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# PEDIATRIC CHRONIC MYELOID LEUKEMIA: UNRAVELING DIVERSE PRESENTATIONS AND MANAGEMENT CHALLENGES IN TWO CASES

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**Abstract**:
This article presents two pediatric cases exemplifying the rarity and complexity of Chronic Myeloid Leukemia (CML) among pediatric population. First patient is a 13-year-old, exhibited classic CML manifestations, including hyper-leukocytosis, hepatosplenomegaly, and molecular confirmation of the BCR-ABL fusion gene. The second patient is an 8-year-old, demonstrated an unusual presentation with dual Philadelphia chromosome-positive Acute Lymphoblastic Leukemia (ALL) and CML in blast phase. Comprehensive investigations, including bone marrow aspiration, flow cytometry, and molecular studies, played a main role in confirming diagnoses, tracking disease progression, and tailoring treatment. These cases highlight the critical role of a multifaceted diagnostic approach in pediatric CML, emphasizing the need for good understanding and individualized management.

**Keywords:** Pediatric Chronic Myeloid Leukemia; CML; Case Report; Hematology; Tyrosine Kinase Inhibitors; Pediatric Oncology

**INTRODUCTION**:
Chronic myeloid leukemia (CML) is a clonal myeloproliferative malignancy (1) characterized by the acquisition of the Philadelphia chromosome (Ph) shown in figure 1* (2), resulting from a reciprocal translocation between chromosomes 9 and 22 (3). While CML is relatively rare in children, accounting for approximately 2-3% of childhood leukemias (4,5), it constitutes up to 15% of all adult leukemias (1). The median age of diagnosis for CML is typically between 60 to 65 years, making it a rare occurrence among children and adolescents, with an annual incidence of 1 case per million in those younger than 15 years (2).

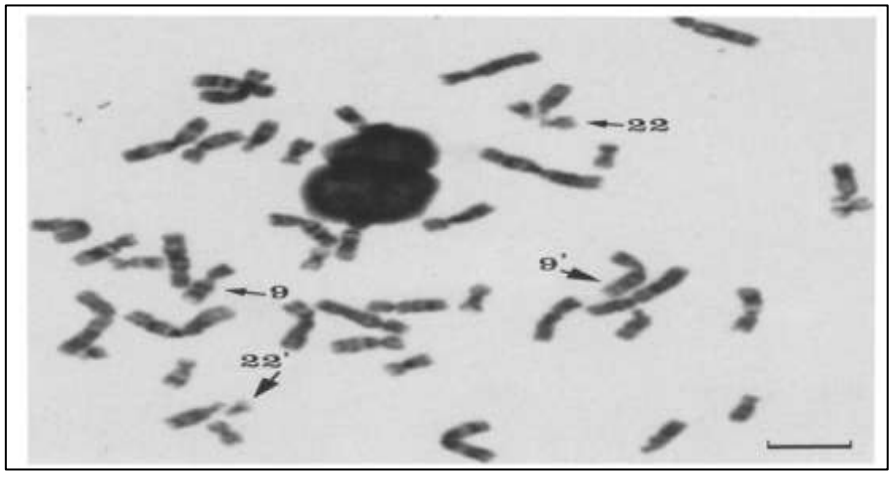


**Figure 1**: The karyotype is 46, XX, t(9; 22)(q34; ql 1). The two derivative chromosomes resulting from the translocation (9' and 22') are indicated by the larger arrowheads. Their normal homologues are also shown (as 9 and 22). 22' is the characteristic Philadelphia chromosome. Bar represents 5 μm.

*Taken from Dobrovic, A., Peters, G.B. & Ford, J.H. Review: Molecular analysis of the Philadelphia chromosome. Chromosoma 100, 479–486 (1991). https://doi.org/10.1007/BF00352198

