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Unveiling the Rarity: Chronic Myeloid Leukaemia in Children and Adults: A Comparative Analysis

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Abstract: ***Chronic myeloid leukemia (CML), also known as chronic myelogenous leukemia, is a blood cancer in which an excessive amount of the white blood cell granulocytes are produced by the bone marrow. CML risk rises with age, and childhood cases are incredibly rare. It is a relatively rare condition that only makes up 3–5% of all pediatric malignancies in children.Because acute leukemias are often more prevalent in children, the term "childhood leukemias" is frequently used to characterize them. Chronic leukemias, such as Chronic Myeloid Leukemia (CML), affect almost exclusively adults. Due to the normal age of diagnosis being around 60 years old in western countries, CML in children is considered to be a very rare condition. The higher leukocyte count that distinguishes children with CML from adults with CML at presentation, together with other symptoms such weariness, fever, awareness of a mass due to splenomegaly, and bleeding signs, is the main difference between the two groups of patients.***

Keywords: leukemia, children, chronic myeloid leukemia

1. Introduction

Chronic myeloid leukemia (CML), also known as chronic myelogenous leukemia, is a blood malignancy in which the bone marrow produces an excessive number of granulocytes, a kind of white blood cell. Normally, bone marrow cells develop into a variety of blood cell types. The normal maturation of blasts, which are younger white blood cells, is blocked in CML. This obstruction prevents the white blood cells from maturing appropriately, which causes them to build up in huge quantities in the bone marrow and blood(1).The median age at diagnosis is 65 years. The risk of CML increases with age, and it is extremely uncommon in children(2). It only accounts for 3-5% of all pediatric cancers in children, making it a relatively uncommon disease(3). The annual incidence of CML varies from 0.4/100,000 persons to 1.75/100,000 persons in different countries(4). With a yearly incidence of 1 and 2.2 cases per million in these 2 age groups, respectively, CML accounts for 2% of all leukemias in children under the age of 15 and 9% of all leukemias in adolescents between the ages of 15 and 19(5). The Philadelphia chromosome, which is the result of a reciprocal translocation between chromosomes 9 and 22, which creates BCR-ABL1, is what distinguishes CML from other types of cancer. BCR-ABL1 is a strong oncogene in addition to being important for CML patients' diagnostics. After a rather passive chronic phase, CML will naturally develop into an accelerated phase and then experience a crisis. Clinical evidence suggests that by targeting BCR-ABL1, long-term remissions can be established with a high rate, at least during the chronic phase (6).

With a breakpoint in the Alu repeat region of BCR, comparable to Ph-positive acute lymphoblastic leukemia (ALL), the disease is aggressive in the pediatric age group. Tyrosine kinase inhibitor exposure causes a higher burden of morbidities in children with CML during their growing years, which can differ from those in adults and calls for cautious monitoring(3). Here, we will discuss three cases of CML in children and early adolescent, taking into account a number of important factors that add to the disease's complexity.

2. Case Reports

Case 1

A 13 years old male, resident of northern part of the state of Assam, presented to Assam Medical College & Hospital with the chief complaints of generalized weakness and distention of abdomen for one month. Examination of the patient revealed pallor, hepatomegaly which was 2cms below costal margin and massive splenomegaly was present crossing the umbilicus. Complete blood count parameters showed hemoglobin 7.2 mg/dl, total count 4,10,000 with neutrophil around 94%, platelet count was 7,00,000 and peripheral blood picture showed plenty of immature myeloid cells with blast 3%, basophils 6%, promyelocyte 7%, myelocyte 20%, metamyelocyte 14% and band cells 6%. The patient was planned for molecular studies for t (9; 22) BCR::ABL status. The BCR::ABL genomic assay was positive and a diagnosis of chronic myeloid leukemia in the chronic phase (CML-CP) was made using all the clinical and laboratory data that was available. Rest of the lab findings are provided in Table1.1

Peripheral blood smear examination findings are shown in Fig 1.1

Imatinib, hydroxyurea, and allopurinol were used as the first line of treatment, along with sufficient transfusion support.

The patient tolerated the treatment well and was discharged in the next week. Hematological remission was seen in one month and molecular testing for remission was also performed for the same. The patient is currently under follow up.

