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Case Report

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Acute Promyelocytic Leukemia Treatment Masking Hepatic Tuberculosis: A Management Dilemma

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Abstract

Acute promyelocytic leukemia is a form of acute myeloid leukemia (AML) that is characterized by presence of a promyelocytic leukemia-retinoic acid receptor alpha fusion. In most patients, this fusion is detected on conventional karyotype as the t(15;17)(q24.1;q21.2) translocation, but some patients have cryptic translocations with a normal karyotype. Historically, AML is associated with a poor prognosis. Treatment with all-trans retinoic acid and arsenic trioxide assures long-term survival in the majority of patients. This treatment is generally well-tolerated but may cause hepatotoxicity. This is usually identified by transaminitis but resolves after temporary cessation of treatment. Our patient's hepatotoxicity did not resolve following all-trans retinoic acid and arsenic trioxide cessation which posed a diagnostic dilemma. This prompted exploration of other possible causes of hepatotoxicity. An eventual liver biopsy identified acid-fast bacilli, confirming a diagnosis of hepatic tuberculosis. A broad differential diagnosis is imperative when investigating abnormalities in liver function, especially in chemotherapy patients when treatment cessation may cause cancer progression.

Keywords: Acute promyelocytic leukemia; Tuberculosis; Hepatotoxicity; ATRA; ATO

Introduction

Acute myeloid leukemia (AML) is classified as a group of hematopoietic neoplasms comprised of cells committed to the myeloid lineage. AML has an incidence of 3.7 per 100,000 persons and accounts for 25% of leukemias in the western world [1]. This malignancy is driven by the accumulation of genetic alterations which combine to halt cell maturation, increase clonal proliferation, and protect against programmed cell death [2]. There exists a large diversity and heterogeneity within AML because leukemic transformations often occur at multiple steps along the cellular differentiation pathway [3]. One of these transformations is responsible for the development of acute promyelocytic leukemia (APL), which is a biologically and clinically distinct variant of AML. Specifically, in APL, the t(15,17)(q24.1;q21.2) translocation produces a promyelocytic leukemia-retinoic acid receptor alpha (PML-RARA) fusion protein that binds with the retinoic acid receptor element in the promoter regions of several myeloid-specific genes and inhibits myeloid differentiation [4, 5]. This distinction of the APL subtype of AML is critically important because, without treatment, APL has a median survival of less than 1 month, often due to uncontrolled bleeding [6]. When recognized and treated appropriately, APL has the highest cure rate among all AML subtypes [5]. Treatment with all-trans retinoic acid (ATRA) and arsenic trioxide (ATO) provides a cure for many patients [5]. It is generally a well-tolerated treatment; however, one notable side effect is hepatotoxicity. Generally, the hepatotoxic side effects improve when holding the medication [7]. We present a case that despite treatment cessation, liver enzymes remained elevated. A dilemma in management ensued with the discovery of coexisting hepatic tuberculosis (TB).

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Case Report

Investigations

A 24-year-old man presented with headache and intermittent fevers of several months duration after immigrating from Africa 1 year prior. Initial laboratory testing revealed a white blood cell count of 26 × 10^9/L, blast cells, neutropenia, severe anemia, and thrombocytopenia. These laboratory findings were concerning for malignancy. A peripheral blood smear was conducted which demonstrated promyelocytes with Auer rods (Fig. 1).

Diagnosis

A follow-up bone marrow biopsy demonstrated hypercellular

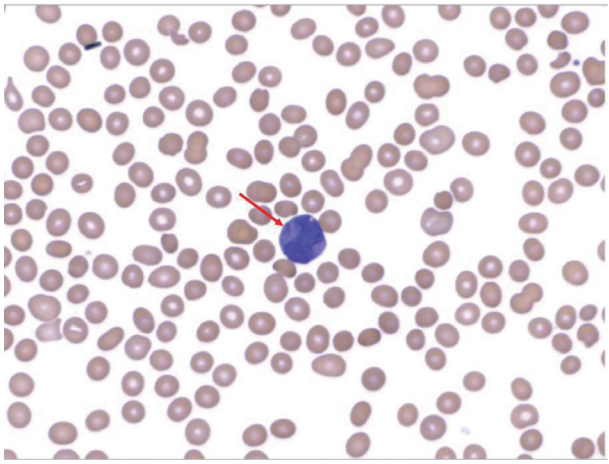

Figure 1. Peripheral blood smear demonstrating Auer rod within a promyelocyte.