In contrast to its prevalence in adults, CML in children presents distinct challenges in terms of diagnosis, treatment, and long-term outcomes (6). The disease's molecular pathogenesis involves the formation of the BCR-ABL1 oncoprotein, a

constitutively active tyrosine kinase that promotes leukemogenesis through the upregulation of various signaling pathways, including RAS, RAF, JUN, MYC, and STAT kinases (3).
Treatment for pediatric CML often involves tyrosine kinase inhibitor (TKI) therapy, which, while effective, necessitates careful consideration due to the potential long-term exposure during active growth years (7). Morbidity can be more frequent in pediatric cases, and treatment decisions need to balance the benefits of TKIs with the associated risks (8). Currently, three US Food and Drug Administration-approved TKIs (imatinib, dasatinib, and nilotinib) are used in pediatric patients, and ongoing clinical trials are exploring next-generation TKIs (9).
WHO stages CML into three phases: chronic, accelerated, and blastic (4). The blastic phase, marked by the presence of at least 20% blasts, signifies an advanced and aggressive stage of the disease (4). Pediatric CML, while presenting less frequently in a blastic phase than in adults, exhibits distinct biological differences, including higher mean white blood cell counts, more pronounced splenomegaly, and a generally more aggressive clinical course (6).
Addressing how peculiar CML in pediatric population; it is worth to mention that recent data indicate that some genetic differences exist in pediatric CML compared to adult disease; for example, 60% of pediatric patients have ASXL1 mutation compared to only 15% of adults (10). Further, children with CML are exposed to their disease and its therapy during periods of growth and development, and a life-long treatment is required in most cases, for a much longer period of time compared to those who are diagnosed at a much later age; assuming that most patients require life-long therapy (10).
In this case report, we present two instances of pediatric leukemia, one illustrating the diagnostic and therapeutic journey of a 13-year-old boy diagnosed with Chronic Myeloid Leukemia (CML), and the other detailing the challenges and complexities faced in the management of an 8-year-old patient diagnosed with Philadelphia-positive Acute Lymphoblastic Leukemia (ALL) in blast phase.

**Case presentation:**

**Case one:**

On February 9, 2023, a 13-year-old boy presented as a referred case from Primary Health Care (PHC) due to hyper-leukocytosis. His history revealed one year of bone pain affecting his daily activities, playing and sometimes he cannot even walk. His bone pain was not investigated before and he used to be given analgesia for it. Last time they asked for medical advice he had CBC done and WBC was 424x10^3/µL then repeated to be 239x10^3/µL so he was referred to our tertiary center. The patient and his family denied history of fever, headache, epistaxis nor cough. He has no previous admissions nor surgeries. Had no family history of hematological or oncological diseases. He is fully vaccinated, studying in secondary school with good school performance.
At the day of his presentation, the patient's clinical examination showed a pale looking male, not jaundiced nor cyanosed, fairly hydrated, with no abnormal facial features. Lymph nodes examination revealed sub-centimetric cervical lymph nodes with no other palpable lymph nodes. Chest auscultation revealed equal bilateral air entry with no added sounds. Cardiac auscultation identified first and second heart sound with associated hemic murmur. Abdominal examination showed distended abdomen with massive splenomegaly of hard consistency and smooth surface, mild hepatomegaly with audible bowl sounds. The remaining of the examination was unremarkable.
Patient was admitted initially to pediatric intensive care unit (PICU) on the same day of his presentation, kept on hydration and started on tumor lysis medications; given hydroxyurea, rasburicase until he was stable and then shifted to pediatric hematology oncology department of Prince Faisal Cancer Center (PFCC) on February 11$^{th}$ 2023
The patient's initial labs indicated hyper-leukocytosis with WBC measuring 397.7 x $10^3$, anemia with hemoglobin of 8.5 mg/dL. Elevated platelet counts at 334 x $10^3$. Peripheral blood smear showed 3% blast cells going with CML. Uric acid, phosphorus, blood urea nitrogen (BUN), calcium, sodium and potassium were all in the normal range. Creatinine was 44 µmol/L. Biochemically, patient displayed mild liver function abnormalities, including elevated ALT (13 U/L) and AST (39 U/L), as well as an elevated LDH level at 1066 U/L. Coagulation studies showed a prothrombin time (PT) of 15.2 seconds and partial thromboplastin time (PTT) of 35.2 seconds. Hemoglobin electrophoresis came back normal, and chest X-ray showed no mediastinal widening. These findings, in conjunction with a comprehensive metabolic panel, formed the basis for the diagnostic workup, guiding subsequent clinical decisions in the context of his CML diagnosis (Table 1).

