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Acute myeloid leukemia with hepatic infiltration presenting as obstructive jaundice

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ABSTRACT

We present the case of a 55-year-old woman who presented with laboratory studies concerning for acute myeloid leukemia (AML) as well as obstructive cholestasis. In similar previously reported cases, concerns of chemotherapy toxicity exacerbated by liver dysfunction or concerns of untreated, concurrent cholecystitis in a neutropenic patient often delay initiation of chemotherapy for full medical workup. At admission, our patient was started on the cytoreductive agent hydroxyurea. By day 10 of her medical workup, her liver function had improved with total bilirubin levels normalizing. At that time, full-dose 7 + 3 induction with cytarabine and daunorubicin was then initiated.

1. Introduction

Extramedullary manifestation of Acute Myeloid Leukemia (AML) is rare, constituting about 1% of all patients with AML. These extramedullary manifestations range from cellular infiltration without effacement of tissue architecture to the growth of a tumor mass, the latter of which is defined as myeloid sarcoma. Furthermore, extramedullary manifestations may affect a wide variety of tissues. Among published cases, otherwise healthy patients have initially presented due to cholestasis with obstructive jaundice, but their symptoms were later confirmed as the primary manifestation of de novo AML [1,2]. In another case, chemotherapy was initiated in a patient with myelodysplastic syndrome who unknowingly had AML infiltration of the liver. This patient observed worsening liver status and faced rapid demise due to liver failure prior to initiation of definitive treatment [3]. These cases highlight the challenges associated with the diagnosis of AML with extramedullary manifestations as well as the perils with timing the initiation of chemotherapy. Currently, no guidelines exist for the initial workup and management of AML with extramedullary manifestations. We describe the unusual case of a patient who presented with studies concerning for AML and obstructive cholestasis. Hydroxyurea was used to address the effects of hyperleukocytosis while completing cholestasis workup prior to initiation of chemotherapy.

2. Case report

Our patient is a 55-year-old female with no significant past medical history who presented to a local community hospital with a 3-week history of upper abdominal pain, fevers, night sweats, gingival swelling with frequent bleeding, and jaundice. Initial studies revealed leukoerythroblastosis with striking leukocytosis (WBC 115.6 $\times 10^3/\mu L$), absolute monocytosis, including immature forms and blasts (60%) (Fig. 1A), anemia (Hgb 9.8 g/dL), normal platelet count (204 $\times 10^3/\mu L$), elevated liver function tests (AST 204/L and ALT 244/L), total bilirubin 3.3 mg/dL, direct bilirubin 2.5 mg/dL, and alkaline phosphatase 1082/L. Flow cytometry immunophenotype analysis showed an expansion of myeloid precursor/blast and monocytic regions (Fig. 1B). Bone marrow biopsy and aspirate were diagnostic for AML with monocytic differentiation (82%), dysmegakaryopoiesis and dyserythropoiesis (Fig. 1C and D). Molecular studies were positive for IDH2 (R140Q), ASXL1, NRAS, ZRSR2, BCOR, and DNMT3A mutations, and an extra copy of KMT2A (MLL)/11q23 was detected by Focused In-Situ Hybridization in 6.5% of

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cells. These findings met the World Health Organization criteria to classify the disease as AML with myelodysplasia-related changes.

CT chest, abdomen, and pelvis revealed biliary distension with biliary sludge, biliary wall thickening, pericholecystic fluid, hepatosplenomegaly, and lesions in the spleen and lungs (Fig. 2). Hepatic viral and autoimmune serologies were negative. She was initiated on piperacillin-tazobactam for acute cholecystitis. Subsequent MRCP demonstrated biliary sludge without intrahepatic or extrahepatic biliary dilation, and no choledocholithiasis or biliary stricture. A HIDA scan revealed a functionally patent cystic duct with moderately severe intrahepatic cholestasis. A percutaneous liver biopsy showed a brisk portal and lobular infiltrate comprised of atypical mononuclear cells (Fig. 1F and E). In addition, the liver parenchyma showed changes suggestive of large duct obstruction, namely bile duct proliferation and portal expansion with edema (Fig. 1F and E). These morphological findings were consistent with AML involvement of the liver.

