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Ultrasound Accelerated Catheter Directed Thrombolytic Therapy in a 15-Year-old Pulmonary Embolism Patient with CLOVES Syndrome

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Dear Editor:

CLOVES syndrome, which stands for Congenital Lipomatous Overgrowth, Vascular malformations, Epidermal nevi and Spinal (scoliosis) and/or Skeletal anomalies, is a rare sporadic segmental overgrowth syndrome currently classified under PROS (PIK3CA-related overgrowth spectrum) disorders.[1,2] The estimated incidence of CLOVES syndrome is less than 1:1,000,000. No gender predilection is reported and the syndrome can be observed in all races and ethnic groups equally. All PROS disorders carry activating somatic mutations of the PIK3CA gene which cause uncontrolled growth of cutaneous, vascular, adipose, neural, and musculoskeletal tissues.[3]

CLOVES syndrome is a rare disorder that carries an increased risk of pulmonary embolism (PE).[4] It has been postulated that potential causes of thrombosis include an underlying hypercoagulable state, the presence of vascular malformations, and the presence of abnormal dilated and incompetent veins. Patients diagnosed with CLOVES syndrome have central and thoracic phlebectasia which is an abnormal outward dilatation of the venous vessel without tortuosity. This leads to incompetent veins and an increased risk of thromboembolism, increasing the risk of pulmonary embolism. A recent institutional observational study revealed that about 9% of patients with CLOVES syndrome suffered from PE cumulatively. Most of these PE episodes were after surgery or sclerotherapy, which all had central phlebectasia. They tolerated anticoagulation well and about 66% had to undergo endovascular treatment.[5]

In this manuscript, we report a pediatric patient with CLOVES syndrome who developed massive pulmonary embolism and was successfully treated with EKOS UCDT, as well as a review of the literature of the pediatric patients who were treated with catheter-directed fibrinolytic therapy.

A 15-year-old male patient, with a history of lymphangiomatosis and a tethered cord with a preoperative diagnosis of progressive double thoracic kyphoscoliosis, was admitted to our hospital for correction of a posterior spinal fusion with instrumentation from second thoracic (T2) to fourth lumbar vertebrae (L4). The procedure was performed without any complications. He was rolled into the supine position and his examination was determined as neurologically intact in the operating room after the procedure. Intraoperative radiological views of the spine obtained during the fusion procedure showed orthopedic hardware overlying the spine, and that the interpedicular screws were positioned. The patient was taken to the intensive special care unit in stable condition for observation overnight.

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A central line was placed and on a chest x-ray, single view on inspiration revealed a right internal jugular line extending into the superior vena cava and no pneumothorax. Additionally, the posterior spinal rods appeared to be in place. Two x-ray views of the thoracolumbar spine showed satisfactory postoperative view of the thoracolumbar spine with posterior spinal rods extending from the level of C7-T1 to L4 and pedicle screws intact at multiple levels. There was improved alignment of the spine, with mild residual curvature remaining in the thoracolumbar region. The patient was under follow-up without any symptoms.

While he was still under observation, he developed intense pain in his chest 24 h after the procedure, just after the removal of a Foley catheter. He was also dyspneic. In physical examination, the patient's vitals were: Temperature 99.2°F, Heart rate 107 beats/min, Respiratory Rate 14/min, BP 98/63 mm Hg, O_2 saturation 98% in room air. The patient was interactive and was in pain while shivering during the exam. The lungs were found to be clear with no wheezes, rales, or rhonchi. There was good bilateral air movement, with no retraction or increased work of breathing. On cardiac examination, there was tachycardia, S1 S2 was normal, and there were no rubs, gallops, or murmurs. His peripheral pulses were 2+, capillary refill was < 2 s. His Abdomen was Soft, non-tender, and non-distended, with bowel sounds. There were no masses. His ear-nose-throat, neck, skin, musculoskeletal, neurologic, endocrine, hematology, and immunology examinations were within normal limits. He had syndactyly of the 2-fourth toes on both feet, flattened and wide feet bilaterally with well-healed scars from soft tissue release.

