Management of bilateral acute iliofemoral venous thrombosis in patients with inferior vena cava agenesis

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Background
Inferior vena cava agenesis (IVCA) is a rare anomaly that presents in 5% of cases of unprovoked lower extremity deep venous thrombosis (DVT), mostly bilateral and significantly under the age of 30 years. Conventional treatment with systemic anticoagulation may not be sufficient in limb-threatening stages. Catheter-directed thrombolysis (CDT) could be the modality of choice in this condition.
Aim
The purpose of this case series is to report our experience with CDT to manage patients with congenital absence of inferior vena cava presented with bilateral acute iliofemoral venous thrombosis.
Patients and methods
From February 2015 to March 2017, three patients were referred to Ain Shams University Hospitals and underwent CDT to treat bilateral iliofemoral DVT with IVCA after failure of treatment with systemic anticoagulation. Periprocedural and postprocedural details were recorded. Follow up with clinical examination and duplex ultrasound was performed regularly for 2 years.
Results
The mean procedural time was 52 h. Technical and clinical success were achieved in all the procedures. No further balloon angioplasty or stent placement was required. No major bleeding occurred. None of the patients had symptoms of pulmonary embolism. The mean postoperative hospital stay was 7 days. During the follow up, none of the patients developed recurrent DVT. Duplex ultrasound showed a patent deep system with only one patient who got unilateral femoral vein reflux, while computed tomography venography showed patency of pelvic and abdominal collaterals in all patients.
Conclusion
CDT is a safe and effective modality of treatment for patients with bilateral acute iliofemoral DVT associated with IVCA. It helps to reestablish the patient's baseline venous drainage for limb salvage, rapid symptomatic relief, and prevention of postthrombotic syndrome.

Keywords:
agenesis, deep venous thrombosis, inferior vena cava, thrombolysis

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Introduction

Congenital absence of inferior vena cava (IVC), known as inferior vena cava agenesis (IVCA), is a rare entity with an estimated prevalence of 0.3–0.5% in the general population [1]. It is also called IVC aplasia or atresia and often occurs together with cardiac and visceral congenital malformations in the form of dextrocardia, atrial septal defects, or asplenia [2]. Its etiology is controversial, either due to embryological dysgenesis or could be a result of intrauterine or perinatal thrombosis [3]. Formation of collateral veins draining to azygos and hemiazygos systems can compensate the absence of IVC; however, these collaterals with their low flow state may not cope with increased blood flow due to major physical exertion, thereby generating venous stasis and increased susceptibility of deep venous thrombosis (DVT) [4]. IVCA may present in 5% of cases of unprovoked idiopathic lower extremity DVT in young adults, mostly bilateral and significantly under the age of 30 years [5]. This could also be exacerbated by inherited factors such as thrombophilia or homocysteinemia or acquired by immobilization, contraceptives, trauma, or malignancy [5,6].

Conventional treatment in the form of anticoagulation and elastic stockings could be sufficient with mild symptoms or unilateral DVT [7], but when the condition approaches limb or life-threatening stages

such as bilateral phlegmasia or venous gangrene, a quick, aggressive, and safe intervention is required to restore deep venous circulation.

In this study, we report our experience with catheter-directed thrombolysis (CDT) to manage patients with congenital absence of IVC presented with bilateral acute iliofemoral DVT.

Patients and methods

From February 2015 to March 2017, three patients were referred to Ain Shams University Hospitals with IVCA and bilateral lower limbs iliofemoral DVT and were admitted for CDT. We got the approval of the scientific and ethical committee of Ain Shams University regarding our research.

The first patient was a 26-year-old housewife, presented with bilateral lower limb phlegmasia cerulea after failure of conventional treatment for 4 days in another hospital. She gave a medical history of oral contraceptive pills intake.

The second patient was a 30-year-old man, accountant by profession, who presented with sudden onset of debilitating bilateral lower limb swelling with severe thigh and calf pain. This was discovered after a hard physical exercise.

The third patient was 28-year-old women, a teacher, presented with tender swollen both thighs and calves after long flight travel. Her symptoms prevented her ambulation. Low molecular weight heparin (LMWH) was taken in another hospital for 1 week and failed to improve these symptoms.