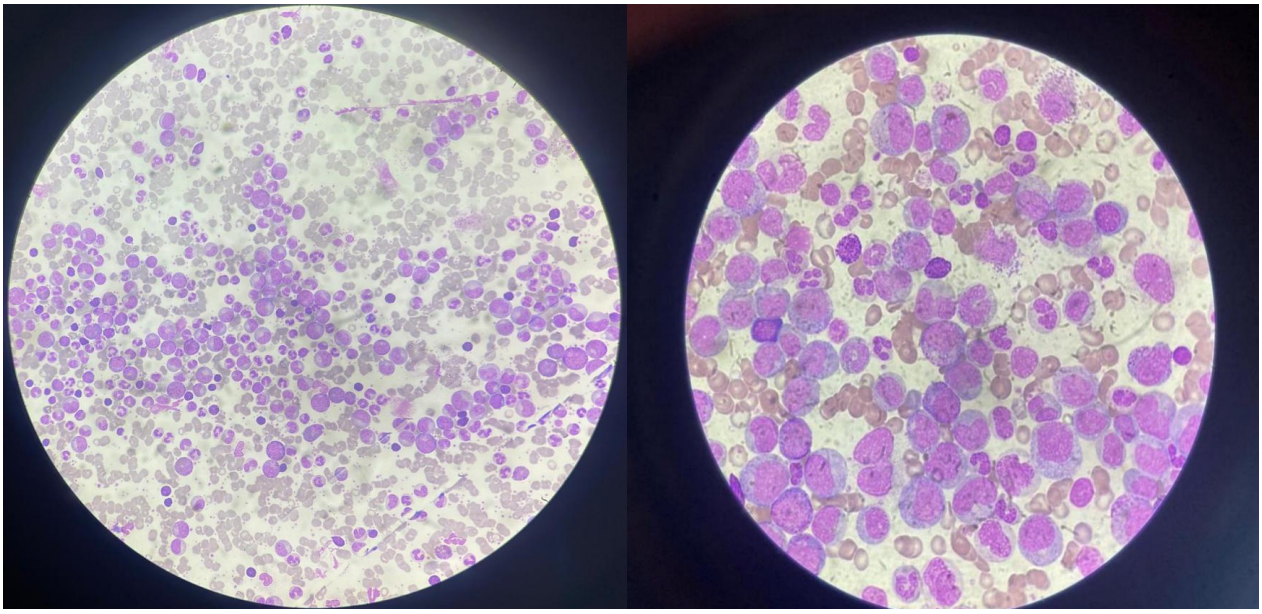

Figure 1.1: Peripheral blood smear picture at 40x and 100x showing immature myeloid cells

Case 2

A 12 years old female, resident of northern part of the state of Assam, presented to Assam Medical College & Hospital with the chief complaints of generalized weakness and distention of abdomen for two months. Examination of the patient revealed pallor with massive splenomegaly (21.5 cm) like our first case. Complete blood picture showed hemoglobin 6.4 gm/dl, total count 3,30,000 with neutrophil around 43%, platelet count of 9,00,000 and peripheral blood picture showed plenty of immature myeloid cells with blast 2%, basophils 17%, promyelocyte 1%, myelocyte 23%, metamyelocyte 5% and band cells 10%. For the patient's t(9;22) mutation, molecular research was planned for status of BCR::ABL. Using all of the available clinical and laboratory data, chronic myeloid leukemia in the accelerated phase (CML-AP) was diagnosed after the BCR::ABL genomic assay revealed a positive result. Rest of the lab findings are provided in Table1.1

Peripheral blood smear examination findings are shown in Fig 2.1

The treatment was initiated with Imatinib, hydroxyurea and allopurinol along with sufficient transfusion support. The patient responded favorably to the therapy and was released after two weeks. Due to financial limitations, molecular testing for remission could not be done after two months of hematological remission. The patient is currently under follow up.