Lab values revealed ABO blood type: O+, Factor VII: 94%, antithrombin III:61% (low), D-dimer:10.7, serum cortisol: 32.7, Homocysteine: 2.9, CK-MB: 20.6, CK: 2319, Troponin 0.02. Coagulation test results revealed activated partial thromboplastin time (APTT):33.9 s, PT: 13.5 with an INR of 1.3, and fibrinogen:296 mg/dL. Additional lab values showed that his Na: 139 mmol/L, K:4.4 mmol/L, Cl:109 mmol/L, Co2: 26 mEq/L, Cr: 0.7 mg/dL, Glucose:126 mg/dL. Blood cultures done three times were reported to be NGTD. Factor II mutation status is unknown at this time point.

The electrocardiography (EKG) was normal. The chest x-ray reported that the patient had recent spinal stabilization surgery with posterior rods with gas within the surrounding soft tissues. There was evidence of leftward scoliosis of the lower thoracic spine. His heart size was normal. There was no evidence of pericardial fluid. A small left pleural effusion with an estimated volume of 300 ml was noted. There is a trace of right pleural effusion. Scoliosis with recent spinal surgery was also reported. A large thrombus load to both the right and left pulmonary arteries was confirmed with CT angiography (Figure 1). A comprehensive bilateral lower extremity Doppler venous ultrasound revealed normal flow, compressibility, and augmentation of the deep venous system. There was no evidence of deep venous thrombosis (DVT). Echocardiography which was performed on postoperative day # 2, revealed normal intracardiac anatomy, moderate tricuspid regurgitation, and mild mitral regurgitation. Based on the tricuspid regurgitation gradient and ventricular septal configuration, the estimated right ventricular pressure was at the level of near systemic pressure. The right ventricular function was moderately decreased and the right ventricle was significantly dilated.

Based on this diagnosis, the patient was started on heparin infusion to maintain APTT between 60–85 s and was given fresh frozen plasma to compensate for low antithrombin III and for effective anticoagulation with heparin. The patient was needed considerable inotropic support in the follow-up with epinephrine at 0.12 mcg/kg per minute, and dopamine at 10 mcg/kg per minute. Due to the diagnosis of massive pulmonary embolus and right heart failure, right heart catheterization with insertion of bilateral infusion/ultrasound catheters (EKOS) was performed on post-operative day #2. Prior to advancing catheters, the femoral vein angiography showed no evidence of thrombus within the femoral vein. The catheter was then advanced to the innominate vein and the hand demonstrated no evidence of thrombus within the innominate vein or the right-sided superior vena cava. The mean right atrial pressure was recorded as 46/26 with a mean of 35 mm Hg. Pulmonary artery saturation was measured at 73% with a superior vena cava saturation of 84% and a right atrial saturation of 84%. A right heart catheterization and pulmonary and venous angiography placement of infusion (ECON)/ultrasound catheter system to right and left pulmonary arteries to facilitate administration of tPA given as a 2 mg bolus to both catheters with an infusion at 0.5 mg/h for 20 h maximum period. After this treatment, the patient acquired immediate symptomatic relief and subsequent clinical improvement and was weaned off of the pressors within 24 h.

A CT angiogram 48 h later demonstrated marked resolution of pulmonary emboli with no significant hematological changes and bleeding (Figure 2). Following this dramatic recovery, the patient was discharged from the hospital and it was recommended to continue follow-up with use of lifelong anticoagulation with direct acting oral anticoagulants (DOAC).

Discussion

This was an extremely rare case of a post-operative pulmonary embolism in a 15-year-old male patient who has CLOVES syndrome. Due to the unique circumstance of being post-operative and the risk of systemic thrombolysis therapy, an alternative approach was used in this case to treat the pulmonary embolism. It was decided to use UCDT and this became the first time it was used to treat PE in a pediatric patient with CLOVES syndrome.