All the three patients' past and family histories were irrelevant. None of them had previous lower limb DVT.

On admission, all the patients continued receiving LMWH as a therapeutic dose (enoxaparin sodium 100 IU/kg twice per day) together with complete bed rest and limb elevation.

Complete laboratory investigations in the form of complete blood picture, platelet count, international normalized ratio, prothrombin time (PT), and biochemical tests for kidneys and liver were done.

Thrombophilia studies were performed in all patients including factor V Leiden mutation, protein C, protein S, prothrombin mutation, antithrombin III, lupus anticoagulant, anticardiolipin antibodies, antinuclear antibody, PT gene mutation, and homocysteine.

Duplex ultrasonography was performed for the three patients which confirmed the diagnosis of bilateral acute iliofemoral DVT. It showed dilated lumbar veins but was not enough to detect agenesis of inferior vena cava (AIVC) in all cases.

Computed tomography (CT) venography showed thrombosis of iliofemoral-popliteal venous tree bilaterally till the iliac confluence, absent IVC lumen, and innumerable venous collaterals communicating with paralumbar, gonadal, retroperitoneal, and abdominal wall veins ascending to azygos/hemiazygos systems and suprarenal portion of IVC if detected.

After confirmation of diagnosis, the patient was transferred to a hybrid OR theater. Both popliteal veins were accessed under ultrasound guidance and local anesthesia via the posterior approach with the patient in prone position. Two (6 Fr) sheaths were inserted and intraoperative venography was done through them which showed thrombus extension from both popliteal veins till the confluence of iliac veins bilaterally. Two standard hydrophilic guide wires (Glidewire; Terumo Medical, Somerset, New Jersey, USA) and angled catheters were advanced through both sheaths till the level of L4 where they could not pass anymore. Another venography was done at that level via diagnostic catheters confirmed the absence of IVC lumen while the venous outflow of both lower extremities was noted to continue through huge collaterals ascending toward azygos and hemiazygos systems or supradiaphragmatic IVC.

Two thrombolysis catheters were then placed bilaterally within the whole length of the thrombus till reaching the iliac confluence. Catheters used were 20 cm multiside hole thrombolysis catheter (Multi-sideport catheter infusion set; Cook, Bloomington, Indiana, USA) or 50 cm multiple side hole Fountain infusion system (Medtronic Inc., Minneapolis, Minnesota, USA). A bolus of 10 mg (10 ml) of recombinant tissue type plasminogen activator (Actilyse; Boehringer Ingelheim, Stockholm, Germany) was administered in each limb into the thrombus using end-hole catheters. This was followed by a continuous infusion of 1 mg/h (1 ml/h) per catheter using a syringe pump. In some cases, during continuous infusion, a pulse spray with 10 mg of Actilyse was used to decrease thrombus load and to fasten the procedure when partial thrombolysis was observed.

