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Case Report

Juvenile chronic myeloid leukemia: a case report

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ABSTRACT

Chronic myeloid leukemia (CML) accounts for 2-3% of leukemias in children under 15 and 9% in adolescents aged 15-19. The diagnosis of CML in children, adolescents, and young adults has several differences compared to that in adults. Juvenile myelomonocytic leukemia (JMML)/ juvenile CML is a rare, malignant myelodysplastic/ myeloproliferative neoplasm (MPN) overlap haemopoetic disorder that presents in infants and toddlers and it must be differentiated from other disorders that can show similar presentation in this age group. JMML is very uncommon and the diagnosis is often difficult to establish. The disease has a rapid course and has a median survival of less than 10 months when untreated or undertreated. In this case report we present a case of a 7-year-old male patient with gingival enlargement and swelling along with mobility of mandibular anterior teeth with various associated systemic factors in which various hematological, biochemical, and radiographic investigations were carried out to differentiate CML from other systemic conditions.

Keywords: Chronic myeloproliferative leukemia, Juvenile CML, Gingival enlargement

INTRODUCTION

Juvenile CML is a relatively rare MPN that amounts to 2-3% of newly diagnosed leukemias in children. Around 95% of children with CML are in the chronic phase (CML-CP).[1-3]

JMML is a myelodysplastic or MPN overlap syndrome of the pediatric age which can be characterized by abnormal, sustained and exaggerated production of myeloid progenitors and monocytes, aggressive clinical course, and poor outcomes. There is no maturation arrest in myeloid differentiation unlike in acute leukemia; therefore, the progenitor cell count in the peripheral blood smear or bone marrow may be low even in the presence of an elevated total leukocyte count. The differentiation pathway is shunted towards the monocytic differentiation and the progenitor colonies of JMML cells show a spectrum of differentiation, including blasts, pro-monocytes, monocytes, and macrophages.[4] CML is an uncommon disease in children and adolescents accounting for 2% to 3% of all leukemias in children younger than 15 years of age and ~9% in adolescents between 15 to 19 years of age.[2,5] The average annual incidence of CML in children younger than 15 years is 0.6-1.0 cases per million and that for patients 15-19 years of age is 2.1 per million. Children, adolescents, and young adults tend to have a more aggressive clinical presentation than adults.[2-7]

Epidemiology

JMML accounts for 1% of all pediatric leukemias, with an incidence of about 1.2 cases per million persons/year. The median age at which it is diagnosed is two years and a male predominance is seen (male: female=2.5). About three-fourths of cases are diagnosed before 3 years of age and by 6 years, 95% of cases are detected. JMML is the most common subtype in children, accounting for 20-40% of pediatric MDS/MPN.[7-11]

CASE REPORT

A 7-year-old male patient reported to Chandra dental college and hospital at the dept of pedodontics with a chief complaint of gingival swelling and mobility of teeth in the anterior mandible region.

The patient was advised oral prophylaxis, after which there was not much significant improvement in his condition. For further investigations and treatment, the patient was referred to dept. of oral and maxillofacial surgery.

The medical history of the patient was non-contributory. On general examination, the patient was conscious, responsive, and well aware of his surroundings. There were no signs of pallor, icterus, cyanosis, clubbing. All the vital signs were within normal limits.

Extraoral examination revealed moon facies, watering eyes, and facial asymmetry due to swelling over the anterior mandibular region. Left submandibular lymph nodes were palpable, measuring 1×1 cm, round in shape, mobile, firm, and non-tender.

Intraoral swelling was present over the lower alveolus, measuring 4×1 cm extending from the right canine region to the left canine region. Swelling was diffused, oval in shape, with well-defined borders. On palpation, intraoral swelling was firm in consistency and non-tender. Generalized mobility was present. Gingival enlargement was generalized. The patient was advised oral prophylaxis which resulted in a slight reduction in gingival swelling.

