

Recurrent Arterial Thrombosis as a Presenting Feature of a Variant M3-Acute Promyelocytic Leukemia

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Acute limb ischemia (ALI) is a common vascular emergency. Hematologic malignancies are commonly associated with derangement of normal hemostasis and thrombo-hemorrhagic symptoms during the course of the disease are common. However, ALI as an initial presenting feature of acute leukemia is rare. Due to the rarity of this presentation, there is a scarcity of prospective randomized data to optimally guide the management of these patients. Current knowledge is mainly based on isolated cases. We report our experience managing a patient who presented with ALI and was found to have occult leukemia. A review of all cases with ALI as a presenting feature of acute leukemia is also presented.

Key Words: Acute limb ischemia, Cold leg, Arterial thrombosis, Acute promyelocytic leukemia, Acute myeloid leukemia-M3

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INTRODUCTION

Acute limb ischemia (ALI), defined as a sudden compromise in limb perfusion with a potential threat to limb viability, is a common vascular emergency [1]. Atherosclerotic thromboembolic disease commonly plays a major etiologic role; however, rarely malignant disorders may lead to vascular thrombosis and ALI. Occurrence of arterial thrombosis as a complication of chemotherapy and specifically, its onset secondary to treatment of acute promyelocytic leukemia (APL) with all-trans retinoic acid (ATRA) is well known [2-4]. However, ALI as a sole initial presenting feature of leukemia, before initiation of chemotherapy and/or ATRA therapy is very rare (Table 1) [5-23]. Due to the rarity of this combination, there is a lack of large prospective data, and current strategies to effectively manage these patients are based on a handful of reported cases (Table 1). We report our experience and review all

reported cases of occult leukemia presenting as ALI from current literature.

CASE

A 75-year-old woman presented to the emergency room with two weeks' duration of acute onset right foot numbness/tingling. Symptoms progressed with increased numbness and worsened right thigh pain over the day prior to her presentation, inciting her to seek medical attention. Past medical history was only significant for arthritis. The patient was not on any home medications. There was no personal or family history of peripheral arterial disease, cardiovascular disease, malignancy or thromboembolism. Her review of systems was positive for the presence of night sweats for the past two years. Her exam revealed absence of palpable femoral and distal pulses on the right lower extremity. The left lower extremity had intact femoral/

Table 1. Reported cases with acute limb ischemia as a presenting feature of acute leukemia

