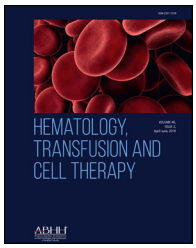
HEMATOLOGY, TRANSFUSION AND CELL THERAPY

www.htct.com.br



Case Report

Reversible cerebral vasoconstriction syndrome after intrathecal cytarabine

Natalia Trombini Mendes *, *Luiza Ramos de Freitas*, *Rônney Pinto Lopes*, *Lohana Santana Almeida da Silva*, *Francisco Tomaz Meneses de Oliveira*

Irmandade da Santa Casa de Misericórdia de São Paulo, São Paulo, SP, Brazil

ARTICLE INFO

Article history:
Received 28 May 2019
Accepted 1 October 2020
Available online 5 December 2020

Introduction

Reversible Cerebral Vasoconstriction Syndrome (RCVS) is a neurological syndrome characterized by a severe acute headache, maximal at onset, associated with diffuse segmental constriction of cerebral arteries. Relapsing headache is the main feature, often qualified as thunderclap headache – severe pain reaching peak in less than one minute – and can be followed by other acute neurological symptoms, particularly transient focal deficits and seizures. Symptoms are usually self- limited and can last up to twelve weeks, but complications such as ischemic lesions and intraparenchymal and subarachnoid hemorrhages can occur.[1]

Most RCVS cases are triggered by an underlying condition or exposure, like complications of postpartum and vasoactive drugs use; some of which particularly implicated are antidepressants, illicit drugs, nasal decongestants and triptans, among many others.[1] Less commonly, the use of chemotherapeutic agents can precipitate RCVS and intrathecal cytarabine has been reported as a rare causative agent in the pediatric population.[2–6]

Even though differential diagnosis is vast, including intracranial hemorrhage, cerebral venous thrombosis, artery dissection, pituitary apoplexy and primary headaches, it can usually be narrowed after neuroimaging and cerebral angiograms. As a self-limiting condition, observation and symptomatic management might be reasonable in patients without clinical deterioration, but follow-up must be warranted to identify early signs of progression and persistence of vasospasm. Other therapeutic strategies that can be considered to relieve arterial narrowing in specific cases include nimodipine, verapamil and magnesium sulphate.[2]

The aim of this study is to report a case of RCVS following intrathecal chemotherapy with cytarabine in an adult patient and to review the literature concerning this topic.

Case presentation

A 28-year-old female diagnosed with primary mediastinal B-cell lymphoma (PMBL) subtype of diffuse large B-cell lymphoma (DLBCL) in May 2017 after experiencing several months of weight loss, fever and fatigue associated with a large

* Corresponding author at: Rua Dr. Cesário Motta Jr., 112. Santa Cecília. 01221-020 São Paulo,SP, Brazil.
E-mail address: natalia.tmendes@gmail.com (N.T. Mendes).
https://doi.org/10.1016/j.htct.2020.10.961