Initial blood investigations revealed Hb% levels of 6.7 gm%, CT, BT within normal limits, WBC 64000 cells/mm^3, PMNs were 20%, lymphocytes, monocytes, eosinophils, and RBSs within normal range. An increase in promyelocytes (04%), myelocytes (28%), and metamyelocytes (05%) was noted. Blood investigations were suggestive of leukocytosis with a shift to the left with thrombocytopenia with anemia. The posterior superior iliac spinal aspirate revealed a myeloid: erythroid ratio of 8:1, suggestive of myeloid hyperplasia.

USG abdomen revealed normal kidneys, slight hepatomegaly, and marked splenomegaly. OPG and lateral cephalogram revealed various unerupted tooth buds and various cystic lesions. CT (plain and contrast) brain and neck revealed a large homogenously enhancing epidural mass lesion with extension along the falx in the parietal region with bilateral orbital soft tissue mass lesions. Also revealed an expansile lytic destruction of the ramus of the mandible on the left side with soft tissue components, suggestive of leukemic infiltrations (chloromas).

All of the above features are associated with the diagnosis of juvenile CML.

After the confirmation of the condition, the patient was hospitalized and symptomatic treatment was started with hyperhydration in order to prevent lysis syndrome. Further he was treated with hydroxyurea, followed by a first generation tyrosine kinase inhibitor, imatinib.

Follow up and outcome of intervention revealed a decrease in the white blood cell count to 63400 cells/mm^3 at the end of first cycle of treatment. The second follow up after 3 months revealed marked decrease in count 61000 cells/mm^3. In further long term follow up of 6 months the leukocyte count was drastically reduced from the initial. Follow up was maintained upto period of 6 years 8 months. The patient and his family was satisfied with the treatment protocol and outcome of the treatment.

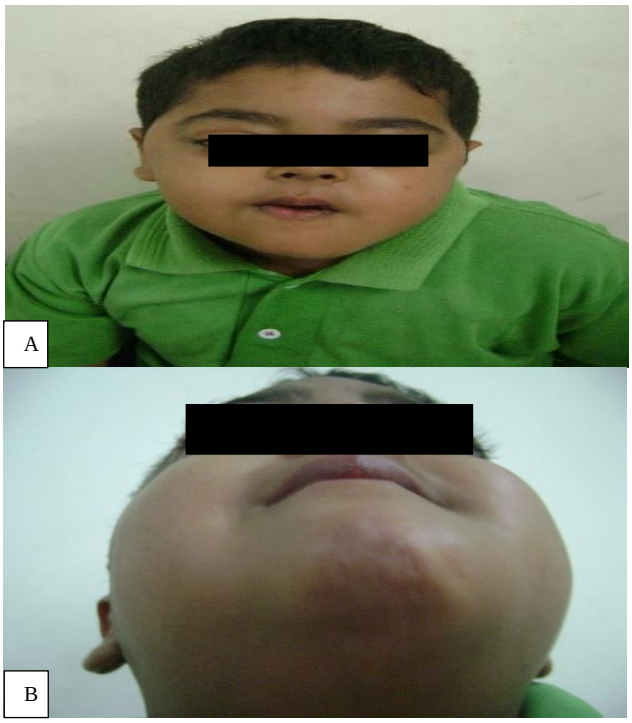

Figure 1 (A and B): Extraoral moon facies appearance.

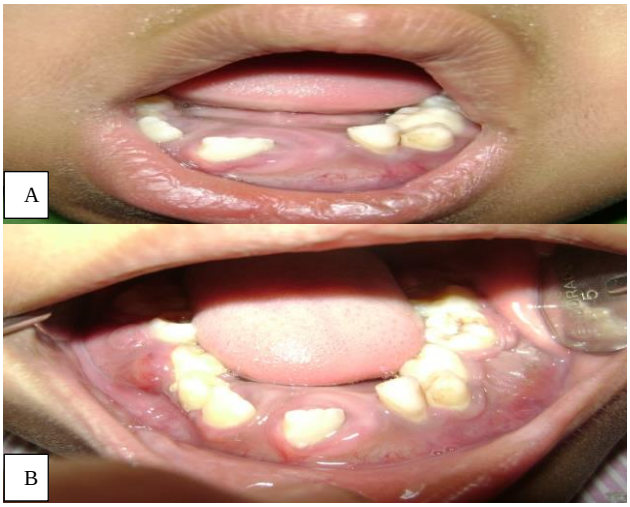

Figure 2 (A and B): Intraoral gingival enlargement and swelling of alveolus.