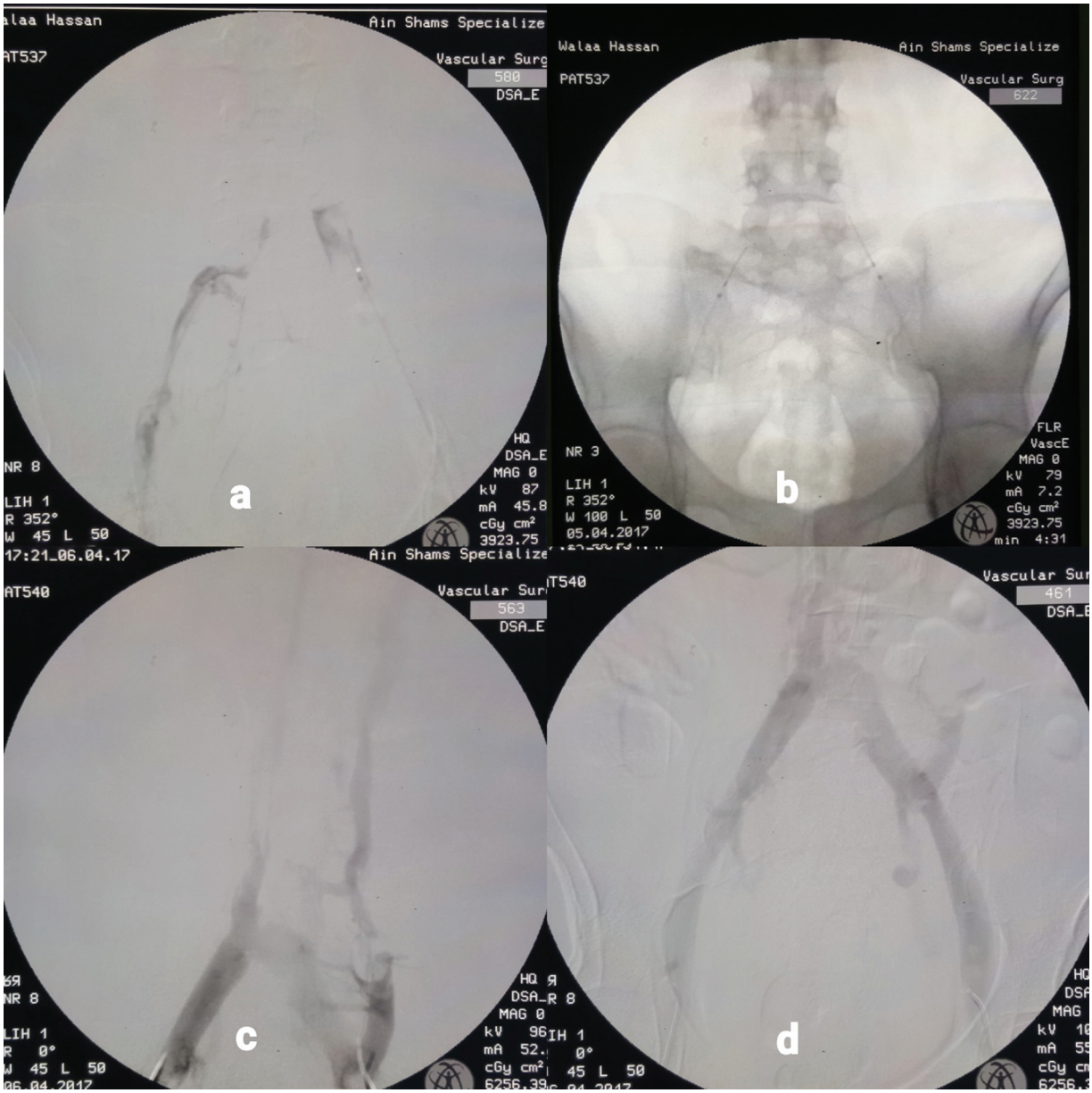
During the procedure, heparin (500 U/h) was continuously infused via the introducer using a separate infusion pump adjusting the PTT to be double normal. Serial fibrinogen and D-dimer levels were monitored during the infusion period. Blood levels of hemoglobin, platelets, and PTT were checked every 6 h.

Repeated venography was performed every 12 h to visualize the degree of thrombus regression. Catheter repositioning was performed when recanalization of the main collateral was noted. Our procedure was terminated when the entire thrombus load was resolved and a satisfactory venous outflow through the collateral vessels was achieved (Figs 1 and 2).

All the patients were monitored all through the procedure either in the theater or in the ICU. The heart rate, blood pressure, puncture sites, and status of the limb were checked at least twice every hour.