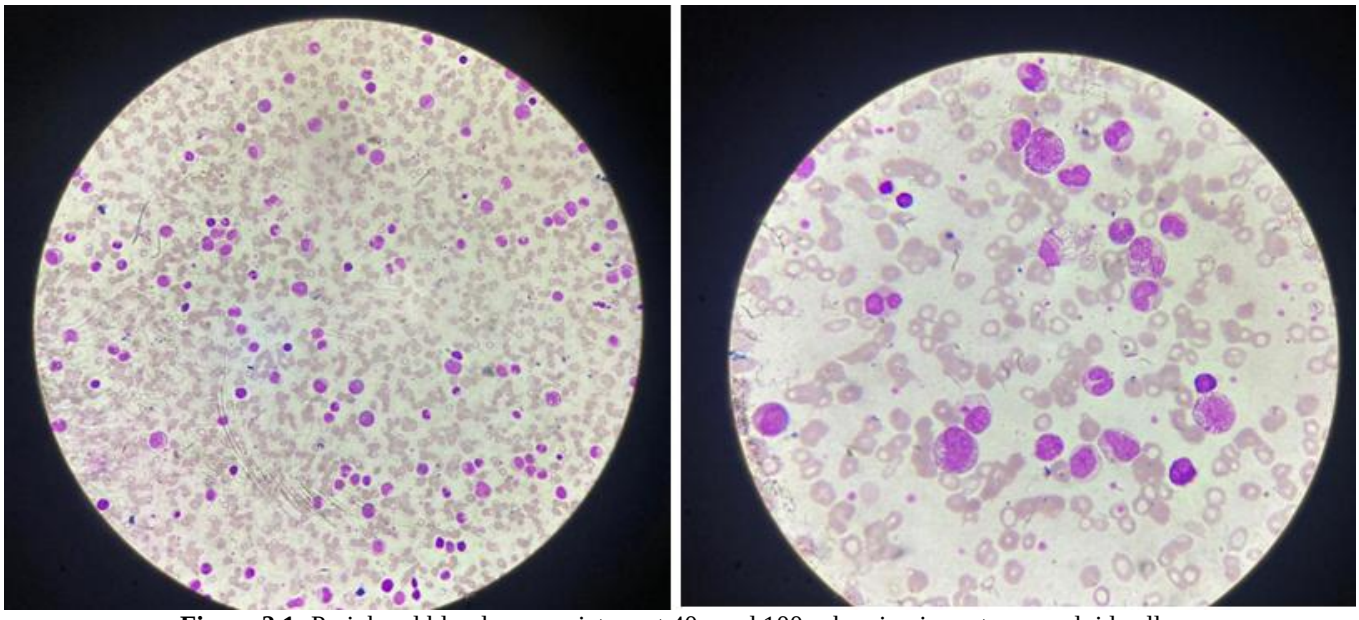

Figure 2.1: Peripheral blood smear picture at 40x and 100x showing immature myeloid cells

Case 3

A 8 years old female, from Assam's northern region presented to Assam Medical College & Hospital with the major complaint of generalized weakness and abdominal distention for two months. Examination of the patient revealed pallor with massive splenomegaly (17.6 cm). Complete blood picture showed hemoglobin 5.5 gm/dl, total count 6,80,000 with neutrophil around 30%, platelet count of 3,60,000 and peripheral blood picture showed plenty of immature cells with blast 3%, basophils 5%, promyelocyte 4%, metamyelocyte 6%, myelocyte 30% and band cells 11%. Chronic myeloid leukemia in the Chronic Phase (CML-CP) was diagnosed using all of the clinical and laboratory data after the results of BCR::ABL genomic assay were favorable. Rest of the lab findings are provided in Table 1.1

Peripheral blood smear examination findings are shown in Fig 3.1

Imatinib, hydroxyurea, and allopurinol were used to start the treatment, along with adequate transfusion support. The patient tolerated the treatment well and after two weeks of therapy, the patient was discharged. Molecular testing for remission could not be performed after two months of hematological remission due to financial restrictions. The patient is currently under follow up.