Author	Age (y)	Sex	Leukemia type	Findings	Management	Outcome
Brinson and Garcia, 1984 [5]	36	M	ALL	Occlusion of infra-renal aorta; CIA. Thrombus composed of fibrin and leukemic cells	Aortic thrombectomy; chemo	Non-fatal
Redmond et al., 1993 [7]	28	M	ALL	Thrombosis of Rt. EIA, profunda femoris and three lower leg arteries	Thrombolysis; heparin; Rt. BKA	Limb loss
Chang et al., 2003 [6]	46	M	AML (no subtype)	Occlusion of Lt. ATA, PTA; gangrenous Lt. 5th toe	Thrombolysis; platelet-pheresis; chemo; Lt. BKA	Limb loss, fatal
Reisch et al., 2007 [8]	39	F	AML (M1)	Recurrent occlusion of Rt. CIA, EIA; Lt. CFA, PFA, SFA; Rt. leg compartment syndrome. White thrombus with leukemic blasts	Multiple thrombectomies; fasciotomy; heparin; AT III; Rt. thigh amputation; chemo	Limb loss
Overton et al., 2012 [9]	57	F	AML (M1)	Bilateral common iliac artery disease, total occlusion on left. Thrombus made of fibrin mesh with entrapped leukemic cells	Multiple bilateral thrombo-embolectomies; heparin; femoro-popliteal bypass; clopidogrel; chemo; Lt. AKA	Limb loss, fatal
Kootte et al., 1986 [10]	42	F	AML (M2)	Occlusion of aorta; Rt. CIA	Aortic thrombectomy	Fatal
Campbell and Mitchell, 1994 [11]	NA	NA	AML (M2)	SFA stenosis, obstruction	Chemo	Non-fatal
Mataix et al., 1996 [12]	42	NA	AML (M2)	Rt. PopA thrombosis	Thrombolysis; multiple thrombo-embolectomies; Rt. AKA	Limb loss
Malnick et al., 1998 [13]	40	F	AML (M5)	Occlusion of Rt. CFA; functional protein C deficiency. Thrombus with no leukemic cells within	Multiple thrombectomies; heparin; oral anticoag; chemo	Fatal
Kafetzakis et al., 2007 [14]	57	M	AML (M5)	Occlusion of Rt. CIA. White clot with leukemic cells	Heparin; leukapheresis; chemo; open thromboembolectomy	Non-fatal
Mar et al., 2013 [15]	63		AML (M5)	Near-complete occlusion of infra-renal aorta; DIC. Fibrin thrombus with leukemic cells	Heparin; aortic thrombectomy	Fatal
Jetha, 1981 [16]	25	F	APL (M3)	NA	Chemo	Fatal
Fass et al., 1992 [17]	10	M	APL (M3)	Recurrent thrombosis of CFA; SFA; PopA. White thrombus with leukemic cells	Multiple thrombectomies; AKA	Limb loss
Rolston et al., 1998 [18]	16	M	APL (M3)	Occlusion of Lt. EIA; PE; intra-ventricular thrombus	Surgical thrombectomy; ATRA; chemo	Non-fatal
DiGiovanni et al., 1999 [19]	16	M	APL (M3)	Acute arterial thrombosis –Lt. SFA; PE. 'Whitish material' retrieved from Lt. femoral artery	Femoral embolectomy; ATRA; chemo; oral anticoag	Non-fatal
Kalk et al., 2003 [20]	47	F	APL (M3)	Total occlusion –Lt. PopA	ATRA; chemo; toe amputation	Non-fatal
Posacioglu et al., 2003 [21]	39	M	APL (M3)	Total occlusion –Lt. CIA; necrotic Lt. big toe. White clot retrieved from femoral artery	Open multiple thrombectomies; heparin; ATRA	Fatal
Belizna et al., 2009 [22]	51	M	APL (M3)	Total occlusion –Lt. femoral, popliteal and peroneal artery; DIC	Surgical thromboembolectomy; chemo; Lt. leg amputation	Limb loss, fatal
Trottier-Tellier et al., 2014 [23]	52	F	APL (M3)	Recurrent thrombosis of Lt. axillary artery+PE +recent DVT	Heparin; multiple thrombolysis; open thrombectomy; Lt. carotido-humeral bypass; ATRA	Non-fatal
Our case 2015	75	F	APL (M3)	Recurrent acute arterial thrombosis –Rt. CIA	Heparin; ATRA; open multiple thrombectomies	Fatal

M, male; F, female; ALL, acute lymphoblastic leukemia; CIA, common iliac artery; chemo, chemotherapy; Rt., right; Lt., left; EIA, external iliac artery; BKA, below-knee amputation; AML, acute myeloid leukemia; ATA, anterior tibial artery; PTA, posterior tibial artery; CFA, common femoral artery; PFA, profunda femoris artery; SFA, superficial femoral artery; AT III, anti-thrombin III; AKA, above-knee amputation; NA, not available; PopA, popliteal artery; +, present; -, absent; DIC, disseminated intra-vascular coagulation; APL, acute promyelocytic leukemia; PE, pulmonary embolism; ATRA, all trans retinoic acid; DVT, deep venous thrombosis.

popliteal/pedal pulses. The right foot was slightly cooler to touch than the left foot; her sensory exam was dulled but intact in the right foot. Motor function throughout the right lower extremity was widely intact. There was no discoloration of skin overlying the right foot and the capillary refill was about two seconds. The rest of the physical examination was unremarkable. Initial laboratory values were remarkable for white blood cell (WBC) count of $43.5 \times 10^9/L$, platelet count $65 \times 10^9/L$, hemoglobin 8.6 g/dL and hematocrit of 25%. Serum chemistry, chest radiograph and electrocardiogram were unremarkable. Peripheral smear showed presence of 90% blasts, 1 Auer rod, tear drop cells, normochromic red cells, and immature red cells. APL was suspected and ATRA therapy was initiated. Concomitantly, a computed-tomographic angiogram (CTA) was obtained and a bone marrow biopsy was performed. CTA revealed occlusive thrombus of the right common iliac artery (Fig. 1). Given the vascular exam and CTA findings, the patient was urgently brought to the operating room (OR).

In the OR, a right femoral artery cut-down was performed, and right ilio-femoral artery thrombectomy was attempted however, we were unable to successfully pass a 4 or 5F Fogarty balloon catheter more than 8-10 cm proximally, and therefore a left-to-right femoral-femoral bypass using an 8 mm ringed Propaten graft (W.L. Gore and Associates, Flagstaff, AZ, USA) was performed. The patient regained palpable pedal pulses with resolution of her lower extremity symptoms.