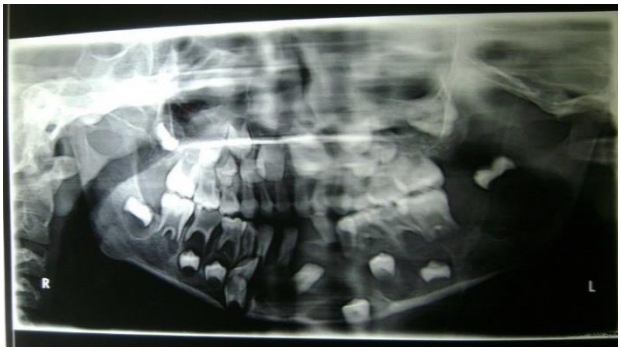

Figure 3: OPG showing multiple unerupted teeth and various cystic lesions.

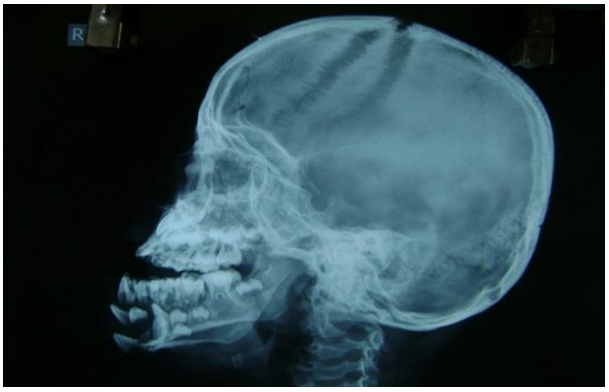

Figure 4: Lateral cephalogram revealing various unerupted tooth buds and various cystic lesions.

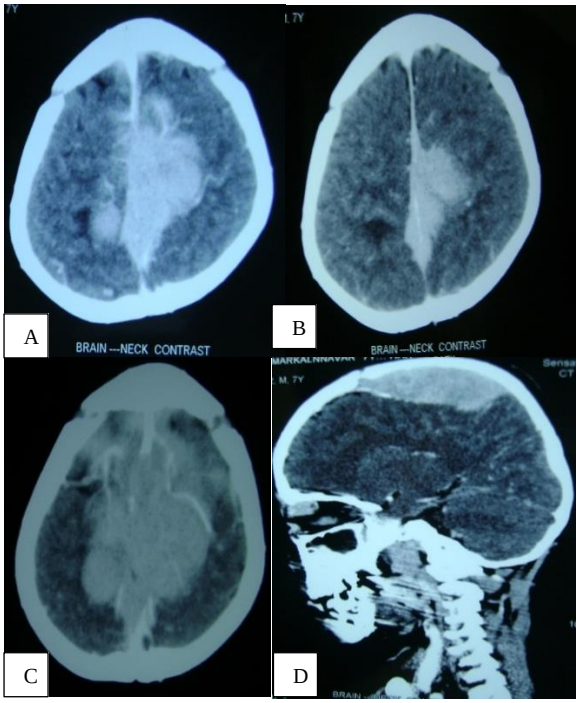

Figure 5 (A-D): Plain and contrast CT brain and neck revealed an epidural mass extension along falx with bilateral orbital soft tissue lesions. Also showing expansile lytic destruction of left mandibular ramus with soft tissue components.