Table 1: Lab reports of case one

| Date | Parameter | Result | Reference Range |
|---|---|---|---|
| 9/Feb/2023 | TLC | 239 x10^3/µL | 4.0 - 11.0 x10^3/µL |
| 9/Feb/2023 | Hb | 8.5 gm/dL | 12.0 - 16.0 gm/dL |
| 9/Feb/2023 | Platelets | 334 x10^3/µL | 150 - 450 x10^3/µL |
| 9/Feb/2023 | BUN | 2.5 mg/dL | 7 - 20 mg/dL |
| 9/Feb/2023 | Creatinine | 44 µmol/L | 44 - 97 µmol/L |
| 9/Feb/2023 | Sodium (Na) | 137 mmol/L | 135 - 145 mmol/L |
| 9/Feb/2023 | Potassium (K) | 3.2 mmol/L | 3.5 - 5.1 mmol/L |
| 9/Feb/2023 | ALT | 13 U/L | 5 - 40 U/L |
| 9/Feb/2023 | AST | 39 U/L | 8 - 38 U/L |
| 9/Feb/2023 | Calcium | 2.3 mmol/L | 2.15 - 2.55 mmol/L |
| 9/Feb/2023 | LDH | 1066 U/L | 313 - 618 U/L |
| 9/Feb/2023 | PT | 14.5 seconds | 11.0 - 15.0 seconds |
| 9/Feb/2023 | PTT | 35 seconds | 25.0 - 36.0 seconds |
| 16/Feb/2023 | Serum Creatinine | 44 µmol/L | 44 - 97 µmol/L |
| 16/Feb/2023 | Uric Acid | 90 µmol/L | 208 - 428 µmol/L |

| | | | |
|---|---|---|---|
| 16/Feb/2023 | Calcium | 2.14 mmol/L | 2.15 - 2.55 mmol/L |
| 20/Feb/2023 | TLC | 4.9 x10^3/µL | 4.0 - 11.0 x10^3/µL |
| 20/Feb/2023 | Hb | 8.5 gm/dL | 12.0 - 16.0 gm/dL |
| 20/Feb/2023 | Platelets | 276 x10^3/µL | 150 - 450 x10^3/µL |
| 23/Apr/2023 | Myeloid Population | 26% | - |
| 23/Apr/2023 | Monocyte Population | 1.7% | - |
| 23/Apr/2023 | Erythroid Population | 4.3% | - |
| 24/Apr/2023 | BCR-ABL Transcripts | Detected | - |
| 8/May/2023 | BCR-ABL Transcripts | 1.81% (IS) | <10% (optimum) |

Abdominal ultrasound done on February 12 reported the liver to be measured about 15 cm (average length for age around 11.5cm) with homogenous echo pattern, smooth surfaces with regular margins and no focal lesions. And the spleen measured about 18.1 cm (average length for age around 9.7 cm). The remaining of pelvic-abdominal ultrasound scan was unremarkable.
Patient's bone marrow aspiration and biopsy reported with flow cytometry, performed on February 13 revealed blast population less than 1%, normal lymphocytes compose 1.8%, basophil 1.9%, normal myeloid populations 95% monocytic population 0.2% erythroid populations 0.3%. BCR/ABL transcript by PCR are detected ratio 0.102, sub type P210. Karyotyping 46 XY, t(9;22). FISH: BCR/ABL1 positive in 98% of nuclei. The results confirmed morphology and phenotyping along with the molecular result confirm the diagnosis of chronic myeloid leukemia in chronic phase.
The patient started on chemotherapy as per AAML0123 protocol, on Imatinib 340mg/m2 on February 27$^{th}$ 2023, which was well tolerated, serial ECG follow-ups showed no prolongation of QT interval of significance, also no electrolytes disturbances found. Regular monitoring through CBC, peripheral blood smear, and bone marrow assessments were scheduled to evaluate treatment response.

Our lab in Prince Faisal Bin Bandar Centre for Pediatric Oncology (PFCC) is following the International Standard for Molecular Response (ISMR) in Bone Marrow Aspirate (BMA) as follows:
- 10% BCR-ABL transcripts in BMA at the end of first 3 months.
- 1% BCR-ABL transcripts in BMA at the end of first 6 months.
- 0.1% BCR-ABL transcripts in BMA at the end of first 12 months.