Prior to transfer to our tertiary institution, the patient had been started on hydroxyurea. Hydroxyurea therapy was continued throughout her workup and both the patient's WBC levels decreased and peripheral blasts were <5% by hospital day 10. Additionally, the patient's liver function panel gradually normalized, with ursodiol added to help improve cholestasis. 7+3 induction chemotherapy with cytarabine and daunorubicin was started when total bilirubin fell below 1.5 mg/dL on hospital day 13. She tolerated therapy well, with initial course complicated by mild mucositis and development of *Clostridium difficile* colitis. The day 14 (from start of 7+3) bone marrow biopsy revealed blast clearance with a hypocellular marrow. A repeat bone marrow biopsy on day 30 revealed profound hypocellularity (<10%), a small foci of early erythroid and granulocytic maturation, and was still clear of residual leukemia. This slow count recovery is attributed to her underlying myelodysplastic syndrome.

3. Discussion

AML with hepatic infiltration is not commonly reported upon and has a poor prognosis. Induction therapy is often delayed for complete cholestatic workup or initiation of chemotherapy may occur in the setting of unknown extramedullary manifestations. Previous cases have highlighted the challenges associated with these situations and there is a paucity in the literature providing recommendations. We describe the use of the cytoreductive therapy hydroxyurea to temporize the effects of hyperleukocytosis while performing a full workup for cholestasis prior to initiation of chemotherapy.

Our patient was found to have AML with monocytic differentiation and MDS-related changes. The presence of monocytic differentiation confers an increased risk of organ infiltration and has been associated with hyperleukocytosis [4]. Additionally, myelodysplastic changes, while not specifically associated with extramedullary infiltration, confer

