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 alteration 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.

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–RARα 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 degrage the PML–RARα fusion protein by acting on the RARα 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 superficial femoral 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.

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  |
Table 2. Hypercoagulable workup.

| Test                                      | Result                          |
|-------------------------------------------|---------------------------------|
| Methylene tetrahydrofolate reductase      | Heterozygous for 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                          |

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.

| Organ Involved                          | Date | Age (years) | WBC        | Platelets |
|----------------------------------------|------|-------------|------------|-----------|
| MI                                     | 1980 | 46          | NA         | NA        |
|                                        | 1986 | NA          | NA         | NA        |
|                                        | 1993 | 38          | 1.7 x 10^9/l | NA        |
|                                        | 2006 | 41          | 5.4 x 10^9/l | 60 x 10^9/l |
|                                        | 2007 | 54          | 0.6 x 10^9/l | 112 x 10^9/l |
|                                        | 2011 | 29          | NA         | NA        |
|                                        | 2012 | 51          | 3.1 x 10^9/l | 85 x 10^9/l |
|                                        | 2013 | 15          | 3.9 x 10^9/l | 27 x 10^9/l |
|                                        | 2015 | 33          | 3.9 x 10^9/l | NA        |
| Acute limb ischemia                    | 1981 | 25          | NA         | NA        |
|                                        | 1992 | 10          | 31.7 x 10^9/l | NA        |
|                                        | 1998 | 16          | NA         | NA        |
|                                        | 1999 | 16          | 2.9 x 10^9/l | 62 x 10^9/l |
|                                        | 2003 | 47          | 4.4 x 10^9/l | 105 x 10^9/l |
|                                        | 2003 | 39          | 19.2 x 10^9/l | 40 x 10^9/l |
|                                        | 2009 | 51          | 8.4 x 10^9/l | 90 x 10^9/l |
| Ischemic stroke                        | 2016 | 75          | 43.5 x 10^9/l | 65 x 10^9/l |
|                                        | 2020 | 71          | 4.6 x 10^9/l | 46 x 10^9/l |
|                                        | 2013 | 23          | 85.0 x 10^9/l | 45 x 10^9/l |
|                                        | 2015 | 38          | 8.6 x 10^9/l | 47 x 10^9/l |
|                                        | 2016 | 10          | 2.4 x 10^9/l | 30 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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References

