# A Very Rare Cerebral Complication of Chemotherapy in a Young Girl: A Difficult Diagnosis

Wala Ben Kridis[*,1], Afef Khanfir[1], Fatma Kammoun[2], Kheireddine Ben Mahfoudh[3], Chahinez Triki[2] and Mounir Frikha[1]

[1]*Department of Oncology, Habib Bourguiba Hospital Sfax, Tunisia*

[2]*Department of Neuropediatrics, Hedi Chaker Hospital Sfax, Tunisia*

[3]*Department of Radiology, Habib Bourguiba Hospital Sfax, Tunisia*

**Abstract:** Sagittal sinus thrombosis (SST) induced by chemotherapy is exceptional. We describe here a new case following the fourth cure of chemotherapy based on cisplatin, bleomycin and etoposide in a 16-year-old patient with no obvious risk factors. Through this uncommon case which forms part of cerebral venous sinus thrombosis (CVST), we propose to study the pathophysiology, the diagnosis and the management of this entity.

The exclusion of the other causes of CVST is important not only for the therapeutic implication but also for the prognosis. Then, accurate documentation of each case induced by chemotherapy is needed to further understanding.

**Keywords:** Cerebral thrombosis, chemotherapy, cisplatin.

## INTRODUCTION

More than 100 causes of cerebral venous thrombosis (CVST) have been described in the literature [1]. The diagnosis of this entity was difficult for more than 100 years. Currently, the imaging has facilitated the diagnosis [1]. The frequency of patients diagnosed with cerebral venous sinus thrombosis (CVST) has increased due to the expanded use of noninvasive brain imaging methods. Sagittal sinus thrombosis (SST) which forms part of CVST is exceedingly rare when it is secondary to chemotherapy. We report here a new case and we propose to study the pathophysiology, the diagnosis and the management of this entity.

## CASE REPORT

A 16 -year-old girl, with a history of a right ovarian cystectomy in 2012, consulted in March 2013 for a pelvic pain. Ultrasound and abdominal CT scan showed multiple pelvic masses measuring 11cm, 10cm and 8.7 cm with low abundant ascites (Fig. **1**). The exploratory laparoscopy showed pelvic masses with adherences to the digestive tract. Biopsy concluded to a grade III immature teratoma with peritoneal gliomatosis (stage IIIc). Carbohydrate antigen 125 (Ca 125) serum level was elevated (252.86ng/l). Alpha fetoprotein (AFP) and human chorionic gonadotropin (HCG) serum levels were negatives. The girl was treated by four cycles of intravenously BEP protocol (bleomycin 30 mg on days 1, 8, and 15 plus etoposide 100 mg/m $^2$ on days 1-5 plus cisplatin 20 mg/m$^2$ on days 1-5; every 21days), with complete clinical and biological response and partial radiological response. Ten day after the fourth and the final cure of chemotherapy, the girl consulted for heaviness in her left hemi body. Clinical examination concluded to a left hemi paresis. Serum calcium, magnesium, sodium and potassium were normal. Cerebral computed tomography showed an endoluminal defect in the superior sagittal sinus (empty delta sign) with hypodensity of the right semi oval center (Fig. **2**). Cerebral MRI concluded to superior sagittal sinus thrombosis without brain metastases (Fig. **3**). The inflammatory and the lipid balances were normal. The protein S and C and antithrombin III serum levels were normal. Antinuclear and Anti-Yo antibodies were negatives. Investigation for systemic vasculitis, disseminated intravascular coagulation, anticardiolipin antibodies and thrombophilia was negative. Cardiac ultrasound was also normal. The D-dimer level was high. Thus, the diagnosis of CVST induced by chemotherapy was retained. Twenty days later, the neurological exam was normal after treatment with anticoagulants.

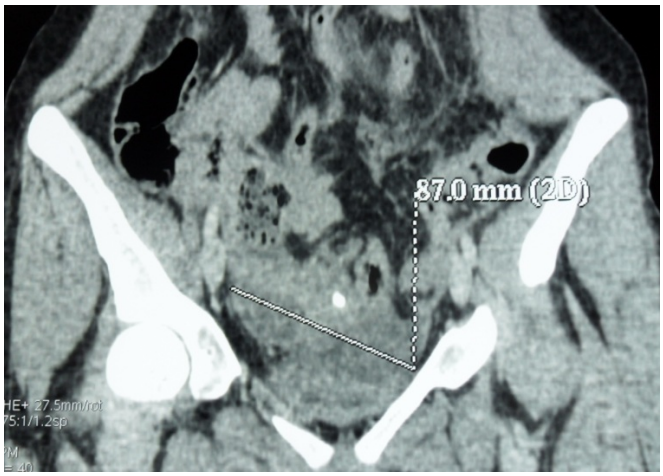


**Fig. (1).** Abdominal CT: Pelvic masses with gliomatosis

*Address correspondence to this author at the Department of Oncology, Habib Bourguiba Hospital Sfax 3029, Tunisia; Tel: ??????????????????????????; Fax: ??????????????????????????; E-mail: walabenkridis@yahoo.fr

