazim IA, AbuFaza M, Hamed MES, Bekmukhambetov Y, Zhurabekova G, Shikanova S. Severe adenomyosis with unexpectedly high CA-125: report of a rare case. *Prz Menopauzalny* 2020;19:144-146.
17. Yamashiro K, Furuya T, Noda K, Urabe T, Hattori N, Okuma Y. Cerebral infarction developing in a patient without cancer with a markedly elevated level of mucinous tumor marker. *Journal of stroke and cerebrovascular diseases* 2012;21:619. e611-619. e612.
18. Lacheta J. Uterine adenomyosis: pathogenesis, diagnostics, symptomatology and treatment. *Ceska Gynekol* 2019;84:240-246.
19. Benagiano G, Habiba M, Brosens I. The pathophysiology of uterine adenomyosis: an update. *Fertil Steril* 2012;98:572-579.
20. Zhao Y, Zhang Y, Yang Y. Acute cerebral infarction with adenomyosis in a patient with fever: a case report. *BMC Neurol* 2020;20:210.
21. Navi BB, Singer S, Merkler AE, et al. Recurrent thromboembolic events after ischemic stroke in patients with cancer. *Neurology* 2014;83:26-33.
22. Naito H, Nezu T, Hosomi N, et al. Antithrombotic Therapy Strategy for Cancer-Associated Ischemic Stroke: A Case Series of 26 Patients. *J Stroke Cerebrovasc Dis* 2018;27:e206-e211.