On the evening of the first post-operative day, the

patient developed acute recurrent foot numbness; exam revealed a cold foot with loss of pulses. She was emergently brought back to the OR and was found to have a “white clot” in her common femoral artery where her graft was anastomosed and additional “white clot” in her bypass graft. Thrombectomy was performed and a clot-free run off was confirmed. Retrieved thrombus material was not sent for histopathologic examination. In addition, when performing our thrombectomies at this point, we again attempted to pass our Fogarty balloon catheter proximally—this time we were able to successfully thrombectomize the right sided native inflow artery. Angiography now confirmed patency of fem-fem bypass and the anastomoses, as well as patency of the right iliac artery system. We elected to leave the fem-fem bypass in place, assuming it would eventually thrombose due to competitive flow. The patient again had resolution of symptoms with intact bilateral lower extremity pulse exam.

Concomitant hypercoagulable work-up including echocardiography and review of her prior CTA failed to demonstrate any clear embolic source. The bone marrow biopsy flow-cytometry confirmed the diagnosis of CD-34- and human leukocyte antigen-DR-negative acute myeloid leukemia (AML) (Fig. 2). Bone marrow fluorescence in-situ hybridization (FISH) result was negative for the t(15:17) translocation seen in the classic French-American-British M3 subtype [24]. FISH analysis for variant subtypes of M3 was not obtained. Cytogenetics was normal female karyotype. A presumptive diagnosis of t(15:17) negative variant of APL was made [25]. ATRA therapy was discontinued at this point.

Within the next 24 hours, however, the patient developed acute onset of bilateral lower extremity pain and



Fig. 1. Three-dimensional reconstruction of computed-tomographic angiogram at presentation showing occlusive thrombus of the right common iliac artery.

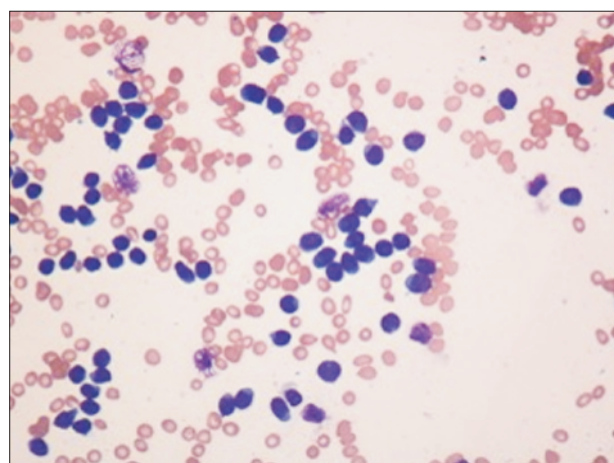


Fig. 2. Bone-marrow aspirate (40 \times) showing blast cells on immunohistochemistry staining for CD34 and human leukocyte antigen antibodies.

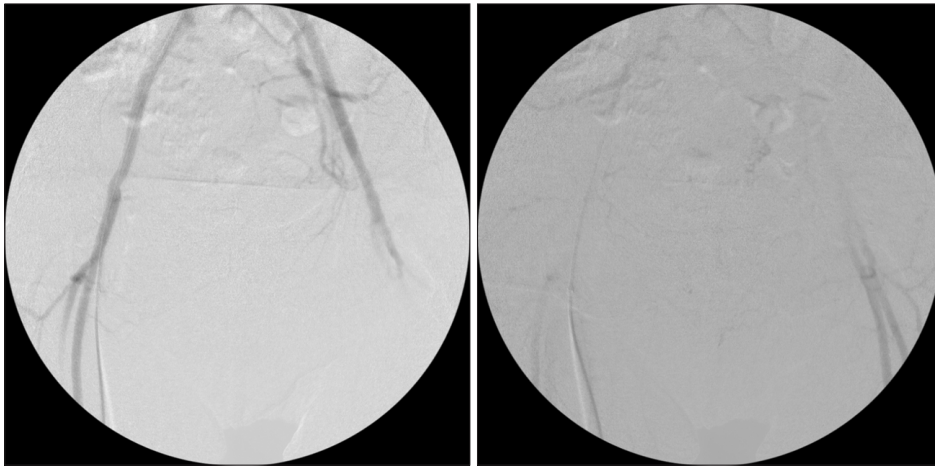


Fig. 3. Final completion angiography once again confirmed widely patent bilateral common femoral arteries and bifurcations.