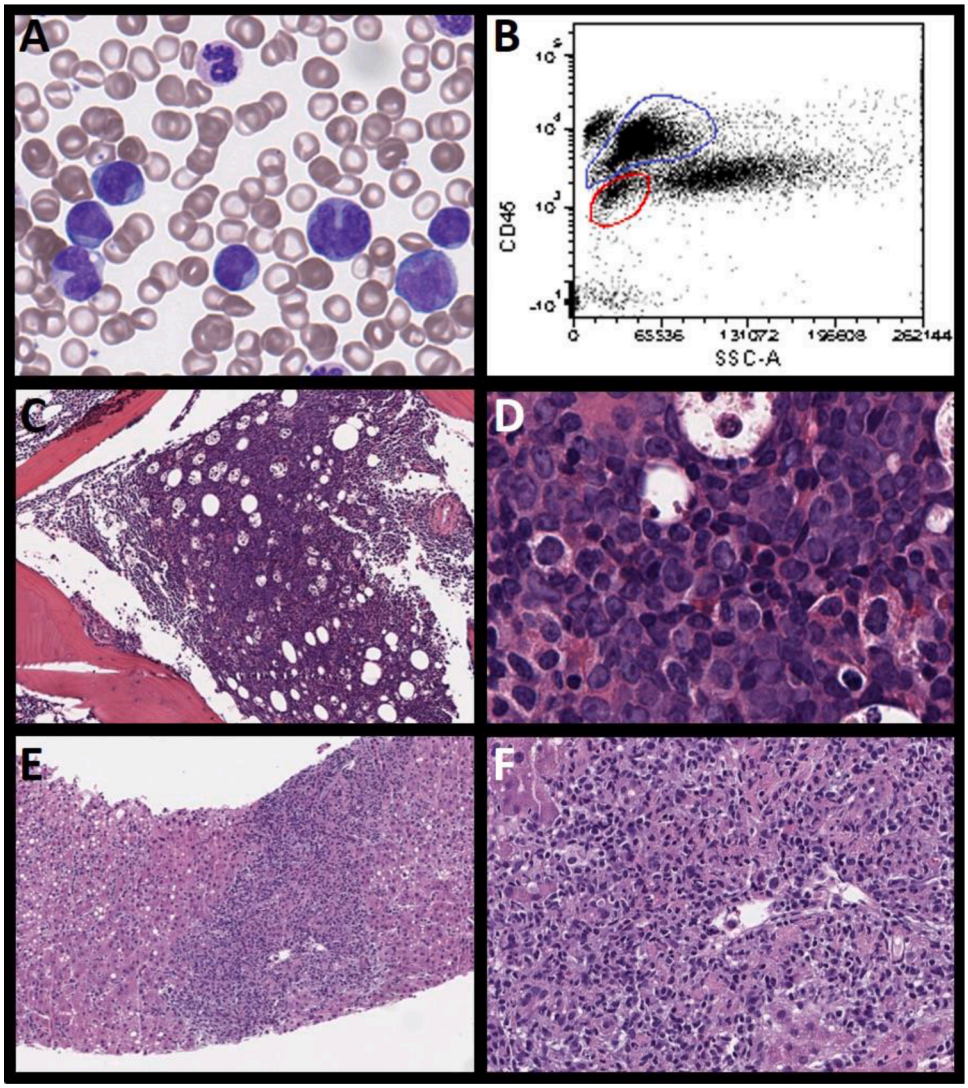

Fig. 1. Histology. (A): Peripheral blood smear Romanowsky stained slide showing immature promonocyte forms with irregular and delicately convoluted nuclear configuration (original magnification x 400). (B): Flow cytometry showing cell populations preliminarily identified by cytoplasmic complexity (side scatter [SSC], displayed on the x-axis) and CD45 expression (displayed on y-axis); expanded blast/myeloid precursor (circled in red) and monocytic (circled in blue) regions are present. (C): Bone marrow biopsy, hematoxylin & eosin (H&E) stained section slide, medium power view showing bone marrow hypercellularity (90–100%) with increase predominance of blast forms (original magnification x 50). (D). Bone marrow biopsy, H&E section slide, High power view showing blasts with high nuclear:cytoplasmic (N:C) ratios, irregular nuclear contours, fine nuclear chromatin and scant cytoplasm (original magnification x 400). (E): Liver biopsy, H&E stained section slide, medium power view showing mild steatosis of the liver (sides) with a brisk portal and lobular infiltrate (center) (original magnification x 40). (F): Liver biopsy, H&E stained section slide, high power view showing an infiltrate comprised of atypical mononuclear cells along with bile duct proliferation and portal expansion with edema (original magnification x 200). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.).

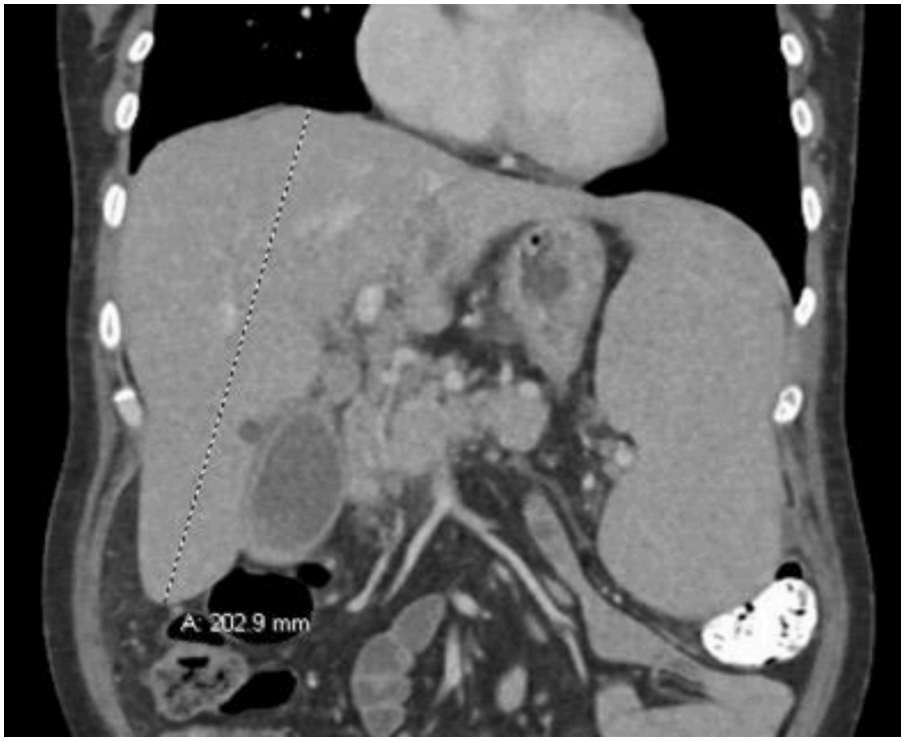

Fig. 2. CT abdomen scan with contrast. The CT abdomen scan demonstrates hepatomegaly, measuring 20.3 cm (as shown by dotted line), with a likely cyst adjacent to the gallbladder. Gallbladder is distended with wall thickening, pericholecystic fluid and sludge within the gallbladder. The CT abdomen scan also demonstrates splenomegaly, measuring 17.3 cm.