This patient suffered from a syndrome named as CLOVES Syndrome and was also found to have antithrombin deficiency.[6–12] In this patient, the diagnosis of CLOVES syndrome is supported by the following: The patient had lipomatous overgrowths at both sides of thorax regions, retroperitoneal microcytic lymphatic vascular malformations at the time of birth, with tethered cord, progressive double thoracic kyphoscoliosis, and club foot.[13–15]

Ultrasound catheter-directed therapy, specifically EKOS, may be used in the treatment of arterial occlusion, DVT, and

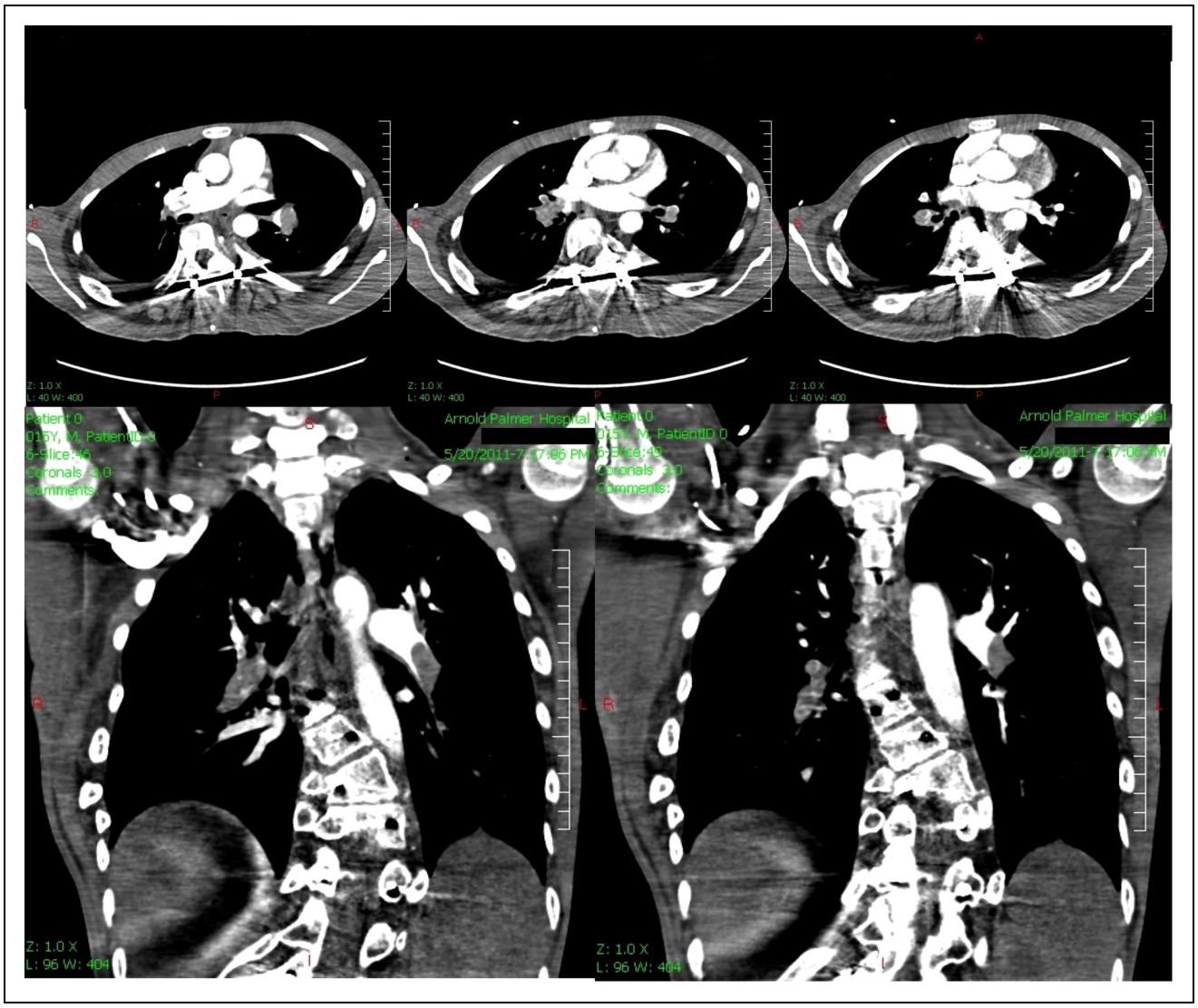

Figure 1. Transverse and vertical sections of CT Angiography represent filling defects in bilateral pulmonary arteries consistent with pulmonary embolism. The patient was suffering from extensive skeletal deformities and kyphoscoliosis the lipomatous overgrowth is prominent on both sides of the thorax.