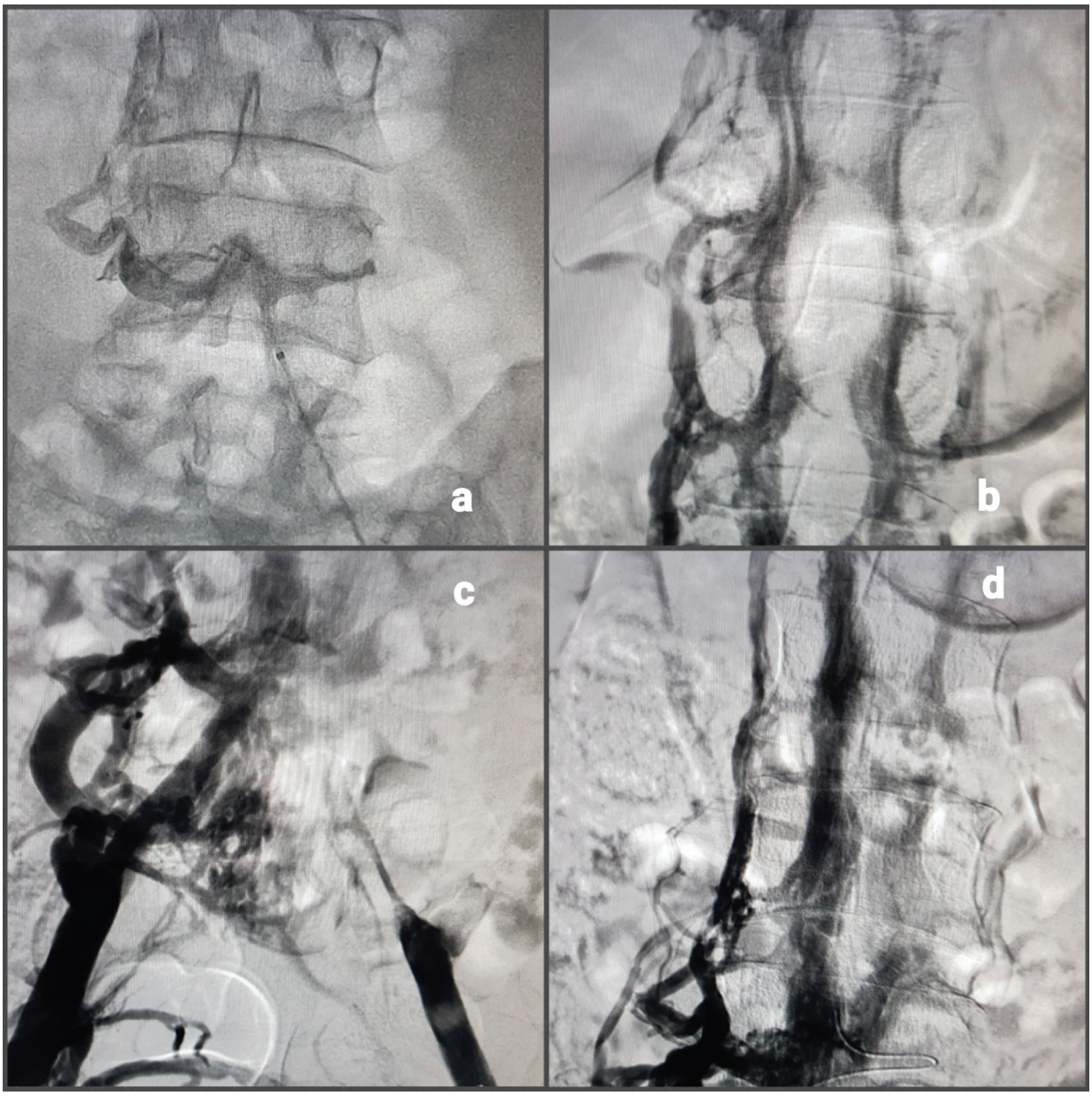
After completing thrombolysis, anticoagulation with LMWH was administered subcutaneously twice daily for 14 days. All patients were fitted with long graduated class II compression stockings. Lifelong warfarin therapy was initiated where the target therapeutic international normalized ratio range was 2–3. Two patients were shifted to rivaroxaban after 6 months of warfarin intake.

Figure 1



(a) Intraoperative venography showing thrombus load in both iliac veins; (b) positioning of both thrombolysis catheters at the most proximal part of iliac confluence; (c) and (d) follow-up venography showing patent iliac veins and ascending paravertebral collaterals with absent IVC. IVC, inferior vena cava.

Figure 2



(a, b) Intraoperative venography showing thrombus load in both iliac veins and patent paravertebral collaterals with absent IVC. (c, d) Follow-up venography showing complete lysis of thrombus in the right iliac vein and partial on the left side. IVC, inferior vena cava.

CT cuts were revised together with echocardiography done to all patients to rule out any associated visceral or cardiac anomalies.

Follow up with clinical examination and duplex ultrasound was performed after 1 week, 6 weeks, 3 months, 6 months, 12 months, and 24 months with a plan of lifelong annual follow-up thereafter. CT venography was done 6 months postoperatively to confirm patency of collaterals.