The molecular response on May 8$^{th}$ 2023, demonstrated an optimal response, with BCR-ABL transcripts at 1.81%. And blast population was 1.47%.
Bone marrow aspiration and biopsy repeated on July 30$^{th}$ 2023 and flow cytometry reported the blast population to be 0.1%, normal lymphocytes compose 47.2 %, normal myeloid populations 45.6%, monocytic population 4.1% and erythroid populations 0.3%. BCR/ABL quantitation by PCR became 0.085%. The patient's clinical course correlated well with the investigative findings. His initial presentation with hyper-leukocytosis, hepatosplenomegaly, and bone pain aligned with the subsequent diagnosis of CML. The treatment response, as evidenced by decreasing BCR-ABL transcripts, supported the effectiveness of Imatinib in controlling the disease.

**Case two:**
On March 27, 2023, an 8-year-old male child presented to the hospital with 3 months history of lower limbs pain, for which he received only analgesia before with no investigations done. One week back he started to spike fever up to 39 Celsius. Responded to paracetamol but associated with mild on and off abdominal pain, no vomiting, nor bleeding from any orifices. Detailed history from the family confirmed weight loss over the past 3 months with drenching night sweats. Further questioning revealed fully vaccinated child with normal developmental history up to his age and no history of previous hospital admissions. His family history did not show any similar complaints among the family members, nor history of hematological diseases nor malignancies.
Upon physical examination at the day of his presentation, the patient looked well with stable vitals and euvolemic status. Has bilateral cervical and submandibular lymphadenopathy. Equal bilateral breath sound bilaterally with no added sounds. Normal first and second heart sounds without an appreciated murmur. Soft distended abdomen with palpable spleen 5 centimeters and palpable liver 3 centimeters below the costal margin respectively. No focal neurological deficits appreciated.
Peripheral blood smear showed marked leukocytosis with left shift maturation and blast cells. The complete blood count (CBC) revealed a white blood cell count (WBC) of 144.8 x 10^3/µL, hemoglobin (Hb) of 8.6 g/dL, and platelets (PLTs) of 307 x 10^3/µL (Table 2).

Table 2: Lab tests of case 2

| Date | Test/Investigation | Results | Reference Range |
|---|---|---|---|
| 27/March/2023 | CBC | WBC: 144.8 x 10^3/µL<br>Hb: 8.6 g/dL<br>PLTs: 307 x 10^3/µL | WBC: 4 - 11 x 10^3/µL<br>Hb: 11.5 - 15.5 g/dL<br>PLTs: 150 - 450 x 10^3/µL |
| 28/March/2023 | Bone Marrow Biopsy | Blast cells: 35% | Not applicable |
| 28/March/2023 | Flow Cytometry | Abnormal blast population: 35% | Not applicable |
| 28/March/2023 | Peripheral Blood Smear (CBC) | WBC: 98 x 10^3/µL<br>Hb: 9.5 g/dL<br>PLTs: 304 x 10^3/µL | WBC: 4 - 11 x 10^3/µL<br>Hb: 11.5 - 15.5 g/dL<br>PLTs: 150 - 450 x 10^3/µL |

| | | | |
|---|---|---|---|
| 4/May/2023 | Peripheral Blood Smear (CBC) | WBC: 2.7 x 10^3/µL<br>Hb: 8.8 g/dL<br>PLTs: 38 x 10^3/µL | WBC: 4 - 11 x 10^3/µL<br>Hb: 11.5 - 15.5 g/dL<br>PLTs: 150 - 450 x 10^3/µL |
| 7/May/2023 | Peripheral Blood Smear (CBC) | WBC: 2.55 x 10^3/µL<br>Hb: 9.3 g/dL<br>PLTs: 26 x 10^3/µL | WBC: 4 - 11 x 10^3/µL<br>Hb: 11.5 - 15.5 g/dL<br>PLTs: 150 - 450 x 10^3/µL |
| 15/June/2023 | CBC | WBC: 4 x 10^3/µL<br>Hb: 9.4 g/dL<br>PLTs: 67 x 10^3/µL | WBC: 4 - 11 x 10^3/µL<br>Hb: 11.5 - 15.5 g/dL<br>PLTs: 150 - 450 x 10^3/µL |
| 15/June/2023 | UE (Urine Examination) | Creatinine: 29 mmol/L<br>Na: 129.4 mmol/L | Creatinine: 20 - 40 mmol/L<br>Na: 135 - 145 mmol/L |