1574-8863/15 $58.00+.00 

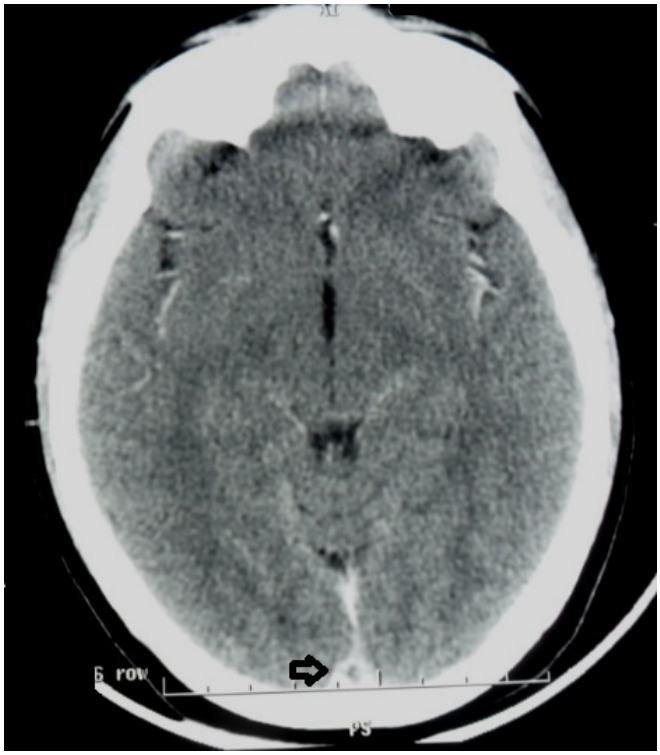

**Fig. (2).** Cerebral CT: Endoluminal defect in the superior sagittal sinus

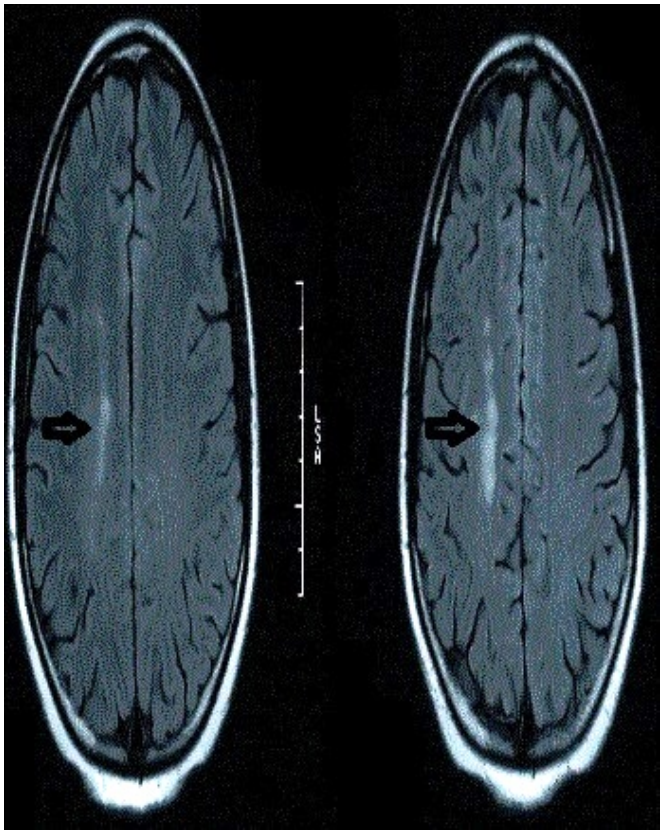

**Fig. (3).** Cerebral MRI: Hyperintensity of the right semi oval center in axial T2 flair (venous infarction).

One month later, repeat cerebral MRI was normal. Then, she underwent surgical resection of the residual pelvic mass. Pathological study concluded to a complete pathologic response after chemotherapy. Our patient is in complete remission with a follow up of 24 months.