[1] de Thé H, Le Bras M, Lallemand-Breitenbach V. The cell biology of disease: acute promyelocytic leukemia, arsenic, and PML bodies. J Cell Biol. 2012 Jul 9;198(1):11–21.
[2] Park J, Juricic JG, Rosenblat T, et al. Emerging new approaches for the treatment of acute promyelocytic leukemia. Ther Adv Hematol. 2011 Oct;2(5):335–352.
[3] Saeed S, Logie C, Stunnenberg HG, et al. Genomewide functions of PML-RA Rs in acute promyelocytic leukaemia. Br J Cancer. 2011 Feb 15;104(4):554–558.
[4] Brown NJ, Ramalho M, Pedersen EW, et al. PML nuclear bodies in the pathogenesis of acute promyelocytic leukemia: active players or innocent bystanders? Front Biosci (Landmark Ed). 2009 Jan 1;14(14):1684–1707.
[5] HK Hillestad. Acute promyelocytic leukemia. Acta Med Scand. 1957 Nov;159(3):189–194.
[6] Mitrovic M, Suvajdzic N, Elezovic I, et al. Thrombotic events in acute promyelocytic leukemia. Thromb Res. 2015 Apr;125(4):588–593.
[7] De Stefano V, Sorà F, Rossi E, et al. The risk of thrombosis in patients with acute leukemia: occurrence of thrombosis at diagnosis and during treatment. J Thromb Haemost. 2005 Sep;3(9):1985–1992.
[8] Lo-Coco F, Avvisati G, Vignetti M, et al. Retinoic acid and arsenic trioxide for acute promyelocytic leukemia. N Engl J Med. 2013 Jul;369(2):111–121.
[9] Wang P, Zhang Y, Yang H, et al. Characteristics of fibrinolytic disorders in acute promyelocytic leukemia. Hematology. 2018 Dec;23(10):756–764.
[10] Menell JS, Cesarmann GM, Jacovina AT, et al. Annexin II and bleeding in acute promyelocytic leukemia. N Engl J Med. 1999 Apr;340(13):994–1004.
[11] Cesarmann GM, Guevara CA, Hajjar KA. An endothelial cell receptor for plasminogen/tissue plasminogen activator (t-PA). II. Annexin II-mediated enhancement of t-PA-dependent plasminogen activation. J Biol Chem. 1994 Aug;269(33):21998–21203.
[12] Barbui T, Finazzi G, Falanga A. The impact of all-trans-retinoic acid on the coagulopathy of acute promyelocytic leukemia. Blood. 1998 May;91(9):3093–3102.
[13] Egbring R, Schmidt W, Fuchs G, et al. Demonstration of granulocytic proteases in plasma of patients with acute leukemia and septicemia with coagulation defects. Blood. 1977 Feb;49(2):219–231.
[14] Wilcox JN, Smith KM, Schwartz SM, et al. Localization of tissue factor in the normal vessel wall and in the atherosclerotic plaque. Proc Natl Acad Sci U S A. 1989 Apr;86(8):2839–2843.
[15] Komiya Y, Pedersen AH, Kiel W. Proteolytic activation of human factors IX and X by recombinant human factor VIIa: effects of calcium, phospholipids, and tissue factor. Biochemistry. 1990 Oct 9;29(40):9418–9425.
[16] Zhu J, Guo WM, Yao YY, et al. Tissue factors on acute promyelocytic leukemia and endothelial cells are differently regulated by retinoic acid, arsenic trioxide and chemotherapeutic agents. Leukemia. 1999 Jul;13(7):1062–1070.
[17] Falanga A, Barbui T. Coagulopathy of acute promyelocytic leukemia. Acta Haematol. 2001;106(1–2):43–51.
[18] Barbui T, Falanga A. Disseminated intravascular coagulation in acute leukemia. Semin Thromb Hemost. 2001;27(6):593–604.
[19] Arbuthnot C, Wilde JT. Haemostatic problems in acute promyelocytic leukaemia. Blood Rev. 2006 Nov;20(6):289–297.
[20] Tallman MS, Kwaan HC. Reassessing the hematologic disorder associated with acute promyelocytic leukemia. Blood. 1992 Feb;79(3):543–553.
[21] Stone RM, Mayer RJ. The unique aspects of acute promyelocytic leukemia. J Clin Oncol. 1990 Nov;8(11):1913–1921.
[22] Runde V, Aul C, Heyl A, et al. All-trans retinoic acid: not only a differentiating agent, but also an inducer of thromboembolic events in patients with M3 leukemia. Blood. 1992 Jan;79(2):534–535.
[23] Bombeli T, Karsan A, Tait JE, et al. Apoptotic vascular endothelial cells become procoagulant. Blood. 1997 Apr;89(7):2429–2442.
[24] Cao M, Li T, He Z, et al. Promyelocytic extracellular chromatin exacerbates coagulation and fibrinolysis in acute promyelocytic leukemia. Blood. 2017 Mar 30;129(13):1855–1864.
[25] Breccia M, Avvisati G, Latagliata R, et al. Occurrence of thrombotic events in acute promyelocytic leukemia correlates with consistent immunophenotypic and molecular features. Leukemia. 2007 Jan;21(1):79–83.
[26] Candelfergher G, Suzzo GL, Visonà A, et al. [Acute myocardial infarct as the first manifestation of acute
myeloid leukemia. Description of an anatomo-clinical case. G Ital Cardiol. 1980;10(10):1403–1407.

[27] Hid S, Stanley A, Pek K, et al. Acute promyelocytic leukemia associated with acute myocardial infarction. A case report. S Afr Med J. 1986 July;70(2):117–118.

[28] Quadir TA, Dhabhar BN, Dhar AK, et al. Acute promyelocytic leukemia with ischemic events. J Assoc Physicians India. 1993 May;41(5):300–302.

[29] Lou Y, Mai W, Jin J. Simultaneous presentation of acute myocardial infarction and acute promyelocytic leukemia. Ann Hematol. 2006 Jun;85(6):409–410.

[30] Altwegg SC, Altwegg LA, Maier W. Intracoronary thrombus with tissue factor expression heralding acute promyelocytic leukaemia. Eur Heart J. 2007 Nov;28(22):2731.

[31] Cahill TJ, Chowdhury O, Myerson SG, et al. Myocardial infarction with intracardiac thrombosis as the presentation of acute promyelocytic leukemia: diagnosis and follow-up by cardiac magnetic resonance imaging. Circulation. 2011 Mar;123(10):e370–2.