a worse overall outcome [5]. Both of these findings support early initiation of hydroxyurea. Unlike previously reported cases, our patient was started on hydroxyurea as her medical work-up was progressing. Hydroxyurea has been shown to provide survival benefit as pretreatment for hyperleukocytosis in AML induction. [6] Additionally, this pretreatment strategy demonstrates the potential value of cytoreduction as a temporizing measure for AML with hyperleukocytosis and extramedullary manifestations. Specifically, AML with hepatic infiltration appears to confer a worse outcome because its rapid progression limits the time available to delineate the etiology of obstructive transaminitis and initiate induction therapy before patient demise [3]. The concerns of initiating 7 + 3 induction therapy when obstructive jaundice is due to non-AML-related causes are two-fold. First, both anthracyclines and cytarabine are primarily metabolized by the liver. Therefore, dose adjustments are recommended for both agents based on the total bilirubin and hepatic transaminase levels to avoid chemotherapy toxicity and worse treatment outcomes [7]. Secondly, initiation of 7+3 induction therapy without proper delineation of the cause of obstructive jaundice increases the risk of calculous cholecystitis, independent of AML, going untreated and becoming a source of infection in a severely neutropenic state. Some published guidelines regarding chemotherapy use for AML in patients with liver disease exist [8]. They suggest daunorubicin can be dose-reduced for bilirubin levels up to 5 mg/dL and is omitted if greater than 5 mg/dL. Cytarabine can also be adjusted to 50% of the total dose for any elevation of AST or ALT, or total bilirubin >2 mg/dL. For example, low-dose cytarabine not exceeding 50 mg/dL daily for 7–10 days can be considered. Hypomethylating agents are not recommended due to their clearance by the liver enzyme cytidine deaminase. Additionally, Venetoclax can be considered. However, it is metabolized in the liver by CYP3A and a trend for increased adverse events was observed in patients with moderate hepatic impairment. [9] A recommended dose has not been determined for severe hepatic impairment, though some suggest 50% dose reduction.

The workup of obstructive transaminitis in the setting of AML can be lengthy. For our patient, the suspicion for acute calculous cholecystitis (ACC) was high even though ACC is typically seen during the neutropenic phase of induction [10]. Management of ACC requires broad-spectrum antibiotics, and either cholecystectomy or cholecystostomy. MRCP ruled out choledocholithiasis and the HIDA scan showed no pattern of cystic duct obstruction, effectively ruling out acute cholecystitis. Thus, we were able to avoid a highly morbid cholecystectomy. In previous cases, cholecystectomy was a common intervention, but it did not improve transaminitis and resolution was achieved only after chemotherapy was initiated. [1,2] Interestingly in our case, liver biopsy showed leukemic infiltration of the portal system resulting in large ductal obstruction despite no obstruction being demonstrated on either MRCP or HIDA scan.

While on hydroxyurea, our patient's liver function improved, as demonstrated by the total bilirubin levels normalizing to 1.6 mg/dL. At that time, full-dose 7 + 3 induction with cytarabine and daunorubicin was started. Her bone marrow biopsy review at 14 and 30 days showed no residual leukemia but there was significant hypocellularity at Day 30 contributing to her slow count recovery and transfusion dependence, which we attributed to her underlying MDS. We plan for her to receive allogenic hematopoietic stem cell transplantation with a goal of curative intent.

The presence of organ dysfunction without clear etiology in the setting of AML is an interesting medical dilemma. On one hand, the negative prognosticators associated with extramedullary infiltration support the utility of hydroxyurea to delineate underlying medical conditions without delaying induction therapy or need for dose reductions. However, early misattribution of unrelated organ dysfunction to extramedullary manifestations of AML may also prove costly. For example, our patient initially presented with elevated transaminases and bilirubin levels which could also have been due to other non-leukemic causes such as infection, clots, drug toxicities, etc. Thus, one must weigh the benefits of initiating hydroxyurea with the risk of misattributing and not treating other medical conditions assumed to be

extramedullary manifestations of AML. Additionally, hydroxyurea presents as a first-line temporizing agent, but is not the only option. In a scenario where acute hepatic failure is likely but not definitively attributable to extramedullary manifestation of AML, there should be consideration of non-hepatotoxic therapies.

4. Conclusion

Challenges exist for the initial workup of AML presenting with extramedullary manifestations. Yet, hydroxyurea remains the gold standard for hyperleukocytosis while working up AML with organ dysfunction when other chemotherapy options do not exist.

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Declaration of Competing Interest

None

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