The manual differential count showed neutrophils to be 68%, lymphocytes 2%, monocyte 4%, eosinophils 2%, basophils 3%, myelocytes 18%, blasts 3%. Red blood cells (RBC) were normocytic normochromic with few nucleated RBCs present. Adequate platelets. White blood cells showed marked leukocytosis with left shift maturation and few blast cells present. Myeloproliferative disorder suspected. Further labs revealed creatinine: 45 mmol/l, uric acid: 328 mmol/l, phosphorus: 1.3 mmol/l, Erythrocyte sedimentation rate (ESR): 54 mm/hour. C-reactive protein (CRP): 116 mg/l. Electrolytes and liver function tests were within normal ranges. Chest X-ray showed no mediastinal widening.

These findings promoted for bone marrow biopsy on the next day which showed findings consistent with Precursor B-cell Acute Lymphoblastic Leukemia (Pre-B ALL) and Chronic Myeloid Leukemia (CML) in blast phase where cellularity is 100%, out of which 70% of the marrow cellularity is replaced by blasts infiltrate. Flow cytometry on the bone marrow aspirate confirmed Pre-B ALL with abnormal blast populations constituting 35% of total cellular events. Blast cells are Positive for CD45 (dim), CD34, CD38, CD19, CD10, CD22, TdT, CD79a, CD58, CD13, CD33 (Partial), CD123 (partial), CD81. This population is negative for CD9, CD20, CD3, CD117, NG2, Kappa, Lambda light chains, MPO and all other antigens. Molecular genetics testing was done on April 9, 2023, and revealed a BCR-ABL ratio of 1.125231, indicative of the P210 fusion transcript associated with t(9:22)(q34:q11) translocation.

Patient's treatment plan included chemotherapy per the Very High-Risk CCG 1961 ARM D protocol. Imatinib was scheduled for introduction on day 14 of induction chemotherapy, following the AALL 1631 protocol. The patient was admitted to the PICU on April 13, 2023, and after three days, he was stable with PEG-asparaginase incorporated into his ongoing chemotherapy regimen.

On April 28, 2023, flow cytometry was repeated to show similar results as before. Normal myeloid and lymphoid populations were also identified. The peripheral blood smear on the same date showed leukopenia with neutropenia. The manual differential count revealed neutrophils/bands at 47%, lymphocytes at 6%, myelocytes at 17%, metamyelocytes at 10%, basophils at 2%, eosinophils at 2%, and blasts at 14%. These findings supported the diagnosis of Chronic Myeloid Leukemia (CML) in blast crisis.

On May 4, 2023, he presented with abdominal pain, dental pain, and lower limb swelling. Examination revealed grade 2 lower limb edema, peripheral neuropathy, and mucositis grade 1. Consultation recommended tooth extraction, and fluconazole was initiated for skin lesions. The CBC at this time showed a WBC of 2.7 x 10^3/µL, Hb of 8.8 g/dL, and PLTs of 38 x 10^3/µL. Clinical correlation during this period involved addressing symptomatic complications arising from the ongoing treatment. The introduction of fluconazole for skin lesions and dental management aimed to alleviate patient discomfort and potential complications.

On June 7, 2023, patient presented with fever and loose bowel motions. Peripheral blood smear showed leukopenia with neutropenia, but no abnormal cells were observed. The CBC showed a WBC of 2.55 x 10^3/µL, Hb of 9.3 g/dL, and PLTs of 26 x 10^3/µL. The manual differential count indicated leukopenia with neutropenia and no abnormal cells. Patent was hospitalized at that time.

