Human Pathology: Case Reports 6 (2016) 32–36

Contents lists available at ScienceDirect

Human Pathology: Case Reports

journal homepage: http://www.humanpathologycasereports.com

Cerebral venous sinus thrombosis due to oral contraceptive use: Postmortem 3 T-MRI and autopsy findings

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ARTICLE INFO

Article history:
Received 6 October 2015
Received in revised form 5 January 2016
Accepted 20 January 2016

Keywords:
Cerebral venous sinus thrombosis
Contraceptive
Postmortem MRI
Autopsy

ABSTRACT

Cerebral venous sinus thrombosis (CVST) is an uncommon form of stroke, and mortality of the acute phase is high. We report the clinical, postmortem 3 T-MRI, and autopsy features of a patient, 20-year-old Japanese woman, with CVST who died shortly after starting to use low-dose estrogen combined hormonal contraceptives (CHCs). A postmortem 3 T-MRI study with our originally developed system revealed abnormal intensities suggestive of thrombi extending throughout the straight sinus and left sigmoid sinus. At autopsy, in accordance with the images, we performed careful preparations of the sinuses. Histological examination revealed an organizing white thrombus occupying the lumen of the left sigmoid sinus, and an acute, red thrombus in the lumen of the left transverse, straight, and tentorial sinuses, and vein of Galen, indicating that the thrombus had developed first in the left sigmoid sinus, then extended retrogradely to the more proximal portion of the sinus system, reaching the vein of Galen. The features of the present CVST patient appear to be informative, when encountering CHC users with neurological symptoms, even in those who begun to use low-dose estrogen CHCs only recently.

1. Introduction

Cerebral venous sinus thrombosis (CVST) is an uncommon form of stroke, accounting for 0.5%–1.0% of all strokes [1]. The clinical manifestations of CVST depend on the location of the thrombus, and may include headache, seizure, focal neurological symptoms, and consciousness disturbance. CSVT is often associated with hemorrhagic infarction in the thalamus and basal ganglia. Thereupon, mortality in the acute phase is high, and ranging from 3% to 15%. CSVT mostly affects young women of childbearing age because they sometimes have several risk factors, including pregnancy and use of oral contraceptives [2]. Recent cohort studies have provided evidence that the relative risk of thrombotic events associated with newly developed, low-dose estrogen combined hormonal contraceptives (CHCs) may be lower than that with conventional CHCs [3,4]. In Japan, low-dose estrogen CHCs were recently approved for use. Therefore, for precise assessment of the risk or safety of this drug for Japanese women, both a large-scale cohort study and information on extraordinarily unexpected cases in this population would be useful.

Recently, we encountered a patient with CVST who died shortly after starting to use low-dose estrogen CHCs. Here we report the clinical, postmortem 3 T-MRI, and autopsy features of this patient.

2. Case report

A 20-year-old Japanese woman with no significant medical history was prescribed an oral CHC tablet, drospirenone (3 mg)/ethinyl estradiol (20 μg) (YAZ®), for dysmenorrhea. In a few days after starting to take the CHC, she developed a headache. On the 9th day of CHC use, her headache worsened and she experienced nausea, appetite loss, and difficulty in walking: therefore she discontinued taking the CHC. In the afternoon of the following day, she was confined to bed, and next early morning, on the 11th day after starting to take the CHC, she was found unconscious and rushed to a hospital. A brain CT and MRI study revealed infarcts with edema in the bilateral thalami and left cerebellar

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http://dx.doi.org/10.1016/j.ehpc.2016.01.002