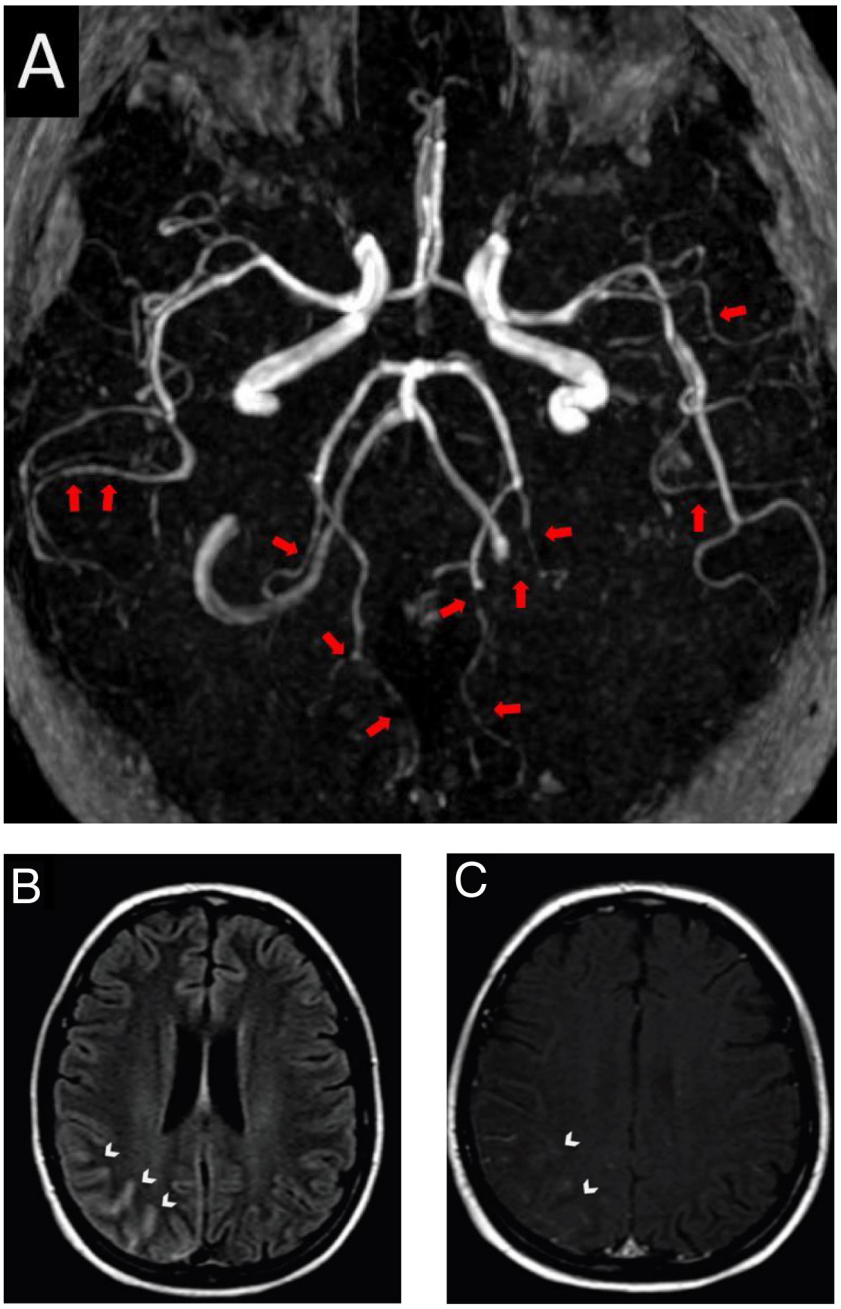


Fig. 1 – Brain magnetic resonance and angiography images. A, Angiography MRI showing segmental arterial constriction (red arrows). B, High intensity signal in the cortical sulcus and gyrus of the right parieto-occipital convexity on T2/Flair (white arrowheads). C, Slight impregnation of contrast in the leptomeningeal adjacent to the right parieto-occipital convexity on T1-GD (white arrowheads).

anterior mediastinal mass infiltrating the right lung and the sternum. Her past medical history was unremarkable. Initial work-up showed metastatic lesions affecting the liver and kidneys and also revealed chronic thrombosis of bilateral internal jugular veins and subclavian veins. Systemic chemotherapy with CHOP-R (6 cycles every 21 days of rituximab 375 mg / m2, cyclophosphamide 750 mg / m2, doxorubicin 50 mg / m2 and vincristine 2 mg) was initiated and intrathecal (IT) chemoprophylaxis with cytarabine 40 mg, methotrexate 15 mg and dexamethasone 4 mg was indicated, once the patient was considered at risk for central nervous system (CNS) relapse.

After four hours of the first IT chemotherapy infusion, the patient presented with severe headache, maximal at onset, described as a frontal and retro-orbital pressure, which persisted despite optimized analgesia, she did not show any other concurrent neurological signs or symptoms and her arterial blood pressure on admission was 110/70 mmHg. Patient had received the last systemic chemotherapy 3 days before symptoms onset and denied receiving any other vasoactive drugs.

Table 1 – Summary of RCVS cases after chemotherapy.

	Case 1 Pound et al.	Case 2 Yoon et al.	Case 3 Sankhe et al.	Case 4 Tibussek et al.	Case 5 Tibussek et al.	Case 6 Aoki et al.	Case 7 This report
Age at onset	7 y	3 y	13 y	3 y	5 y	7 y	28 y
Hematologic diagnosis	ALL	ALL	ALL	ALL	ALL	ALL	DLCBL
Chemotherapy protocol	COG AALL 0331	Not started	N.D.[a]	COG AALL 0932	COG AALL 0932	JPLSG ALL-B12	CHOP-R
IT cytarabine Dose	Yes 70mg	Yes 70mg	N.D.	Yes 70mg	Yes 70mg	Yes[b]	Yes 40 mg
Symptom onset after infusion	3 d	10 d	4 d	4 d	11 d	6 d[b]	4 h
Associated Symptoms	Aphasia, visual hallucinations, hemiparesis	Headache, visual loss, hemiparesis	Seizures	Limb weakness	Headache, hemiplegia, gaze deviation, speech arrest	Headache	Headache
Complications	AIS	AIS	PRES	AIS	AIS	None	SAH
Neurologic Outcomes	Full recovery	Full recovery	Full recovery	Full recovery	Persistent hemiplegia	Full recovery	Full recovery

