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LETTER TO THE EDITOR

Acute promyelocytic leukaemia presenting with subarachnoid haemorrhage and complicated by central nervous system involvement

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Acute promyelocytic leukaemia (APML) is a condition classically characterised by t(15;17) (q22, q21), with disseminated intravascular coagulopathy (DIC) being a major cause of death. Central nervous system (CNS) involvement with APML commonly occurs in relapse; however, it is rarely seen at presentation, with only six reported cases in the literature. This case is the first to describe a patient with APML who presented with a subarachnoid haemorrhage and had CNS involvement early at diagnosis.

A 65-year-old woman was admitted with headache, generalised bruising and DIC. Her blood film and bone marrow examination were consistent with classic APML, while MRI scan confirmed a sub-arachnoid haemorrhage. Consequently she was commenced on all-*trans* retinoic acid (ATRA), idarubicin and aggressive blood product support.

Her treatment was initially complicated by ATRA differentiation syndrome and then extensive pulmonary emboli causing hypoxia, resulting in commencement of unfractionated heparin while maintaining a platelet count $>50\times10^9$/l.

During her induction she underwent serial MRI scans that, although confirmed no extension of her subarachnoid haemorrhage, showed persistent abnormal meningeal thickening. Lumbar puncture revealed an infiltrate of immature granular leucocytes and CNS involvement was confirmed by both immunophenotyping and cytogenetic analysis via fluorescent *in situ* hybridisation (FISH) (Figure 1). Consequently she went on to have six cycles of triple intrathecal therapy with methotrexate, cytarabine and hydrocortisone until her cerebrospinal fluid was clear of leukaemic cells, as confirmed by immunophenotyping and FISH.

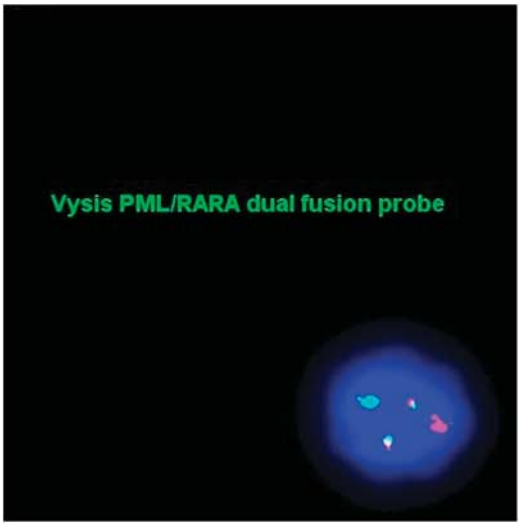

Figure 1 PML/RARα translocation identified in the patient's cerebrospinal fluid by fluorescent *in situ* hybridisation (FISH).

Bone marrow examination post induction confirmed complete morphological and cytogenetic remission, at which point she was commenced on arsenic trioxide and ATRA for her subsequent consolidation and currently she remains in remission.

Acute promyelocytic leukaemia is frequently associated with clotting abnormalities and carries a high risk of intracranial haemorrhage.[1] Bleeding involving the CNS is often catastrophic and is the main cause of death in induction for APML.[1–4]

CNS involvement in APML is extremely rare at presentation but not infrequent at relapse, and associated factors include raised white cell count ($>10\times10^9$/l), prior CNS haemorrhage, microgranular variant and bcr3 PML/RARα type.[5,6] Currently lumbar puncture is not carried out during induction when the risk of haemorrhagic complications is high. Instead it is reserved for patients with neurological symptoms or on relapse if CNS involvement is suspected.[7] Some strategies have included CNS prophylaxis in patients with high-risk features, although the benefit from this as yet remains to be established. An Italian report describes the use of routine lumbar puncture at the end of induction in newly diagnosed APML patients with a white cell count $>10\times10^9$/l. Seven patients underwent lumbar punctures and two were identified with CNS involvement;[6] both of these patients were in molecular remission in their marrows. The authors concluded that routine lumbar puncture may be recommended for patients with high risk features in order to identify occult CNS disease.

Our case supports that high-risk patients, in particular those who have intracranial haemorrhage and high white cell count ($>10\times10^9$/l) at presentation, should have diagnostic lumbar puncture performed earlier once the coagulopathy has resolved. This approach may allow earlier detection and treatment of occult CNS disease and consequently reduce the risk of future relapse.

Conflict of interest

The authors declare no conflict of interest.

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References

1 Chen CY, Tai CH, Tsay W, Chen PY, Tien HF. Prediction of fatal intracranial haemorrhage in patients with acute myeloid leukaemia. *Ann Oncol* 2009; **20**: 1100–1104.
2 Di Bona E, Avvisati G, Castaman G, Vegna ML, De Sanctis V, Rodeghiero F *et al*. Early haemorrhagic morbidity and mortality during remission induction with or without all-trans retinoic acid in

acute promyelocytic leukaemia. *Br J Haematol* 2000; **108**: 689–695.
3 Rodeghiero F, Avvisati G, Castaman G, Barbui T, Mandelli F. Early deaths and anti-haemorrhagic treatments in acute promyelocytic leukaemia. A GIMEMA retrospective study in 268 consecutive patients. *Blood* 1990; **75**: 2112–2117.
4 Kim H, Lee JH, Choi SJ, Kim WK, Lee JS, Lee KH. Analysis of fatal intracranial haemorrhage in 792 acute leukaemia patients. *Haematologica* 2004; **89**: 622–624.
5 Montesinos P, Diaz-Mediavilla J, Deben G, Prates V, Tormo M, Rubio V *et al*. Central nervous system involvement at first relapse in patients with acute promyelocytic leukaemia treated with all-trans retinoic acid and anthracycline monotherapy without intrathecal prophylaxis. *Haematologica* 2009; **94**: 1242–1249.
6 Breccia M, Carmosino I, Diverio D, De Santis S, De Propris MS, Romano A *et al*. Early detection of meningeal localisation in acute promyelocytic leukaemia patients with high presenting leucocyte count. *Br J Haematol* 2003; **120**: 266–270.
7 Sanz MA, Grimwade D, Tallmann MS, Lowenberg B, Fenaux P, Estey EH *et al*. Management of acute promyelocytic leukaemia: recommendations from an expert panel on behalf of the European LeukaemiaNet. *Blood* 2009; **113**: 1875–1891.