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CASE REPORT **Open Access**

The Silent Hematologic Emergency: Delayed Diagnosis of Acute Promyelocytic Leukemia

Lisa Malina Mang[1*] and Rainer Schöfl[2]

Abstract

The following case study depicts the case of a 29-year-old female patient who presented with severe neutropenia, elevation of D-Dimer as well as a decrease in fibrinogen. After several weeks of blood tests without a diagnosis, as well as the exclusion of a pulmonary embolism, a bone marrow biopsy was conducted. The result was acute promyelocytic leukemia (APL). The disease was effectively treated with all trans retinoid acid (ATRA) as well as arsentrioxide (ATO).

*Correspondence:
Lisa Malina Mang
University of Roehampton, United Kingdom

1. University of Roehampton, United Kingdom
2. Professor of Gastroenterology, Private Practice, 4020 Linz, Austria

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Introduction

Acute promyelocytic leukemia, also called M3, represents 10% of all leukemia cases. It is a special subtype of acute myeloid leukemia with a distinct coagulopathy. Due to modern treatment regimens, the once particularly deadly disease is now highly treatable with cure rates of 97% [1]. Early death is, apart from potential long-term toxicity, still a major concern and one of the biggest hurdles in APL [2].

Case report

History and diagnosis

In January 2024, a 29-year-old female, who was announced and urgently sent to the hematological-oncological station by a private hematologist, arrived visibly distressed and anxious.

Four weeks ago, routine blood work was done (see table 1) showing an absolute neutropenia, marginally diminished thrombocytes and marginally diminished erythrocytes. The patient did not exhibit any kind of symptoms.

HEMATOLOGY

Blood Count:

White blood cells	↓ **1.3**	G/l	4.0-10.0
Platelets	162	G/l	150-350
Red blood cells	↓ **3.6**	T/l	3.8-5.2
Hemoglobin	↓ **11.9**	g/dl	12.0-16.0
Hematocrit	↓ **0.33**	l/l	0.35-0.47
MCV (mean cell volume)	90	fl	78-98
MCH (mean cell hemoglobin)	33	pg	27-33
MCHC (mean cell Hb. conc.)	36	g/dl	32-36
Red cell distribution width	13	%	11-16
Neutrophils (abs.)	↓ **0.2**	G/l	2.0-7.5
Lymphocytes (abs.)	1.0	G/l	1.0-4.0
Monocytes (abs.)	0.1	G/l	< 1.2
Eosinophils (abs.)	0.00	G/l	< 0.40
Basophils (abs.)	0.0	G/l	< 0.2
Neutrophils (rel.)	↓ **16**	rel %	50-75
Lymphocytes (rel.)	↑ **80**	rel %	25-40
Monocytes (rel.)	4	rel %	< 12
Eosinophils (rel.)	0.0	rel %	< 4.0
Basophils (rel.)	0.0	rel %	< 2.0

Table 1

Her general practitioner believed in a laboratory's mistake due to the fact that the diagnosis of absolute neutropenia did not fit the patient's appearance and behavior. The blood was taken again with the same results. Therefore, the patient went to a public hospital for further diagnostics. For three consecutive weeks, the patient had appointments and was sent home every time without any results. A pulmonary embolism was ruled out via contrast CT, which was necessary due to the rising D-Dimer.

Since her D-Dimer was 7.55 mg/L (81 mg/L at admission 5 days later) (normal range: 0.00 – 0.50 mg/L), her fibrinogen was already 0.85 g/L (normal range: 1.50 – 3.50 g/L) and factor XIII had almost entirely vanished, by the end of week three, she decided to visit a private hematologist.

The new hematologist did extended bloodwork again, diagnosed an asymptomatic disseminated intravascular coagulation (DIC) and suspected a parvovirus infection. She would however still call another doctor to confirm her suspected diagnosis, since the patient's bloodwork was highly suspicious.

Later that evening, the patient got a call that she urgently needed to arrive at the hematological oncological station of a recommended hospital. The private hematologist had already called them and secured a bed.

At arrival, new blood was drawn and based on the existing lab results, the following steps were taken: i.v. substitution of fibrinogen, i.v. substitution of factor XIII as well as starting empirical treatment (40 mg of All-trans retinoid acid), for which the patient's consent was needed.

A bone marrow biopsy was scheduled for the next day. The patient was still highly anxious and under great distress which is why Midazolam was used for the procedure. The results arrived later the same day and confirmed the doctor's presumptive diagnosis. The patient's bone marrow biopsy read as follows: "Weak erythro- and thrombopoiesis as well as little to none granulopoiesis in combination with a substantial increase in atypical promyelocytes.
Proof of translocation t(15;17) (q24;q21) in 70% of nuclei".