ALL: Acute Lymphocytic Leukemia; DLCBL: Diffuse Large B-cell Lymphoma; COG: Children's Oncology Group; JPLSG: Japanese Pediatric Leukemia/Lymphoma Study Group; N.D._ Not described; AIS: Acute Ischemic Stroke; PRES: Posterior Reversible Encephalopathy Syndrome; SAH: Subarachnoid Hemorrhage.

[a] Protocol not described. Patient received daunorubicin, vincristine and steroids before symptoms onset.

[b] Patient received IT cytarabine more than 3 weeks before symptoms onset (dose not described) and it was not implicated by the authors as the triggering factor.

Head computed tomography (CT) did not show any abnormalities, thus symptoms were initially attributed to post puncture headache. As she persisted presenting recurrent headache in the following days, a brain magnetic resonance imaging (MRI) and angiography was obtained 11 days after symptoms onset. Images showed signs of diffuse arterial vasospasms consistent with RCVS (Fig. 1A) with secondary subarachnoid hemorrhage (Figs. 1B and 1C). The patient was treated symptomatically and experienced gradual improvement of the headache within three weeks. Neuroimaging after twelve weeks showed complete resolution of the vascular findings and the previous hemorrhage.

Discussion

RCVS is diagnosed by detecting diffuse cerebral vasospasm in the absence of aneurysmal subarachnoid hemorrhage (SAH) and reversion of symptoms within 12 weeks.[1] We report a case of a 28-year-old woman diagnosed with RCVS, with typical clinical and radiological findings, after receiving treatment with IT cytarabine. Brain MRI identified SAH as a complication of RCVS, with no brain aneurysms. Neurotoxicity is a common side effect of chemotherapy and symptoms differ according to drug class and dosage. Cytarabine has been associated with an array of neurotoxic effects, including myelopathy, peripheral neuropathy, seizures, encephalopathy and acute cerebellar syndrome,[7] but cerebral vasospasm is not a frequently reported complication. We identified, throughout an extensive literature review in major medical databases (PubMed and LILACS), six previously reported cases of RCVS following chemotherapy,[2–6] all in children with LLA. IT cytarabine was implicated as the probable causative agent in four of the cases[3–5]; in one other case, patient had received IT cytarabine more than three weeks before symptoms onset, therefore it was not held responsible for triggering the event.[6] The clinical characteristics of the six reported cases as well as the present case are summarized in Table 1.

We could not find other reports of RCVS after chemotherapy with cytarabine in the adult population in current literature; although, comparable cases of posterior reversible encephalopathy syndrome (PRES) following treatment with cytarabine have been described in older adults.[8,9] A recent study by Sun et al.[10] used transcranial Doppler ultrasound to evaluate signs of subclinical cerebral vasospasm in a subset of children with hematologic malignancies who receive intrathecal cytarabine. Among the 18 enrolled subjects, four (22%) met the criteria for subclinical vasospasm within four days of IT cytarabine administration, suggesting that this complication may not be as rare as once thought and that it is probably underdiagnosed. Unlike the aforementioned reports, the majority of patients in this study with cerebral vasospasm (three of the four) had acute myeloid leukemia (AML) and only one had ALL.

Other chemotherapeutic agents have been implicated as triggers for RCVS. The patient in question had also been exposed to rituximab, cyclophosphamide, doxorubicin, vincristine, and methotrexate. There are reports of other chemotherapy drugs possibly implicated with RCVS, including methotrexate,[11] cyclophosphamide,[12] daunorubicin and vincristine.[2] Rituximab is most often related to paresthesia, dizziness, and anxiety. Cyclophosphamide is most often related to encephalopathy, seizures, dizziness, peripheral neuropathy, and myelopathy. Doxorubicin is implicated with

cerebrovascular disease peripheral neurotoxicity. Vincristine tends to have dose-dependent neurological effects, which are mainly peripheral symptoms and cranial neuropathy, but can also be associated with seizures, cerebellar dysfunction, and movement disorders. Methotrexate can be related to several types of neurotoxicity, specially leukoencephalopathy and chemical meningitis.[13] In the present case, the patient did not show any symptoms after exposure to the other chemotherapeutic agents and presented the symptoms with an intimate temporal relationship to the exposure to cytarabine, not presenting any complaints after continuing therapy with methotrexate alone. Thus, we consider that the patient's symptoms were caused by diffuse cerebral vasospasm probably after IT cytarabine.

