

# A 39-year-old woman with atypical variant of Klippel–Trénaunay syndrome and progressive thromboembolic pulmonary hypertension, successfully treated by pulmonary thromboendarterectomy (RCD code: II-1A.5)

**Małgorzata Poręba\*, Marcin Misztal, Andrzej Biederman, Agnieszka Skrzypek, Piotr Szatkowski, Ewelina Pirsztuk, Danuta Czernecka-Mroczek, Andrzej Gackowski, Jadwiga Nessler**

John Paul II Hospital, Department of Coronary Artery Disease of the Jagiellonian University, Medical College, Krakow, Poland

## Abstract

We present a case of 39-year old female with Klippel-Trenaunay syndrome (KTS) complicated by chronic thromboembolic pulmonary hypertension (CTEPH). Our patient was operated in adolescence by vascular surgeons and severe varicosities of her leg were excised. After second pregnancy she manifested pulmonary embolism (PE) and was treated with vitamin K antagonists (VKA) and implantation of vena cava filter. Despite chronic VKA therapy she developed pulmonary embolism again. We present our TTE studies, X-ray and CT scans confirming diagnosis of pulmonary hypertension. Because of worsening of her cardiopulmonary status she was send to Cardiac Surgery Department and underwent pulmonary thromboendarterectomy. Extensive quantities of chronic thromboembolic material were cut out from both pulmonary arteries. At one year follow-up her functional status returned to NYHA class I. Control TTE demonstrated normal diameter and function of her right cardiac chambers.

We conclude that vascular anomalies existing in KTS although present locally are responsible for general hypercoagulability. We also wonder what should be proper treatment and which diagnostic tests should be perform to prevent from severe thromboembolic pulmonary hypertension. JRCD 2013; 1 (2): 61–68

**Key words:** Klippel–Trénaunay syndrome, chronic thromboembolic pulmonary hypertension, pulmonary endarterectomy

## Background

Klippel–Trénaunay syndrome is a rare congenital vascular malformation of the veins, capillaries, and lymphatic vessels, which can be associated with thromboembolic events. We report a case involving a woman with Klippel–Trénaunay syndrome and severe complications.

## Case presentation

A 39-year-old woman with previously diagnosed Klippel–Trénaunay syndrome affecting her right lower extremity was admitted to our hospital due to a significant deterioration in exercise tolerance and progressive dyspnea. The symptoms had been aggravating slowly for about a week.

Conflict of interest: none declared.

\* Corresponding author: Department of Coronary Artery Disease, John Paul II Hospital, Pradnicka str. 80, 31-202 Krakow, Poland; tel: +48 12 614 22 18;

email: sekr\_kchw@szpitaljp2.krakow.pl

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**Figure 1.** Recurrent lateral varicosity of the right lower extremity due to Klippel-Trenaunay syndrome. Normal size (no hypertrophy) of the leg is present



**Figure 2.** Chest X-ray image. Main pulmonary artery enlargement and prominent vascular hili

Varicose veins in her right lower limb were diagnosed in childhood and the patient underwent a three-staged procedure of varicose vein removal at the age of 17 years. She gave birth to 2 children, without complications, at the age of 19 and 21 years, respectively. At the age of 36 years, she experienced the first episode of pulmonary embolism (PE) treated in a public hospital with unfractionated heparin, and later, she was switched to warfarin therapy.

