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Case Report

CASE REPORT

An unusual headache: CSF negative APML relapse in the brain

Dr Thomas Quinn[1,*], Dr Manish Jain[2] and Dr Ming-Te Lee[3]

[1]Department of Neurology, Leeds Teaching Hospitals Trust, Leeds, UK, [2]Department of Haematology, Leeds Teaching Hospitals Trust, Leeds, UK, [3]Department of Haematology, Leeds Teaching Hospitals Trust, Leeds, UK

*Corresponding address. Department of Neurology, Leeds Teaching Hospitals Trust, Leeds LS9 7TF, UK. Tel: 0113 243 2799; E-mail: thomas.quinn@nhs.net

Abstract

Acute Promyelocytic Leukaemia (APML) is a subtype of Acute Myeloid Leukaemia (AML), responsible for around 10% of cases of the disease in adults. Extra medullary disease (EMD) occurs infrequently in APML, but where EMD does occur, the central nervous system is one of the most commonly infiltrated sites. Our case describes a man in his 40s undergoing post-therapy surveillance for APML who presented to follow-up clinic with a headache, which was ultimately found to be caused by a tumour comprised of APML cells. His case presented a diagnostic challenge due to the benign appearances of the lesion on initial computed tomography brain imaging and the non-diagnostic cerebrospinal fluid analysis. The diagnostic difficulties described in our case emphasizes that clinicians working with APML patients must approach new neurological symptoms with a high degree of suspicion to prevent diagnostic delay.

INTRODUCTION

Acute Promyelocytic Leukaemia (APML) is a relatively uncommon subtype of Acute Myeloid Leukaemia (AML); in adults it is responsible for around 10% of cases of the disease [1]. Due to its unique sensitivity to treatment with ATRA (all-trans retinoic acid), around 80% of patients who survive induction therapy can now be expected to achieve complete remission [2]. Post-therapy patients can be stratified into different relapse risk categories to help guide follow up, and it is common practice for patients to undergo minimal residual disease (MRD) monitoring with a highly sensitive reverse transcription polymerase chain reaction (RT-PCR) test for the DNA translocations characteristic of APML to guide this follow up [2].

The literature on APML suggests that extra medullary disease (EMD) occurs infrequently, at around 3–5% of cases and most EMD occurs in post-therapy relapse. Where EMD does occur, the central nervous system (CNS) is one of the most commonly infiltrated sites, occurring in 0.6–2% of all APML cases [3]. As such, any APML patient presenting with new neurology or intracranial pressure symptoms will prompt the clinician to consider appropriate imaging and cerebrospinal fluid (CSF) examination for morphological and molecular evidence of disease (with exception given to those with the coagulopathy of acute illness or other absolute contraindication) [1].

We report a case of a man in his 40s who developed an isolated extra-medullary relapse of APML within the CNS which unusually had no detectable CSF involvement. He had previously received treatment for high-risk APML with ATRA and chemotherapy, and for a subsequent hematologic relapse he was given ATO (arsenic trioxide) and ATRA. His post-therapy MRD monitoring period had been completed without evidence of any further recurrence.

This late presentation of an isolated CNS relapse presented a diagnostic challenge as the EMD radiologically mimicked a benign solid tumour on initial computed tomography (CT) imaging, and his CSF had no detectable disease. Additionally, at the