Therefore, the diagnosis of acute promyelocytic leukemia (M3) was confirmed. The final diagnosis is based on finding a balanced reciprocal

translocation between chromosomes 15 and 17 (t(15;17)). The result is the production of a functional PML/RARA protein and a fusion transcript of the retinoic acid receptor alpha (RARA) and promyelocytic leukemia (PML) genes. For tracking and diagnosis, the detection of this fused PML/RARA genomic DNA sequence was a revolution. PML/RARA is either detected using fluorescence in situ hybridization (FISH) or by the detection of the PML/RARA fusion transcript using reverse transcriptase polymerase chain reaction (RT-PCR) [3].

Since the patient had a white blood cell count < 10.000 µL, she was considered low risk. [3]. She had no comorbidities, no family history of cancers or blood related diseases and had been healthy up to this point.

After an induction phase with arsentrioxide (0.15 mg/kg/d) as well as all-trans retinoid acid (2x40mg), which lasted 20 days, the patient was allowed to go home for a week but had to come back for another 7 days in the hospital, for observation as well as further treatment. The rest of the treatment was done in the walk-in clinic. During the first phase of treatment, the blood parameters started to normalize. The leukocytes which were affected the most slowly climbed from 0.9 G/l to 2.5 G/l at the time of release.

After induction therapy with arsentrioxide and all-trans retinoid acid was completed, a second bone marrow biopsy was conducted with a promising result showing 36.9% of PML-RARA left. The third and last biopsy was done after the first round of consolidation and showed full molecular remission.
According to guidelines, a fourth biopsy after consolidation was planned but not conducted due to a highly anxious patient, which had already made the three prior biopsies challenging.

Pathophysiology and Complications
In 1976, first steps were made to understand the physiopathology of APL. Fluorescence banding of bone marrow samples showed a deletion of the long arm of chromosome 17. Later it was found that APL cells had a balanced chromosomal translocation between the long arms of chromosomes 15 and 17 [4].

Some years later the RARA gene was found at the 17q21 position, confirming a specific rearrangement in patients with APL. Eventually, this gene fusion was called promyelocytic leukemia (PML). Through further investigation, it was found that RARA plays an important role in hematopoiesis. In physiological conditions, RARA's role is to slow down granulopoiesis and is ATRA's target. Together, it was shown that PML and ATRA cause numerous subtle effects on hematopoietic differentiation and self-renewal. Up to this day, it is still not clear which RARA genes are responsible for APL pathogenesis [4].

PML-RARA was found to be the crucial factor in the development of the disease by inhibiting myeloid differentiation [4].

APL is associated with severe coagulopathy and very high and rapid mortality, which makes a fast diagnosis and treatment crucial. Patients often present with a particular hemorrhagic syndrome due to hyperfibrinolysis, DIC as well as thrombocytopenia. Disease-related complications, such as catastrophic hemorrhage, differentiation syndrome as well as infection still are the main reason for deaths in APL patients [3] [2].

Patients often die within the first 30 days of diagnosis (early death). Therefore, an ongoing focus of treatment is to decrease the number of early deaths. Untreated, APL has a median survival of under one month [5].

High risk patients (white blood cell count >10 × 109/L) as well as patients above 60, run a greater risk of fatal bleeding. If APL is suspected, even without confirmation, ATRA should be administered, in order to avoid early death. In addition, blood transfusions as well as platelets and fibrinogen should be administered.

Treatment
Since time is of upmost importance with this kind of leukemia, treatment had already commenced, the evening before the confirmation of the diagnosis with a dose of all trans retinoid acid, fibrinogen i.v as well as factor XIII i.v.
Hematopoietic stem cell transplantation (HSCT) was once widely used in front-line therapy before the use of ATRA in APL. However, it is now virtually rejected for patients receiving contemporary medications. The excellent cure rates

now achieved in APL patients through contemporary treatments with ATRA combined with chemotherapy or ATRA plus ATO indicate that HSCT has no place in initial therapy. The use of HSCT has been limited to consolidation for relapsed patients who attain a second complete remission following salvage treatment whenever feasible [6].

After confirmation, the patient was given 80 mg of ATRA every day - 40 mg in the morning and 40 mg in the evening. In addition, the patient started induction therapy with a daily dose of 9 mg of ATO (0.15 mg/kg/d) for 20 days. Both medications were later reduced by 50% due to hepatotoxicity and not raised again during consolidation. Moreover, fibrinogen needed to be substituted once more on day 5. The treatment followed the PETHEMA/PALG treatment plan of APL. High dose glucocorticoids (Dexamethasone) were administered in order to prevent differentiation syndrome.

After induction therapy a second bone marrow biopsy was conducted. The results were promising showing: '36.9% PML-RARA quantity left'. After induction, four rounds of consolidation therapy followed. One round consisted of 4.5 mg i.v ATO over the course of 2 hours every day, except the weekends, for one month. Between each round, one month was off. In addition, ATRA had to be taken every two weeks, for two weeks. 20 mg in the morning and 20 mg in the evening.