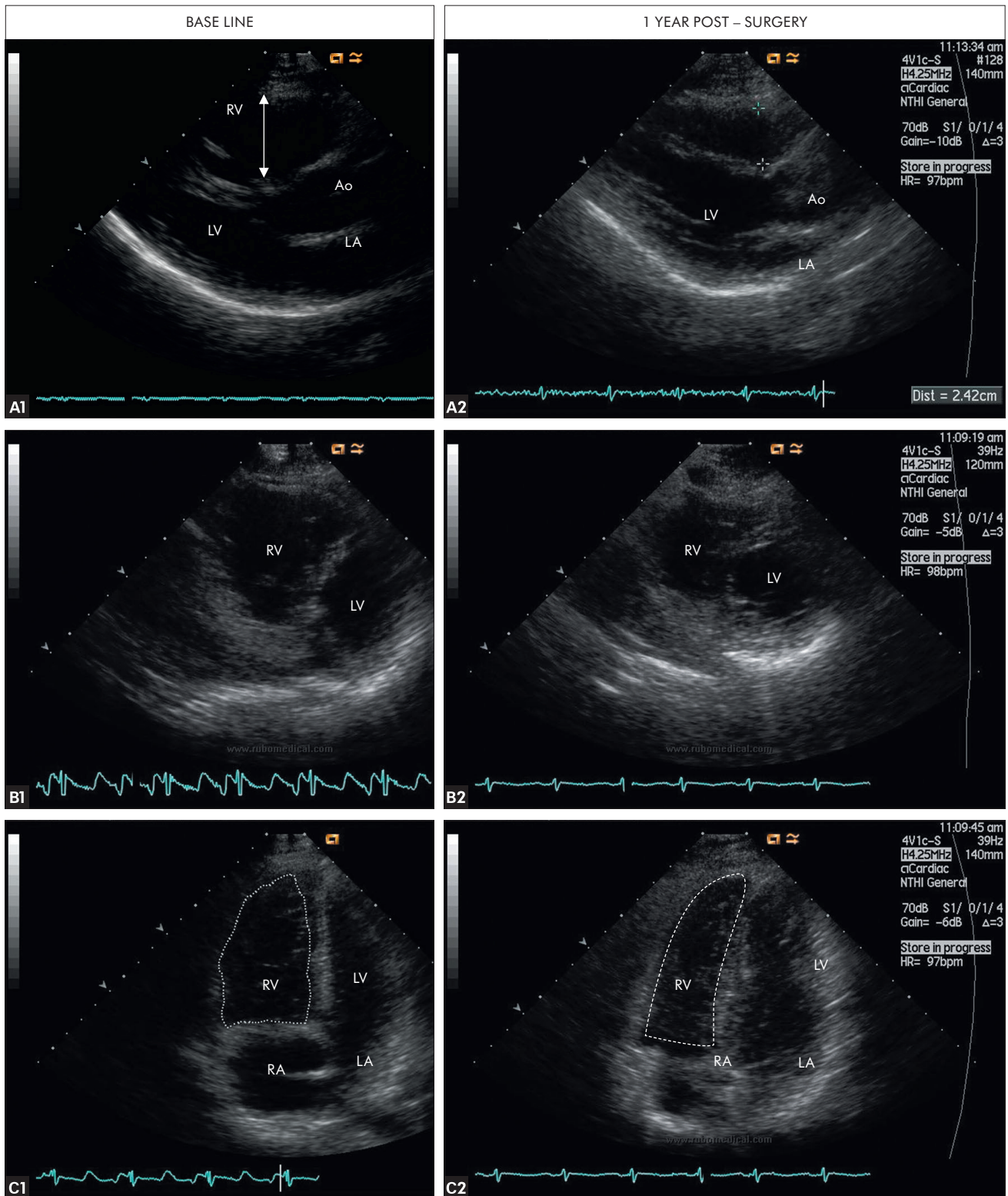
At the age of 37 years, she gave birth to the third child by cesarean section without complications. The following year, she miscarried at 10 weeks of the next pregnancy. Two months later, despite treatment with oral anticoagulant, she had another episode of PE (international normalized ratio [INR] values were not recorded).

Antiphospholipid syndrome and thrombophilia were excluded. An inferior vena cava filter was implanted to prevent recurrent PE and warfarin therapy was continued.