[32] Sargsyan Z, Higgins C, Alexandrescu S, et al. Acute promyelocytic leukemia as a cause of intracoronary drug-eluting-stent thrombosis. Tex Heart Inst J. 2012;39(3):416–419.

[33] Thomas TO, Ramachandran P, Jefferies JL, et al. Prompt recognition and percutaneous coronary intervention leads to favorable myocardial recovery after ST-segment elevation myocardial infarction secondary to acute promyelocytic leukemia: pediatric case report. Pediatr Cardiol. 2013;34(8):2047–2051.

[34] Li Y, Suo S, Mao L, et al. Acute myocardial/cerebral infarction as first/relapse manifestation in one acute promyelocytic leukemia patient. Int J Clin Exp Med. 2015;8(8):14210–14213.

[35] Jetha N. Promyelocytic leukaemia with multiorgan infarctions and large-vessel thrombosis. Arch Pathol Lab Med. 1981 Dec;105(12):683–684.

[36] Fass R, Haddad M, Zaizov R, et al. Recurrent peripheral arterial occlusion by leukemic cells sedimentation in acute promyelocytic leukemia. J Pediatr Surg. 1992 May;27(5):665–667.

[37] Rolston DD, Rubin S, Topolsky D, et al. Arterial occlusions as a presenting feature of acute promyelocytic leukemia. Am J Clin Oncol. 1998 Oct;21(5):436–437.

[38] DiGiovanni RJ, Crilley P, Kerstein MD. Peripheral arterial occlusion in acute promyelocytic leukemia. Cardiovasc Surg. 1999 Mar;7(2):21198–21203.

[39] Kalk E, Goede A, Rose P. Acute arterial thrombosis in acute promyelocytic leukaemia. Clin Lab Haematol. 2003 Aug;25(4):267–270.

[40] Posacioglu H, Apaydin A, Buyukkececi F, et al. Recurrent Peripheral Arterial Occlusion in Acute Promyelocytic Leukemia. EJVES Extra. 2003;6(5):100–102.

[41] Belzna C, Pistorius MA, Planchon B. Lethal limb ischaemia in leukaemia. Case report and review of the literature. J Thromb Thrombolysis. 2009 Oct;28(3):354–357.

[42] Chotai PN, Kasangana K, Chandra AB, et al. Recurrent Arterial Thrombosis as a Presenting Feature of a Variant M3-Acute Promyelocytic Leukemia. Vasc Specialist Int. 2016 Jun;32(2):65–71.

[43] Chavez MA, Heidari B, Thacker S, et al. Acute Promyelocytic Leukemia Presenting as Bilateral Acute Limb Ischemia and ST Elevation Myocardial Infarction: a Case Report. Cureus. 2020 Jun;12(6):e8495.

[44] Carella AM, Antonucci G, Conte M, et al. A case of ischemic stroke in acute promyelocytic leukemia at initial presentation. Relevance of all-trans retinoic acid treatment. Cardiovasc Hematol Disord Drug Targets. 2010 Mar;10(1):1–6.

[45] Kapoor R, Pati HP, Gupta SK, et al. Acute promyelocytic leukaemia presenting as ischemic stroke in young. Indian J Hematol Blood Transfus. 2013 Jun;29(2):93–95.

[46] Kishore M, Kumar V, Marwah S, et al. Unusual Presentation of Acute Leukaemia: a Tripod of Cases. J Clin Diagn Res. 2016 Oct;10(10):ED04–ED08.

[47] Trottier-Tellier F, Durand M, Kolan C, et al. Recurrent arterial and venous thromboemboli as initial presentation of acute promyelocytic leukemia. J Clin Med Res. 2014 Oct;6(5):388–391.

[48] Vaid AK, Batra S, Karanth SS, et al. Acute promyelocytic leukemia presenting as pulmonary thromboembolism: not all APLs bleed. Avicenna J Med. 2015 Oct-Dec;5(4):131–133.

[49] Jandial A, Mishra K, Lad D, et al. Deluging thrombosis: an unusual presentation of acute promyelocytic leukemia. Indian Journal of Medical and Paediatric Oncology. 2020;41(2):282–284.

[50] Bandyopadhyay S, Bandyopadhyay D. Acute Budd-Chiari syndrome as an initial presentation of acute promyelocytic leukemia. J Cancer Res Ther. 2010 Oct-Dec;6(4):567–569.