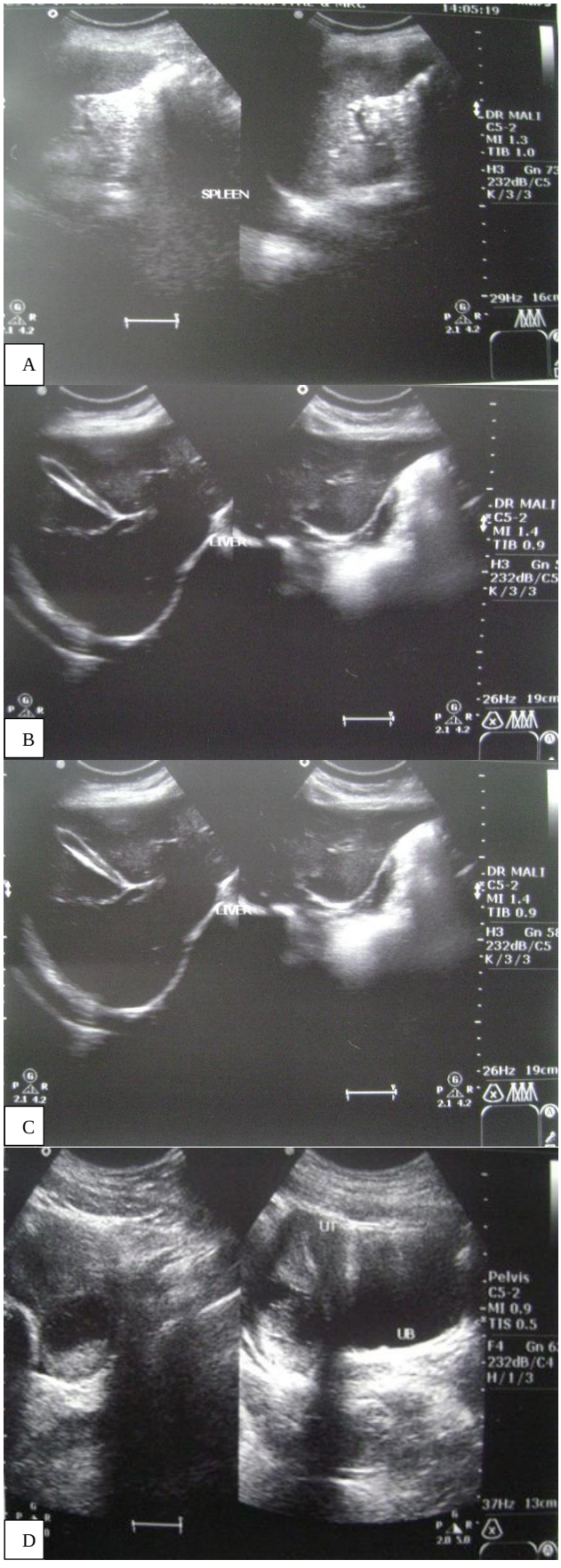

Figure 4 (A-D): USG abdomen showing marked splenomegaly and slight hepatomegaly.

DISCUSSION

A number of studies have reported clinical findings in children and young adults with CML that suggest either a different leukemia cell or host biology compared with CML in adults.[5,6,12-14] Although it might be reasonable to assume that CML in an 8-month-old, which may also involve congenital factors, will have a different biology from CML in a 70-year-old, there is little data to support this, and the biology of CML in children has been assumed to be identical to that in adults.[12] There are also host differences in adult patients as compared with young, expeditiously developing pediatric and adolescent patients that may affect CML development, response to treatment, and detrimental effects of treatment.

Patients of JCML might present with pallor, infections, fever, cough, hepatomegaly, splenomegaly, lymph-adenopathy, and rash. Splenomegaly is found in all cases and is an expedient for the diagnosis of JMML. Skin rash and lymphadenopathy caused by leukemic infiltration and are seen in about 50% and 80% of cases, respectively.[15]