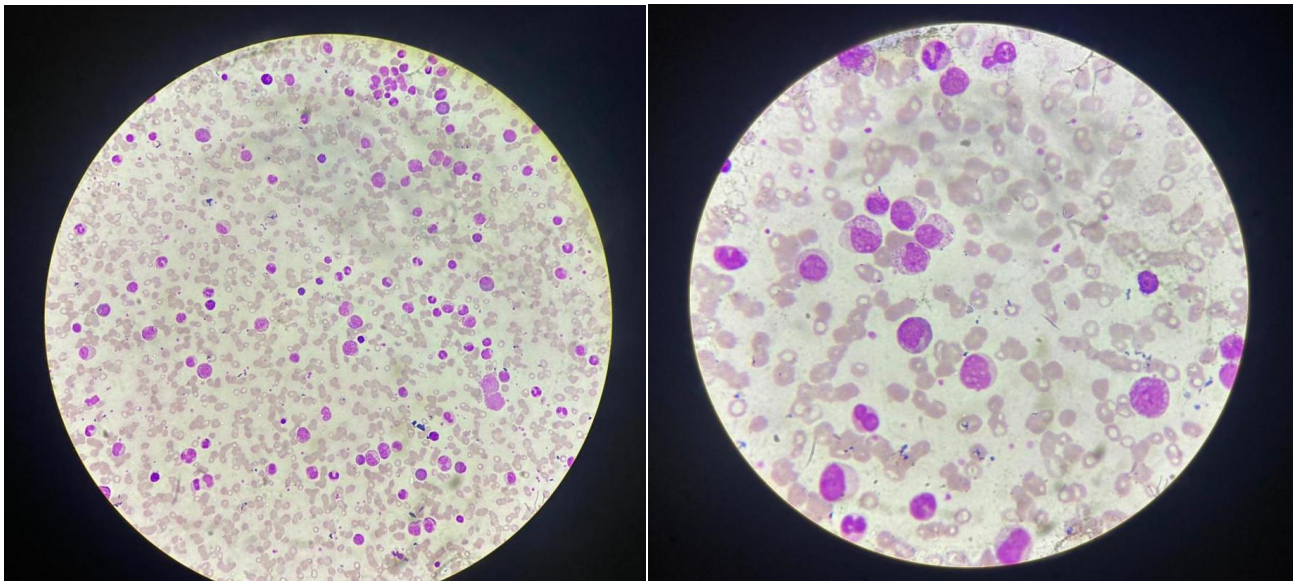

Figure 3.1 Peripheral blood smear picture at 40x and 100x showing immature myeloid cells

Case 4

A 16 years old female, resident of northern part of the state of Assam, presented to Assam Medical College & Hospital with the chief complaints fever and non-productive cough for 5-6 days. Examination of the patient revealed pallor, distension of abdomen with massive splenomegaly (16.9cm) with no significant chest findings. Complete blood picture showed hemoglobin of 8.0 gm/dL, total count 2,80,000 with neutrophil around 39%, platelet count of 5,10,000 and peripheral blood picture showed plenty of immature cells with blast 4%, basophils 4%, promyelocyte 5%, metamyelocyte 7%, myelocyte 27% and band cells 09%. Fever profile for the most common diseases in our area was found to be negative. Using all available clinical and laboratory information, Chronic Myeloid Leukemia in the Chronic Phase (CML-CP) was identified incidentally, following the BCR::ABL genomic results were positive. Rest of the lab findings are provided in Table 1.1

Peripheral blood smear examination findings are shown in Fig 4.1

The initial course of therapy included imatinib, hydroxyurea, and allopurinol, as well as sufficient transfusion support, along with other supportive measures for fever and dry cough. After two weeks of therapy, the patient was discharged since she had tolerated the treatment well.Current follow-up on the patient is ongoing.

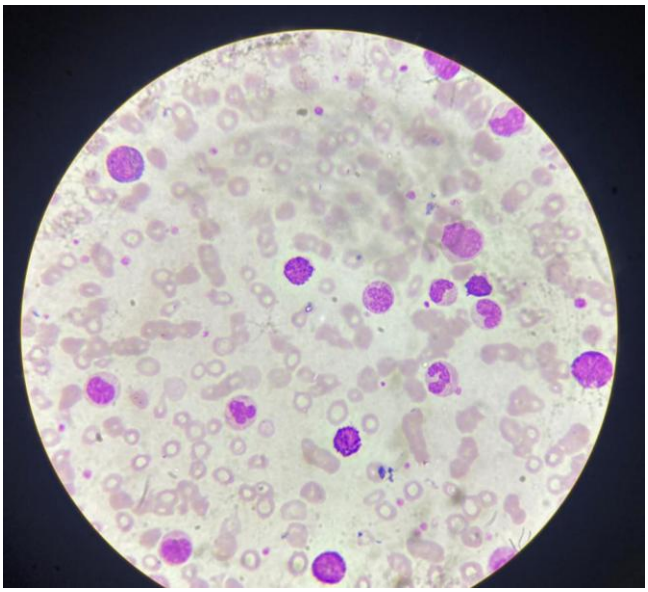

Figure 4.1: Peripheral blood smear picture at 100x showing immature myeloid cells

