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CASE REPORT

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Acute promyelocytic leukemia presenting as recurrent venous and arterial thrombotic events: a case report and review of the literature

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ABSTRACT

Acute promyelocytic leukemia (APL) is a distinct subtype of acute myeloid leukemia characterized by a translocation of chromosomes 15 and 17, creating an alternation in the retinoic acid receptor-alpha (RAR-alpha) gene. This leads to excessive medullary production of promyelocytic blasts, which are frequently associated with the hemorrhagic complications seen in APL. In contrast, APL-associated thrombosis occurs much less frequently and is an underappreciated life-threatening manifestation of the disease. Most thrombotic events occur during induction chemotherapy with all-transretinoic acid and are rarely seen as the initial presentation on APL. Here we report an exceedingly rare case of a patient with recurrent venous and arterial thrombotic events, including deep vein thrombosis, bilateral segmental pulmonary embolism, an ischemic stroke, splenic infarcts, and renal infarcts, later found to have APL. We aim to discuss the most recent understanding of the pathogenesis of APL-associated thrombosis and to summarize the literature of this rare presentation of APL.

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1. Introduction

Acute promyelocytic leukemia (APL) is a malignant hematologic disorder of the acute myeloid leukemia (AML) group, identified by the French-American-British classification as AML-M3. APL is cytogenetically characterized by a specific balanced reciprocal translocation that always involves the retinoic acid (RA) receptor a (RARA) gene on chromosome 17 to create a variety of X-RARA fusions. The most common translocation, which is associated with more than 98% of all APL cases, is noted to be t(15,17), a fusion between promyelocytic leukemia (PML) gene and retinoic acid receptor alpha (RARA) gene, encoding as PML/RARA[1]. The second most common translocation is t(11,17) encoding promyelocytic leukemia zinc finger PLZF/RARA t(11,17)[1]. Distinguishing between these two translocations is important because patients with the variant translocation t(11;17) are almost invariably resistant to all-trans retinoic acid (ATRA)[2]. In APLs driven by the t(15,17) translocations, PML/RARA is most often the only driving genetic alteration. This fusion protein induces excessive medullary production of hypergranular promyelocytes, which can be found in the bone marrow and peripheral blood. In normal cells, PML is a main constituent of nuclear bodies, which are matrix-associated multi-protein containing domains involved in various biological functions like DNA-damage response, senescence, stem-cell self-renewal, apoptosis, lipid metabolism and microorganism resistance through regulation of a wide range of proteins, among which are various transcription factors[3]. In contrast, in APL, the expression of PML–RARa fusion disrupts the localization of the wild-type PML from nuclear bodies to numerous micro speckles resulting in maturation blockade at the promyelocytic level, defects in apoptosis, stem-cell cell renewal and FT3 activating mutations all driving towards leukemogenesis[4].

APL is a very aggressive malignancy, with a median survival of less than 1 month without treatment[5]. Since the advent of ATRA, and more recently arsenic trioxide (ATO), significant improvement in patient outcomes have been achieved, and APL has become the most curable subtype of AML. Both ATRA and ATO degrade the PML–RARa fusion protein by acting on the RARa and PML moieties, respectively. ATRA mainly degrades the protein through proteosome-mediated pathways and caspases, while ATO-induced degradation is initiated through sumoylation of the PML moiety. Both treatments ultimately lead to restoration of PML nuclear bodies[3].

Despite incredible advances in diagnosis and treatment, the coagulation and bleeding complications

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associated with APL continue to cause significant morbidity and mortality. The high rate of complications from bleeding and infection often overshadows the thrombotic complications, which occur much less frequently. Most thrombotic events occur during induction chemotherapy with ATRA and are rarely seen as the initial presentation. In a retrospective chart review of 63 APL patients, 13 had thrombosis, but only 1 (1.6%) occurred prior to receiving therapy for APL[6]. In another observational cohort study, thrombosis was the clinical presenting manifestation in 3 of 31 (9.6%) of patients with APL[7]. The coagulopathy in APL is complex and thought to occur due to an interplay of various factors.