A third bone marrow biopsy was conducted after the first round of consolidation and revealed the following: 'Erythropoiesis strong and good maturation, thrombopoiesis strong, granulopoiesis strong and good maturation. Currently no sign of acute promyelocytic leukemia, consistent with complete remission.'

The treatment started in the beginning of February 2024 and ended in October 2024.
During induction phase, a break of five days from ATRA was necessary due to severe hepatotoxicity (Stage III). The dosage was then adjusted (from 80 mg per day to 40 mg). The ATO dosage was equally reduced (from 9 mg to 4.5 mg) for the consolidation therapy.

Due to a risk of QT time extension, the patient was under regular ECG supervision.

Besides the hepatotoxicity, the patient reported strong fatigue, a tingling sensation in her hands and feet as well as worsening of her vision. She was sent to the ophthalmologist but nothing pathological was found on the eyes.

The history of the all-trans retinoid acid plus arsenic trioxide therapy

The treatment of APL is a success story of medicine. Originally this type of leukemia was considered one of the most aggressive and deadly leukemias in existence. With the introduction of the ATO plus ATRA therapy, it is now the most curable kind of acute myeloid leukemias, with curation rates up to 98% [4].

An earlier success was daunorubicin, which APL was sensitive to with 55% of patients achieving complete remission and even long – term remission in some cases. However, in about 2/3 of patients, APL resurfaced within a year, which decreased the event free survival to 25-55%. In addition, chemotherapy was sometimes the cause of early mortality, due to an exacerbated bleeding diathesis, calling for safer alternatives [4].

In the 1980s, the high clinical efficiency was proven, when used on chemotherapy-resistant APL patients. In 1988, it was found that ATRA monotherapy could induce long term CR by helping the leukemic blasts mature into granulocytes, without showing any of the blood related risks caused by daunorubicin. Unfortunately, in most cases, patients relapsed within the first five months. Therefore, ATRA was used in combination with chemotherapy. This therapy proved to be superior (up to 80% curation rate) to anthracycline monotherapy, which was therefore ceased in general [4] [7] [1].

The most important side effect of the ATRA regimens are differentiation syndromes ('ATRA syndrom'), which are fatal, presenting as respiratory distress, peripheral edema, dyspnea with interstitial pulmonary infiltrates, pleuropericardial effusion, hypotension as well as acute renal failure. Differentiation syndrome usually occurs during induction due to differentiating agents on leukemic blasts and leads to a systemic inflammatory response syndrome [2].

In modern protocols, differentiation syndromes are prevented by the use of corticosteroids (most commonly dexamethasone) [2].

Arsenic is a metal which has been used for centuries to treat certain conditions, including ulcers, tuberculosis or infectious diseases. Since arsenic is an important part of traditional chinese medicine, Chinese researchers started trials with the ATO in the treatment of APL with highly beneficial outcomes by promoting promyelocytic differentiation and apoptosis [2].

In the mid 1990s, western countries conducted clinical trials for the first time achieving the same result (73% of CR for newly diagnosed patients).
The combination of ATO and ATRA was an overwhelming success with a 97% CR rate and increased event free survival [7] [4] [1].
Regarding risk stratification: APL can be divided into low-risk, intermediate-risk and high-risk based on the white blood cell count as well as platelet count: low risk white blood cells ≤ 10.000/μL plus platelets 40.000/μL or more and high-risk white blood cells >10.000/μL [8].

Follow up and Outcome

The patient achieved complete molecular remission in April 2024, after the initial induction plus one month of consolidation therapy. In October 2024, she finished her last round of ATRA and ATO.
Ever since, she has had regular checkups with the walk-in clinic. First, every month and later every three months until two years later. During these checkups the molecular marker PML RARA is checked within the blood, in order to catch a potential relapse early on.

Even after cessation of therapy, the mild polyneuropathy as well as a worsened vision, persisted. Other than that, the patient is currently healthy and resumed her life.
The combination of ATO and ATRA is gold standard in APL therapy for patients with low-risk and cures 97% of patients [4].
Even though the long-term toxicity profile of ATO plus ATRA is superior to protocols with chemotherapy, more research is needed in order to assess the long-term toxicity profile of ATO. Liver function should periodically be monitored after ending treatment, in particular for patients who had liver toxicity. In addition, patients should be periodically checked for diabetes and hypertension as well as screened for secondary malignancies (breast cancer, colon cancer, melanoma and prostate cancer) [2].

Despite the excellent outcomes with ATO plus ATRA regimen, more research as well as careful monitoring and management of toxicity after therapy is necessary [2].

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