Definitions and study endpoints

The goal of CDT in patients with bilateral iliofemoral DVT was to reestablish the patient's baseline venous drainage for limb salvage, symptomatic relief, and prevention of postthrombotic syndrome (PTS).

'Technical success' was defined by anterograde flow restoration with complete or near-complete lysis of thrombus without major complication that indicate termination of the procedure.

'Clinical success' was defined as the relief of clinical symptoms and successful limb salvage.

'Major bleeding' was defined as intracranial bleeding, bleeding resulting in death or bleeding requiring transfusion or cessation of thrombolytic therapy. Small or postprocedural hematomas (with no clinical

consequences on the procedure) were not considered as major bleeding.

Results

The three patients presented in the study had a mean age of 28 years, two women and one man. Past and family histories were irrelevant. Risk factors for DVT detected were major physical exertion, long flight travel, or oral contraceptive intake. Hereditary thrombophilia was identified in one patient who was heterozygous for factor V Leiden mutation. No concomitant cardiac or visceral defects were detected in any of the patients.

None of the patients had symptoms of pulmonary embolism, neither on presentation nor while undergoing thrombolysis.

Duplex ultrasound confirmed bilateral acute iliofemoral DVT but was not able to detect IVCA, which was diagnosed by CT venography or later intraoperatively through conventional venogram. Absence of infrarenal segment of IVC with preservation of the suprarenal part was detected in the male patient, while absence of the entire IVC was found in the other two women. All patients had collateral veins in the abdomen and pelvis, some of which were thrombosed, with distinguished paravertebral collateral veins connecting to the azygos and hemiazygos system. Involvement of the proximal part of the popliteal vein was noticed in two patients.

The mean procedural time was 52 h (36–72 h). Technical success was achieved in all the procedures. Final venogram showed patency of the iliac, femoral, and popliteal veins in all cases, and restoration of flow into the pelvic and abdominal collaterals. No attempts for further balloon angioplasty or stent placement were required.

Clinical success was noticed in the three cases. No major bleeding occurred. One patient experienced mild hematuria by the end of the procedure which did not require any intervention. Small hematoma at the puncture site occurred in one case and was managed conservatively. The mean postoperative hospital stay was 7 days (5–10 days).

During the follow up for 2 years, none of the patients developed recurrent DVT. Follow up with duplex ultrasound showed a patent deep system. CT venography done after 6 months showed patency of collaterals in all patients together with patent lower limb venous tree (Figs 3 and 4). One patient had marked edema in one leg. On duplex examination he got reflux in the femoral vein.

Discussion

Congenital venous malformations occur in 1% of the population, approximately half of the cases accounts for IVC abnormalities [8]. The most common types of which are isolated left IVC, double IVC, segmental or total agenesis (atresia) of IVC, and azygos or hemiazygos continuation of the IVC [9].