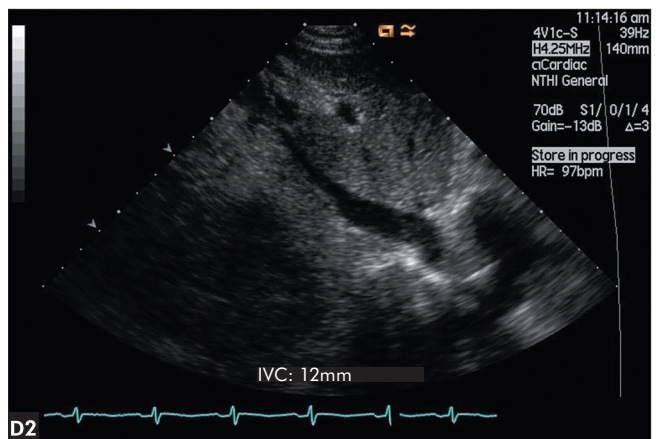
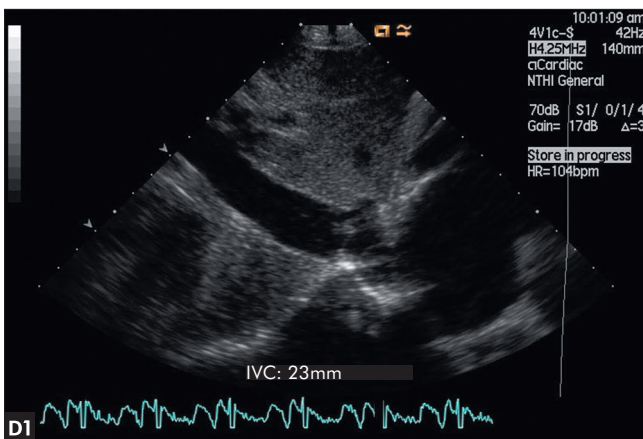
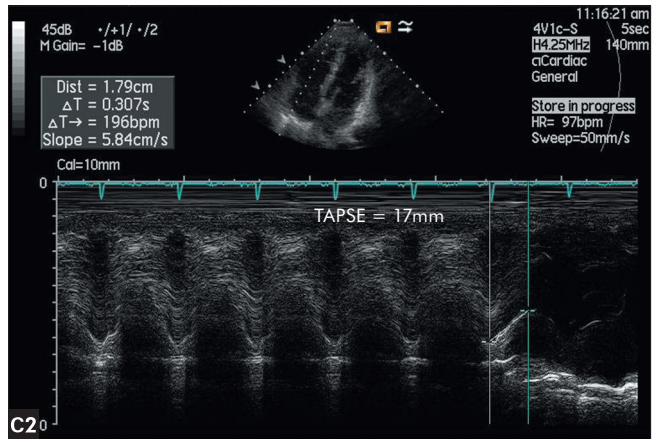
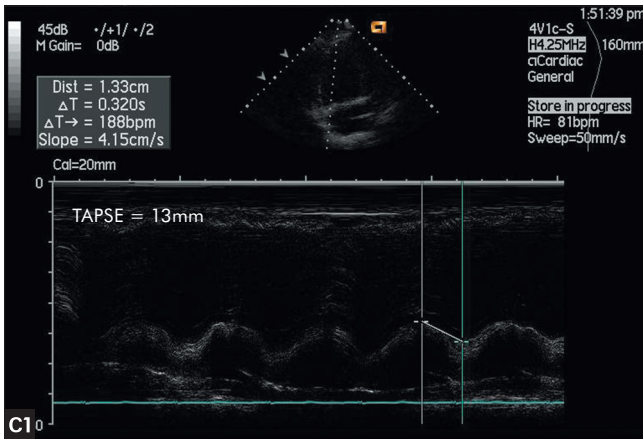
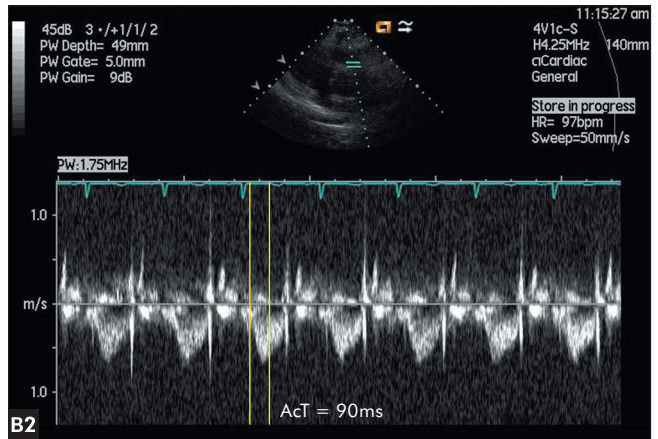
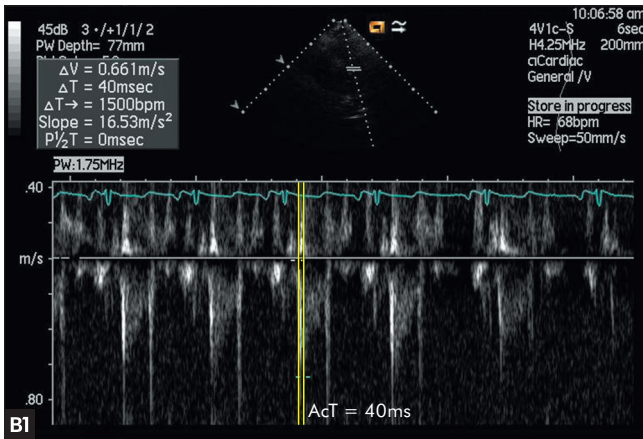
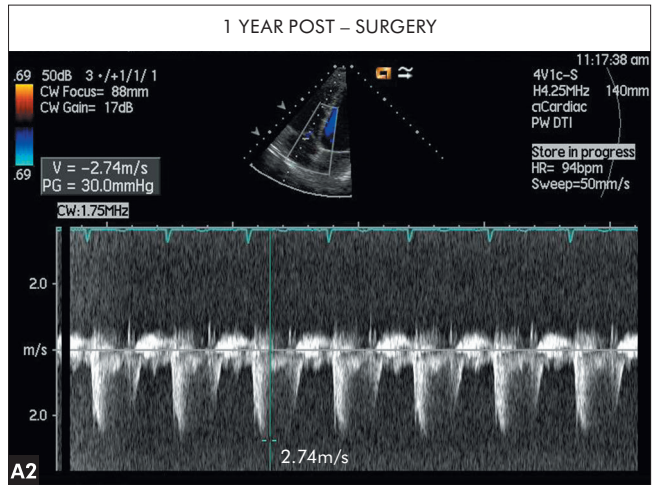
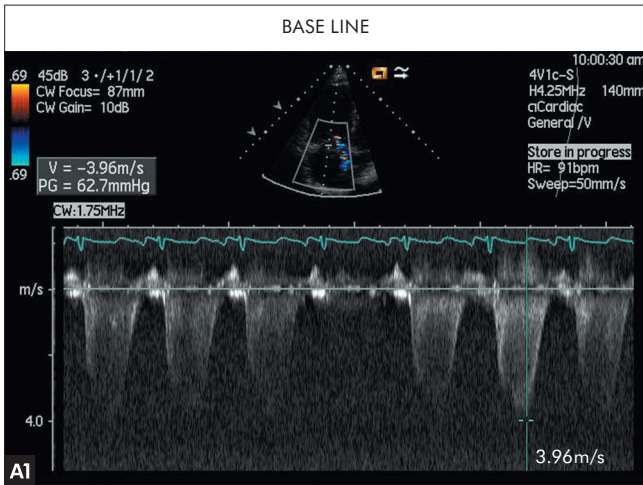
A day before admission, the INR ratio was 1.86. The patient reported that INR levels were not systematically measured during the preceding period.