pulmonary emboli.[13] The way ultrasound therapy works are by using cavitation-induced microstreaming. This mechanism works by loosening the fibrin strands ultimately causing the mechanical breakdown of the clot. Additionally, it exposes more plasminogen receptors by increasing surface area, therefore, allowing for easier breakdown by biological mechanisms. This also allows for the enhancement of the breakdown of a clot by allowing an increase in the permeability of thrombolytic agents.[14,15] The major complications documented with this therapy are hematoma at the access site, injury to any artery specifically pulmonary artery, pulmonary hemorrhage, and retroperitoneal hematoma. These complications are similarly seen in multiple catheter-based approaches.[16]

In the management of pulmonary emboli, the three approaches may be systemic anticoagulation, catheter-directed therapy, and surgical embolectomy. One of the ways PEs are managed is with the EKOS device, which is a version of catheter-directed thrombolysis. This device utilizes ultrasound to mechanically break up the clot. One of the most important advantages of this approach, as seen in this case, is the avoidance of potential complications of systemic anticoagulation therapies.[13] This is especially beneficial when managing post-operative patients where systemic therapy may be contraindicated. However, although it has been found that catheter-directed therapy had less in-hospital mortality than systemic thrombolysis in treatment PE, the evidence for pediatric population is lacking.[17] We urge further investigation on whether UCDT is superior to systemic anticoagulation in the pediatric population.

In the pediatric populations, pediatric studies assessing the efficacy and safety of using the EKOS approach in PE are lacking compared to adult literature. In a particular