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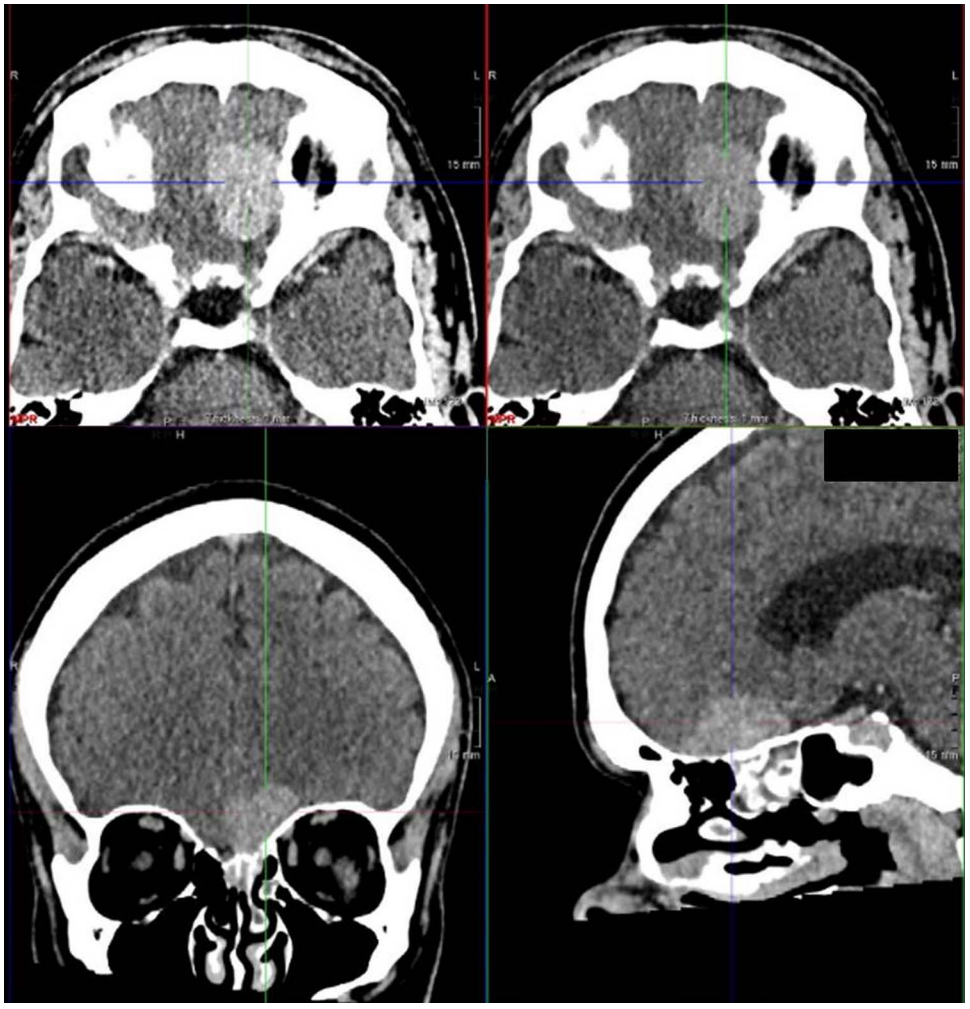

Figure 1: CT Head—Initial CT images showing a single enhancing and well-circumscribed lesion in the anterior cranial fossa floor.

time of presentation with his CNS relapse, our patient had no detectable disease in the bone marrow (including a negative RT-PCR for PML-RARA fusion gene).

CASE REPORT

A 45-year-old man presented to the Emergency Department in March 2014 with central 'pressure-like' chest pain and was discharged after chest X-ray, ECG and Troponin testing showed no overt cause of the pain. He re-presented 7 days later with worsening exercise-induced chest pain and shortness of breath, now associated with headache, pain in his right leg and sweating. His physical examination was unremarkable. Blood counts revealed he was very mildly anaemic (Hb 133 g/L), had a moderate thrombocytopenia (63 $\times 10*9$/L) and manual differential showed he had 54% circulating blasts. His coagulation screen showed DIC (borderline-low Clauss Fibrinogen level of (1.1 g/L) and a D-dimer of 2475 ng/ml). His bone marrow biopsy showed the classical t(15;17) translocation, confirming APML. He received induction and maintenance chemotherapy according to the AML-17 trial protocol with ATRA, Idarubicin and Mitoxantrone, which initially provided a good response.

Unfortunately, during follow-up, a bone marrow biopsy showed evidence of morphological relapse around 6 months after completing treatment. He received further treatment with ATRA and additional ATO (arsenic trioxide), which was completed in October 2015. During this time his CSF was tested and showed no evidence of APML. Again, he achieved a good response with molecular remission, and no markers suggestive of relapse in any subsequent bone marrow biopsies, which were taken every three month for 2 years.