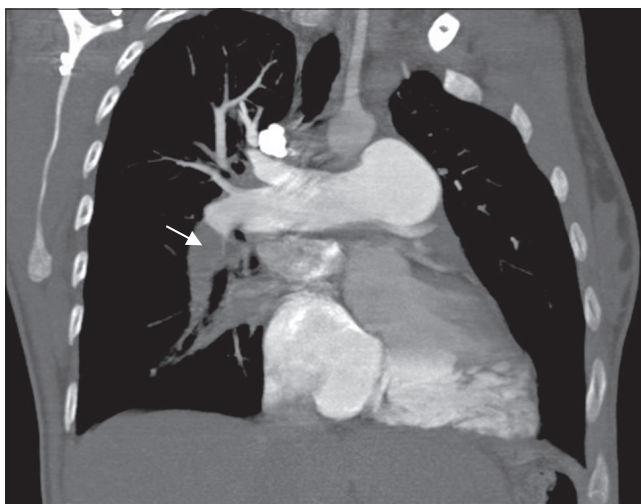
On admission, the patient was in New York Heart Association (NYHA) functional class IV, with resting dyspnea, tachypnea (26 breaths/min), tachycardia (heart rate, 102/min), and SaO<sub>2</sub> of 85%. Moreover, we observed central exertional cyanosis and 2 irregular hemangiomas in the sacral region and varicose veins of the lower extremities without the signs of inflammation or thrombosis (fig. 1). The systemic blood pressure was 108/80 mm Hg, but soon after admission the patient developed hypotension of 80/45 mm Hg. On palpation, there was tenderness of the right subcostal region.