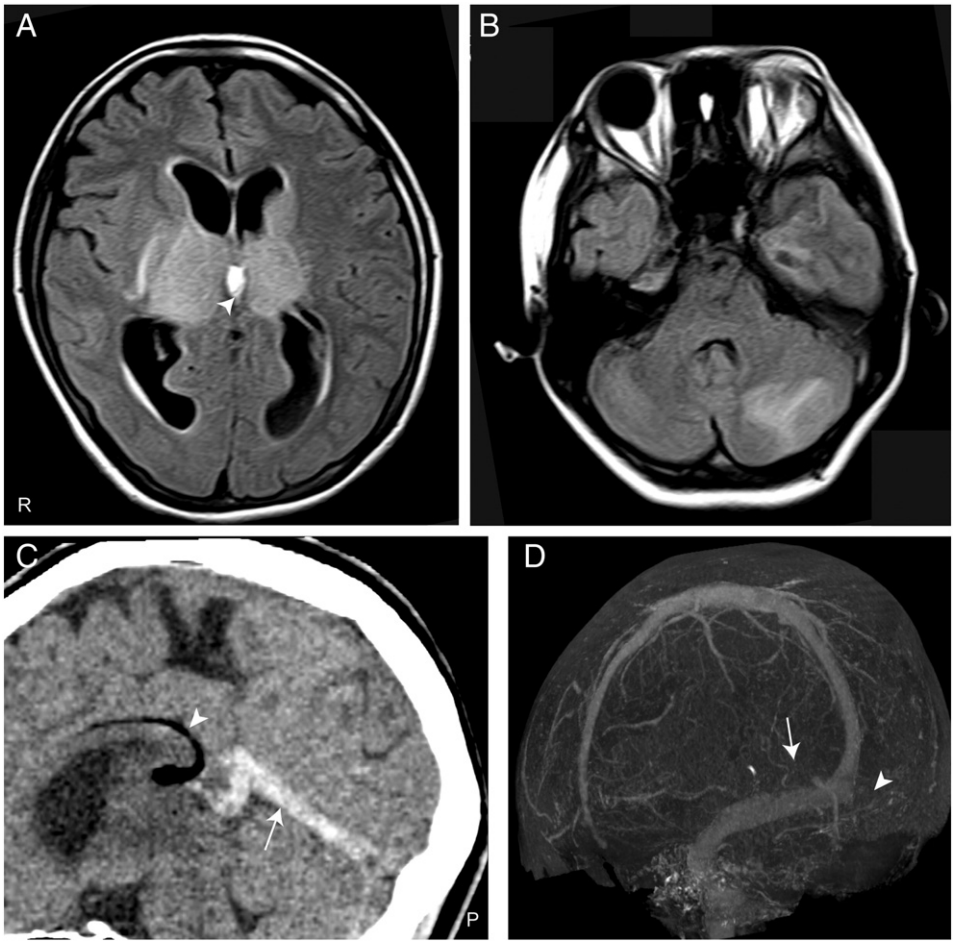

Fig. 1. Axial MRI (A, B), sagittal CT (C), and CT venography (D) images of the patient taken on admission to hospital. Lesions with edema in the bilateral thalami (A) and left cerebellar hemisphere (B) appearing hyperintense on the fluid-attenuated inversion recovery (FLAIR) image. A mid-line lipoma (*arrowhead* in A). (C) A large thrombus in the vein of Galen and straight sinus (*arrow*). Hypointense lesion (*arrowhead* in C), suspicious of pericallosal lipoma, is evident. (D) Absence of flow in the straight (*arrow*) and left transverse (*arrowhead*) sinus.

hemisphere (Fig. 1A and B). Then, under a tentative diagnosis of CVST, she was transferred immediately to Niigata University Hospital. On admission, the patient was suffering from generalized convulsions and was administered diazepam. She then became comatose and quadriplegic. A CT scan disclosed a large thrombus in the vein of Galen and straight sinus (Fig. 1C), and CT venography clearly demonstrated absence of flow in the vein of Galen, straight sinus, and left transverse and sigmoid sinus (Fig. 1D), leading to a diagnosis of CSVT. A serological examination demonstrated a low level of hemoglobin (7.3 g/dL), and an elevated D-dimer level (6.8 μg/mL), but the titers of several autoantibodies, including antinuclear, anti-cardiolipin, and anti-β2-glycoprotein I were normal. Despite administration of anticoagulants shortly after admission, on the second day she developed respiratory failure and required artificial respirator support thereafter. She died on the third day.

