AOSIS

Acute myeloid leukaemia with myelodysplasia-related change in a child living with human immunodeficiency virus infection, a transformation from underlying juvenile myelomonocytic leukaemia

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Juvenile myelomonocytic leukaemia (JMML) is an aggressive clonal haematopoietic disorder that presents in early childhood. It is classified by the World Health Organization (WHO) as an overlap myeloproliferative or myelodysplastic disorder. The pathogenesis of JMML has been well-explained at the molecular level using clear diagnostic criteria. There is limited literature on JMML in the context of HIV infection. The only curative modality for the majority of patients with JMML is allogeneic haematopoietic stem cell transplant (HSCT). The role of other chemotherapeutic approaches is to ameliorate the disease but they are no substitute for allogeneic HSCT. We report a case of a 59-month-old child with vertically transmitted HIV-infection who was referred to the authors' institution for further management.

Keywords: paediatric oncology; leukaemias; myeloproliferative/myelodysplastic; JMML; HIV infection.

Introduction

Juvenile myelomonocytic leukaemia (JMML) is a clonal haematopoietic disorder of early childhood.[1,2] It is classified by the World Health Organization (WHO) as an overlap myeloproliferative or myelodysplastic disorder.[3] Juvenile myelomonocytic leukaemia constitutes about 2% – 3% of all childhood leukaemias.[2] The incidence of JMML in South Africa is not known, as the published paediatric tumour registry combines all the leukaemias in one group.[4] There is limited literature on JMML in a background of HIV infection. The only curative modality for the majority of patients affected with JMML is allogeneic haematopoietic stem cell transplant (HSCT) with an event free survival of 50%.[2] We report a case of a 59-month-old child who was managed at the authors' institution.

Case report

Presentation

A 59-month-old female child was referred to a tertiary-level care hospital in Gauteng, Johannesburg, South Africa with a history of epistaxis for 2 weeks. The child also had a long-standing history of abdominal distension.

The child was born at term with a normal birthweight. The mother tested HIV negative during pregnancy but seroconverted during breastfeeding. The child was diagnosed with HIV infection at 17 months of age following recurrent illnesses. She was commenced on first-line highly active antiretroviral therapy (HAART) (abacavir, lamivudine and lopinavir/ritonavir) and demonstrated good virological control. At the time of her presentation to our unit she was virologically suppressed.

Physical examination

The child was critically ill, pyrexial, tachypnoeic, tachycardiac and hypoxic (a condition that improved with supplemental oxygen). She was not dysmorphic but was severely underweight-for-age with moderate stunting and wasting. She had significant generalised lymphadenopathy

with the largest node in the left axilla, measuring 2 centimetres (cm) in diameter. She had bounding pulses and auscultation revealed normal heart sounds with a grade 2/6 systolic murmur at the apex. Crackles were heard in the left lower zone. The abdomen was distended with a 14 cm splenomegaly and 10 cm hepatomegaly. Neurologically, she was lethargic but had no focal neurological signs.

Laboratory investigations

The initial full blood count revealed a leukocytosis (57.66×10^9/L), with a severe normocytic anaemia (haemoglobin 5.0 grams per decilitre [g/dL], mean corpuscular volume (MCV) 85.9 femtolitre [fl]) and severe thrombocytopaenia (Platelet 8×10^9/L). The differential count revealed a neutrophilia (28.8×10^9/L) and a striking monocytosis (9.22×10^9/L) with 12% blasts and promonocytes (blast equivalents), 5% granulocyte precursors and 74 nucleated red blood cells/100 white blood cells. Review of the peripheral smear revealed pseudopelgerisation of the neutrophils and significant dysplasia of the circulating erythroblasts (Figure 1). The lactate dehydrogenase was markedly elevated at > 2500 units per litre (U/L). In addition, septic markers were also elevated with a C-reactive protein

Note: Stained with May-GrünwaldGiemsa, 500 × magnification.

FIGURE 1: Images from the peripheral blood showing disordered neutrophils (black arrows), blasts (white arrows), a granulocyte precursor (black arrowhead), monocytes (white arrow heads) and a dysplastic erythroblast.

of 146 milligrams (mg)/L and procalcitonin of 15.9 microgram (µg)/L. There was no growth from blood cultures after 5 days of incubation. Serology for both cytomegalovirus and Epstein–Barr virus wase positive for IgG but negative for IgM. Bone marrow (BM) aspirate culture for *Mycobacterium tuberculosis* was also negative. The haemoglobin F (HbF) level was normal (0.5%).