marrow with increased promyelocytes and aspirate showed promyelocytes. PML-RARA fusion protein was detected by fluorescence *in situ* hybridization (FISH). Flow cytometry also showed CD34 negative, CD117 positive, human leukocyte antigen (HLA)-DR negative, and CD33 negative, suggestive of APL. Treatment with idarubicin, ATRA, and ATO was initiated. His clinical course was complicated by progressively worsening transaminitis (Table 1), prompting the decision to hold therapy with ATRA and ATO, given their known potential for hepatotoxicity. Despite holding these agents, his transaminitis persisted. Given the patient's recent immigration from an endemic TB region, an interferon-gamma release assay was performed and returned positive. Chest X-ray and computed tomography (CT) demonstrated no acute cardiopulmonary findings or findings suggestive of TB. Serial sputum acid-fast bacillus (AFB) smears were negative. Given the clinical uncertainty between drug-induced liver injury (DILI) versus an infiltrative process, a liver biopsy was performed. It demonstrated caseating granulomas with AFB, confirming the diagnosis of hepatic TB (Fig. 2).

Treatment

TB treatment was initiated with rifampin, isoniazid, pyridox-

Table 1. Laboratory Values

Day	Significant event	SGOT (14 - 33 IU/L)	ALT (10 - 42 IU/L)	TB (0.2 - 1.0 mg/dL)	Alkaline phosphatase (40 - 129 IU/L)
1		33	26	1.5	91
2	ATRA started	22	22	1.2	78
3	Idarubicin started	22	20	1.2	75
4		40	21	1.3	83
9		66	102	1.9	112
10	ATO started	61	89	1.2	121
11		70	91	1.3	122
25		146	136	2.8	254
26		172	146	3.6	259
27	Chemotherapy held	192	167	3.8	261
30		232	231	3.4	380
33		364	542	4.4	408
34	ATRA + 50% ATO dose restarted	320	574	4.9	382
36		198	510	4.6	355
38	Hepatic TB diagnosed; chemotherapy held	149	443	6.7	445
39	TB treatment started	153	403	5.0	414
43		244	521	4.1	487
44	ATRA resumed	179	501	4.4	497
47		244	496	3.1	414
49	ATO restarted at 50% dose	163	413	2.5	334
51		125	337	2.9	312
56		83	164	2.4	405
76	ATO resumed at 100%	58	57	2.3	441
156		31	62	0.8	81

ATO: arsenic trioxide; ATRA: all-trans retinoic acid; SGOT: serum glutamic-oxaloacetic transaminase; TB: total bilirubin.