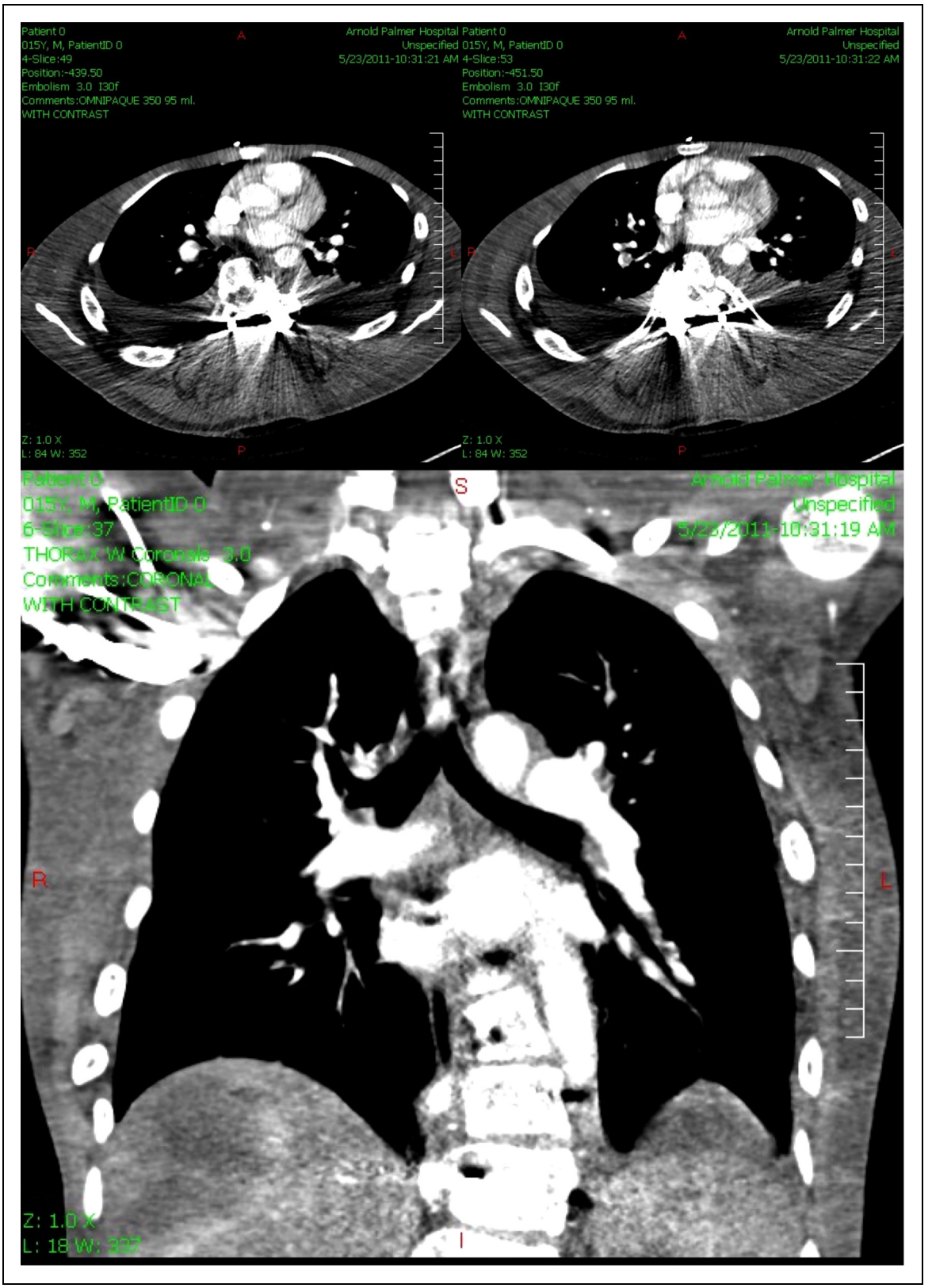

Figure 2. Transverse and vertical sections of CT Angiography represent the complete resolution of pulmonary embolism.

retrospective study, they used six CDT interventions on five pediatric patients, particularly, five of those procedures used the EKOS software in treating pulmonary embolism. It was found that all the patients had improvement in the clinical parameters and all of them had no long-term mortality or treatment-related complications.[18] As this study by Bavaria

Table 1. Summary of Data on Catheter-Directed Thrombolysis in Pediatric Patients with Pulmonary Emboli.

Author, Year	Patients Age and Description	Location	Thrombolysis tPA Dose and Duration	Outcome and Follow-up
Hubara, 2021[20]	8 month, hypoplastic left hard syndrome with Glenn procedure	Left pulmonary artery	Catheter-directed therapy (EKoS) 0.2 mg/kg/h TPA for 18 h, disconnected due to mild bleeding at sheeth site.	Initial treatment success, with reoccurrence on day 6. Treatment on day 6 had complete resolution and no complications after treatment of reoccurrence. 3 weeks later catheterization and balloon dilation for rehab of pulmonary tree. Discharged with long-term anticoagulation with heparin.
Belsky, 2020[21]	5 patients, (3 years, 13 years, 15 years, 17 years, 21 years)	Variable	Suction thrombectomy or mechanical clot disruption followed by catheter-directed therapy (EKoS) 0.03 mg/kg/hr alteplase (max dose 2 mg/hr) with 10 u/kg/hr heparin during alteplase infusion	4 complete resolution 1 partial resolution No complications Transitioned to therapeutic anticoagulation with low molecular weight heparin. Follow up at thrombosis clinic at 6 weeks, 3 months, and 6 months post-discharge.
Bavare, 2014[18]	5 patients (11 years, 15 years, 16 years, 17 years, 17 years)	Variable	Catheter-directed therapy (EKoS) 0.75 mg/kg/hr–1 mg/kg/hr tPA. Systemic tPA 10 mg	3 complete resolution 2 partial resolution No mortality No complications and anticoagulation of heparin bridged to enoxaparin or warfarin +/− aspirin
Ji, 2019[22]	9 patients (6 years, 9 years, 11 years, 14 years, 16 years, 16 years, 17 years, 17 years, 19 years)	5 bilateral and 2 unilateral pulmonary arteries	Catheter-directed therapy (EKoS) 0.03–0.06 mg/kg/hr tPA (max dose 1 mg/hr). During catheter-directed therapy low dose heparin 10 u/kg/hr was given. Low dose heparin infusion (2 u/ml) was administered constantly at the vascular sheath to prevent thrombus formation within the sheath. Mean time for tPA infusion was 29 h (16–73 h)	4 complete resolution 5 partial resolution and no complications. One of the ECMO patients required mechanical thrombectomy due to failure of catheter-directed therapy after 37 h, which showed chronic calcified thrombi bilaterally. All other patients were started on heparin and bridged to enoxaparin. One patient with inherited antithrombin deficiency required rivaroxaban. There was no recurrence of PE
Akam-Venkata, 2018[19]	9 patients 12 years, 14 years, 15 years, 16 years, 16 years, 17 years, 17 years, 18 years, 20 years)	Variable	Catheter-directed therapy (EKoS or pigtail) initial bolus dose of 2 mg followed by infusion rate of 1 mg/hr with concomitant low dose IV 500 u.hr heparin.	2 patients immediately died due to massive PE burden and 7 patients responded to catheter-directed therapy and concomitant anticoagulation with heparin with complete resolution. Of those 7, 6 patients were discharged with enoxaparin and one with apixaban. Median follow-up at 11 months (3–36 months). 2 patients with systemic lupus erythematosus had pulmonary embolism recurrence while on enoxaparin. 2 patients had GI bleeds from local tPA.
Kajy, 2019[23]	12-year-old Hereditary spherocytosis	Right pulmonary artery	EKOS Catheter-directed 10.5 mg of recombinant tissue plasminogen activator (r-tPA) delivered over 8 h second course due to minimal clinical improvement: 25 mg of r-tPA for additional 24 h	Marked clinical and hemodynamic improvement with clot resolution. Discharged and remained asymptomatic
Claveria, 2013[24]	2 patients, (17 years, 6 years) who developed PE after damage	Multiple, Variable	17-year-old: CDT tPA was infused at 30 mg/h for 2 h, giving a total dose of	Case 1: complicated by transfusion-manageable bleeding. However, improvement in hemodynamics