Table 1.1: Laboratory profile of patients

Investigations	Case 1	Case 2	Case 3	Case 4
Hemoglobin (gm/dL)	7.5	6.4	5.8	8.0
Total count (mm^3)	4,10,000	3,30,000	6,80,000	2,80,000
Peripheral Blood Smear	Blast 3%, Basophils 6%, Promyelocyte 7% Myelocyte 20%, Metamyelocyte 14% and Band cells 6%	Blast 2%, Basophils 17%, Promyelocyte 1%, Myelocyte 23%, Metamyelocyte 5% and Band cells 10%.	Blast 3%, Basophils 5%, Promyelocyte 4%, Metamyelocyte 6%, Myelocyte 30% and Band cells 11%.	Blast 4%, Basophils 4%, Promyelocyte 5%, Metamyelocyte 7%, Myelocyte 27% and Band cells 09%
Corrected Retic count (%)	2.8	2.0	3.1	2.8
Platelet count (mm^3)	7,00,000	9,00,000	3,60,000	5,10,000
RBC count (mm^3)	2.6 million	3.1 million	1.8 million	2.4 million
LDH	>1000	>1000	>1000	>1000
Total Bilirubin (mg/dL)	0.66	0.37	0.81	0.48
Hemoglobin typing (%)	Adult Hb 85.6	Adult Hb 84.9	Adult Hb 85.9	Adult Hb 87.4
Creatinine (mg/dL)	0.68	0.47	0.52	0.80
Urea (mg/dL)	34.82	12.73	13.74	19.22
Uric acid (mg/dL)	6.56	6.08	6.88	6.94
Sodium (mmol/L)	138.28	134.56	137.63	135.65
Potassium (mmol/L)	3.27	3.55	3.49	3.60
BCR::ABL status	Positive	Positive	Positive	Positive

3. Discussion

Myelogenous leukemia, often known as chronic myeloid leukemia (CML), is a malignancy of the white blood cells. It is a type of leukemia characterized by the buildup of myeloid cells in the blood as well as the accelerated and uncontrolled proliferation of these cells in the bone marrow. A bone marrow stem cell disorder is CML. It is linked to the Philadelphia chromosome, a distinctive chromosomal translocation. Parts of two chromosomes—the 9th and 22nd—switch positions in this translocation. The outcome is the "fusion" gene BCR::ABL, also known as a tyrosine kinase, which is produced when a portion of the BCR ("breakpoint cluster region") gene from chromosome 22 is fused with the ABL (“Abelson”) gene on chromosome 9(7). The term "childhood leukemias" is frequently used to describe acute leukemias because they are typically more common in children. Almost exclusively adults are affected by leukemias of chronic variants, including Chronic Myeloid Leukemia (CML). CML in children is regarded as an extremely unusual illness because the typical age of diagnosis in western nations is about 60years(7). Approximately 2–3% of newly diagnosed cases of child leukemia are pediatric CML instances. For the age range of 0-14 years, the age-adjusted Surveillance, Epidemiology and End Results (SEER) cancer incidence rate from 2010 to 2014 was 1.4 per 1,000,000, whereas for the age group of 0-19 years, it was 2.1 per 1,000,0005. CML is quite uncommon in children younger than one year old. Children older than 12 years old in India are typically affected with CML. There is no distinct data collection for pediatric CML because the National Cancer Registry Program of India registers all cases of pediatric leukemia as a single group(8). The key distinction between children with CML and adults with CML at presentation was the increased leukocyte count in the children; other accompanying symptoms were fatigue, fever, awareness of a mass owing to splenomegaly, and bleeding signs(9). Out of the four patients we had, three were in the chronic phase and one was in the accelerated phase.