Here we report an exceedingly rare case of a patient with recurrent venous and arterial thrombotic events, including deep vein thrombosis (DVT), bilateral segmental pulmonary embolism (PE), an ischemic stroke, splenic infarcts, and renal infarcts, later found to have APL.

2. Case presentation

We report the case of a 50-year-old male with a past medical history of mild, intermittent asthma, obstructive sleep apnea on continuous positive airway pressure therapy and dyslipidemia. He initially presented to the Emergency Department (ED) for dyspnea on exertion associated with heart palpitations, and left calf pain. He denied long-haul air travel or prolonged immobilization. The patient was hemodynamically stable. His initial complete blood count with differential can be seen in Table 1. His troponin was <0.01 ng/mL, serum pro-brain natriuretic peptide was <5 pg/mL, and D-dimer (Dd) was 3251 ng/mL. His COVID-19 polymerase chain reaction (PCR) swab was negative.

Legend: WBC, white blood cells; RBC, red blood cells, MCV, mean cell volume.

Lower extremity ultrasonography revealed an acute DVT in the left proximal popliteal vein and left peroneal vein, as well as acute superficial thrombosis in the left gastrocnemius vein. Computer tomography (CT) angiography of the chest revealed bilateral segmental lower lobe PE with no evidence of right heart strain (Figure 1). The patient was started on therapeutic enoxaparin and transitioned to apixaban 10 mg twice daily (BID).

Legend: P is for posterior; Yellow arrows pointing at the pulmonary embolism.

The patient was discharged home with a diagnosis of acute, unprovoked left lower extremity DVT and bilateral PE. He followed up at the hematology clinic where he was encouraged to undergo age and sex appropriate cancer screening.

Three months later, the patient presented to the ED for acute onset of dysarthria and expressive aphasia. His National Institutes of Health Stroke Scale score was 2. He admitted to missing several doses of apixaban. Magnetic resonance imaging (MRI) of the head revealed multiple small and punctate acute infarcts within the bilateral cerebellar hemispheres, two small foci of signal abnormality within the right frontal lobe likely reflecting small subacute infarcts, and small rounded focus of signal abnormality within the right occipital lobe, potentially reflecting a subacute infarct. There was no evidence of antiphospholipid syndrome and the panel for hypercoagulable workup was normal, except for heterozygosity for C677T mutation in the methylenetetrahydrofolate reductase (MTHFR) gene (Table 2). A transthoracic echocardiogram was performed and was negative for a patent foramen oval and no thrombus was seen. The patient was diagnosed with acute embolic stroke of unknown source. His symptoms resolved, and he was discharged home on apixaban 5 mg BID and aspirin 81 mg.

The patient returned to the ED the following day with acute-onset abdominal pain. His complete blood count with differential can be seen in Table 1. White blood cells (WBC) were 3.58 K/µl (normal: 4.80–10.80 K/µl). CT abdomen revealed wedge-shaped defects of the spleen consistent with infarcts (Figure 2), as well as foci of renal peripheral hypoenhancement bilaterally which were suspicious for small infarcts and thus embolic phenomenon. The

Table 1. Complete blood count with differential throughout clinical course.

Test	1st Admission (5/10/20)	2nd Admission (8/1/20)	3rd Admission (8/15/20)	Reference Range
WBC Count	4.40	2.82	3.58	4.80–10.80 K/µL
RBC Count	5.12	4.81	4.65	4.70–6.10 M/µL
Hemoglobin	15.8	15.1	14.3	42.0–52.0%
MCV	86.5	89.4	86.9	80.0–94.0 fL
Platelets	300	352	194	130–400 K/µL
Neutrophils	2.58	1.17	2.55	1.40–6.50 K/µL
Lymphocytes	1.30	1.22	0.78	1.20–3.40 K/µL
Monocytes	0.27	0.17	0.18	0.10–0.60 K/µL
Eosinophils	0.22	0.07	0.05	0.00–0.70 K/µL
Basophils	0.03	0.08	0.01	0.00–0.20 K/µL