Laboratory tests revealed slightly elevated plasma D-dimer levels of 644 µg/L (normal value <486 µg/L). The arterial blood gas analysis showed pO<sub>2</sub> of 59 mm Hg, pCO<sub>2</sub> of 23 mm Hg, pH of 7.47, and SaO<sub>2</sub> of 91.5%. On admission, the electrocardiogram showed sinus tachycardia (115/min), right axis deviation, high P-wave voltage, incomplete right bundle branch block, left posterior fascicular block, and right ventricular (RV) hypertrophy. Chest radiography showed main pulmonary artery enlargement and prominent vascular hili (fig. 2). Colour duplex ultrasonography did not show venous thrombosis in the lower limb. Transthoracic echocardiography (TTE) revealed dilatation of the RV with the proximal RV outflow tract diameter of 40 mm, thickening of the RV free wall of up to 7 mm, flattening and paradoxical motion of the interventricular septum, and reduced RV systolic function with tricuspid annular plane systolic excursion (TAPSE) of 13 mm. An estimated RV systolic pressure was 80 mm Hg and pulmonary flow acceleration time (AcT) was 40 ms (fig. 3, 4: left panels). Computed tomographic (CT)



**Figure 3.** Transthoracic echocardiography. Examination on admission (left panel) and 1 year after the surgery (right panel). A1, 2. Parasternal long-axis view. B1, 2. Parasternal short-axis view. C1, 2. Apical four-chamber view. Significant decrease of the right ventricular (RV) and right atrial (RA) dimensions after the surgery can be observed. LV – left ventricle, LA – left atrium



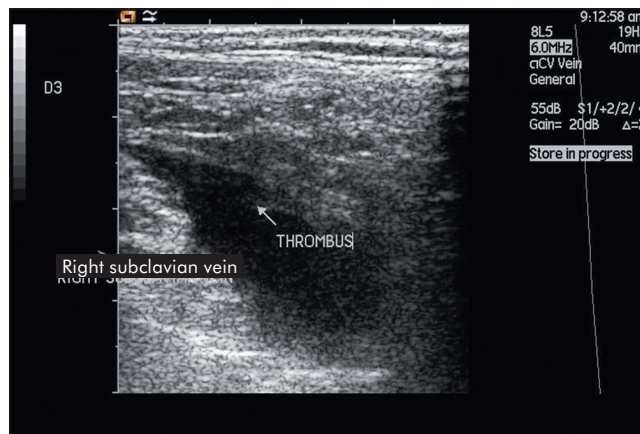


**Figure 5.** Computed tomography. Thrombotic material in the right lobal pulmonary artery (arrow)

angiography of the chest showed PE (fig. 5). In particular, it showed multiple intraluminal filling defects (emboli) localized in the pulmonary artery of the middle lobe and in the segmental arteries of the middle and lower lobes of the right lung. Based on the clinical course and CT results, the diagnosis of chronic thromboembolic pulmonary hypertension (CTEPH) was suggested. Due to a gradual improvement on enoxaparin therapy, the attending physician did not administer thrombolytic treatment. Prior to pulmonary endarterectomy, the patient was referred for right heart catheterization. Due to the presence of the inferior vena cava filter, we used the internal jugular vein access. Before the puncture, color duplex ultrasonography was performed and revealed multiple thrombi in the jugular and subclavian veins so the procedure was aborted due to the risk of thrombus mobilization (fig. 6). As no central PE was found, the consulting cardiac surgeon did not recommend urgent pulmonary thrombectomy. The patient was referred to the Department of Chest Medicine in Warsaw for further evaluation and treatment. The previous findings were confirmed.