Written informed consent for postmortem imaging and autopsy, and subsequent use of the images and tissue samples for research purposes was obtained from her parents. We performed a postmortem MRI study with our originally developed system. Briefly, the body was packed in a sealable polyethylene bag, and placed supine in a polycarbonate coffin, which was maintained at 7.5–8.5 °C with circulating cooled dry air. The whole body within the coffin was imaged with a SIGNA 3 T MRI (GE Healthcare, Waukesha, WI, USA) using a body coil. Acquisition of the head was performed using a T1-weighted (T1W) image (axial—TSE, TE 3.2 ms, TR 7.5 ms, 1.5-mm thickness) and a T2W image (axial—TSE, TE 81.0 ms, TR 4000 ms, 4.0-mm thickness), followed by T2W imaging of the neck, abdomen, thighs, and legs. The total acquisition time was about 7 h. Consistent with the antemortem images (Fig. 1), hemorrhagic or anemic infarcts and edema in the bilateral thalami and left cerebellar hemisphere (Fig. 2A and B), and abnormal intensities suggestive of thrombi extending throughout the straight sinus (Fig. 2H and I) and left sigmoid sinus (Fig. 2N and O) were evident. No thrombus was observed in the right sigmoid sinus (Fig. 2T and U), body or extremities.

A general autopsy was performed. The fresh brain was severely swollen and soft. Fresh hemorrhagic or anemic infarcts involving the bilateral thalami, midbrain tegmentum and base on the left side, and the left cerebellar hemisphere, were confirmed. In accordance with the postmortem images, we performed careful preparation of the sinuses and found that a continuous thrombotic substance occupied the lumen of the vein of Galen, and straight, tentorial, left transverse, and left sigmoid sinuses (Fig. 2C-E). Histological examination revealed an organizing white thrombus occupying the lumen and involving the wall of the left sigmoid sinus (Fig. 2P and Q), and an acute, red thrombus in the lumen of the left transverse, straight, and tentorial sinuses, and vein of Galen (Fig. 2J and K), indicating that the thrombus had developed first in the left sigmoid sinus, then extended retrogradely to the more proximal portion of the sinus system, reaching the vein of Galen. No thrombus was evident in the right transverse sinus.

