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The Importance of Diagnostic Vigilance Amid Cultural Barriers in Pediatric Oncology: A Case of Atypical B-ALL

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ABSTRACT: Pediatric cancers have the ability to spread rapidly, however, they also respond well to chemotherapy, and can have incredible success rates when diagnosis and intervention are implemented early. This case report describes an unusual presentation of B-ALL in a patient whose treatment was initially delayed due to barriers of cultural origin. The child initially presented with high fevers and vomiting, with mild abdominal distention and tenderness. With concern for sepsis or the need for surgical intervention, the pediatrician urged the family to proceed to a tertiary care center for further workup. The family felt these processes were unnecessary and felt that he would recover at home with over-the-counter medications. As the boy remained ill, emergency care was sought, and further investigations revealed a diagnosis of B-cell acute lymphoblastic leukemia. With this case report, we examine the importance of diagnostic vigilance amongst physicians to ensure a prompt and accurate diagnosis, while remaining mindful of cultural factors that may complicate clinical assessment and compliance.

KEYWORDS: B-ALL, cultural barriers, diagnostic vigilance, pediatric oncology, rural healthcare

1. INTRODUCTION

Cancer is one of the most devastating and terrifying diagnoses an individual and their families can receive. However, when it comes to children, they tend to be much more resilient, with an incredible ability to recover from even the worst situations. Pediatric cases also do not have nearly a fraction of the comorbidities seen in adult populations, allowing for an increased availability of treatment options, and the ability to treat more aggressively. In contrast to adults, pediatric cancers tend to have shorter incubation periods and can disseminate more rapidly, with a tendency to be invasive, but also responding well to chemotherapy.[1] In these cases, the key to having positive outcomes is contingent on early detection and diagnosis. If detected early, there is an ~80-85% success rate for potential cure of all childhood and adolescent cancer types.[1]

When it comes to leukemia, there are a series of diagnostic steps that take place. Initially, clinical exams may reveal fatigue, easy bruising, and increased infections. The patient may also present with enlarged lymph nodes, joint pain, and hepatosplenomegaly. These findings will prompt the provider to order blood work which will often reveal abnormal blood counts, such as leukopenia or leukocytosis. Bone marrow aspiration and biopsy are diagnostic, and for leukemia, the bone marrow will contain 20% or more blast cells. Following this bone marrow finding, immunophenotyping and cytogenetics can be conducted to determine lymphoid vs. myeloid, T or B lymphocyte affected, and any chromosomal results that can be used to help determine treatment.[2] The ability to reach this stage of diagnosis is not only up to the provider ordering the correct tests, but compliance on behalf of the family to ensure all the testing is done. Acute lymphoblastic leukemia is one of the most common childhood cancers, with survival rates that can exceed 90%.[3] However, as previously mentioned, these survival rates are strongly dependent on early detection and diagnosis so that treatment can begin.

An issue faced by many physicians is patient compliance to follow through and complete the tests that have been ordered. This becomes a more serious issue in pediatrics, when the affected children rely on their parents in order to have them done. This issue is often exacerbated when cultural barriers begin to play a role. A recent study focusing on the health of immigrants and low socioeconomic status populations in the United States identified that there is a significant underrepresentation in the United States health data for these groups, which has led to poor documentation of their unique health needs and disparities. Cancer screening rates in these individuals are consistently lower, often driven by cultural modesty, limited provider recommendation, lower health literacy, and trust issues.[4] Ali et al., conducted a study assessing the knowledge and practices regarding self-medication in these

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same populations and found that more than 50% of these individuals were self-medicating, majority of which was with antibiotics. The reasons for this self-medication involved seeing symptoms as minor, feeling of having enough experience or knowledge, and lack of time, money, or insurance. More than 50% understood that there were dangers associated with self-medicating that may mask a more serious illness, but they continued to self-medicate anyway.[5] Another recent study was done to assess the literacy of appropriate antibiotic use in refugee and immigrant populations. They found that those from low to middle income countries scored significantly lower and had higher rates of inappropriate antibiotic use, most commonly attributed to culture factors, healthcare access, and communication challenges.[6] Many of these families were found to view antibiotics as proof of being taken seriously by their physician. General practitioners treating these patient populations were found to prescribe antibiotics, even when not needed, in order to build trust-based relationships with these patients, to avoid conflict, and to compensate for diagnostic uncertainty, especially when language barriers played a role.[7]