A BM aspirate revealed active, but disordered (10% – 50%) erythro- and granulopoiesis, with a reversed myeloid: erythroid ratio. Megakaryocytes were present, but under-represented without striking dysplastic change. Blasts and blast equivalents comprised 18% of the cells present. Similar features were seen in the trephine biopsy, and blasts were seen to comprise 20% of the cells present on immunohistochemistry for CD34. Flow cytometry confirmed the blasts to be of myeloid lineage and demonstrated aberrant CD7 expression.

Fluorescent *in situ* hybridisation (FISH) analysis was positive for monosomy 7, and negative for KMT2A rearrangement and the classical Philadelphia chromosome, *t*(9;22). Karyotypic analysis confirmed the presence of monosomy 7 in 10/13 metaphases, with a normal female karyotype in the remaining metaphases.

Next-generation sequence (NGS) revealed Tier I mutations in *PTPN11* (variant allele frequency [VAF] 41.4%), *SETBP1* (VAF 43.1%), *ASXL1* (VAF 40.5%) and a tier III mutation in *STAG2* (VAF 55%). Collectively, the results supported a diagnosis of acute myeloid leukaemia with myelodysplasia-related change. This was suspected to have transformed from underlying JMML in view of the peripheral blood and clinical features together with the presence of the *PTPN11* mutation detected on NGS.

Progress

Allogeneic HSCT is the only option that offers the child a chance for cure. The child does not have any siblings. In view of the massive hepatosplenomegaly resulting in respiratory compromise, she was put on metronomic therapy by using prednisolone and thioguanine as a bridging therapy whilst making arrangements with a transplant centre for HLA typing. Oral etoposide that is part of this therapy was not available. The organomegaly decreased to 5 cm splenomegaly and 8 cm hepatomegaly 2 months after starting the metronomic therapy. At 3 months the spleen was barely palpable. Platelet and red blood cell transfusion requirements have decreased from weekly to once a month. She was maintained on HAART.

Ethical consideration

The publication of case study reviews was carried out with permission and ethical clearance from the Human and Research Ethics Committee of the University of the Witwatersrand, reference number: M1906102.
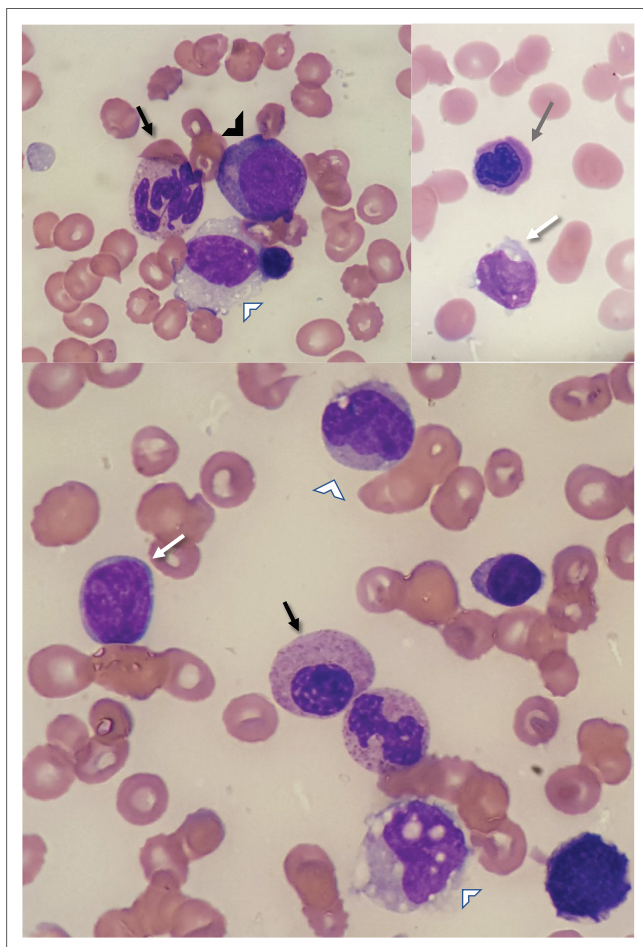
Discussion

Juvenile myelomonocytic leukaemia is a rare, aggressive haematopoietic disorder of infancy or early childhood caused by excessive production of cells of the monocytic and granulocytic lineages.[1,2] The median age at presentation is 2 years. Males are more commonly affected as compared to females (male: female ratio 2–3:1).[5,6] Patients usually present with fever, failure to thrive, thrombocytopenia, leucocytosis, splenomegaly, lymphadenopathy with or without respiratory symptomatology. This is a result of leukaemic infiltrates in the liver, spleen, lymph nodes and lungs.[7] Although about 9% of children may present without splenomegaly, it usually becomes evident within weeks to a month of diagnosis. Gastrointestinal infiltrates may result in diarrhoea and cutaneous infiltrates result in non-specific lesions (including eczematous eruptions and indurated raised lesions). Leucocytosis is common, with a reported median white cell count of 35×10^9/L but white cell counts less than 10×10^9/L may occur.[5,6] Examination of the peripheral smear usually reveals a neutrophilia and monocytosis, along with metamyelocytes, promyelocytes and immature monocytes.[5] Bone marrow findings are non-specific, typically showing hypercellularity with a predominance of granulocytes during all stages of maturation. Dysplastic change is usually not prominent.