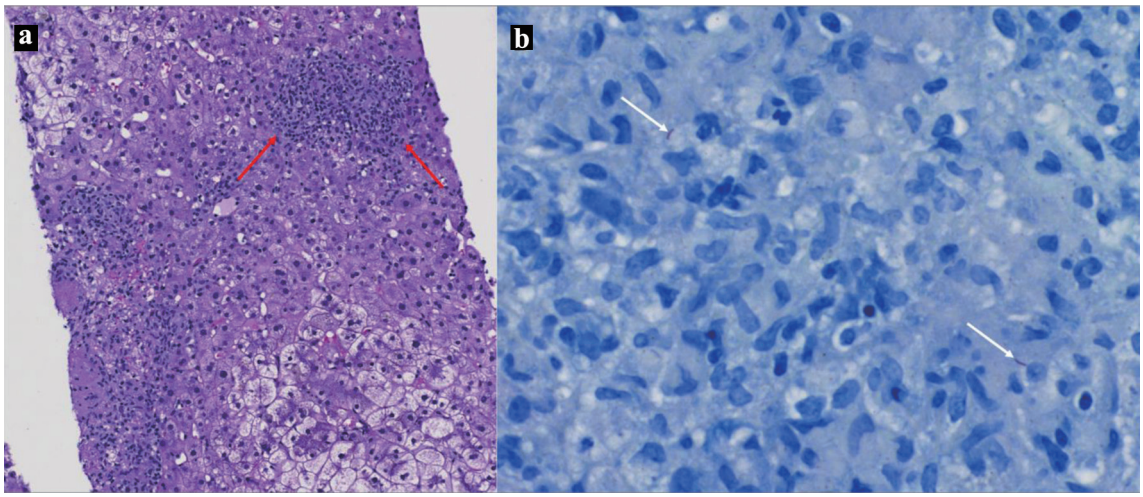

Figure 2. (a) H&E of liver biopsy specimen demonstrating necrotizing granulomas (red arrows). (b) Liver biopsy demonstrating two acid bacilli (white arrows).

ine, and ethambutol, as he did not have multidrug-resistant disease. ATRA and ATO were temporarily held for 1 and 2 weeks, respectively until liver enzymes improved. The dose of ATO was adjusted to half of the original dose once reinitiated, then increased to his therapeutic dosage when liver function normalized.

Follow-up and outcomes

The patient had an excellent hematological response to ATRA and ATO induction with repeat bone marrow showing molecular remission. Treatment was subsequently followed by a consolidation phase of therapy. He remained on his TB medication to complete a 6-month duration of therapy.

Discussion

ATRA/ATO has improved survival in APL by reducing the early treatment related mortality and risk of relapse. This treatment has been shown to improve survival when compared to ATRA with chemotherapy [7]. Arsenic trioxide binds the promyelocytic leukemia protein component of PML-RARA oncoprotein leading to apoptosis of leukemic promyelocytes [7]. ATRA then binds the RARA component of the PML-RARA oncoprotein, which is believed to cause degradation [8]. This subsequently causes the maturation of the APL cells into granulocytes [9-11].

Drug toxicities due to ATRA/ATO are generally minor, but potential adverse effects include hepatotoxicity, leukopenia, QT time prolongation, and differentiation syndrome [6]. When compared to ATRA-chemotherapy, it is associated with fewer cases of neutropenia, thrombocytopenia, mucositis, and infections [6, 7]. The hepatotoxicity associated with ATRA/ATO has been estimated to affect anywhere from 24% to 75% of patients, in comparison to 6% of patients treated with ATRA-chemotherapy [6, 7, 12, 13]. Lo-Coco et al described grade 3 or 4 hepatotoxicity occurring in 63% of patients receiving ATRA/ATO. Grade 3-4 hepatotoxicity was defined as an increase in serum bilirubin and/or serum glutamic-oxaloacetic transaminase (SGOT) and/or alkaline phosphatase > 5 times the upper limit of normal [7]. Hepatic toxicity usually resolves after temporary discontinuation and dose adjustments [7, 12-15]. Some cases of hepatic toxicity have resolved spontaneously even in the setting of continuing treatment [6]. Lo-Coco et al describe the re-initiation of ATRA/ATO treatment at 50% of the previous dose for 7 days once the serum bilirubin and/or SGOT and/or alkaline phosphatase had decreased to below four times upper limit of normal [7]. Subsequently, ATRA/ATO was resumed at full dosage, in the absence of worsening of previous toxicity. If hepatotoxicity recurred, ATRA/ATO was discontinued [7]. The first 3 weeks following induction of therapy have been described as important periods of monitoring for hepatic toxicity [12]. Zacholski et al identified a correlation between increased ATO dosages and the development of neurotoxicity; however, there was no increased incidence of hepatotoxicity identified following dose fluctuations [16]. It is critical to differentiate DILI from secondary causes of liver toxicity as delay in treatment can increase the risk for severe bleeding events or lead to cancer progression [17].