## DISCUSSION

Atherosclerotic vascular disease, blood dyscrasias, deficiencies of protein S, C and antithrombin III, infections, penetrating head trauma, pregnancy and systemic diseases are the principle causes of CVST [1]. Only 7.4% of CVST were associated with cancer particularly in patients with hematologic malignancies. SST in cancerous patient may be caused by direct tumor compression, tumor invasion of sagittal sinuses, confinement to bed and paraneoplastic syndrome.

Chemotherapy may induce SST exceptionally. Factors identified by multivariate analysis to increase the risk of thrombosis in patient receiving chemotherapy were: advanced age, lower Karnofsky Performance Status score, the presence of a central venous catheter and higher Khorana score [2]. Compared to adult, thrombosis is a rare event in childhood. Children with cancer are exposed to thrombosis 600 time that the general pediatric population. Unal *et al.* had reported a case of cerebral venous sinus thrombosis in a 16-year-old adolescent girl with Ewing sarcoma treated with chemotherapy protocol consisting of Cisplatin, Ifosfamide, adriamycine and vincristine [3].

We describe here a new case of SST following chemotherapy based on cisplatin, bleomycin and etoposide in a 17-year-old patient with no obvious risk factors described above.

To our knowledge, the first reported case of cerebral stroke secondary to chemotherapy dates back to 1983 and the implicated product was Cisplatin [4]. By Goldhirsch *et al.*, the stroke incidence in patients on chemotherapy represent 0.137% [5]. Middle cerebral arterial stroke was the most common type. CVST induced by chemotherapy is exceedingly rare. It was described from some case reports. Most of CVST occurred within 10 days after chemotherapy which concord to our patient. Thus, it occurred following the first cycle.

Cancer and cisplatin chemotherapy are well-recognized risk factors for coagulation disorders and thrombosis. Several reports suggest that cisplatin is associated with an increased risk of thromboembolism. A meta-analysis of 8,216 patients from 38 randomized trials had included prospective randomized phase II and III trials evaluating cisplatin-based *versus* non–cisplatin-based chemotherapy in patients with solid tumors. This meta-analysis of Seng *et al.* revealed that those receiving cisplatin-based chemotherapy had a 1.67-fold increased likelihood of experiencing a thromboembolic event. Exploratory subgroup analysis revealed the highest relative risk of thrombosis in patients receiving a weekly equivalent cisplatin dose > 30 mg/m$^2$ [6].

Cisplatin is not well known to be associated with cerebral sinus thrombosis. Karam *et al.* had reported two cases with cerebral dural sinus thrombosis following cisplatin therapy. The first patient was a 33-year-old man with a germ-cell carcinoma of the testis. The second was a 60-year-oldwomanwith hypertension, hypercholesterolemia and

diabetes mellitus who were diagnosed with poorly differentiated pericardial carcinoma [7].

Cisplatin may induce CVST by reducing the protein C 4 activity [8], which has been known to increase the hyper coagulability state. Additionally, cisplatin infusion releases free radicals, which cause direct vascular endothelial injury, leading to the release of endothelial and platelet and the initiation of a cascade of platelet aggregation and vasoconstriction [9]. Cisplatin is also known to induce hypomagnesemia, which increases the vascular smooth muscle contraction contributing to vascular toxicity. However, in our case the magnesium levels were normal. Furthermore, liver metastasis and high dose of corticosteroids increase thrombo-embolic complications in cancerous patients having germ cell tumour during chemotherapy administration [4].

The majority of authors suggested cisplatin as the causative agent of CVST and SST [10]. To our knowledge, there are no reports that clearly link etoposide to neurovascular adverse reactions. Bleomycin may cause myocardial infarction, coronary heart disorder and bleeding disorders in the brain. In our case, neuroimaging didn't show cerebral bleeding and cardiac ultrasound was normal. Based on this information, cisplatin appears to be the most likely candidate for having caused the severe cerebrovascular complication in our patient. So, clinicians should be aware of the potential neurovascular adverse effect of this drug.

Clinical presentation is variable. SST occurs over hours to a few weeks after drug administration. The principal clinical sign in our case was paresis. In the Dutch-European study, the most frequent revealed symptom was headache (95%) [11]. But, our patient consulted for heaviness in her left hemi body without headache. In fact, there are other signs described in the literature such us focal seizures with or without secondary generalization, paresis and papillo-edema [11]. The diagnosis of SST is based on neuroimaging. In our patient, the cerebral CT showed the typical empty delta sign which occurs only in 20% of cases in the literature.