paralysis. She had cool, pulseless legs; and imaging confirmed occlusion of the femoro-femoral bypass, but also with thrombus occluding bilateral common femoral arteries. She was again returned emergently to the OR, and underwent bilateral ilio-femoral thrombectomies and excision of her femoro-femoral bypass with patching of bilateral common femoral arteries. Again, pulses and exam was restored to baseline. Of note, at this time the patient's WBC count had peaked at over $80 \times 10^9/L$. Within the next 15 hours, she again developed bilateral lower extremity numbness, right sided paralysis, and loss of bilateral pulses distally. She was once again returned to the OR emergently, where she underwent bilateral ilio-femoral thrombectomies, resection of her right common femoral artery with dacron interposition grafting, and bovine pericardial patch angioplasty of the left common femoral artery. Completion angiography once again confirmed widely patent bilateral common femoral arteries and bifurcations (Fig. 3). The patient was maintained on therapeutic anti-coagulation through the entire clinical course.

Within the next 12 hours however; the patient once again developed right foot and leg pain and numbness, as well as paralysis with loss of pulses. At this point, further operative attempts were felt to be futile. After extensive discussions with the patient, her family, the hematologists, as well as the opinion of a national cancer center, the patient elected to go to inpatient hospice, where she subsequently expired one week later.

DISCUSSION

Development of malignancies is commonly associated with disturbances in normal hemostasis [26]. Acute leukemias are known to be more commonly associated with bleeding and disseminated intravascular coagulation than with thrombosis. However, recent studies indicate

that thrombotic events may be more prevalent in acute leukemias than previously reported [27-29]. The incidence of venous thromboembolism in untreated leukemia patients is ~2%-3%, however occurrence of arterial thrombosis in these patients is not common [27,29]. Thrombogenic properties of leukemic cells are attributable to expression of procoagulant activities (PCA) including tissue factor (TF) and cancer procoagulant, fibrinolytic and proteolytic mediators, as well as inflammatory cytokines leading to activation of the clotting cascade [26,30,31]. Additionally, cancer chemotherapy may also predispose leukemia patients to thrombosis by direct toxic effects on vascular endothelium, direct induction of tumor cell TF, and a decrease in physiologic anticoagulants [30]. Reports describing arterial thrombosis associated with leukemia have described these thrombi as "white thrombi". These thrombi are platelet- and fibrin-rich, but lack erythrocytes unlike "red thrombi". The exact mechanism remains unknown but it is hypothesized that severe leukocytosis and abnormal accumulation of lymphocytes, may trigger leukemic cell sedimentation followed by aggregation of platelets to complete the clot formation which eventually leads to arterial occlusion and ischemia [14,17,19]. Pre-clinical studies have proven that conventional thrombolytic therapy is more effective on the "red" thrombus compared to the fibrin-rich "white" thrombus [32].

In an observational cohort study, 13 of 379 (3.4%) newly diagnosed leukemia patients were found to have venous or arterial thrombosis as the initial presentation. Four patients had arterial thrombosis manifesting as ischemic stroke, but none presented with ALI [27]. In another retrospective review of 63 APL patients, 13 presented with thrombosis, however none presented with ALI [28]. Only a handful of cases of occult leukemia initially presenting as acute thrombosis of major arteries have been reported. Our literature search revealed twenty such cases, including our

case (Table 1). Of these twenty cases, two were associated with acute lymphoblastic leukemia and eighteen (90%) were associated with AML. Among the AML subtypes, APL (M3) was the most frequent (50%, 9/18 cases), followed by M5 (17%), M2 (17%), and M1 (11%) subtypes presenting with ALI (Table 1). This was similar to findings from the above mentioned study, which reported that APL was the most frequently associated subtype with arterial thrombosis as an initial presentation [27]. Recently, in a review of all cases of APL-associated thrombosis, 94 cases were identified [3]. Only six of the 94 patients (6%) had associated major arterial thrombosis, of which, four had ALI as an initial feature of occult APL. The thrombogenic property of APL is attributed to hyper-expression of PCA, including TF, in the leukemic cells [26,30].