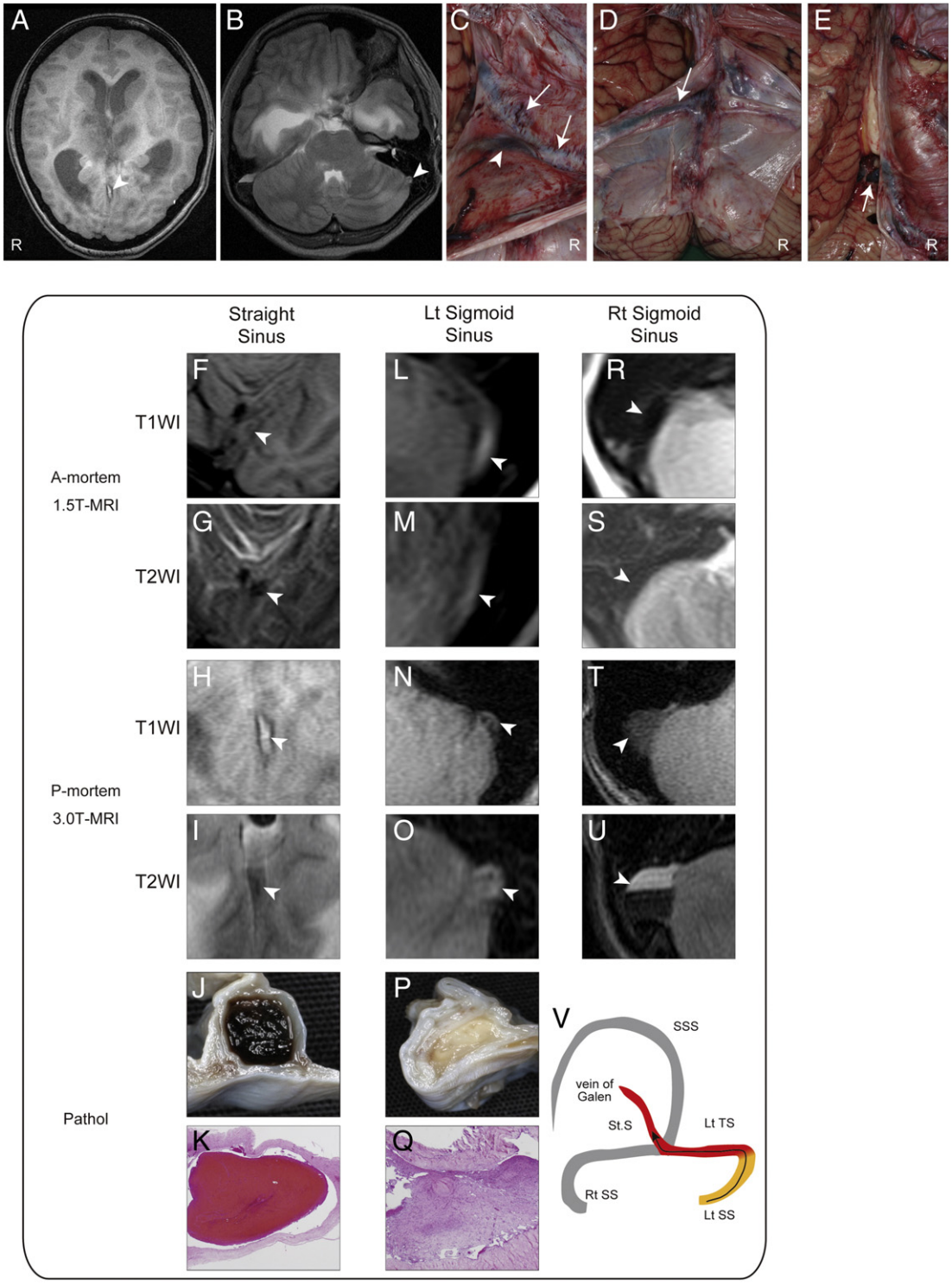

Fig. 2. MRI and autopsy findings. T1-weighted (T1W) (A, F, H, L, N, R, T) and T2W (B, G, I, M, O, S, U) images of post-mortem 3 T MRI (A, B, H, I, N, O, T, U) and ante-mortem 1.5 T MRI (F, G, L, M, R, S). The gross appearance (C–E), cut surface (J, P), and histology images of the sinuses (K, Q). Images of the straight (F-K: *arrowheads* in F-I), left sigmoid (L-Q: *arrowheads* in L-O), and right sigmoid (R-U: *arrowheads*) sinuses. *Arrowhead* in B indicates the left sigmoid sinus. *Arrowhead* and *arrows* in C indicate the vein of the left tentorium cerebelli and straight sinus, respectively. *Arrows* in D and E indicate the left transverse sinus and vein of Galen, respectively. Note the difference in signal intensity between the ante- and postmortem MRI. In the straight sinus, the thrombus shows low (F) and high (H) intensity on T1W images, respectively, and similar low intensity (G, I) on T2W images, representing the red thrombus (J, K). In the left sigmoid sinus, the thrombus shows high (L) and heterogeneously low (N) intensity on T1W images, respectively, and high (M) and heterogeneously high (O) intensity on T2W images, respectively, representing the white thrombus (P, Q). (V) A schematic representation of temporal extension of the thrombus (*yellow*: old, white thrombus, *red*: relatively fresh, red thrombus). The *long, curved arrow* indicates retrograde extension of the thrombus within the sinus system.

Comparative images of the antemortem 1.5 T-MRI and postmortem 3.0 T-MRI, histopathologic pictures of the corresponding sinuses, and a schematic representation of the sinus thrombosis are shown in Fig. 2F–V.