Cerebral MRI is the imagery of choice for the diagnosis of dural sinus thrombosis. In our case, paresis disappeared few days after treatment by low molecular weight heparin. Then, we introduce oral anticoagulant. By reviewing the literature, the treatment of SST is based on anticoagulation to avoid blood clot formation. In patients with suspected CVT, routine blood studies consisting of a complete blood count, chemistry panel, prothrombin time, and activated partial thromboplastin time should be performed. In our case the protein S and C and antithrombin III serum levels were normal. A normal D-dimer level may be considered to help identify patients with low probability of CVST.

Clinical practice guidelines recommend low molecular weight heparin or heparin in the initial treatment, followed by warfarin [12, 13]. The duration of warfarin treatment varied from 6 to 12 months. However, warfarin treatment may need to continue indefinitely in case of absence of disappearance of thrombosis. Endovascular therapy may be considered in patients with absolute contraindications for anticoagulation therapy or failure of initial therapeutic doses of anticoagulant therapy. Endovascular treatment of venous sinus thrombosis may include the use of a double lumen balloon, as it allowed direct infusion of continuous in situ tissue plasminogen activator through the balloon catheter without having to exchange the balloon for a microcatheter. Successful recanalization substantially helps to achieve good clinical outcome in patients with CVST. The prognosis was good in our case which concord with data of the literature with a low rate of recurrence (2.8%) [13].

## CONCLUSION

SST is a common complication in cancer patients because of multiple risk factors. Chemotherapy is a very rare etiology of SST. Therefore, the exclusion of the other causes is important not only for the therapeutic implication but also for the prognosis. It is difficult to recognize CVST at an early stage due to its diverse clinical presentations. Neuroimaging may be helpful for the diagnosis. Epilepsy and papilla-edema are potentially independent predictors for the 12-month functional outcome of patients with CVST. Then, accurate documentation of each case is needed to further understanding.

## CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

## ACKNOWLEDGEMENTS

Declared none.

## REFERENCES

[1] J. Kimber. Cerebral venous sinus thrombosis. QJ Med 2002:137-42.

[2] Moore RA, Adel N, Riedel E, *et al*.: High incidence of thromboembolic events in patients treated with Cisplatin-based chemotherapy: a large retrospective analysis. J Clin Oncol 2011; 29: 3466-73.

[3] Unal E, Yazar A, Koksal Y, Caliskan U, Paksoy Y and Kalkan E: Cerebralvenous sinus thrombosis in an adolescent with Ewing sarcoma. Childs Nerv Syst 2008, 24: 983-86.

[4] Li SH, Chen WH, Tang Y, *et al*. Incidence of ischemic stroke post-chemotherapy: a retrospective review of 10,963 patients. Clin Neurol Neurosurg. 2006;108(2):150-6.

[5] Goldhirsch A, Joss R, Markwalder TM, Studer H, Brunner K: Acute cerebrovascular accident after treatment with cis-platinum and methylprednisolone**.** *Oncology* 1983, 40:344-45.

[6] Seng S, Liu Z, Chiu SK, *et al.*: Risk venous thromboembolism in patients with cancer treated with Cisplatin: a systematic review and meta-analysis. J Clin Oncol 2012, 30:4416-26.

[7] Karam C and Koussa S: Cerebral dural sinus thrombosis following cisplatin chemotherapy. J Clin Neurosci 2008, 15: 1274- 75.

[8] Licciardello JT, Moake JL, Rudy CK, Karp DD, Hong WK. Elevated plasma von Willebrand factor levels and arterial occlusive complications associated with cisplatin-based chemotherapy. Oncology 1985;42(5):296-300.

[9] Periard D, Boulanger CM, Eyer S, Amabile N, Pugin P, Gerschheimer C, Hayoz D. Are circulating endothelialderived and platelet-derived microparticles a pathogenic factor in the cisplatin-induced stroke? Stroke 2007; 38(5):1636-8.

[10] Russmann S, Winkler A, Lovblad KO, Stanga Z, Bassetti C. Lethal ischemic stroke after cisplatin-based chemotherapy for testicular carcinoma and cannabis inhalation. Eur Neurol 2002:178-80.

[11] De Bruin S, de Haan R, Stam J. Clinical features and prognostic factors of cerebral venous sinus thrombosis in a prospective series of 59 patients. J Neurol Neurosurg Psychiat 2001; 70:105-8.

[12] Saposnik G, Barinagarrementeria F, Brown RD Jr, Bushnell CD, Cucchiara B, Cushman M, deVeber G, Ferro JM, Tsai FY. Diagnosis and management of cerebral venous thrombosis: a statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2011:1158-92.

[13] Martinelli I, Franchini M, Mannucci PM. "How I treat rare venous thromboses". *Blood.2008 :* 4818-23.

Received: December 24, 2014 Revised: May 15, 2015 Accepted: May 18, 2015