These cultural barriers can result in significant mistrust in Western medicine, resulting in diagnostic uncertainty, and a hesitancy to comply with additional testing. Oftentimes, families will discuss diagnoses amongst themselves and extended family, and may decide against initial provider treatment plans, opting to wait-it-out, or get a second opinion. Whilst secondary opinions should never be opposed by providers, and are often encouraged to ensure patients feel comfortable with their treatment plans, it can result in a delay in diagnosis. Children of immigrant or low socioeconomic status families can be difficult to treat, especially if one or both of the parents are in the medical field themselves. Childhood illnesses are complicated in that more serious illnesses can be masked, often presenting as a more common condition. When symptoms appear to be benign, such as presenting as a cold or flu, parents, and even some providers, are often more content with trying a course of antibiotics as opposed to a series of tests for a more sinister underlying cause. As physicians, we must remain diligent in explaining the standard of care, reasoning and evidence, and the importance of trust in the treatment plan in a way that they will accept and will not delay treatment. Through the presentation of our case, we aim to highlight the importance of remaining vigilant in obtaining a correct diagnosis for patients, even amidst cultural barriers.

2. CLINICAL PRESENTATION

On 8/6/2024, a 3-year-old boy was brought to his pediatrician by his mother with the chief complaint of fever of 103. The boy had decreased oral intake, vomiting, and decreased activity levels. The primary exam revealed an alert but fussy, slightly pale boy. HEENT was unremarkable, chest was clear to auscultation with normal S1/S2 and regular rate and rhythm. Blood pressure was 105/60 and respiratory rate was 22. Abdomen was mildly distended and diffusely tender with no rebound or guarding. No organomegaly was seen on primary examination.

Concerned about the potentiality of this being a surgical case or sepsis, the pediatrician referred the mother to a tertiary care center for a sepsis workup, including CBC, cultures, possible spinal tap, and to start antibiotics.

8/7/2024, the following day, the doctor tried to find out about the results, however, the family had not taken the boy in. He called the family and asked why they had not gone to the tertiary center for the testing, to which they advised the doctor they decided to give him Tylenol and Motrin and were waiting to see if he improved. The doctor asked the parents to bring the boy back to the office. On the exam, he was still having high fevers, pale, fussy, abdominal pain, decreased oral intake, vomiting and abdominal tenderness. The pediatrician emphasized the importance of sending to the tertiary care center for full workup, otherwise CPS would be called.

On 8/8/2024, the boy presented to the emergency department and was admitted for fever and abdominal pain. During the clinical workup, the mother noted the boy remained constant with fevers at 103-104 for the past three days. His fever was not resolved with acetaminophen or ibuprofen. He had increased lethargy and was not eating or drinking. She noted his stomach pain began over the past two days.

Clinical workup in the hospital revealed leukocytosis (22 x10^3/uL), platelets (119 x10^3/uL), normal CMP, and elevated procalcitonin. A CT scan of the abdomen with IV contrast was unremarkable from a surgical standpoint with no identifiable masses, appendicitis, or any other abnormalities. Chest x-ray was unremarkable. The diagnosis was listed as enteritis.

The patient was given a bolus of intravenous fluids (IVF) and was started on a continuous IVF drip. He was given a dose of

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ceftriaxone empirically and was started on piperacillin/tazobactam. The patient was admitted overnight for further observation and evaluation.

The next day, 8/9/2024, the patient's fever was unrelenting, requiring numerous doses of Motrin and Tylenol. His abdominal pain continued, and he began having diarrhea. A GI panel was conducted and was positive for Giardia. Further lab results showed elevated D-dimer, ferritin, LDH, BNP, CRP and ESR.