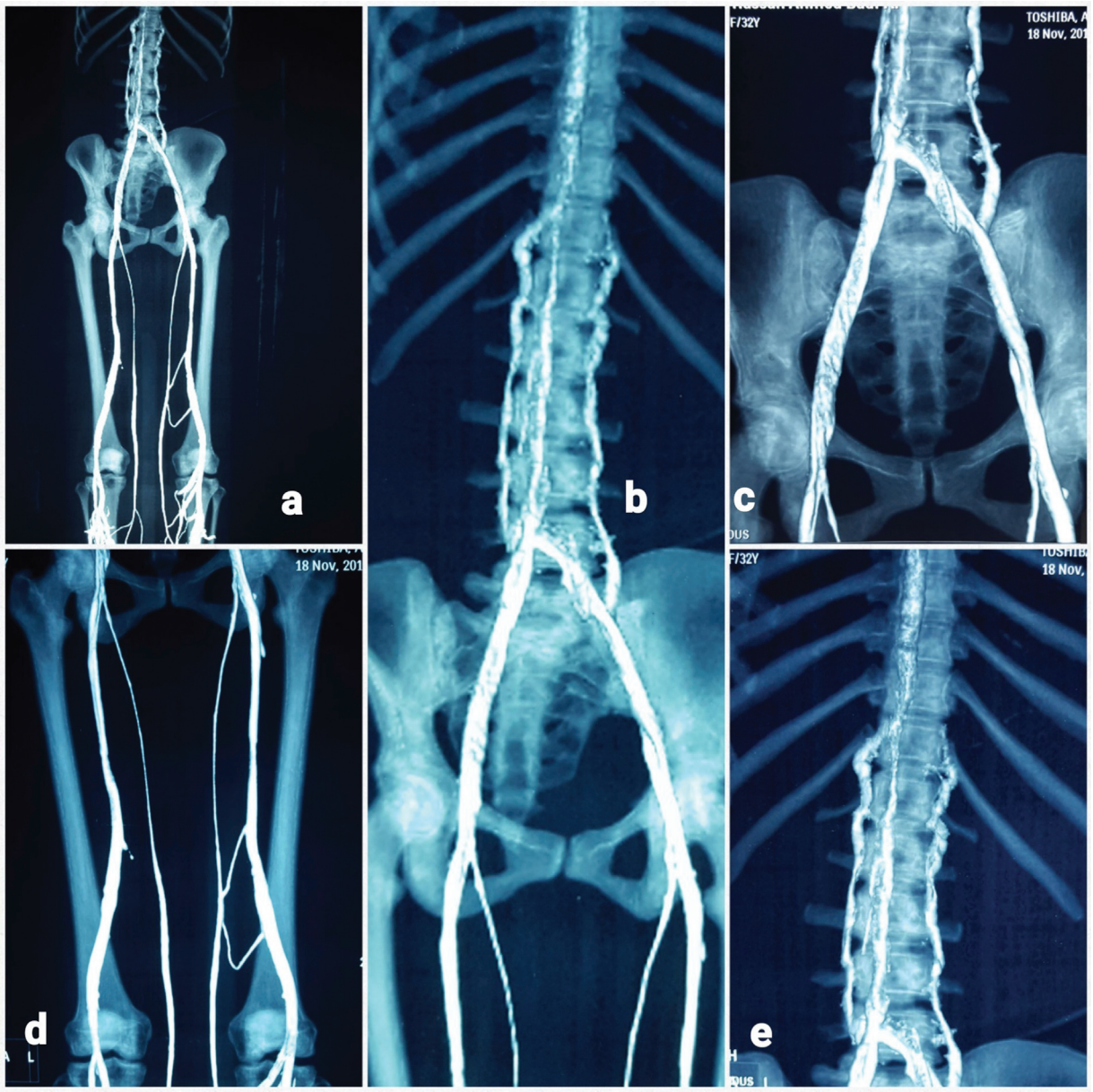
The development of IVC starts at the sixth week of embryogenesis. Three pairs of primitive veins (supracardinal, subcardinal, and postcardinal) form extensive collaterals during development, followed by regression, leaving one continuous vessel. Debing and colleagues stated that IVC can be divided into four segments: hepatic, prerenal, postrenal, and the renal collar. The supracardinal part gives rise to the postrenal IVC, hemiazygos and azygos veins. The subcardinal part gives rise to the prerenal portion of IVC. Hepatic sinusoids are derived from the hepatic segment, while the renal collar is formed by both subcardinal and supracardinal veins [10].

IVCA is caused by failure of anastomosis of one (segmental IVCA) or multiple (total IVCA) segments of the IVC [9]. It is a rare anomaly, with a prevalence rate ranging from 0.3 to 0.5% in the general population [1]. IVCA is usually accompanied by other congenital anomalies of organs which develop at the same week of gestational life, most of them are cardiac such as dextrocardia and atrial septal defects or visceral such as agenesis of the right kidney, asplenia, polysplenia or lung dysgenesis [2]. Rarely, it may be a part of KILT syndrome (kidney and IVC abnormalities with leg thrombosis) which may present with acute loin or back pain with hematuria and venous thrombosis [11,12].

Most of the patients with IVCA are asymptomatic due to the extensive network of the collateral venous system that develops to compensate for inadequate blood return through retroperitoneal and abdominal wall vessels. However, this alternative pathway may not be sufficient especially in case of increased demands, such as vigorous physical exertion or when additional risk factors for thrombosis are concomitantly present, such as immobilization, malignancy, trauma, major surgery, or oral contraceptive intake thereby generating venous stasis and clotting [13].

