CASE REPORT

Cerebrospinal fluid involvement in acute promyelocytic leukaemia at presentation

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SUMMARY

In acute promyelocytic leukaemia (APL), extramedullary disease (EMD) is rare but can occur in those who relapse following therapy. Although the most common site of EMD in APL is central nervous system (CNS) and skin, CNS involvement in recently diagnosed patients with APL is very rare and rarely described. We report cerebrospinal fluid involvement in a case of APL, on day 3 of induction therapy.

BACKGROUND

Acute promyelocytic leukaemia (APL) is a condition classically characterised by a specific balanced chromosomal translocation, $t(15;17)(q22,q12)$, resulting in abnormal fusion gene PML/RAR α . With the use of all-trans retinoic acid (ATRA) and improved survival in patients with APL, extramedullary relapse following therapy have been reported more frequently.¹ We describe cerebrospinal fluid (CSF) involvement in a case of APL on day 3 of induction therapy which is rarely reported in literature.

CASE PRESENTATION

A 30-year-old woman presented in the medicine outpatient department of School of Medical Science and Research, Greater Noida with a 1-month history of fever, weight loss, fatigability and episodes of epistaxis. Physical examination did

not reveal any lymphadenopathy, gum hypertrophy or organomegaly. Her complete blood counts revealed—haemoglobin: 6.0 g/dL, platelet count: $30 \times 10^9/L$ and total leucocytes count (TLC): $85 \times 10^9/L$ with 92% promyelocytes. Prothrombin time was 12 s, activated partial thrombin time was 36 s and thrombin time was 12 s. Consequently, she was immediately put on induction therapy comprising of ATRA, daunorubicin and aggressive blood product support. Her bone marrow examination and flow cytometry were consistent with the diagnosis of APL (hypergranular type). Presence of $t(15;17)(q22,q12)$ was confirmed by cytogenetic analysis. On day 3 of induction, she reported headache and dizziness. Non-contrast CT scan did not show any intracranial bleed or any other abnormality. Although lumbar puncture should not be performed in a case of APL during the induction phase, it was performed in our case due to persistent headache, in the absence of coagulopathy and after ensuring a normal coagulation profile. Informed consent was obtained for the same. CSF cytology revealed presence of promyelocytes (figure 1A–D) and myeloperoxidase positivity (figure 1E). Complete blood count on day 3 of induction revealed 60% promyelocytes, TLC $60 \times 10^9/L$, haemoglobin 7.5 gm/dl and platelet count $70 \times 10^9/L$. Repeat CSF examination on day 4 of induction also showed promyelocytes. Subsequently, she received six cycles of triple

Figure 1 (A–D) Cytospin cerebrospinal fluid smears showing promyelocytes (Jenner-Giemsa stain, $\times 100$). (E) Strong myeloperoxidase positivity in a promyelocyte ($\times 100$).

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intrathecal therapy with methotrexate, cytarabine and hydrocortisone until her CSF was clear of leukaemic cells and her neurological symptoms subsided.

OUTCOME AND FOLLOW-UP

She is presently on ATRA and chemotherapy as maintenance. Her complete blood count and bone marrow show remission till date.

DISCUSSION

Extramedullary disease (EMD) is a rare complication in APL. It is estimated that about 3–5% of patients suffer EMD with central nervous system (CNS) being the most common site.² It is believed that ATRA induces differentiation of promyelocytes and is responsible for upregulation of cellular adhesion molecules such as VLA-4 and LFA-1. Adhesion of promyelocytes to the endothelium is further increased by interleukin 1 due to the effect mediated by increased expression of intercellular adhesion molecule 1 (ICAM-1) and vascular cell adhesion molecule 1 (VCAM-1) on CNS endothelium.² Thus upregulation of these adhesion molecules might promote passage of ATRA-treated promyelocytes across the blood–brain barrier causing CNS relapse.² Moreover it is speculated that ATRA therapy induces expression of adhesion molecules such as CD11c, CD13 and CD56 on promyelocytes, leading to extramedullary relapse.^{3–5}

CNS prophylaxis for patients in high-risk setting may be appropriate as majority of CNS relapses occurs in patients with APL with hyperleucocytosis. As lumbar puncture at initial presentation and during induction is extremely hazardous, CNS prophylaxis should be started after achieving complete remission.² However, in our patient lumbar puncture was performed on day 3 of induction therapy because of persisting headache and dizziness. Also, the patient and her husband were explained

Learning points

- ▶ Extramedullary involvement by acute promyelocytic leukaemia (APL) is relatively rare and the common sites of involvement are central nervous system and skin.
- ▶ Diagnostic lumbar puncture is not recommended and prophylactic intrathecal chemotherapy is not routinely administered during induction phase but can be performed in selective cases with persistent neurological symptoms, after obtaining informed consent and ensuring normal coagulation profile.
- ▶ Cerebrospinal fluid involvement in APL has been attributed to upregulation of cellular adhesion molecule such as VLA-4 and LFA-1 by all-trans retinoic acid therapy.

about the procedure and reason for doing it during the induction phase. They were also informed about the possible hazardous complication (death) that could occur following the procedure. It is important to ensure normal coagulation profile before starting diagnostic and therapeutic lumbar puncture because of associated coagulopathy with APL.

In short this case describes CSF involvement in a case of APL, on induction therapy which is quite rare. It also describes the possible mechanism by which malignant promyelocytes cross blood–brain barrier and reach CSF.

Contributors JM diagnosed the case, did literature search, and wrote and reviewed the manuscript. MG did the literature search, and edited and reviewed the manuscript.

Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

Patients perspective

- ▶ The family (patient, her husband and an 8-year-old son) was well educated, financially strong and had a non-medical background. When the diagnosis of blood cancer was revealed to them, they were very much tensed (husband was in tears). They were of the view that blood cancer is incurable and these patients do not survive. However, the doctors counselled them and advised them not to lose hope and start treatment immediately.
- ▶ Presently the patient is able to perform her routine activities.

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