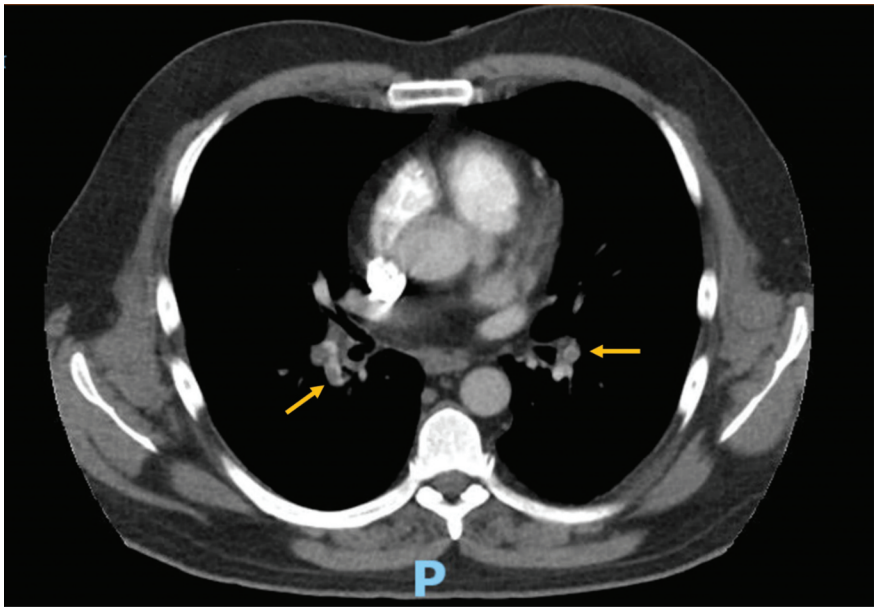

Figure 1. Computer tomography angiography of the chest demonstrating bilateral segmental lower lobe pulmonary embolism.

Table 2. Hypercoagulable workup.

Methylenetetrahydrofolate reductase (MTHFR) gene	Heterozygous for the C677T mutation
Factor V Leiden gene	Absence
Prothrombin gene	Absence
Beta-2 glycoprotein antibodies	Negative
Anti-cardiolipin antibodies	Negative
Protein C Functional Assay	135% (Normal: 65–129%)
Protein S Free Activity Assay	117% (Normal: 70–150%)
Antithrombin III Assay	144% (Normal: 85–135%)
Silica Clotting time	Normal
Dilute Russell's Viper Venom time	Normal

patient was started on unfractionated heparin and transitioned to warfarin.

Legend: P is for posterior; Yellow arrows pointing at the wedge-shaped defects in the spleen.

To further evaluate the patient's neutropenia, human immunodeficiency virus was tested and was negative. JAK-2 mutation was negative. Flow cytometry, which included cytogenetics, was negative for paroxysmal nocturnal hemoglobinuria but revealed t(15;17)(q26;q25), consistent with APL. The patient underwent a bone marrow biopsy which demonstrated diffuse infiltration of abnormal promyelocytes (Figure 3(a-c)). Before treatment for APL could be initiated, the patient developed left lower extremity and right upper extremity pain. Ultrasonography revealed thrombosis of the right cephalic vein, left basilic vein, and a superficial thrombosis of the left great saphenous vein. International normalized ratio was therapeutic at 2.80. Patient was transitioned from coumadin back to unfractionated heparin. Aspirin was discontinued due to the high-risk of bleeding.

The patient completed induction chemotherapy with ATRA and arsenic trioxide (ATO) according to the Lo-Coco protocol[8]. Results from repeat bone marrow showed remission and fluorescence in situ hybridization was negative. The patient is currently undergoing consolidation therapy with ATRA and ATO. The patient is doing well on apixaban 5 mg and has not had any further thrombotic events.

