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A Case of Chronic Thromboembolic Pulmonary Hypertension in a High-Altitude Dweller

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Abstract

Sydykov, Akylbek, Kubatbek Muratali Uulu, Abdirashit Maripov, Meerim Cholponbaeva, Tatyana Khan, and Akpay Sarybaev. A case of chronic thromboembolic pulmonary hypertension in a high-altitude dweller. *High Alt Med Biol* 00:000–000, 2019.—Chronic hypoxia causes sustained pulmonary vasoconstriction and vascular remodeling leading to development of pulmonary hypertension in high-altitude residents. Although pulmonary hypertension is of mild to moderate degrees in most cases, some high-altitude residents may develop severe pulmonary hypertension. We report a case of a 47-year-old female highlander of Kyrgyz ethnicity who presented with exertional breathlessness and echocardiographic signs of severe pulmonary hypertension, who was diagnosed as having chronic thromboembolic pulmonary hypertension (CTEPH). To the best of our knowledge, this is the first documented case of severe CTEPH in a high-altitude dweller. This case illustrates that causes other than hypoxia may underlie and/or contribute to severe pulmonary hypertension in residents of high altitude.

Keywords: chronic thromboembolic pulmonary hypertension; computed tomography; echocardiography, high altitude; Kyrgyz

Introduction

Chronic hypoxia causes sustained pulmonary vasoconstriction and vascular remodeling leading to development of pulmonary hypertension in high-altitude residents. Pulmonary hypertension due to high-altitude hypoxia is classified as group 3 pulmonary hypertension. Although pulmonary hypertension is of mild to moderate degree in most cases, some high-altitude residents may develop severe pulmonary hypertension (Maripov et al., 2013). An exaggerated hypoxic pulmonary vasoconstriction is generally thought to underlie severe pulmonary hypertension in high-altitude residents. However, causes other than hypoxia may potentially underlie and/or contribute to severe pulmonary hypertension at high altitude. Literature data on other forms of pulmonary hypertension in high-altitude dwellers are very scarce. In this study, we report for the first time a case of severe chronic thromboembolic pulmonary hypertension (CTEPH) in a high-altitude dweller.

Case Report

A 47-year-old woman of Kyrgyz ethnicity presented with exertional breathlessness, chest pain, and fatigue for the past 4 years during our field expedition to high-altitude area (3000 m, Sary-Mogol, Kyrgyzstan). She was a resident of a high-altitude village located at 2500 m (Chak, Kyrgyzstan). Her medical history was significant for recurrent lower limb deep vein thrombosis and poorly controlled hypertension. She underwent emergency postpartum hysterectomy for uncontrolled postpartum hemorrhage 4 years before the presentation. The patient had no history of drug abuse or cigarette smoking and denied taking any medications.

Physical examination revealed elevated jugular venous pressure, varicose veins in both legs. The patient walked 256 m on a 6-minute walk test. Her blood group was identified as A. Complete blood count results were as follows: hemoglobin 15.0 g/dL, hematocrit 46.5%, red blood cell count 4.86×10^{12}/L, platelet count 310×10^{9}/L, and white

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blood cell count 6.8×10^9/L. Erythrocyte sedimentation rate was 14 mm/h. An electrocardiogram showed normal sinus rhythm, right atrial enlargement, and right ventricular (RV) hypertrophy. Pulmonary function tests were within normal limits. A transthoracic echocardiogram disclosed hypertrophied and severely dilated right-sided chambers, and an increased tricuspid regurgitation peak gradient of 113 mmHg (Fig. 1A, B) indicated severe pulmonary hypertension. RV systolic function was impaired with RV fractional area change (RVFAC) of 29%, tricuspid annular plane systolic excursion (TAPSE) of 1.35 cm, and peak systolic velocity at the lateral tricuspid annulus S′ of 11.2 cm/s (Fig. 1C, D). The ratio of early tricuspid inflow to annular diastolic velocity E/Ea was markedly increased at 16.5. Doppler ultrasound study of lower limbs disclosed lower extremity deep venous thrombosis. The patient was diagnosed as having severe pulmonary hypertension and was referred to the National Center of Cardiology and Internal Medicine (NCCIM) in Bishkek (760 m) for further assessment and investigation.

At the NCCIM, echocardiogram showed tricuspid regurgitation peak gradient of 81 mmHg, suggesting contribution of hypoxic pulmonary vasoconstriction to the pulmonary hypertension at high altitude in this patient. Right heart catheterization confirmed severe pulmonary hypertension with mean pulmonary artery pressure of 86 mmHg (123/37) and mean atrial pressure of 19 mmHg, whereas the pulmonary capillary wedge pressure was normal at 8 mmHg. The values of pulmonary vascular resistance and the cardiac index were 1024 $dyn \cdot s \cdot cm^{-5}$ and 3.39 $L \cdot min^{-1} \cdot m^{-2}$, respectively. Pulmonary angiography disclosed obstruction in the left lower lobe pulmonary artery. Furthermore, computed tomography pulmonary angiography revealed filling defects corresponding to thrombus in the left lower lobe pulmonary artery (Fig. 2). Blood coagulation tests (prothrombin time, thrombin time, activated partial thromboplastin time, and fibrinogen level) were normal. Finally, the patient was diagnosed as having CTEPH.