On June 15, 2023, oral examination demonstrated the resolution of oral mucositis. Patient remains stable, and Imatinib and Septra are temporarily on hold due to low counts. His CBC shows a WBC of 4 x 10^3/µL, Hb of 9.4 g/dL, and PLTs of 67 x 10^3/µL. The absolute neutrophil count (ANC) is 420. He is in the second block of consolidation for Philadelphia-positive ALL, following the EsphALL 2017 COG protocol. Imatinib is part of the treatment plan, as outlined in the AALL 1631 protocol. Clinical correlation during this phase involves careful monitoring of his response to treatment, adjusting the course as necessary based on laboratory findings and managing any emergent complications. The decision to temporarily hold Imatinib and Septra reflects a personalized approach to his care, considering his specific clinical parameters and ongoing treatment challenges.

**DISCUSSION**:

The most prevalent malignancy among children and adolescents is leukemia accounting for 28.8% of all cancers (figure 2). Acute lymphoblastic leukemia (ALL) constitutes the majority of childhood leukemias accounting for 80% while acute myeloid leukemia (AML) follows to be 5-20% (11). CML is an uncommon paediatric disease representing 3% of childhood leukemias and is characterized by an aggressive clinical progression (12). Diagnosis and treatment of paediatric leukemia, a varied group of hematologic malignancies, are exceptionally difficult (13). This case report aims to highlight this rare entity and discuss the recent advances and research in it.