3. Discussion

In the present study, we demonstrated the features of the sinus thrombosis in detail using our originally developed postmortem 3 T-

MRI system, and then investigated the corresponding lesions in histopathologic preparations (Fig. 2).

The patient had acute symptoms possibly associated with the development of thrombus shortly after starting to take the CHC. In general, venous thrombosis tends to develop in women who have used oral contraceptives for a prolonged period [4]. However, a population-based, case–control study revealed that women who use oral contraceptives, and who have inherited clotting defects (deficiencies of protein C, protein S, or antithrombin, or otherwise mutations of factor V Leiden or prothrombin 20,210 A) may develop venous thrombus significantly earlier than those without such defects [5]. Considering the fact that this patient developed sinus thrombosis immediately after starting to take the CHC, she may have had certain underlying risk factors, even though no such factors were apparent, as described above. We were unable to perform further examinations of other coagulation factors, including protein C, protein S, or antithrombin III, in view of the patient's serious condition. In response to three lethal cases of thrombosis, including the present one, in women taking YAZ® in Japan as of January 2014, the Ministry of Health, Labor and Welfare has issued safety communication about the risk of thrombosis associated with the use of YAZ® combination tablets for dysmenorrhea [6].

We speculated that the thrombus had initially developed in the left sigmoid sinus and extended retrogradely (Fig. 2V). Hemorrhagic infarcts in the bilateral thalami appeared to have developed when the thrombus reached the straight sinus. In the present study, we successfully demonstrated alterations in the MRI signal intensity of the sinus thrombus (Fig. 2), reflecting the phases of thrombus organization [7,8]. In the straight sinus, the thrombus showed low (Fig. 2F) and high (Fig. 2H) intensity in T1W ante- and post-mortem images, respectively, indicating that the thrombus was fresh. On the other hand, in the left sigmoid sinus, the thrombus demonstrated high (Fig. 2L) and heterogeneously low (Fig. 2N) intensity in the ante- and post-mortem T1W images, respectively, indicating that the thrombus was relatively well organized. These images seemed to be consistent with the histopathologic features (Fig. 2J, K, P and Q), and supported the idea of thrombus extension (Fig. 2V).

As demonstrated in the present study, our postmortem 3 T MRI system is practically useful for detection of brain lesions. This system can keep the whole body in a refrigerated state during the long acquisition time required. Following MRI, we performed a complete autopsy. This reflects our policy of combining both high-resolution imaging and pathology studies in order to gain a better understanding of the pathophysiology in individual cases. To our knowledge, another postmortem 3 T MRI system mainly targeting cardiopulmonary disorders has been reported in Switzerland [9].

It is unclear whether the white thrombus developed after the patient had begun to take the CHC, or whether it had already been present. The patient had no medical history that suggested she might be at risk of CVST. Moreover, histological examination revealed that the proximal portion of the thrombus in the left sigmoid sinus contained an admixture of both organizing and fresh thrombi (images not shown), suggesting temporal continuity of thrombus organization. The diameter of the left transverse and sigmoid sinuses appeared much smaller than that of the right sinus. Therefore, the main venous flow may have been through the right sinus, and if so, such hemodynamics could have posed a risk of CVST in the left sigmoid sinus.

In the present patient, a lipoma on the body of the corpus callosum was evident (Fig. 1C). To our knowledge, there is no evidence indicating a close association between the presence of lipoma and development of CSVT.

The clinical, postmortem 3 T-MRI, and autopsy features of the present patient appear to be informative. When encountering patients with headache and other symptoms suggestive of increased intracranial pressure, even in those who have begun to use low-dose estrogen CHCs only recently, and while recognizing that such cases are rare, careful follow-up, including MRI of the sinus system, should be conducted for accurate and prompt diagnosis of CSVT. If applicable, further surgical intravascular approaches may be considered for such patients.

Disclosure

The authors have stated that they have no conflicts of interest.

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