Ventilation/perfusion lung scintigraphy showed multiple areas of ventilation/perfusion mismatch at the segmental and subsegmental levels. Right heart catheterization revealed elevated pulmonary artery pressure (56 mm Hg), elevated pulmonary vascular resistance (1636  $\text{dyne} \times \text{s} \times \text{cm}^{-5}$ ), and cardiac output of 2.2 L/min. Pulmonary angiography revealed signs of distal chronic thromboembolism (fig. 7). As central PE was not observed, the patient was discharged in a stable medical condition. The follow-up examinations were repeated after a month. Treatment with nadroparin at a dose of  $2 \times 5700$  IU was continued.

Three weeks later, the patient was admitted to the Department of Cardiac Surgery in Warsaw in critical condition due to the next episode of severe PE. The arterial blood gas analysis revealed  $\text{pO}_2$  of



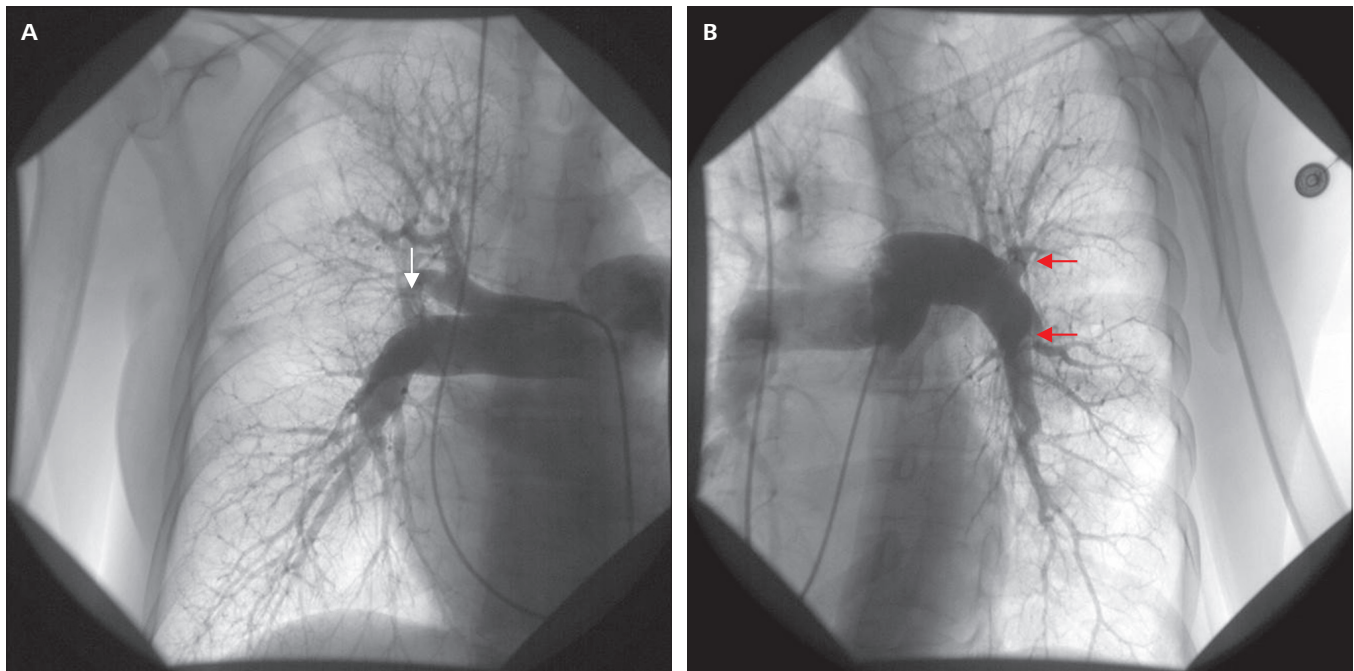
**Figure 6.** Ultrasonography. Mural thrombus in the subclavian vein