The patient was switched from piperacillin/tazobactam to metronidazole. A follow-up abdominal ultrasound was conducted and showed trace fluid and splenomegaly, but no other significant findings. All blood cultures for the previous 48 hours had been negative.

8/10/2024, the patient's mother reported that the boy was still having abdominal pain and his fever was not improving. Repeat labs showed normal electrolytes, kidney function, and consistently elevated WBCs with neutrophilia. At this point, the patient was reported to have prolonged fevers for several days with no identified source, aside from Giardia. A discussion between the providers and the family was done regarding the risk and benefit of starting the patient on IVIG treatment while waiting on results. Given that all cultures had been negative for 48 hours, a collaborative decision was made to start IVIG treatment. Results pending were for COVID antibodies, Epstein-Barr Virus titers, Hemophagocytic Lymphohistiocytosis-related labs, including natural killer cell function and soluble interleukin-2 receptor levels.

The boy tolerated the IVIG infusion well without any complications, however, he continued to spike fevers, and his abdominal pain and irritability remained. The patient was still having poor oral intake since admission, as well as vomiting episodes.

Given his clinical course, a decision was made to transfer the patient to a children's hospital for a more comprehensive assessment, including a bone marrow aspirate and biopsy, infectious disease, and rheumatology consultation, a crucial part of the workup for fevers of unknown origin.

The patient was admitted to the children's hospital on 8/12/2024. Clinical workup with flow cytometry revealed 75% blasts, and bone marrow biopsy confirmed a diagnosis of B-cell acute lymphoblastic leukemia (B-ALL) with 95% blasts. CNS with blasts on his initial lumbar puncture confirmed staging at CNS-2 disease. Table 1 shows the labs from the patient's admission to the children's hospital.

3. MANAGEMENT AND TREATMENT

Upon admission to the children's hospital and confirmation of B-ALL diagnosis, the patient was started on The Children's Oncology Group (COG) AALL1731 protocol (COG AALL1731). He did well with his chemotherapy, and received blood products as needed. He received lumbar puncture with intrathecal chemotherapy on 8/16/2024, 8/20/2024, 8/23/2024, and 8/27/2024 prior to discharge. On the day of discharge, he was stable and doing well. Table 2 shows the labs on day 15 of the chemotherapy protocol prior to discharge from the children's hospital.

The patient returned to the infusion center for the remainder of induction on 9/3/2024 and 9/10/2024. He received another bone marrow biopsy on 9/10/2024 and his mediport was placed on 9/13/2024.

In addition to his chemotherapy regimen with the AALL1731 protocol, he received ondansetron for chemotherapy induced nausea/vomiting, famotidine for acid-suppression, and polyethylene glycol for constipation. He received trimethoprim-sulfamexazole for pneumocystic prophylaxis. He was also given oxycodone as needed for pain.

He was closely monitored for any evidence of neuropathic pain or neuropathy as a potential side effect of the Vincristine. His treatment course was complicated by a bout of hemorrhagic cystitis, a potential side effect of the chemotherapy protocol, managed with IV fluids, oxybutynin and tamsulosin.

4. OUTCOME

The patient is currently being treated in a children's hospital and has improved significantly. His treatment is ongoing and he continues to follow-up with his primary care doctor.

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5. DISCUSSION

As a physician, you will undoubtedly face difficult patients and cases. It is important to ensure that you remain vigilant with your communication of the treatment plan to the family and emphasize the importance of the complete workup and compliance with management and treatment plans.

When patients do not follow the recommended treatment or fail to comply with testing, follow-up and explain again what it is that you are looking for and the potential consequences of delaying diagnoses. They must understand that some illnesses do require further workup, not just from the primary care physician, but through consultations with other specialties to ensure the correct diagnosis is achieved.

If the initial treatment plan is decided but there is no resolution and the problem persists, this necessitates further workup. As seen in our patient initially treated with antibiotics, the persistent fever for several days required ongoing exploration, even when the patient does not yet meet the criteria for fever of unknown origin.