During routine follow-up in June 2018, he reported he had been experiencing recurrent headaches for approximately 1 month. The pain was sharp and frontally localizing. This had been associated with the sensation of nasal congestion but no focal neurology. The only other concerning feature had been the onset of night sweats, sometimes requiring a change of pillow case.

He underwent a CT head scan, which showed a single enhancing well-circumscribed lesion in the anterior cranial fossa floor with no vasogenic oedema (see Fig. 1). Radiologically this was classified as a probable meningioma. CSF was analysed, which at this time showed no molecular or morphologic evidence of disease recurrence. He was subsequently seen in a neurosurgical clinic and a magnetic resonance imaging (MRI) was planned to determine a surgical or surveillance approach for the presumed meningioma.

In September the MRI scan (see Fig. 2) showed the lesion had grown significantly. It now extended across the cribriform plate,

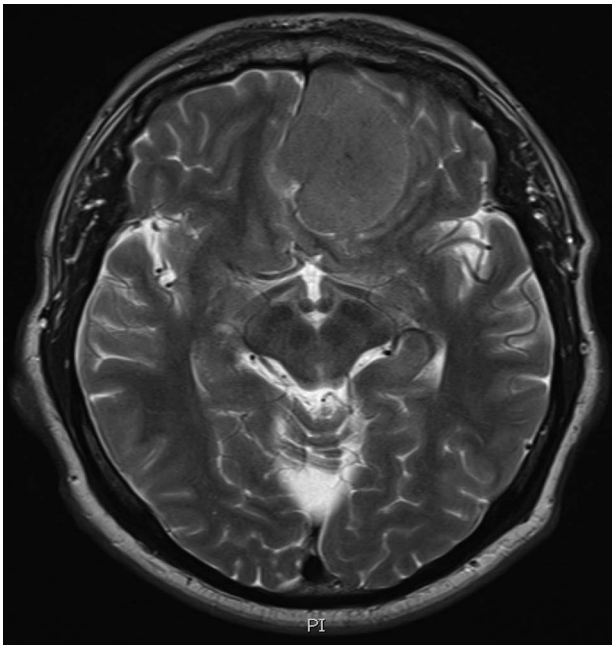

Figure 2: MRI Head—Subsequent MRI imaging of the brain which showed progression of the mass with associated bony lysis.

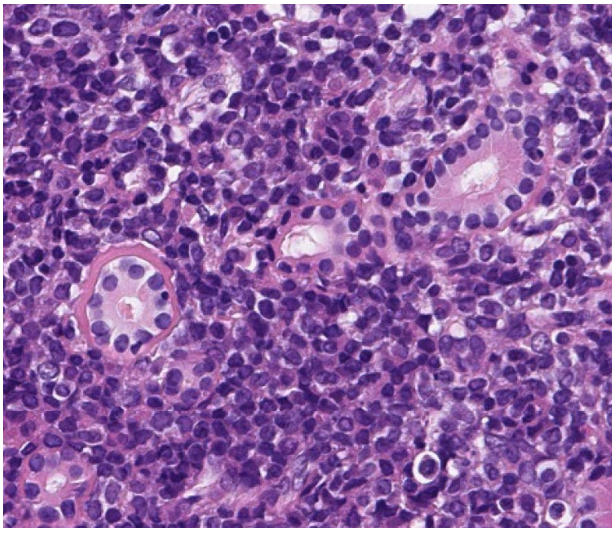

Figure 3: Biopsy—Tissue from the mass with H&E Stain under ×40 magnification.

into the nasal cavity and it demonstrated associated bony lysis. These aggressive changes made the diagnosis of meningioma unlikely; as such, a transsphenoidal biopsy was obtained.

Initial staining of the acquired tissue showed diffuse infiltration with monomorphic cells around glands of the respiratory mucosa (see Fig. 3). Subsequent FISH (Fluorescence *in situ* Hybridization) analysis of the biopsied tissue showed a t(15;17)(q22;q11–12) PML-RARA rearrangement which confirmed that the lesion was in fact a CNS relapse of APML (see Fig. 4). Despite the confirmed EMD in the brain parenchyma, both bone marrow biopsy and CSF analysis showed no morphological or molecular evidence of leukaemia.

