CASE REPORT

Bilateral subdural hygromas following administration of intrathecal methotrexate chemotherapy

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Accepted 1 May 2015

SUMMARY

We report the case of a previously well 58-year-old man who presented with headache and confusion 4 days postadministration of intrathecal methotrexate. He was undergoing intensive chemotherapy (CODOX-M/IVAC, cyclophosphamide, doxorubicin, vincristine, methotrexate, etoposide, ifosfamide, cytarabine) for the treatment of leukaemic phase CD20 negative diffuse large B-cell lymphoma. A CT of the head demonstrated the presence of bilateral subdural hygromas complicated by haemorrhage resulting from coexisting chemotherapy induced thrombocytopenia. Surgical drainage of the hygroma was undertaken but the patient died of overwhelming sepsis. In patients with high-risk lymphoma, directed central nervous system (CNS) therapy is administered either systemically or intrathecally. It is thought that subdural hygromas result from cerebrospinal fluid (CSF) accumulation in the inner dural layers of the cerebral convexities from CSF leak and reduction in CSF pressure post-lumbar puncture. We describe a rare but potentially fatal complication of intrathecal chemotherapy that haemato-oncologists need to be mindful of.

BACKGROUND

Intrathecal (IT) chemotherapy is delivered using a standard lumbar puncture (LP) technique. Common complications, especially post-LP headache are well known to those with experience in the procedure. The nature and persistent nature of the patient's symptoms was disproportional to those expected after uncomplicated administration of IT chemotherapy. The radiological findings were unexpected highlighting the rarity of subdural hygroma formation in such context.

CASE PRESENTATION

We report the case of a previously well 58-year-old man who presented with a short history of rapid-onset breathlessness and weight loss. Clinical investigation led to a diagnosis of leukaemic c-myc negative, CD20 negative diffuse large B-cell lymphoma (DLBCL). His performance status at diagnosis was 3 (WHO/ECOG). He was treated with the intensive CODOX-M/IVAC (cyclophosphamide, doxorubicin, vincristine, methotrexate, etoposide, ifosfamide, cytarabine) protocol¹ which includes IT and high-dose intravenous methotrexate as central nervous system (CNS) directed prophylactic therapy. The patient had an excellent clinical response to initial treatment achieving a complete remission after the first course of chemotherapy. There was no evidence of CNS disease at diagnosis

or during treatment based on repeated flow cytometry and cytospin testing of cerebrospinal fluid (CSF). At the time of IT chemotherapy administration, his coagulation screen was normal (prothrombin time 13 s, activated partial thromboplastin time 32 s, fibrinogen 6.1 g/L).

Four days after a routine, uncomplicated end of cycle IT methotrexate of CODOX-M of his second course, the patient presented with headache, nausea, mild confusion and unsteadiness.

INVESTIGATIONS

A CT scan of the head demonstrated the presence of bilateral subdural hygromas (figure 1). No radiological evidence of a congenital cause for low-pressure CSF such as an Arnold–Chiari malformation was present.

In the absence of clinical features of CNS involvement at presentation, CNS directed radiological investigation was not warranted and hence previous CT scan of the head was not available to compare with the diagnostic scan.

His haematological indices revealed a marked neutropenia and thrombocytopenia compatible with recent exposure to myelosuppressive chemotherapy (haemoglobin 103 g/L, white cell count $0.1 \times 10^9/L$, platelet $18 \times 10^9/L$, neutrophil $0.0 \times 10^9/L$). The coagulation profile was again normal (prothrombin time 13.5 s, activated partial thromboplastin time 31 s, fibrinogen 5.0 g/L).

DIFFERENTIAL DIAGNOSIS

In this scenario, complications potentially arising include:

- ▶ Post-LP headache and nausea
- ▶ CNS infection
- ▶ Secondary CNS lymphoma involvement
- ▶ Subdural hygroma

Figure 1 CT scan showing extensive supratentorial bilateral subdural collections.

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To cite: Lewis H, Mahdi AJ, Rowntree C. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2014-205059

TREATMENT

Presurgical optimisation included platelet transfusion support with two adult platelet doses resulting in a platelet count of $78 \times 10^9/L$. The collections were drained of blood-stained CSF under general anaesthetic via bilateral burr holes. Postoperatively, no drains or spinal patches were used. The operation note commented that the appearances were more compatible with hygromas rather than pure haemorrhage. There was also mention of reduced opening pressures on immediate drainage although an objective CSF pressure measurement was not undertaken.

OUTCOME AND FOLLOW-UP

Despite neurosurgical intervention, the patient continued to deteriorate with a fluctuating conscious level and persistent fever. The postoperative period was complicated by neutropenic sepsis with the likely source being pulmonary. The patient died 7 days later on the intensive care unit of multiorgan failure as a result of overwhelming sepsis.

DISCUSSION

Despite survival rates for patients with DLBCL increasing significantly over the past decade with the introduction of immunochemotherapy, approximately 5% of patients will relapse within the CNS² and the outlook for this group of patients remains poor. Consequently, the use of CNS directed prophylactic therapy continues to be recommended for patients who are deemed to have a high risk of developing secondary CNS lymphoma.³ However, IT chemotherapy is not without risks.

The mechanism for post LP bilateral hygromas is poorly understood but is presumed to involve a lumbar CSF leak with a reduction in CSF pressure, resulting in downward displacement of the brain with CSF accumulation in the inner dural layers of the cerebral convexities (hygromas).

Bilateral subdural hygromas have been described before in patients post-LP, including following administration of prophylactic IT methotrexate.⁴ A study of patients with subdural hygromas post haemopoietic stem cell transplant concluded that patients were at increased risk of developing subdural collections if they had an LP with or without IT chemotherapy administration, prior to or during transplantation.⁵ It is estimated that the risk of symptomatic subdural hygroma to be 1–2% after LP.⁶

In the absence for evidence of a structural cause for reduced CSF pressure, notably CNS involvement and/or congenital malformation, the IT administration of chemotherapy in this patient was most likely the causative mechanism of hygroma formation. In addition, haemorrhage into the fluid-filled pocket as a result of chemotherapy induced thrombocytopenia further complicated the presentation.

It should be remembered that the procedure of delivering IT chemotherapy is not without clinical risk. Clinicians are aware of the clinical governance risks around safe administration of IT chemotherapy, as well as the more common complications of

methotrexate induced encephalopathy and arachnoiditis. We describe a rare but potentially fatal complication of IT chemotherapy that haemato-oncologists also need to be mindful of. In the majority of cases described in the literature, post-LP headache was reported by the patients prior to the diagnosis of hygroma and should, therefore, be regarded as a potential warning sign. Coexisting thrombocytopenia poses an additional risk for haemorrhagic complication in this patient population.

Learning points

- ▶ Clinicians should be aware of the common risks associated with lumbar puncture including headache, nausea and pain to the local.
- ▶ Those patients presenting with persistent headache and/or significant signs of raised intracranial pressure should undergo brain imaging.
- ▶ Surgical drainage of symptomatic subdural hygroma should be considered.
- ▶ Concurrent thrombocytopenia in patients with haematological malignancies increases the risk of spontaneous bleeding and risks of surgical intervention.

Contributors HL acted as main author. AJM and CR both reviewed and coauthored the manuscript.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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