As the mechanism of chemotherapy-associated neurotoxicity is not well known, specific therapeutic and prevention strategies are a challenge and have not yet been developed.

Conclusions

Previous studies strongly suggest a true association between RCVS and IT cytarabine; however, it may be underdiagnosed. This seem to be the first reported case in the adult population and further research is needed to confirm this association.

The knowledge and early recognition of RCVS in patients undergoing chemotherapy is important for all neurologists, hematologists, and emergency physicians once it could potentially prevent subtle and severe neurologic consequences.

Conflicts of interest

The authors declare no conflicts of interest.

REFERENCES

1. Ducros A. Reversible cerebral vasoconstriction syndrome. Lancet Neurol. 2012;11:906–17.
2. Sankhe S, Kamath N, Sahu A. A rare case of chemotherapy induced reversible cerebral vasoconstriction syndrome in a patient of acute lymphocytic leukemia. Journal of Cancer Research and Therapeutics. 2015;11:1012.
3. Pound CM, Keene DL, Udjus K, Humphreys P, Johnston DL. Acute encephalopathy and cerebral vasospasm after multiagent chemotherapy including PEG-asparaginase and intrathecal cytarabine for the treatment of acute lymphoblastic leukemia. J Pediatr Hematol Oncol. 2007;29:183–6.
4. Tibussek D, Natesirinilkul R, Sun LR, Wasserman BA. Brandão LR, deVeber G. Severe Cerebral Vasospasm and Childhood Arterial Ischemic Stroke After Intrathecal Cytarabine. Pediatrics. 2016;137:e20152143.
5. Yoon JH, Yoon JHY, Park HJ, Son MH, Kim S-H, Kim W, et al. Diffuse cerebral vasospasm with infarct after intrathecal cytarabine in childhood leukemia. Pediatrics International. 2014;56:921–4.
6. Aoki T, Koh K, Arakawa Y, Mori M, Oguma E, Hanada R. Reversible Cerebral Vasoconstriction Syndrome during Chemotherapy for Acute Lymphoblastic Leukemia. J Pediatr. 2017;180:284, http://dx.doi.org/10.1016/j.jpeds.2016.09.045.
7. Baker WJ, Royer GL, Weiss RB. Cytarabine and neurologic toxicity. Journal of Clinical Oncology. 1991;9:679–93.
8. Henderson RD, Rajah T, Nicol AJ, Read SJ. Posterior leukoencephalopathy following intrathecal chemotherapy with MRA-documented vasospasm. Neurology. 2003;60:326–8.
9. Saito B, Nakamaki T, Nakashima H, Usui T, Hattori N, Kawakami K, et al. Reversible posterior leukoencephalopathy syndrome after repeat intermediate-dose cytarabine chemotherapy in a patient with acute myeloid leukemia. American Journal of Hematology. 2007;82:304–6.
10. Sun LR, Ziai W, Brown P, Torriente AG, Cooper S, Gottesman RF, et al. Intrathecal chemotherapy-associated cerebral vasospasm in children with hematologic malignancies. Pediatr Res. 2020.
11. Wang X, Zhang Y, You H, Zhu T, Zhou D. A Case of Reversible Vasoconstriction Syndrome Triggered by High-Dose Methotrexate in a Boy With Lymphoma. Headache. 2019;0:1–6, http://dx.doi.org/10.1111/head.13526.
12. Ducros A, Boukobza M, Porcher R, Sarov M, Valade D, Bousser MG. The clinical and radiological spectrum of reversivle cerebral vasoconstriction syndrome. A prospective series of 67 patients. Brain. 2007;130:3091–101.
13. Stone JB, DeAngelis LM. Cancer Treatment Induced Neurotoxicity: A Focus on Newer Treatments. Nat Rev Clin Oncol. 2016;13(2):92–105.