He subsequently received FLAG-Ida (Fludarabine, Cytarabine, Idarubicin) chemotherapy, intrathecal cytarabine and craniospinal radiotherapy. He later underwent an allogeneic

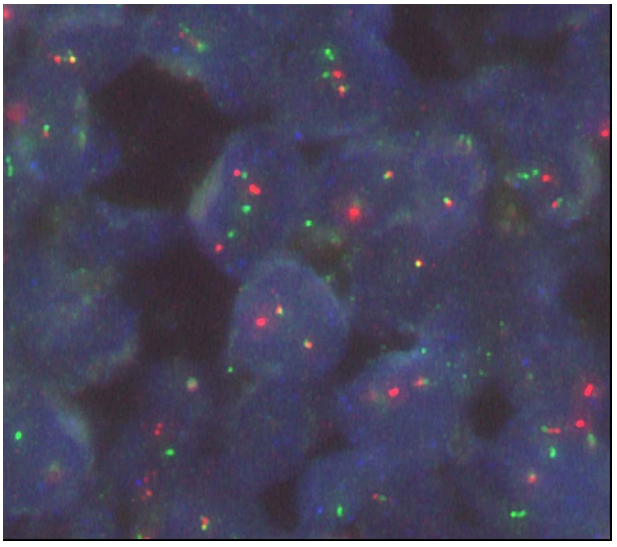

Figure 4: Biopsy with FISH—Fluorescence *in situ* hybridization showing targeted florescence of the PML-RARA fusion gene.

peripheral stem cell transplant with successful engraftment. Unfortunately, he went on to develop paraplegia secondary to treatment induced myelitis.

DISCUSSION

Since the advent of ATRA transformed survival in APML, there have been a growing number of cases of extra-medullary relapse [2–4]. Sources disagree on whether the most commonly affected site is CNS or skin, but cases have been reported in the spine, lungs, thymus, gingiva, breast, pelvis, lymph node, mediastinum and middle ear [5–7]. One study found that the 5-year cumulative incidence of CNS involvement ranged from 0 to 5.5% depending on the risk stratification at presentation [8]. Although relapse of APML within the CNS remains overall an uncommon entity, given the potential consequences of delaying diagnosis, any new neurology should trigger prompt investigation.

Certain factors detectable at presentation of APML have been purported to put a patient at a higher risk CNS relapse, including: a peripheral WBC $> 10 \times 10*9/L$, high circulating blast count and presence of the BCR3 PML/RARα type [8]. Other evidence links CNS haemorrhage during induction with an increased risk and thus it could be suggested that lumbar puncture, especially a traumatic tap, may risk introducing disease into the CSF [8]. However, there is currently no consensus on how these factors should be used to stratify individuals in order to target CNS prophylaxis.

In addition to intrathecal chemotherapy, treatment of CNS relapse in APML usually involves the same systemic therapy given for haematologic relapse. This is because even apparently isolated extramedullary disease will rarely remain within the afflicted tissue or organ system; as such, systemic treatment aims to prevent wider relapse [5].

In all forms of leukaemia, infiltration of the CNS typically produces either leptomeningeal disease or intravascular lesions [9]. As demonstrated in this case, APML can also less commonly form a discrete tumour mass with benign-looking radiological features (e.g. absence of vasogenic cerebral oedema or lytic bone destruction) [10]. As such, it is important to maintain a high

suspicion of CNS infiltration during follow-up and reassuring radiological appearances alone should not deter from performing a lumbar puncture and CSF analysis. Unfortunately, as seen in our case, even the absence of detectable malignancy in the CSF does not guarantee that there is no relapse of the primary disease; as our patient's diagnosis was only made once a tissue sample had been obtained via transsphenoidal biopsy.

CONSENT STATEMENT

Written informed consent was obtained from the patient for this submission.

Conflict of interest statement. None declared.

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ETHICAL APPROVAL

There was no formal ethical approval sought prior to the writing of this case report.

GUARANTOR

Dr Thomas Quinn.

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