IVCA constitutes for 5% of cases of unprovoked lower limb DVT in young adults aged between 20 and 40

Figure 3



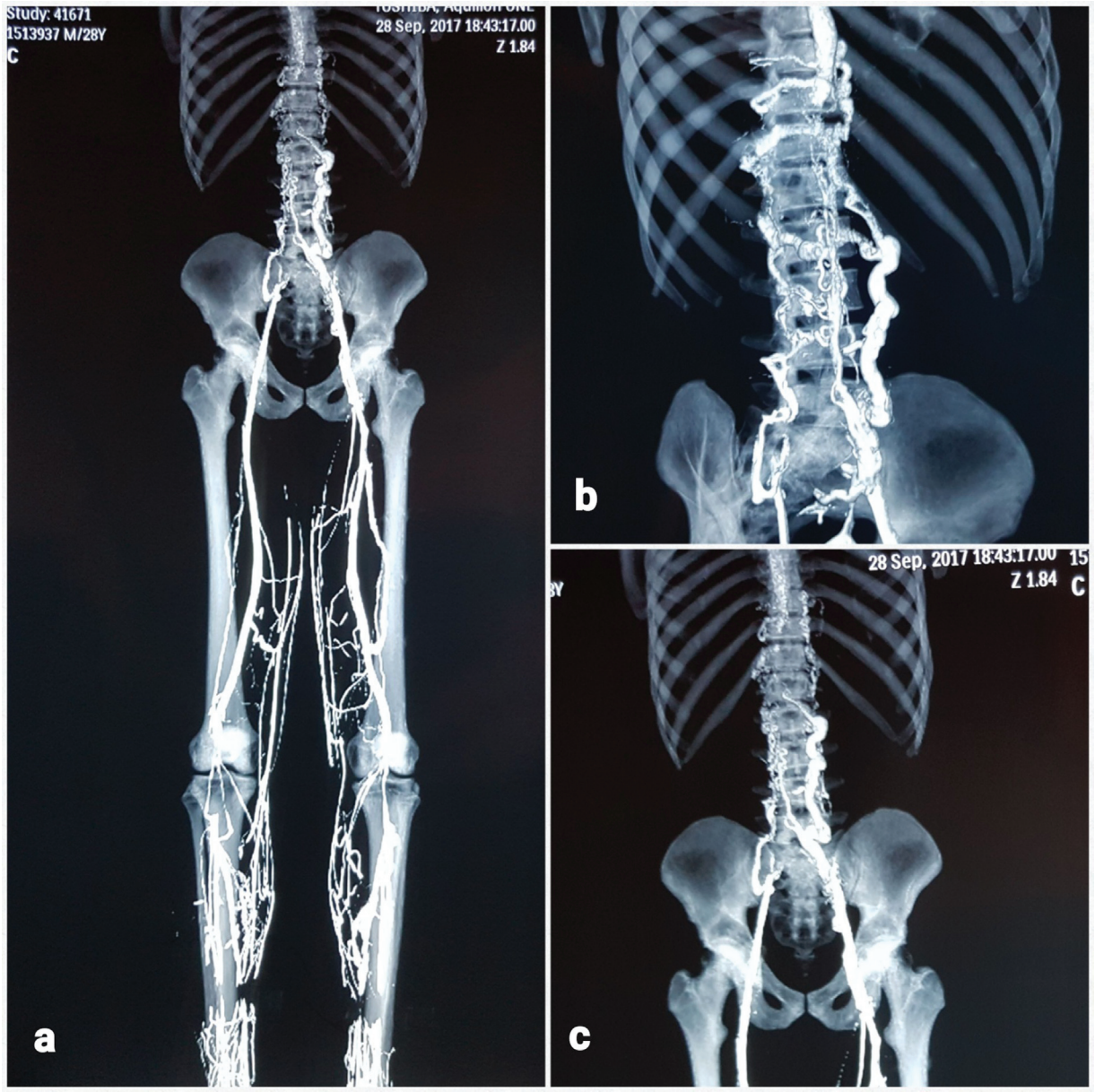
Follow-up CT venography showing absent prerenal IVC, patent both iliac and femoral veins with patent collaterals draining to the supra-diaphragmatic portion of postrenal IVC. CT, computed tomography; IVC, inferior vena cava.

years. Bilateral DVT has been reported in more than 50% of cases [14]. Most published reports stated that approximately one-third of patients with IVCA had hypercoagulable disorders especially those associated with hyperhomocysteinemia and factor V Leiden mutation [15]. Hence screening is recommended for inherited thrombophilia. Our three patients in the study had mean age of 28 years, all were presented with bilateral acute iliofemoral DVT. One of them was presented with bilateral lower limb phlegmasia cerulea. Heterozygosity factor V Leiden was identified in one patient.