3. Discussion

Patients with APL typically present with symptoms related to complications of pancytopenia, including weakness and fatigue, infections, and/or hemorrhagic complications. The hemorrhagic complications in APL can be profound and life-threatening and represent a medical emergency. The exact pathophysiology of the coagulopathy in APL is poorly understood and remains controversial. At present, there are several different, yet inter-related potential mechanisms of coagulation complications such as activation of the coagulation system, increased fibrinolytic activity, and increased nonspecific proteolytic activity. [9]

Recent studies have reported leukemic promyelocytes in APL to have an abnormally high expression of annexin II receptor, a phospholipid-binding protein[10]. Annexin II receptors bind tissue plasminogen activator and plasminogen and increases plasmin generation by a factor of 60, therefore leading to increased fibrinolysis[11]. Additionally, the pathway of non-specific proteolysis has also been shown to lead to increased bleeding tendency in patients with APL [12,13]. The PML-RARα fusion gene in APL cells can induce tissue factor (TF)

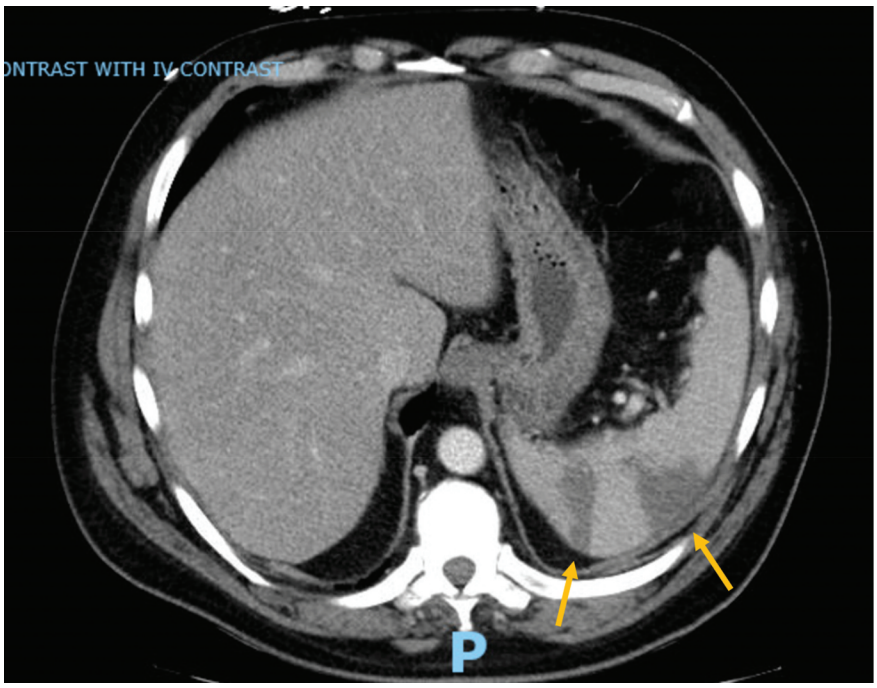

Figure 2. Computer tomography abdomen revealing wedge-shaped defects of the spleen consistent with infarcts.

