Cerebral venous thrombosis after first Methotrexate administration by lumbar puncture in a patient with large B cell lymphoma

Thrombose veineuse cérébrale après la première administration de Méthotrexate par ponction lombaire

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Abstract

Cerebral venous thrombosis is a rare consequence of lumbar punctures for intrathecal therapy. We report a patient treated for diffuse large B cell lymphoma with cerebral venous thrombosis after intrathecal Methotrexate administration. In this patient, intrathecal treatment was discontinued and he was successfully treated with high-dose low-molecular-weight heparin subcutaneously.

Haematologist must be aware about neurological symptoms of cerebral venous thrombosis as a complication of lumbar puncture especially among patients with high coagulopathy state. If neurological symptom occurs, patient should be referred early to neurologist to avoid fatal outcome and neurological deficit.

Key words: Cerebral venous thrombosis, diffuse large B cell lymphoma, intrathecal Methotrexate, lumbar puncture.

Résumé

La thrombose veineuse cérébrale est une complication rare des ponctions lombaires. Nous rapportons le cas d'un patient traité pour un lymphome B diffus à grandes cellules et présentant une thrombose veineuse cérébrale après l'administration intrathécale de Méthotrexate. Le traitement intrathécal a été interrompu et le patient a été traité avec succès par l'héparine de faible poids moléculaire administrée par voie sous-cutanée.

L'hématologue doit être conscient des symptômes neurologiques de la thrombose veineuse cérébrale en tant que complication de la ponction lombaire, en particulier chez les patients présentant un état d'hypercoagulopathie.

En cas de symptômes neurologiques, le patient doit être adressé rapidement à un neurologue afin d'éviter une issue fatale et un déficit neurologique.

Mots clés: Thrombose veineuse cérébrale, Lymphome diffus à grande cellules, Methotrexate intrathecal, ponction lombaire

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INTRODUCTION

Lumbar puncture (LP) is an invasive procedure that could assess the spread of lymphoma and allow the administration of intrathecal chemotherapy (1). LP has common side effects such as headaches, infection local hematoma and leg numbness (2). Cerebral venous thrombosis (CVT) is a rare complication of LP (3). The etiology seems to be multifactorial, and several disorders, including diagnostic and therapeutic procedures, have been proposed as risk factors (4).
Herein, we describe a patient who developed CVT after lumbar puncture with intrathecal administration of Methotrexate (MTX).

CASE REPORT

A 24-year-old man, with no significant past medical history, presented to our department for superior vena cava syndrome. A computed-tomography scan of the thorax revealed a large right-sided dominant mediastinal mass measuring approximately 15.3 x 9.7 x 13.2 cm. Fine-needle aspiration and scan-guided core biopsy of the mediastinal mass were performed which revealed the presence of diffuse large B cell lymphoma (DLBCL). The patient was diagnosed with Ann Arbor stage IV DLBCL which is treated with the R-CHOP regimen (Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone). The patient didn't initially receive intrathecal injection of chemotherapy because he suffered from dyspnea. A complete clinical response was achieved with regression of vena cava syndrome.
The patient had her first LP for CNS prophylaxisis during his 4th R CHOP with intrathecal injection of 15 mg of MTX and 20 mg of corticosteroid. The cerebro-spinal-fluid (CSF) was normal, with a normal cell count, protein and glucose. Microscopic examination showed no malignant cells. On day 4 of the treatment, our patient presented a generalized seizure with a persistent post ictal coma that required his transfer to the intensive care unit. Clinical examination revealed right hemiparesis. Non-contrast brain Computed Tomography (CT) scan revealed a left frontal intraparenchymal hematoma measuring 20 x 8 mm with perilesional edema.
Brain Magnetic Resonance Imaging (MRI) showed CVT of the superior sagittal sinus and right lateral sinus extending to the homolateral jugular vein and causing a left frontal parenchymal hematoma, with no evidence of secondary cerebromedullary localization due to lymphoma (Figure 1).

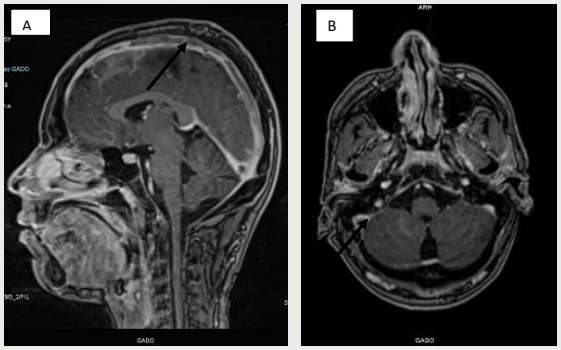

Figure 1. Sagittal (A) and axial (B) MRI T1-weighted images of the brain after gadolinium administration showed thrombus in the superior sagittal sinus (A) extending to the right lateral sinus and jugular vein (B).