Finally, you will come across complex cases with families who are non-compliant, question your decisions, and have little faith in the treatment process. It is crucial to remain humble and patient with the family and focus on strong communication when explaining to them that they have a right to understand and make decisions for their child, however, if these choices put the child at harm, CPS may need to be involved if a resolution cannot be made in the best interest of the child.

6. CONCLUSION

With significant persistence from the pediatrician, a thorough workup was able to be conducted and our patient was able to be accurately diagnosed, with proper intervention rapidly initiated. Even with many negative tests and an initial differential of enteritis, the diagnostic vigilance of the physicians working this case allowed for a more sinister diagnosis to be revealed in a seemingly benign clinical presentation. This case strongly emphasizes the importance of ensuring every patient is fully evaluated and that clinical reasoning is never compromised, even amidst cultural barriers that may complicate workup.

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8. DATA AVAILABILITY

This article is freely available and may be used by all members of the scientific and medical community.

Consent to participate

The patient is under the age of 18, therefore, verbal informed consent was obtained by the patient's parents to write and publish this case report. The informed consent was obtained by Kid Care, Department of Pediatrics.

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Table 1: Pertinent labs upon admission to the children's hospital on 8/12/2024

TESTS	RESULT	REFERENCE INTERVAL
WBC	22.9 (H)	5.1 - 13.4 x10^3/uL
HGB	9.2 (L)	10.2 - 12.7 g/dL
HCT	27.9 (L)	31.0 - 37.7%
PLATELET COUNT	93 (L)	202 - 403 x10^3/uL
RBC	3.60 (L)	3.89 - 4.97 x10^6/uL
MCV	77.5	71.3 - 84.0 fL
MCHC	33.0	32.0 - 34.7 g/dL
MCH	25.6	23.7 - 28.3 pg
RDW-CV	13.2	12.5 - 14.9%
RETICULOCYTE COUNT (%)	0.50 (L)	0.80 - 1.50%
RETICULOCYTE COUNT ABS	17.9 (L)	36.4 - 68.0 x10^3/uL
IMMATURE RETIC FRACTION	9.5	8.4 - 21.7%
RETICULOCYTE HEMOGLOBIN EQUIVALENT	30.1	28.0 - 38.0 pg
MPV	8.7 (L)	9.0 - 10.9 fL
PMN'S	1	%
LYMPHOCYTES	51	%
EOSINOPHIL	0	%
MONOCYTES	4	%
BASOPHILS	0	%
BLASTS	40 (H)	<=0%
METAMYELOCYT ES	3 (H)	%
MYELOCYTES	1 (H)	%

(H): Data is abnormally high, (L): Data is abnormally low

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Table 2: Pertinent labs on day 15 (8/27/24) of chemotherapy after chemotherapy initiation per The Children's Oncology Group (COG) AALL1731 protocol on 8/12/24

TESTS	RESULT	REFERENCE INTERVAL
WBC	1.2 (L)	5.1 - 13.4 x10^3/uL
HGB	9.9 (L)	10.2 - 12.7 g/dL
HCT	28.7 (L)	31.0 - 37.7%
PLATELET COUNT	73 (L)	202 - 403 x10^3/uL
RBC	3.61 (L)	3.89 - 4.97 x10^6/uL
MCV	79.5	71.3 - 84.0 fL
MCHC	34.5	32.0 - 34.7 g/dL
MCH	27.4	23.7 - 28.3 pg
RDW-CV	15.4 (H)	12.5 - 14.9%
PMN'S	43.4	%
LYMPHOCYTES	54.1	%
EOSINOPHIL	0.0	%
MONOCYTES	2.5	%
BASOPHILS	0.0	%
BLASTS	0.0	<=0%
IMMATURE GRANULOCYTE %	0.0	0.0 - 1.0 %
IMMATURE GRANULOCYTE #	<0.10	<0.10 x10^3/uL

(H): Data is abnormally high, (L): Data is abnormally low

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