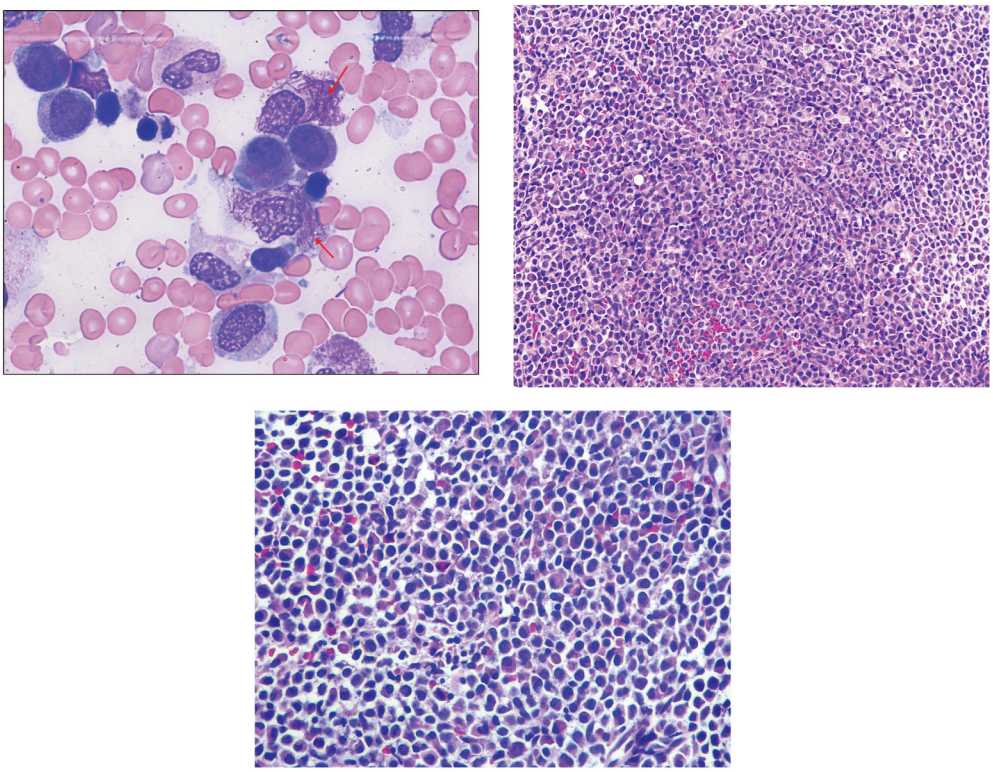

Figure 3. **a**.Bone marrow aspirate smear showing promyelocytes with ovoid to monocytoid nuclei, abundant cytoplasm with numerous pink, red or purple granules that obscure the nuclear outline. the cells contain numerous intertwining auer rods (arrows). **b**. The bone marrow biopsy showing hypercellularity with aggregates of promyelocytes (x200). **c**. High power image showing promyelocytes with relatively abundant cytoplasm and convoluted nuclei that are often eccentrically located (x400).

expression, which is an essential integral membrane glycoprotein expressed in various cells[14]. Under normal circumstances, TF serves as an initiator in coagulation pathways via interaction with coagulation factor VII (F VII) and its activated form (F VIIa) and plays a primary role in both normal hemostasis and thrombosis. [15] However, in pathologic conditions such as AML, TF is often expressed at a relatively high levels by monocytes, macrophages and endothelial cells, thereby initiating a series of enzymatic reactions resulting in enhanced clot formation and vascular sealing. [16]

In addition to bleeding, disseminated intravascular coagulation (DIC), has been shown to cause localized or multiorgan thrombosis in patients with acute leukemia [17,18]. The release of tissue factor and procoagulant factors by promyelocytic cells is thought to be the main thrombogenic factor leading to the thrombotic events in DIC [19–21]. The induction of tumor cell differentiation with ATRA, the cornerstone of therapy in APL, has also been associated with a prothrombotic state[22]. In contrast to the hemorrhagic complications in APL, the thrombotic complications occur much less frequently and are less well studied. It has been proposed that the administration of ATRA causes increased secretion of inflammatory cytokines such as interleukin-1β and tumor necrosis factor-α, which interact with the vascular endothelium, inducing the expression of tissue factor on the endothelial cells and inducing a pro-coagulable state [12,23]. Recent studies have shown that APL blasts undergo ETosis, a novel cell death pathway distinct from apoptosis or necrosis, which releases intact chromatin into the extracellular space in response to stimulation in which resulted in extracellular chromatin having a big influence on the fibrinolytic and procoagulant activity (PCA) after ATRA treatment. The interaction between promyelocytic extracellular chromatin and endothelial cells results in endothelium damage and can also exacerbate coagulopathy[24]. A higher WBC count, prevalence of the break cluster region 3 (BCR3) transcript type, Fms related receptor tyrosine kinase 3-internal tandem duplication (FLT3-ITD), and expression of cluster differentiation 2 (CD2) and cluster differentiation 15 (CD15) on the leukemic cells have been shown to be associated with an increased risk of thrombosis[25].