The study of chromosomes and chromosomal disorders is known as cytogenetics. The diagnosis of CML is confirmed by the discovery of the Ph (Philadelphia) chromosome in the bone marrow cells, a high white blood cell count, and other distinctive blood and bone marrow test results. The BCR::ABL1 gene can be detected and quantified in blood or bone marrow samples using the most sensitive test, qPCR. Even when the Ph chromosome cannot be found by cytogenetic testing in blood or bone marrow cells, it can detect extremely modest levels of the BCR::ABL1 gene. One CML cell among 100,000 normal cells can be found using this method. Another test used to look at genes and chromosomes in cells is called fluorescence in situ hybridization (FISH). Compared to the common cytogenetic tests used to identify the Ph chromosome, it is a somewhat more sensitive approach for identifying CML(10). The fusion gene BCR-ABL1 is present in both pediatric and adult CML patients, and its breakpoints are spread throughout a large intronic distance (encompassing >200 kb) in the ABL1 gene and the same main breakpoint cluster areas (M-BCR) in the BCR gene on chromosome 2(11).

Leukemoid reaction and juvenile myelomonocytic leukemia (JMML) are included in the differential diagnosis of CML in pediatric age groups. Leukemoid reactions have a high TLC but no myelocyte bulge. A diagnosis of CML can be ruled out by toxic granulation and normal or elevated leukocyte esterase levels. While JMML lacks the distinctive Philadelphia chromosome of CML, it still exhibits fever, hepatosplenomegaly, and anemia. Only 1.9% of pediatric CML patients are in the accelerated phase, which is quite uncommon. On the basis of morphology and immunophenotyping alone, it can be challenging to differentiate between a pediatric CML in lymphoid blast crisis and a Ph-positive ALL. As Ph+ ALL typically exhibits p190 transcript, the presence of myelocyte bulge, basophilia, splenomegaly, and p210 transcript aids in differentiating (3).

Tumor lysis syndrome, which typically comes with high WBC and is treated with hydration, recombinant urate oxidase (rasburicase), and allopurinol, is a common

complication that could arise or be the presenting characteristic of CML. In CML, tumor lysis is uncommon and often only happens during the blast crisis or the advanced accelerated phase. Second, hyperleukocytosis causes priapism, inappropriate circulation, giddiness, headaches, and dyspnea and is treated with hydroxyurea (50–75 mg/kg/day) and/or leukapheresis. When WBC >600,000/mm^3, leukapheresis is advised (12).

With the therapeutic use of TKIs, the survival of patients with pediatric CML has considerably increased in recent years. Global treatment recommendations have taken into account the therapeutic responses to TKIs at particular time points as crucial prognostic assessment markers for CML patients. Hematologic, cytogenetic, and molecular indications at 3, 6, and 12 months were used to categorize the response criteria as ideal, warning, and failure. The finest long-term results are those that result from the optimal response. To ensure the prompt identification of treatment failure during the warning reaction, close monitoring is necessary. In the event of failure, patients should be quickly shifted to alternative treatments to lower the risk of illness development and mortality(13). Children who receive imatinib treatment show better results. Allogeneic stem cell transplantation (allo-SCT) is now a third-line treatment as a result of the recent approval of the second-generation TKIs (2G-TKIs) dasatinib and nilotinib as first-line treatments in children. This has increased treatment choices. However, because they are still actively growing while on TKIs, children are more likely to experience certain adverse effects, such as growth disturbance, than are adults. Adult patients may be able to stop using TKIs if they have a profound and long-lasting molecular response. This strategy would probably be more advantageous in pediatrics for reducing TKI-related side effects, but there is a paucity of data, primarily anecdotal experiences from patients who stopped TKI due to poor adherence and a small percentage of kids who successfully stopped TKI.It is necessary to do prospective research on the stopping of TKIs in CML pediatric patients (14).

4. Conclusion

Due to the relative rarity of chronic myelogenous leukemia (CML) in children and the paucity of reliable clinical research evidence, care of CML in children is not standardized and frequently follows adult-developed guidelines. Finally, it is important to note that adult and pediatric CML are biologically distinct from one another. The first-line therapy is TKI, additionally, there are special problems that are more relevant to CML in children and adolescents, such as a detrimental influence on bone growth, uncertainty regarding the long-term consequences of TKI therapy, difficulties with adherence to medication, fertility and family planning problems, and psycho-oncology. The complexity of treating this illness is heightened by all these different key factors.

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Conflicts of Interest: None

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