42 mm Hg,  $\text{pCO}_2$  of 21.1 mm Hg, pH of 7.49, and  $\text{SaO}_2$  of 81%. TTE showed severe right atrial and RV enlargement, severe tricuspid regurgitation, RV systolic pressure of 85 mm Hg, moderate pulmonary regurgitation, TAPSE of 12 mm, AcT of 45 ms, and dilatation of the inferior vena cava without inspiratory collapse. CT pulmonary angiography demonstrated massive thrombi in the branches of the right pulmonary artery (in the upper lobe pulmonary artery, in the interlobar artery, and in the arteries of the basal segments of the lower lobe). The N-terminal pro-B-type natriuretic peptide (NT-proBNP) level was 6390 pg/mL. Repeated Doppler ultrasound of the lower extremities showed no evidence of deep vein thrombosis.

The patient underwent urgent pulmonary endarterectomy. Extensive amounts of chronic thromboembolic material were removed from both pulmonary arteries. The early postoperative period was complicated by respiratory distress because of the right lung edema; moreover, the patient required dialysis due to acute renal failure. Nine days after pulmonary endarterectomy, a rethoracotomy had to be performed to evacuate a postoperative mediastinal hematoma.

Postoperative TTE demonstrated a significant improvement in the RV function. The NT-proBNP level decreased to 498 pg/mL. The improvement was confirmed by right heart catheterization. The mean pulmonary artery pressure was 12 mm Hg, pulmonary vascular resistance dropped to 210  $\text{dyne} \times \text{s} \times \text{cm}^{-5}$ , and cardiac output was 4.05 L/min. The patient was discharged on the 45th postoperative day and life-long enoxaparin treatment was recommended. The dose of heparin was adjusted based on anti-Xa levels. The functional status of the patient significantly improved at 1 year of follow-up, and, currently, she is classified as NYHA class I. TTE showed normal diameter and function of right cardiac chambers. An estimated RV systolic pressure was 35 mm Hg (fig. 3, 4 – right panels).

← **Figure 4.** Transthoracic echocardiography. Examination on admission (left panel) and 1 year after the surgery (right panel). A1,A2. Significant reduction of tricuspid regurgitant jet velocity. B1,B2. Significant increase in pulmonary valve acceleration time (AcT). C1,C2. Increase of the tricuspid annular plane systolic excursion (TAPSE). D1,D2. Reduction of the inferior vena cava (IVC) diameter. LV – left ventricle, LA – left atrium, TAPSE – tricuspid annular plane systolic excursion, IVC – inferior vena cava



**Figure 7.** Pulmonary angiography. Examination performed before operation. A. Narrowing of the right segmental pulmonary arteries (arrow). B. Amputation of left segmental pulmonary arteries (red arrows)

## Discussion

In the literature, there are only a few reports on Klippel-Trénaunay syndrome, which was first described in the beginning of the 20th century [9]. It is a rare congenital condition with mixed vascular malformation of the veins, capillaries, and lymphatic vessels. The typical triad of symptoms in Klippel-Trénaunay syndrome consists of capillary malformations (port-wine stains, hemangiomas), atypical, severe lateral varicosity, as well as soft tissue and bone hypertrophy of the limbs [1,2,11–14,38].

A unilateral manifestation in the lower limb is present in about 95% of the cases but the arm, trunk, head, or neck can also be affected [1]. The prevalence of Klippel-Trénaunay syndrome is estimated to be 1/20 000 to 1/100 000.

A review of the literature showed that Klippel-Trénaunay syndrome has been associated with venous thromboembolism in 8% to 22% of the cases [3–9]. The underlying mechanism of hypercoagulability in vascular malformations is still unclear. Inadequate formation of the vascular tree, abnormal vein function, abnormalities in the endothelial structure, and segmental widening of the venous system are likely responsible for stagnation of blood and activation of thrombosis. This combination of factors can lead to thrombi migration and worsening of recurrent PE and CTEPH in this vicious circle of venostasis, thrombosis, and embolism [2,3,34,35].

Chronic presentation and lack of adequate treatment can lead to CTEPH [25–30]. The early diagnosis of recurrent PE is crucial for proper treatment and prevention of CTEPH [3,26]. Another severe complication is recurrent bleeding from vascular malformations [31–33].