It is very rare however, for the thrombotic event to occur prior to the initiation of ATRA and is one of the reasons that this case is unique. A summary of the literature of patients presenting with thrombosis and later found to have APL, can be seen in Table 3. Furthermore, to present with multiple recurrent venous and arterial events, including a DVT, bilateral segmental PEs, an ischemic stroke, splenic infarcts, and renal infarcts further contributes to the rarity of this case.

Table 3. Review of the literature of patients with acute promyelocytic leukemia (APL) presenting with thrombosis.

Organ Involved	Date	Age (years)	WBC	Platelets
MI	1980[26]	46	NA	NA
	1986[27]	NA	NA	NA
	1993[28]	38	1.7 X 10^9/l	NA
	2006[29]	41	5.4 X 10^9/l	60 X 10^9/l
	2007[30]	54	0.6 X 10^9/l	112 X 10^9/l
	2011[31]	29	NA	NA
	2012[32]	51	3.1 X 10^9/l	85 X 10^9/l
	2013[33]	15	3.9 X 10^9/l	27 X 10^9/l
	2015[34]	33	3.9 X 10^9/l	NA
Acute limb ischemia	1981[35]	25	NA	NA
	1992[36]	10	31.7 X 10^9/l	NA
	1998[37]	16	NA	NA
	1999[38]	16	2.9 X 10^9/l	62 X 10^9/l
	2003[39]	47	4.4 X 10^9/l	105 X 10^9/l
	2003[40]	39	19.2 X 10^9/l	40 X 10^9/l
	2009[41]	51	8.4 X 10^9/l	90 X 10^9/l
	2016[42]	75	43.5 X 10^9/l	65 X 10^9/l
	2020[43]	71	4.6 X 10^9/l	46 X 10^9/l
Ischemic stroke	2010[44]	49	6.9 X 10^9/l	151 X 10^9/l
	2013[45]	23	85.0 X 10^9/l	45 X 10^9/l
	2015[6]	38	8.6 X 10^9/l	47 X 10^9/l
	2016[46]	10	2.4 X 10^9/l	30 X 10^9/l
DVT, acute limb ischemia	2014[47]	52	NA	NA
DVT, PE	2015[48]	48	14.8 X 10^9/l	NA
DVT, LV thrombus	2020[49]	20	1.6 X 10^9/l	334 X 10^9/l
Hepatic vein thrombosis	2010[50]	14	23.4 X 10^9/l	80 X 10^9/l
DVT, PE, ischemic stroke, splenic infarct, renal infarct	Our case	50	2.0 X 10^9/l	244 X 10^9/l

Legend: WBC, white blood count; MI, myocardial infarction; NA, not available; DVT, deep vein thrombosis; LV, left ventricle; PE, pulmonary embolism

4. Conclusion

Thrombotic events in APL are rare and poorly understood. We report a rare case of DVT, bilateral segmental PE, an ischemic stroke, splenic infarcts, and renal infarcts prior to diagnosis and treatment of APL. To the best of our knowledge, this is the first such case reported in the literature. Our case highlights an unusual cause of recurrent venous and thromboembolic events, which can easily go undiagnosed in routine clinical practice. A high degree of suspicion for underlying malignancy must be maintained for timely diagnosis and treatment.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Patient consent

Consent was obtained from the patient prior to drafting of this manuscript.

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