CASE REPORT

RUNX1-RUNX1T1-positive acute myeloid leukaemia presenting as bilateral proptosis and multiple cranial nerve palsy

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SUMMARY

We describe a unique presentation of acute myeloid leukaemia (AML) with myeloid sarcoma (MS), manifested as proptosis with multiple cranial nerve palsies in a 9-year-old boy. MRI of the brain revealed multiple enhancing lesions and bilateral mastoiditis, in addition to sagittal sinus thrombosis. Peripheral blood smear demonstrated blasts showing Auer rods. Bone marrow examination confirmed the diagnosis of AML. PCR was positive for RUNX1-RUNX1T1. Neurological deficits improved with induction chemotherapy for AML. Extramedullary MS can present simultaneously with or antedate AML. Common genetic aberrations include t(8;21) and inv(16). Therapy is akin to AML. An effect of MS on survival outcomes is variable.

Figure 2 Contrast enhanced MRI of the brain revealed multiple, enhancing lesions in the frontal, left frontoparietal (A, black arrows) and central skull base regions. There was evidence of superior sagittal sinus thrombosis (B, black arrow) and bilateral mastoiditis.

BACKGROUND

Extramedullary myeloid sarcoma (MS) is an infrequent phenomenon encountered in patients with

acute myeloid leukaemia (AML).¹ MS may predate or present concomitantly with AML.¹ Extramedullary involvement of the central nervous system (CNS) in paediatric AML is commonly described with M4, M5 types (French-American-British classification) and the chromosomal aberration inv(16).² The cytogenetic aberration t(8;21) resulting in the fusion gene *RUNX1-RUNX1T1* has been associated with increased incidence of MS, particularly in the orbits and the CNS.^{1,3} We describe a unique presentation of RUNX1-RUNX1T1-positive AML in a child. The exceptional features included multiple cranial nerve palsies; radiological evidence of solid deposits in the brain parenchyma associated with cerebral sinus venous thrombosis; and circulating myeloblasts identified in the peripheral smear in the absence of significant cytopaenias.

CASE PRESENTATION

A 9-year-old boy presented with fever, painless, progressive swelling of the eyes and reduced hearing for the past 3 weeks. Clinical examination revealed bilateral proptosis and mild pallor (figure 1). There was no lymphadenopathy, evidence of skin/mucosal bleeding or hepatosplenomegaly. Neurological examination revealed right lower motor neuron facial nerve palsy (figure 1) and sensorineural hearing loss in the left ear. Additionally, there was diminished gag reflex suggestive of a bulbar palsy. The higher mental functions were intact, and there were no motor/sensory deficits.

Figure 1 Clinical photograph of the patient demonstrating bilateral proptosis. Proptosis is more marked on the left side. Deviation of the angle of mouth to the left side and loss of right-sided nasolabial fold is apparent, secondary to right-sided facial nerve palsy.

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Figure 3 (A) Peripheral smear demonstrated blasts with Auer rods (arrow; original magnification $\times 100$, Wright-Giemsa stain). (B) Bone marrow aspirate smear showing a myeloblast with single long slender Auer rod (arrow; May-Grunwald Giemsa stain, $\times 1000$). Inset showing myeloperoxidase positivity in the blast and an Auer rod (myeloperoxidase stain, counterstained with haematoxylin, $\times 1000$).

INVESTIGATIONS

An MRI of the brain revealed multiple, enhancing lesions in the frontal, left frontoparietal and central skull base regions (figure 2A). There was evidence of superior sagittal sinus thrombosis (figure 2B) and bilateral mastoiditis. Cerebrospinal fluid (CSF) cytology was unremarkable. Complete blood count showed haemoglobin: 8.4 g/dL, white cell count of $4.8 \times 10^9/L$ with 34% neutrophils, 42% lymphocytes, 16% monocytes, 4% eosinophils, 8% immature granulocytes and a platelet count of $158 \times 10^9/L$. Peripheral smear demonstrated blasts with Auer rods (figure 3A). Bone marrow aspiration and trephine biopsy were performed revealing 30% blasts which were myeloperoxidase positive (figure 3B). Long, slender Auer rods were visible within the blasts, confirming the diagnosis of AML with maturation (French-American-British classification M2). Flow cytometry revealed positivity for the following markers: CD13, CD33, CD117, anti-MPO, CD19, CD34, HLADR and CD38. Reverse transcriptase PCR of the bone marrow aspirate demonstrated positivity for RUNX1-RUNX1T1.

TREATMENT

Child was started on induction chemotherapy as per the AML 15 Medical Research Council protocol, which included cytarabine, daunorubicin and etoposide. He received six intrathecal doses of triple therapy (hydrocortisone, methotrexate and cytarabine) within the first 3 weeks of treatment, followed by monthly triple therapy for the subsequent 4 months. Proptosis and cranial nerve deficits significantly improved within 2 weeks of treatment. The repeat bone marrow performed after induction was in morphological remission. He later received the second induction course, followed by two courses of high-dose cytarabine-based consolidation. Cranial radiotherapy (2400 cGy) was administered for the CNS involvement, after completion of chemotherapy.