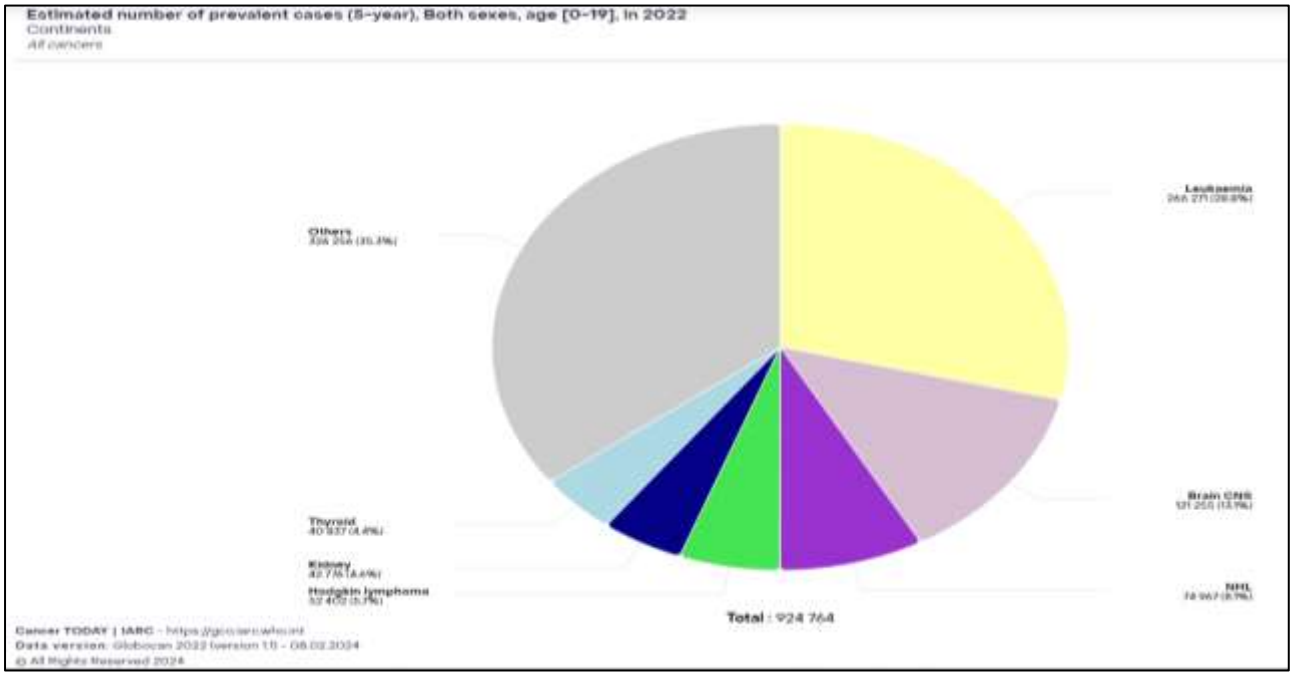


**Figure 2:** pie chart of prevalence of types of cancers among the population of 5-19 years old

The circumstances surrounding the first patient aged 13 years old, who was identified as having Chronic Myeloid Leukemia (CML) during its chronic phase, and the second patient aged 8 years old, who confronted the uncommon combination of Philadelphia positive Acute Lymphoblastic Leukemia (Pre-B ALL) and CML during a blast crisis. A limited number of isolated case reports exist about paediatric CML that manifested as myeloid blast crisis or underwent such a transformation. A comprehensive search for similar papers discussing same conditions over the past few years from the aspect of laboratory and clinical data comparison, we found the following six cases which are almost matching our two cases illustrated here in our literature, each accompanied by comprehensive laboratory and clinical information (6–9,14,15). A comprehensive summary of the six cases is shown in Table 3.

Table 3: The results of previous studies providing cases of CML

| Case Study | Patient Age/ gender | Presenting Symptoms | Diagnostic Findings | Treatment | Outcome |
|---|---|---|---|---|---|
| Carolina Pavão et al. (8) | 9-year-old boy | Pallor, B symptoms, hepatosplenomegaly | CML diagnosis: Translocation (9;22), BCR-ABL fusion gene | Imatinib, then Dasatinib | Sustained major molecular response |
| Biswajit Dey, and Anirban Dutta (6) | 3-year-old male | Abdominal swelling, hand and feet swelling, weakness | CML in myeloid blast crisis | Imatinib | Died due to febrile neutropenia |
| Uma Bhatta and Dosti Regmi (7) | 3-year-old female | Low-grade fever, weight loss, abdominal distension | CML diagnosis: t(9;22), BCR-ABL1 positive | Chemotherapy | Under treatment with regular follow-up |
| Suejung Jo et al. (9) | 8-year-old girl | Hyperleukocytosis, hepatosplenomegaly | CML-CP diagnosis: t(9;22), EUTOS low-risk | Dasatinib | Isolated CNS lymphoblastic crisis, then allogeneic HSCT |
| B R Shanthakumari, et al. (14) | 9-year-old male | Low-grade fever, abdominal distention | CML-CP diagnosis: t(9;22), BCR/ABL1 positive | Imatinib, hydroxyurea, allopurinol | Hematological remission, no relapse for 24 months |
| Gholamreza Bahoush et al. (15) | 15-month-old male | Asymptomatic, increased WBC | Ph1-positive CML diagnosis: Philadelphia chromosome | Imatinib Mesylate | Under treatment after diagnosis |

Translocation between chromosomes 9 and 22, which results in the creation of the Philadelphia (Ph) chromosome, is the defining feature of CML. The breakpoint cluster region (BCR)-ABL1 chimaera messenger RN is produced by this translocation, which confers growth advantages to leukemic cells. CML typically manifests between the ages of 60 and 65. The natural history of untreated CML is biphasic or triphasic with most cases diagnosed in the initial CML-chronic phase (CP) followed by an accelerated phase (AP), a blast phase (BP), or both. The common symptoms are fatigue, weight loss, abdominal fullness, bleeding, purpura, splenomegaly, leukocytosis, anemia, and thrombocytosis. The BCR-ABL1 fusion gene is anticipated to be identified in mature neutrophils in CML, as opposed to blasts in de novo AML (1). In addition,

mature eosinophils and basophils exhibit proliferation in CML due to the presence of the BCR-ABL1 fusion gene. Typically, one BCRABL1 gene in CML encodes the p210 fusion transcript (b3a2/e14a2 junction) (16,17). In addition, 2-4 percent of childhood acute lymphoblastic leukemia patients also have this mutation, which is often p190 in nature (17). The examination explores their clinical manifestations, research discoveries, and treatment reactions, which are consistent with prior scholarly works (6–9,14,15).

A year-long struggle with bone pain marked the beginning of the first patient's medical journey, who was 13 years old, which ultimately identified hepatosplenomegaly and hyperleukocytosis. The patient's diagnostic strategies, which encompassed a CBC, bone marrow aspiration, and molecular research, provided further support for the chronic phase of CML. Indicators of CML included hyperleukocytosis, preponderance of myeloid cells, and the presence of BCR-ABL transcripts. Flow cytometry was utilized to identify a myeloid neoplasm, hence confirming the morphological observations. The bone marrow aspiration of the patient revealed a predominance of myeloid cells with 3% blasts, which is in disagreement with the chronic phase of Chronic Myeloid Leukemia (CML) (6). Moreover, the presence of proliferative myeloid neoplasm confirms the diagnosis with CML (3,18). Eosinophilia, basophilia, and myeloid hyperplasia with a left-shift in maturation were observed in the aspirate. The touch preparation highlighted the preponderance of myelocytes, hence supporting the participation of the myeloid lineage.