APL is a distinct subtype of acute leukemia characterized by a balanced reciprocal translocation- t(15:17) resulting in formation of the leukemogenic fusion gene promyelocytic leukemia/retinoic acid receptor (PML/RAR α) [25,26,30]. Studies have identified variants of M3 without the classical t(15:17) translocation as well as without the PML/RAR α fusion gene [25]. Interestingly a higher incidence of coagulopathy and hemorrhage related deaths have been reported in APL patients with M3-variants compared to classical M3 patients [25]. Our patient presented with arterial thrombosis and leukocytosis as the sole presenting feature of the APL. We postulate that this was a variant subtype of M3, as the classic t(15:17) translocation was not present on the FISH analysis. No further FISH testing was obtained to confirm the rare variant subtypes of APL [25]. Presence of M3-variant and a WBC $>10\times 10^9$ /L were indeed found to be significant risk factors for thrombosis in a previously reported study [33].

Management of acute leukemia presenting as ALI requires a multidisciplinary care approach. In view of threat to limb viability, vascular management generally takes precedence; however, concomitant medical management should be initiated promptly. A hematology consult should be obtained along with a peripheral smear exam. Aggressive supportive treatment using blood products should be initiated to maintain target platelet count above 30×10^9 /L and fibrinogen level above 1.5 g/L [34]. Presumptive diagnosis of APL can be made from presence of characteristic clinical presentation, peripheral smear and bone marrow biopsy findings [34,35]. Targeted bi-functional therapy using ATRA should not be delayed while waiting for cytogenetic or molecular confirmation of APL in order to prevent hemorrhage related deaths [3,27,34-36]. The use of ATRA has been shown to induce complete remission as well as rapid reversal of coagulopathy in APL patients [26,34,35,37]. ATRA is also effective in treating

elderly patients above 60 years with co-morbidities [38]. Paradoxically, incidence of thrombosis in APL has increased in the post-ATRA era [2]. This may be attributed to ATRA-induced differentiation syndrome and ATRA-associated sustenance of a low-level pro-thrombotic state [26,31,39]. In our patient, ATRA was started immediately once APL was suspected however, it was stopped once bone marrow FISH results were negative for t(15:17) translocation. We postulate that the initial thromboses as well as subsequent recurrent episodes were not associated with ATRA in our case.

The initial surgical evaluation of these patients should follow the inter-society consensus for the management of peripheral arterial disease recommendations and include a clinical determination of limb viability and timing of intervention based on clinical classification of ALI [1,40]. An immediate Doppler assessment of peripheral pulses, measurement of ankle-brachial index and prompt evaluation by a vascular specialist should follow [1]. Degree of limb viability and associated co-morbidities greatly influence the decision whether to manage these patients operatively or non-operatively. No randomized studies are available due to the rarity of this presentation, however experience from the limited number of cases reported (Table 1) and from studies involving patients with solid malignancies presenting with ALI, may guide decision making [4,41]. A conservative management approach has been advocated by some based on studies showing poor outcomes with post-operative mortality as high as 80%-100% when malignancy associated ALI is treated surgically [42,43]. In contrast, recent retrospective studies have favored an early surgery-based limb salvage approach in malignancy associated ALI [4,41]. Mouhayar et al. [41] reported a 47% amputation free survival in cancer patients with ALI when treated surgically. Similarly, Tsang et al. [4] also reported a one-year survival of 44% and a 37% limb-loss rate favoring early operative limb salvage. Our review of reported cases of occult leukemia presenting with ALI revealed that 75% (15/20) patients underwent operative management; almost half (45%, 7/15) of these patients met with a fatal outcome and almost one-fifth (20%, 3/15) of patients progressed to limb loss. About a half (53%, 8/15) of these patients developed recurrent thrombosis and required multiple re-thrombectomies with bypass grafting (Table 1). Our patient also had a fatal outcome after developing multiple recurrences of thrombosis involving bilateral lower limb vessels as well as the femoral-femoral bypass graft and taken to the OR multiple times. The recurrent thrombosis was not a result of a technical or mechanical failure as the patency of the peripheral vasculature was assured by clinical improvement, return of distal pulses as well as satisfactory return of distal flow on completion angiograms

after each operative intervention (Fig. 3).

In summary, acute leukemia should be included in the differential diagnoses of patients presenting with ALI without an obvious etiology. A multidisciplinary approach including a prompt initiation of aggressive supportive treatment is recommended. If APL is suspected, ATRA induction therapy should be started immediately. Managing the ALI in these patients is an added challenge and decision

regarding when to operate should be individualized. In most cases, early surgical intervention may be prudent, however outcome is guarded secondary to likelihood of recurrent thrombosis and increased risk of limb-loss or fatality. Vascular surgeons and hematologists should discuss this in great details with the patient and/or family members to optimally guide decision making.

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