OUTCOME AND FOLLOW-UP

The patient has had a disease-free survival of 1 month after completion of therapy. There are no residual neurological deficits on follow-up. He is planned for a close follow-up and monitoring based on clinical examination and complete blood counts.

DISCUSSION

Incidence of extramedullary involvement in paediatric AML ranges from 6.7% to 23.3%.⁴ An extramedullary myeloid tumour is referred to by varying nomenclature including

myeloid sarcoma (MS), granulocytic sarcoma and chloroma.¹ Skin and orbit are the most common sites of manifestation of paediatric MS, in addition to bones, lymph nodes, gastrointestinal tract and CNS.⁴ CNS involvement in AML can occur in 6%–29% of children with AML.⁵ CNS-positive AML may present with neurological symptoms such as headache, visual disturbance, cranial nerve palsies or cord compression; leptomeningeal infiltration; intracranial solid tumours or asymptomatic detection of leukaemic cells in the CSF.² The index patient had extramedullary involvement of the orbit and CNS.

Our patient presented with cranial nerve palsies and proptosis with anaemia as the sole haematological manifestation. Meticulous peripheral smear examination revealed the presence of blasts with Auer rods, prompting a bone marrow. This underscores the importance of complete blood count and peripheral smear as a simple investigation to establish diagnosis in suspected cases of MS/AML. In a large study of 1459 children with AML conducted by the Children's Oncology Group (COG), 1% had MS of the CNS and 2% had orbital MS.³ Merely 0.3% had CNS MS with CNS3 status (blasts in CSF with cell count ≥ 5).³ Children with orbital and CNS MS were likely to be in the age group of 3–10 years and had lower incidence of hepatosplenomegaly.³ Our patient was 9 years old, did not have hepatosplenomegaly and his CSF cytology did not reveal blasts. Of 33 patients identified with CNS-positive AML in a Nordic study, 58% presented with neurological symptoms.² Facial nerve was the most common cranial nerve involved.² Intracranial solid tumours similar to our patient were seen in 2 out of the 22 patients who had neuroimaging available in this study.² Our patient had bulbar palsy and sensorineural hearing loss in addition to facial nerve palsy which was distinctive. A peculiar finding in our child was the evidence of bilateral mastoiditis, which was observed in almost all the children with facial nerve palsy in the Nordic study.²

The French-American-British categories M2, M4 and M5 are classically associated with MS, which was exemplified by our case who demonstrated M2 morphology.^{3,4} The most common genetic association is with t(8;21) (RUNX1-RUNX1T1), followed by inv(16) (CBF β /MYH11) and 11q23 abnormalities.^{1,4} Our patient was positive for RUNX1-RUNX1T1, which was significantly associated with orbital and CNS MS in the COG study.³ Therapy for MS with/without associated AML involves conventional chemotherapy as for AML.^{1,4} Radiotherapy is used for consolidation, if remission of MS is not achieved postinduction.¹ Varying effects of extramedullary involvement on survival

Learning points

- ▶ Extramedullary myeloid sarcoma can involve the orbits and central nervous system.
- ▶ Meticulous peripheral smear examination aids in clinical suspicion of acute myeloid leukaemia (AML) in patients with extramedullary presentation.
- ▶ M2 type and presence of RUNX1-RUNX1T1 are associated with myeloid sarcoma.
- ▶ Treatment of myeloid sarcoma is similar to that of acute myeloid leukaemia (AML).
- ▶ The influence of extramedullary involvement in AML is variable.

in paediatric AML have been reported. The COG study reported significantly better 5-year event-free survival (EFS) in patients with orbital and CNS MS (76% and 52%), as compared with non-CNS MS and non-MS AML, independent of cytogenetics (34% and 40%, $p=0.004$).³ A Japanese study showed no difference in 3-year EFS between children with and without extramedullary involvement in AML (53.3 ± 6.7 vs 62.5 ± 3.6 , $p=0.117$).⁶ A Nordic study demonstrated similar 5-year EFS in patients with or without extramedullary involvement in AML (54% vs 45%, $p=0.57$).⁷ However, in the same study, 5-year overall survival was lesser (64% vs 73%, $p=0.04$) and induction mortality was greater (8% vs 1%, $p=0.002$) in children with AML with extramedullary involvement.⁷

Contributors ST: wrote the primary manuscript. PB: edited the manuscript and provided the peripheral smear image. SS: provided the image of the bone marrow and contributed to the description of investigations in the manuscript. The authors have contributed equally to the manuscript.

Competing interests None declared.

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