The peripheral blood film examination is crucial for establishing the diagnosis of JCML. Anemia with the presence of nucleated RSCs, leukocytosis, monocytosis, a shift towards immaturity in the granulocytes, and thrombocytopenia are characteristically present in patients with JCML. A myeloid shift to the left is present and blasts including promonocytes constitute less than 5% of all cells. Absolute monocytosis of >1000/mm^3 is a diagnostic criterion for JMML but in isolation, it is neither specific nor sensitive because it can be a feature of infections. A common finding of JCML is thrombocytopenia which is occasionally severe. Bone marrow examination may support the diagnosis of JMML but is not specific. There is a myeloid predominance and hypercellularity. Myeloid to erythroid (M:E) ratio might show variation from 0.1 to >94. The number of myeloid progenitor cells, blast cells, including promonocytes are increased but blast cell count is less than 20%. Auer rods are not seen. Monocytes comprise 5-10% of marrow cells and nonspecific esterase or immunohistochemistry for CD14 may help to highlight the monocytic component. Erythroid progenitors are megaloblastic. Megakaryocytes are decreased in number.[16] Some other frequently affected organs are lymph nodes, skin, and the respiratory tract. Liver and spleen infiltration is found in the majority of cases. Myelomonocytic infiltration of the lungs is also accompanied by infections, occasionally resulting in significant morbidity. Rarely, the gastrointestinal tract can also be involved.[16]

The skin involvement presents as eczema, xanthoma, café-au-lait spots, and juvenile xanthogranuloma. The café-au-lait spots may also be present in children with germline mutations in the NF-1 and CBL gene and melanocytic lesions can be observed in patients with germline mutations in genes involved in the RAS signaling pathway.[17]

Gastrointestinal involvement can also be demonstrated as intractable diarrhea, hemorrhagic manifestations, and infections. These patients might also present with cough and respiratory distress. The chest x-ray reveals findings such as peribronchial and interstitial pulmonary infiltrates. Although central nervous system (CNS) involvement in JMML is rare, a few patients have been reported with CNS leukemic infiltration, ocular granulocytic sarcoma, diabetes insipidus, and facial palsy.[9]

Unlike other myeloproliferative disorders such as polycythemia vera, specific diagnostic criteria for JCML have not been widely accepted. Broad criteria used in pediatric oncology group JCML protocol (#9265), activated in 1992, include: Leukocytosis with absolute monocytosis (>450//uL), presence of immature myeloid cells in peripheral circulation, <25% marrow blasts, no demonstrable chromosomal abnormalities in bone marrow except for presence of monosomy 7 and negative studies for viral infections (CMV, rubella, EBV).[18]

Diagnosis is challenging in such situations, where it has to be established by viral polymerase chain reaction and genetic mutation analysis. Occasionally, association of concurrent viral infections with underlying JMML results in poor outcomes. Presence of viral infections must be excluded in all cases of JMML by serological tests and PCR.[17]

Except for the ones with monosomy 7, the majority of the JMML patients have higher HbF levels. About 50% of patients have hypergammaglobulinemia. One-fourth of patients may show autoantibodies and positive direct antiglobulin test.[17]

One such criteria helpful in establishing the diagnosis of JMML is JAK2-activated hyperphosphorylation of STAT-5 in response to GM-CSF which has been identified as a hallmark of JMML. Phosphospecific flowcytometry in CD33+/CD34+ or CD33+ CD14+CD38 (low) cells has been validated to detect hyperphosphorylation of STAT-5 protein in BM (or PB) cells in response to low doses of GM-CSF.[19]

Table 1: Diagnostic criteria for JMML per the 2016 revision to world health organization classification.[20]

S. no.	JMML diadnostic criteria
1	**Clinical and hematological features (all 4 features mandatory)**
	PB monocyte count ≥ 1x10 /L
	Blast percentage in PB and BM < 20%
	Splenomegaly
	Absence of Philadelphia chromosome (BCR/ABL 1 rearrangement)

Continued.

S. no.	JMML diadnostic criteria
2	**Genetic studies (1 finding sufficient)**
	Somatic mutation in PTPN 11* or KRAS* or NRAS*
	Clinical diagnosis of NF1 or NF1 mutation
	Germ line CBL mutation and loss of heterozygosity of CBL₸
3	**For patients without genetic features, besides the clinical and hematologic features listed under 1, the following criteria must be fulfilled**
	Monosomy 7 or any other chromosomal abnormality or atleast 2 of the following: Hemoglobin F increased for age, myeloid or erythroid precursors on PB smear, GM-CSF hypersensitivity in colony assay and hyperphosphorylation of STAT5

Modified from Locatelli and Niemeyer, *Germ line mutations (indicating Noonan syndrome) need to be excluded, ₸Occasional cases with heterozygous splice site mutations