Exhaustive biological tests panel for etiological assessment of CVT, including thrombophilia and immunological tests, were normal. The patient was treated with high-dose low-molecular-weight heparin subcutaneously during 6 months. Oral anticoagulation also vitamin K antagonist were avoided because of the risk of interaction with chemotherapeutic agents. MRI after 2 months of treatment showed resolution of the thrombosis (Figure 2).

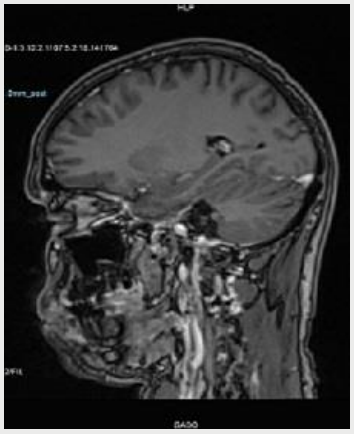

Figure 2. Sagittal MRI T1-weighted images of the brain after gadolinium administration showed a resolution of the thrombus

Unfortunately, the lymphoma was refractory to two lines of chemotherapy with rapid and aggressive progression leading to the death of our patient.

DISCUSSION

We report a case of CVT following lumbar puncture with intrathecal administration of MTX for treatment of a diffuse large B cell lymphoma. Known complications of LP include headaches, infection, local hematoma and leg numbness (2). CVT is a rare complication after LP (3). In our case, the CVT could be favored by LP regarding the chronology of clinical signs after this procedure. On reviewing the published literature for LP followed by CVT, 54 cases were identified. Two major groups were described: an obstetric group and non-obstetric group, including post-diagnostic lumbar puncture, spinal or epidural anesthesia, lumbar intrathecal injection for myelography or chemotherapy espacially MTX (6). Severe adverse events affecting CNS have been noted in approximately 3–40% of patients receiving intrathecal MTX including arachnoiditis, leukoencephalopathy, cerebral edema and/or hematoma and superior sagittal sinus thrombosis (7). No cases of systemic lymphoma with CVT after intrathecal MTX injection have been reported. Only thirteen cases of acute lymphoblastic leukemia with CVT were found (8).
Additional risk factors for CVT have been described including oral contraceptives, infections, malignancies, postpartum conditions and hereditary thrombophilia that can even causes CVT (6). Our patient presented with a DLBCL which may be associated to hypercoagulability state (3). This is the first case of vascular complication after LP and intrathecal injection of MTX described in a patient with lymphoma in our series. The normality of Cerebrospinal fluid analysis and the significant clinical response after heparin therapy in our case exclude the responsibility of lymphoma for the development of CVT in our case.
CVT presents with a wide spectrum of clinical symptoms, including headaches, focal neurologic deficit, seizure and coma (3). The time interval between LP and the onset of symptoms, which was 4 days in our case, vary from a few hours to several days(3). MRI of the Brain is the procedure

of choice for the diagnosis of CVT (9).
Several mechanisms of CVT have been described. First, LP may lead to a decrease in intracranial pressure and ,consequently, a decrease in venous blood flow velocities, causing a downward displacement of the brain and traction on the cortical veins and the superior sagittal sinus (3). Second, intrathecal administration of the MTX could chemically irritate the venous sinus and induce local thrombosis (3). Third, LP induces a negative cranial–spinal pressure gradient with intracranial hypotension, which may cause local traction on the meninges and damage the venous endothelial wall inducing the development of subdural hematomas (3) . The fact that the thrombus was located in the superior sagittal sinus in our case supports the first theory.
Anticoagulation with low molecular weight heparin is safe and effective in the treatment of venous thromboembolism even when hematoma is present (10).
Clinical outcomes vary widely. Patients may recover completely or develop severe and permanent neurologic deficits (3). Our patient was successfully treated with low-molecular-weight heparin subcutaneously and thrombosis regressed after 2 months of anticoagulation.

CONCLUSION

Although neurologic complications after administration of Methotrexate by lumbar puncture are very rare, the diagnosis of CVT should be considered to avoid fatal outcomes and neurological deficits.

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