The infrequency with which childhood leukemias manifest with dual diagnosis is emphasized in the literature, highlighting the criticality of employing comprehensive diagnostic strategies. The 13 years old patient's condition is consistent with the chronic phase of CML in juvenile patients, which is distinguished by a gradual onset and frequently nonspecific symptoms. The significance of molecular investigations, including BCR-ABL testing, in verifying the diagnosis and providing guidance for targeted therapy is underscored in the literature.

Conversely, the 8 years old patient's clinical manifestations of abdominal distension, joint pain, and weight loss led to the concurrent diagnoses of Pre-B ALL and CML in blast crisis. The second patient's inquiries unveiled a distinctive obstacle in the form of the simultaneous presence of Pre-B ALL and CML during a blast crisis. Flow cytometry, marked leukocytosis, and blast cells in a peripheral smear all verified the presence of multiple diseases. Molecular investigations, specifically BCR-ABL testing, furnished molecular substantiation for both diagnoses, where it has revealed a BCR-ABL ratio of 1.125231, indicative of the P210 fusion transcript associated with t(9:22)(q34:q11) translocation.

The second patient's situation, characterized by the simultaneous presence of Pre-B ALL and CML during a blast crisis, is an exceptional and complex case. Dual diagnoses are infrequent in childhood leukemias; therefore, comprehensive investigations, such as those employing molecular testing and flow cytometry, are critical for clarification of this complexity, as supported by the available research. The bone marrow biopsy of the second patient, performed on March 28, revealed the presence of a blast phase, which is diagnostic of Chronic Myeloid Leukemia and Precursor B-cell Acute Lymphoblastic Leukemia (Pre-B ALL) (CML). The presence of blast infiltration substantially diminished the cellularity of the bone marrow, accounting for 35% of the overall cellular events. Pre-B ALL was confirmed by the aspirate of bone marrow, which revealed an aberrant blast population that accounted for 35% of the total cellular events. The results emphasize the aggressive characteristics of the disease, as seen by the significant presence of blast cells.

The flow cytometry results collectively highlight the distinct immunophenotypic features of CML in the first case and the coexistence of Pre-B ALL and CML in blast phase in the second case. Flow cytometry serves as a powerful tool for leukemia classification, providing detailed information about cell surface markers and aiding in the identification of specific subtypes (21,22). The combination of flow cytometry with other diagnostic modalities, such as bone marrow aspiration and molecular studies, enhances the precision of leukemia diagnosis and guides the formulation of targeted treatment strategies (23).

In both cases, the molecular studies were integral in confirming the diagnoses, offering insights into the specific genetic alterations, and guiding therapeutic decisions. Monitoring BCR-ABL transcripts served as a valuable tool for evaluating the response to Imatinib therapy in the first CML case. The identification of the P210 fusion transcript in the second case provided essential information about the underlying genetic abnormalities contributing to the dual leukemia diagnosis (24).

**CONCLUSION**:

In this study, we presented two cases, which offer insights into the diverse spectrum of pediatric leukemia presentations. Thorough investigations, including molecular studies, are essential for accurate diagnoses and tailoring treatment strategies. The rarity of dual diagnoses, as seen in the second case, necessitates multidisciplinary collaboration and ongoing monitoring to adapt treatment approaches. Both cases highlight the crucial role of molecular studies in confirming diagnoses and guiding targeted therapies, underscoring the evolving landscape of pediatric leukemia management.

**Data availability**: The original contributions presented in the study are included in the article material. Further inquiries can be directed to the corresponding author.

**Confliction of interest**: No conflict of interest in the current study.

**Ethics statement**: Written informed consent was obtained from the minor's legal guardian/next of kin for the publication of any potentially identifiable images or data included in this article.

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