(continued)

Table 1. (continued)

Author, Year	Patients Age and Description	Location	Thrombolysis tPA Dose and Duration	Outcome and Follow-up
	control laparotomy after perihepatic packing.		60 mg. 6-year-old found to have extensive thrombus from the infrarenal IVC to the right common femoral vein. unfractionated heparin titrated to PTT of 40–60 s Patient transitioned to enoxaparin treatment after procedures. Hospital day 25 patient was found to have asymptomatic PE. enoxaparin dose was readjusted then transitioned to warfarin therapy prior to discharge home.	and ventilation Case 2: anticoagulated and no CDT was used
Kuo, 2019[25]	16 years antithrombin III deficiency.	bilateral segmental pulmonary artery embolism and DVT	Unfractionated heparin followed by CDT. CDT is used to treat remaining PE after UFH and DVT is treated with IVC filter.	Under CDT, heart rate decreased with resolution confirmed on angiography
Ruud, 2003[26]	12 years developed PE 9 years after Complex heart defects treated with Fontan Circulation	Left pulmonary embolus completely restricting flow to left lung	Continuous infusion of low-dose alteplase initially at 0.008 mg kg/ h/ And after day one due to minimal resolution was doubled to 0.016 mg kg/ h/ and continued for 5 days.	After 5 days thrombus disappeared with no complications

mentioned, we have also had success in treating this pediatric patient with EKOS with no long-term mortality and treatment complications.

Through our literature review of pediatric patients who developed PE and were treated, we included 34 pediatric patients who had been treated for PE. 33 of these patients were treated with a form of CDT. 8 out of 33 patients (24%) treated with CDT had a partial response and 25 (76%) had complete resolution of PE with CDT. There were 3(9%) total complications in the patients treated with CDT, two being GI bleeds that did not need transfusions and one being transfusion manageable bleeding. Two patients in the Akam–Venkata study were not included because of immediate death due to massive PE, possibly due to delayed treatment.[19] Of the 34 patients mentioned, none had died. Two patients with prior history of systemic lupus erythematous had developed a recurrent PE. The summary data of CDT in pediatric patients are presented in Table 1.

Conclusion

The utilization of EKOS in treating PE in the pediatric population is important in the management of PE as there are promising results and minimal side effects. This treatment modality was successful in treating our case of pediatric PE in this patient with CLOVES syndrome, and the overall complications were found to be low in our literature review. Due to the overall efficacy and success of EKOS UCDT, it seems that it is an important consideration to utilize in the treatment of the pediatric population.

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