Hepatic TB is a rare form of infectious hepatic disease. Hepatic involvement of disseminated TB is known as secondary hepatic TB [18]. This type of intra-abdominal TB occurs in 3.5% of cases [17]. Primary hepatobiliary TB is even more rare, occurring in 1% of cases [17]. The primary complaint by patients is often abdominal pain, although other common symptoms include abdominal distention, weight loss, ascites, diarrhea, nausea, and vomiting [19]. Hepatic TB can cause elevated transaminitis or alkaline phosphatase depending on the involvement of liver parenchyma or porta and ducts [17]. Diagnosis of hepatic TB can be challenging as symptomatology may be broad and nonspecific. Imaging studies, such as computerized tomography or ultrasound, may be helpful to establish the diagnosis; however, they have been found to be sensitive but not specific [17]. The diagnosis usually requires

a liver biopsy or positive culture of a liver specimen, as in the case of our patient [18].

Few cases have been described of patients with APL and TB. Palta et al described a patient with dyspnea who was diagnosed with TB and subsequently found to have APL after abnormalities were seen on complete blood count differential [20]. Abdullah et al described a case of a patient with APL and persistent fevers. After extensive testing, without explanation for fever, a lung biopsy was performed which was consistent with TB [21]. Our patient initially presented without any symptoms suggestive of a TB diagnosis and had leukocytosis on initial laboratory testing which was thought to be explained by APL. No other laboratory or imaging findings suggested a diagnosis of TB until the transaminitis occurred and persisted following APL treatment. Hematological malignancies may predispose to a risk for activation of latent TB or opportunistic infections. Coburn et al found that 4.6% of patients with hematological disease had active TB compared to 0.2% of patients without hematological disease [22].

Medications used to treat TB are often involved in drug-drug interactions due to their metabolism by cytochrome p450 enzymes [23]. Minimal information has been reported in literature to describe drug interactions between TB treatment and ATRA/ATO. However, both drug regimens increase risk for hepatotoxicity [6, 7, 23]. Conversely, ATRA has shown to be efficacious in the treatment of TB both *in vitro* and *in vivo* [24]. Treatment mechanisms of ATRA relate to the activation of host innate and adaptive immune responses while stimulating the release of proinflammatory cytokines [24]. The pro-inflammatory environment created within the hepatic parenchyma secondary to the targeted attack of the infection may have caused persistent transaminitis despite the cessation of APL therapy. This conclusion was made whilst considering that the patient had normal liver function prior to its initiation while still harboring the infection.

Learning points

Chemotherapy-related side effects can be difficult to differentiate from clinical or laboratory indicators of an underlying infectious etiology. In our case, treatment of APL revealed a transaminitis causing concern for a DILI. However, because the transaminitis remained despite the cessation of ATRA-ATO, it prompted further investigation into the liver dysfunction. Identifying the underlying pathology of TB allowed our patient to be treated for both concurrent disease states. Making the distinction between drug-induced and other secondary causes of liver injury is imperative when the goal of treatment is curative as in the case of APL. The presence of unexplained abnormalities in liver function should prompt a broader differential diagnosis, which may include extrapulmonary TB in certain at-risk patient populations.

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None to declare.

Financial Disclosure

None to declare.

Conflict of Interest

The authors declare that they have no conflict of interest.

Informed Consent

Written informed consent has been obtained.

Author Contributions

Kimberly Boldig and Walter Quan conceptualized the project. Kimberly Boldig and Amy Kiamos wrote the initial manuscript draft. Trevanne Matthews-Hew edited the manuscript. Reeba Omman provided pathologic images. Walter Quan was senior editor of the manuscript.

Data Availability

All data underlying the results are available in the article, and no additional source data are required. Further inquiries can be directed to the corresponding author.

Abbreviations

AFB: acid-fast bacillus; AML: acute myeloid leukemia; APL: acute promyelocytic leukemia; ATO: arsenic trioxide; ATRA: all-trans retinoic acid; CT: computed tomography; DILI: drug-induced liver injury; FISH: fluorescence *in situ* hybridization; PML-RARA: promyelocytic leukemia-retinoic acid receptor alpha; SGOT: serum glutamic-oxaloacetic transaminase

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