Our patient had an atypical manifestation of Klippel-Trénaunay syndrome with only 2 of the 3 components, namely, cutane-

ous hemangiomas and vein malformation without hypertrophy of the limb. It might have been caused by the removal of abnormal veins at an early stage. After that procedure, the patient was followed-up by her general practitioner and she gradually developed new (recurrent) varicose veins in the area of the lateral marginal vein and presented with shortness of breath. After the second childbirth, she had another episode of PE.

It is still unknown whether hypercoagulability in vascular malformations is the sole cause of thromboembolism in patients with Klippel-Trénaunay syndrome. Our patient did not have any signs of vein thrombosis in the lower limbs on Doppler ultrasound. Interestingly, we identified the signs of deep vein thrombosis in the upper extremity when the patient was prepared for angiography. It can lead to a conclusion that vascular anomalies in Klippel-Trénaunay syndrome may be responsible not only for local but also for general hypercoagulability.

The implantation of vena cava filters could be recommended for patients with Klippel-Trénaunay syndrome and a history of thrombosis [12]. Unfortunately, our patient had recurrent PE despite adequate anticoagulation and implantation of the filter. Awad et al. [35] observed a single case of anomalous venous communication between the lower extremities and the inferior vena cava, which bypassed the filter [35–37]. Currently, magnetic resonance venography seems to be the optimal method to detect such malformations. Another explanation of the recurrent PE may be thrombosis within the veins proximal to the filter or patency of the filter to small emboli [26].

According to the current management of Klippel-Trénaunay syndrome, the absolute indications for surgical treatment of vascular malformations are: hemorrhage, infections, acute thromboembolism, or intractable ulcers. The relative indications include pain,

functional impairment, chronic venous insufficiency, limb asymmetry, and other cosmetic defects [12].

It is difficult to diagnose PE because of nonspecific signs and symptoms [15–18,23,24]. CTEPH is rare in the general population, and only from 0.5% to 5% of the patients after acute PE develop pulmonary hypertension [20,21]. CTEPH may be detected in up to 50% of the patients without previous history of clinically symptomatic acute PE or deep vein thrombosis [19,22].

The incidence of chronic venous thromboembolism and CTEPH among patients with Klippel-Trénaunay syndrome is unknown [3]; however, it is certain that without early diagnosis and treatment the prognosis in CTEPH is very poor. It is known that the presence of large phlebectasia in the deep venous system is a risk factor for PE [1,2]; therefore a strict follow-up of patients is recommended. Patients with Klippel-Trénaunay syndrome should possibly undergo CT venography or contrast magnetic resonance imaging of the venous system because duplex ultrasound may not be sensitive enough to identify all venous malformations and thrombosis.

Guidelines for secondary prophylaxis in patients with vascular malformations after the first episode of venous thromboembolism are still under discussion. Mazoyer et al. [36] proved that use of low-molecular-weight heparin and compression therapy might be better than that of unfractionated heparin or vitamin K antagonists. Furthermore, the recommended INR range is still debated; perhaps, higher INR levels (2.5–3.5) should be considered. The role of novel oral anticoagulants has not been tested in this setting.

Another controversial issue is superior vena cava filter implantation in patients with vascular malformations (i.e., those with Klippel-Trénaunay syndrome) after thromboembolic episodes. Surprisingly, in our case, we observed jugular vein thrombosis. Therefore, superior vena cava filter implantation could be beneficial although the precise risk-to-benefit ration of this therapy it is still unknown [39,40,10]. No prospective studies involving patients with Klippel-Trénaunay syndrome have been published so far.

## Management strategy

The presented case confirms that recurrent thromboembolic events are possible in patients with Klippel-Trénaunay syndrome and may persist despite the implantation of an inferior vena cava filter. Proper anticoagulation and search for additional vascular anomalies and atypical thrombosis sites are necessary. Pulmonary thromboendarterectomy performed by experienced staff may be a safe and effective method of treatment in patients with Klippel-Trénaunay syndrome and CTEPH. To conclude, patients with Klippel-Trénaunay syndrome require a multidisciplinary diagnostic and therapeutic approach to manage this rare disease at a very early stage.

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