Table 2: Prognostic factors in JMML.[17]

Standard risk	High risk
Young age	Older age of presentation
Normal HbF	High HbF
Peripheral blood and bone marrow blasts< 20%	Peripheral blood and bone marrow blasts > 20%
Germline NRAS, KRAS and PTPN11	NF-1 mutation
CBL mutation	Somatic NRAS, KRAS and PTPN11 mutation
Low methylation profile	High methylation profile
Monosomy 7	Double RAS variants
Spontaneous regression (good prognosis) or resolution with minimal chemotherapy (good prognosis)	Complex cytogenetics AML genetic signatures
Remission after HSCT	Relapse after HSCT/refractory disease after HSCT

JMML: Juvenile myelomonocytic leukemia; NF1: Neurofibromin-1; CBL:Casitas B-lineage lymphoma; PTPN11: Protein tyrosine phosphatase non-receptor type; NRAS: Neuroblastoma rat sarcoma; HSCT: Hematopoetic stem cell transplant.

Children with CML are exposed to their disease and its therapy during their periods of growth and development, and a life-long treatment is required in most cases, for a much longer period compared to those who are diagnosed at a much later age; assuming that most patients require life-long therapy.

Jin Kang et al in Korea proposed a new regimen for newly diagnosed JCML cases lacking access to transplantation. In this 3-week standard regimen they offered a combination of chemotherapy (Ara-C, etoposide, and vincristine) and differentiation therapy (isotretinoin). If the disease relapsed or progressed, they continued to deliver the regimen of chemotherapy (Ara-C, etoposide) and the differentiation therapy (low-dose Ara-C) in 3-4 weeks intervals. This regimen was safe and effective, but the study was only done on 5 JMML patients.[21] Another regimen was tested in China by Feng et al which consisted of decitabine, cytarabine, and fludarabine. It was reported that this regimen is safe, effective, and feasible with a response rate of 97%. Although, the complete remission rate was low and primarily partial.[22] It is believed that DNA hypermethylation of specific genes contributes to the aggressiveness of JMML, azacytidine (AZA), a DNA hypomethylating agent, has been tested as a potential treatment for JMML. Cseh et al conducted a retrospective study in which they treated 9 JCML patients with low-dose azacytidine before HSCT and emphasized two complete remissions and two partial remissions. However, there were several adverse events (severe neutropenia, skin rash, and gastrointestinal problems.[23]

Recently in March 2022, the food and drug administration (FDA) approved azacitidine for JMML therapy. Some patients with JMML showed complete clinical remission after the use of Azacitidine therapy. A study by Niemeyer et al. stated that azacitidine monotherapy is a suitable option for children with newly diagnosed JMML.[24] Fabri et al. in Slovakia tested a novel approach using azacytidine 75 mg/m^2, i.e., on days 1-7 of a 28-day cycle as a bridging therapy before HSCT, and reported a good response and favorable toxicity.[25] Some studies report sustained remission after azacitidine therapy 26 and the disappearance of the monosomy 7 clones in JMML without HSCT 27. Azacitidine is currently the standard of care for most patients with JMML prior to HSCT.

Tyrosine kinase inhibitors (TKI) are now the standard of care for patients with CML in chronic phase.[28-30] They act on the fusion protein of BCR-ABL1, as well as have off-target inhibition of other tyrosine kinases like platelet-derived growth factor receptor (PDGFR), vascular endothelial growth factors receptors (VEGFR), c-KIT etc., which share pathways for bone growth and metabolism and other endocrine functions.[31,32] The long-term effects of TKI on developing children are currently not known. Also, it is likely to be different than what is observed in adults. Although therapies that are newer and safer are desired for the treatment of JMML in children, it is imperative to

define the safety and efficacy of TKIs. However, currently, there are no evidence-based guidelines for the diagnosis and management of CML in children and adolescents.

CONCLUSION

Since the clinical features of juvenile CML strongly resemble the gingival hypertrophy and periodontal diseases, it is imperative that the disease be identified and diagnosed as early as possible using the necessary aid, because the management for both the conditions require different modalities.

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