The diagnostic criteria are summarised in Box 1.[2] Our patient met three of the four clinical and haematological criteria at presentation as she had a peripheral monocytosis, absolute count > 1000/L, splenomegaly and absence of the breakpoint cluster region to Abelson (BCR-ABL1) fusion gene. However, her BM blast percentage was found to be 20% on trephine histology, which was speculated to represent JMML transformation. The HbF is usually elevated in cases of JMML associated with a normal karyotype. In our patient (who had monosomy 7), the HbF was normal.

More than 90% of patients with JMML show somatic or germline mutations in *PTPN11, KRAS, NRAS, CBL* or *NF1* in their leukaemic cells.[1,2,8] These mutations are mutually exclusive, and they act by activating the RAS-signaling pathway. The germline mutations are sometimes termed RASopathies or neuro-cardio-facio cutaneous syndromes,[2] with *NF 1* and Noonan syndrome being the most frequently encountered. *PTPN11* mutations are the most common in JMML, occurring in about 35% of patients,[1] and have been shown to be associated with poorer disease outcomes compared to *NRAS* and *CBL* mutations[1,2,9,10] (where spontaneous resolution of the haematologic abnormalities occasionally occurs[2]). The *PTPN11* proto-oncogene encodes Src-homology tyrosine phosphatase 2 (SHP-2) a phosphatase that has a role in signal transduction and haematopoiesis through the RAS pathway.[6,11]

Our patient also had a *SETBP1* mutation. This has been described in JMML where it is proposed to play a role in disease progression (rather than functioning as a driver mutation).[2,9,12,13] *SETBP1* mutations have been associated with poor outcome.[1,9,14]

Most patients with JMML (65%) have a normal karyotype[5,15] whilst monosomy 7 and other abnormalities are found in 25% and 10% of cases, respectively.[5]

Allogeneic HSCT offers the best curative option with an event-free survival of about 52%.[15] A case report of JMML on a background of vertically transmitted HIV, with successful HSCT has been published.[16] In adults, the outcomes of HSCT in individuals living with HIV for other haematological malignancies have been found to be comparable to individuals not living with HIV.[17] Other chemotherapeutic approaches have limited role in JMML.[2,6] They may be used to ameliorate the disease but do not substitute allogeneic HSCT. They include 6-mercaptopurine and cytarabine[10] as well as AML-type combination therapy.[6] The use of *13-cis* retinoic acid as a differentiating agent has been shown to reduce organomegaly and targeted therapy with monoclonal antibodies targeting various points in the RAS-signaling pathway including JAK3 inhibitors has been used in clinical trial settings.[10] Spontaneous resolution has been described but is uncommon.[18,19] Poor outcome is predicted by a lower platelet count (< 33 000/L), age > 2 years at diagnosis and a high HbF (> 40%) at presentation.[5]

Conclusion

The pathogenesis of JMML has been well explained at the molecular level with clear diagnostic criteria. Next generation sequence testing is now available in South Africa making diagnosis easier. The only curative option is HSCT.

Acknowledgements

Competing interests

BOX 1: Juvenile myelomonocytic leukaemia diagnostic criteria.[2]

1. Clinical and haematologic criteria (all four mandatory)
   - Peripheral blood monocyte count > 1×10^9/L
   - Blast percentage in peripheral blood or bone marrow > 20%
   - Splenomegaly
   - Absence of Philadelphia chromosome (BCR/ABL rearrangement)
2. Oncogenetic studies (one finding sufficient)
   - Somatic mutations in *PTPN11, KRAS* or *NRAS*
   - Clinical diagnosis of neurofibromatosis-1 of *NF1* mutation
   - Germline CBL mutations or loss of heterozygosity of *CBL*
3. For patients without genetic features, besides the clinical and haematologic features listed under I, at least two of the following criteria must be fulfilled
   - Monosomy 7, or any other chromosomal abnormality
   - Haemoglobin F increased for age
   - Myeloid or erythroid precursors on peripheral smear
   - GM-CSF hypersensitivity in colony assay
   - Hyperphosphorylation in STAT5

BCR/ABL, breakpoint cluster region to Abelson; GM-CSF, granulocyte-macrophage colony-stimulating factor.

Authors' contributions

All authors contributed equally to this work.

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Data availability statement

Data sharing is not applicable to this article as no new data were created or analysed during this study.

Disclaimer

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