The incidence of pulmonary embolism is very low with IVCA. The fragmented thrombus cannot embolize to the pulmonary circulation because it gets trapped in the azygos/hemiazygos system [4]. Only one report described pulmonary showers in a patient with IVCA [16]. In our study, none of the patients had symptoms of pulmonary embolism, neither on presentation nor while undergoing thrombolysis.

Although duplex ultrasound is the initial imaging modality to diagnose DVT, it could miss the anomalies of IVC [17]. To avoid underdiagnosis, all young patients with unprovoked DVT should undergo CT or MRI to rule out IVCA [13]. These modalities are more accurate as they could assist in diagnosing other concomitant anomalies and of great use for follow-up [18]. Venography is more invasive. Hence,

Figure 4



Follow-up CT venography showing complete absence of IVC, patent both iliac and femoral veins with patent collaterals draining to the azygos and hemiazygos system. CT, computed tomography; IVC, inferior vena cava.

it is reserved for confirmation of diagnosis and in case of further endovascular intervention [19]. In our series, we used duplex ultrasound in the diagnosis and follow-up. CT and intraoperative venography were used to confirm IVCA. We used to perform CT venography after 6 months postoperatively to detect patency of lower limb venous tree and ascending collaterals.

Owing to rarity of the disease, there are no standard guidelines to treat IVCA-associated DVT. Most case reports used conservative anticoagulation therapy for treatment [17,18]. Lambert and colleagues published one of the largest case series of DVT with IVCA, they recommended medical treatment in the form of LMWH followed by lifelong oral anticoagulation together with elastic stockings and leg elevation to relieve symptoms, decrease venous stasis, and prevent thrombotic recurrence or chronic venous insufficiency and ulceration [4].

Recent guidelines from the American College of Chest Physicians recommend the use of CDT as the preferred treatment for acute iliofemoral DVT. Comerota and colleagues showed that CDT in the treatment of classical iliofemoral DVT can result in rapid thrombus lysis, decreased incidence of DVT recurrence, preservation of valvular competency, and, consequently, a lower incidence of PTS compared with systemic anticoagulation alone for the treatment.

Broholm *et al.* [20] described the efficacy of CDT for rapid thrombus removal in patients with IVCA with acute iliofemoral DVT, especially involving iliofemoral venous thrombosis. Similar reports stated that CDT provides immediate relief of symptoms and significant decrease in thrombus burden [21,22].

Ly and colleagues reported failure of CDT in three patients with IVCA and therefore recommended against the use of this treatment in these patients [25]. Some authors assumed that the reason for unsatisfactory outcome in some studies may be due to the long duration of symptoms before the start of CDT, resulting in a lower degree of thrombus lysis [22]. In our study, we achieved 100% technical and clinical success. No major complications occurred and during follow-up, none of our patients developed recurrent DVT.Recently, pharmacomechanical CDT has been used, where CDT could be combined with mechanical thrombectomy using Trellis or Angioget to deal with extensive iliofemoral DVT. It showed promising results; however, more research trials are required to confirm long-term efficacy [19,23,26].

Precise duration of postoperative oral anticoagulation is still controversial [4]. Most reports recommend long-term vitamin K antagonist in combination with elastic stockings [2,5]. Lifelong anticoagulation is required in case of hereditary thrombophilia or other acquired risk factors to avoid the probability of recurrent thrombosis [24]. In our study, we preferred to offer our patients lifelong oral anticoagulation.

Conclusion

CDT is a safe and effective modality of treatment for patients with bilateral acute iliofemoral DVT associated with IVCA. It helps to reestablish the patient's baseline venous drainage for limb salvage, rapid symptomatic relief, and prevention of PTS.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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