The patient was recommended to move to lowland with the purpose of alleviation of hypoxic pulmonary hypertension. In addition, therapeutic warfarin and sildenafil due to unavailability of riociguat were commenced. Furthermore, assessment of her operability in an expert center for pulmonary endarterectomy was recommended, but the patient refused surgical treatment.

Six months later, the patient was investigated at high altitude. The patient showed significant improvement of effort tolerance with a distance of 416 m on 6-minute walk test compared with 256 m before treatment. Repeat echocardiogram showed improvement in several parameters of RV function: TAPSE increased to 1.8 cm and E/Ea to 6.8, whereas tricuspid regurgitation peak gradient, RVFAC, and S′ remained unchanged (116 mmHg, 29%, and 10 cm/s, respectively).

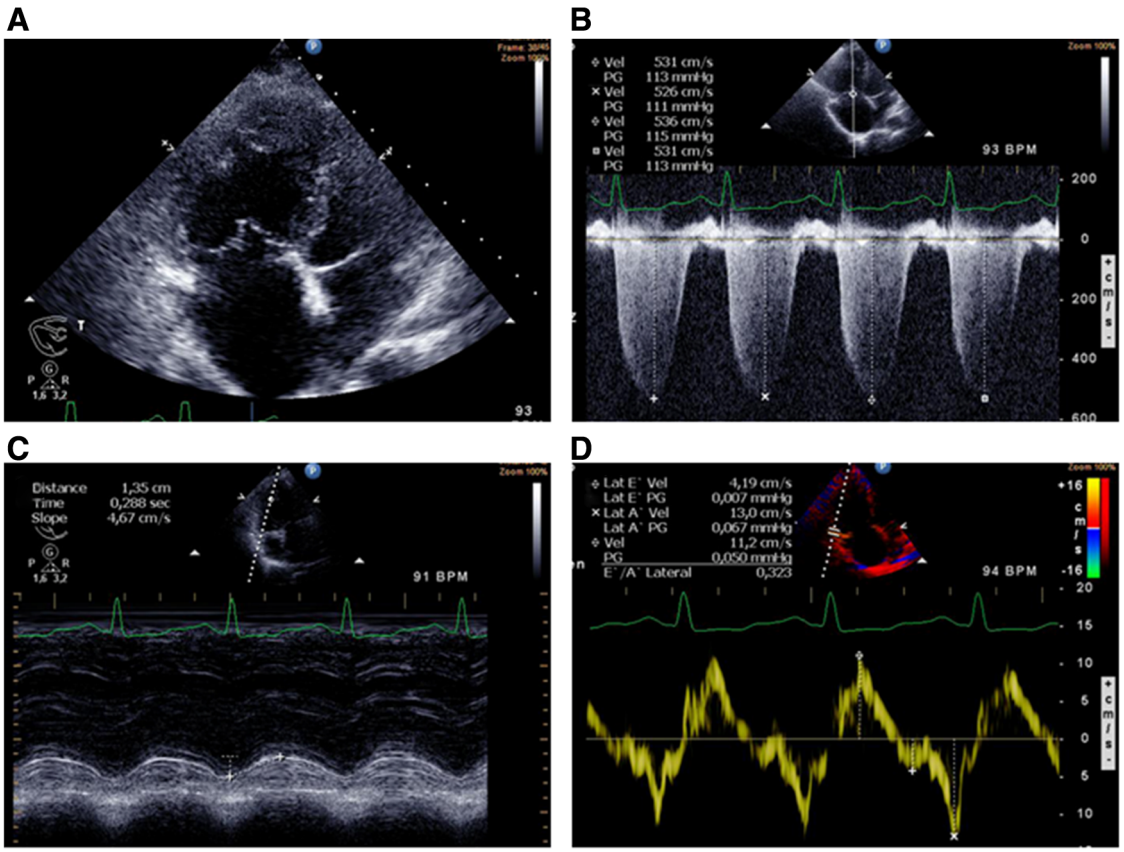

FIG. 1. Initial echocardiography performed at high altitude showing severe pulmonary hypertension and dilated right-sided chambers. **(A)** An apical four-chamber view. **(B)** Maximal tricuspid regurgitant jet velocity, measured from the spectral profile of the tricuspid regurgitation jet. **(C)** Tricuspid annular plane systolic excursion using M-mode of the tricuspid annulus. **(D)** Lateral tricuspid annular motion velocity using pulsed wave tissue Doppler imaging.

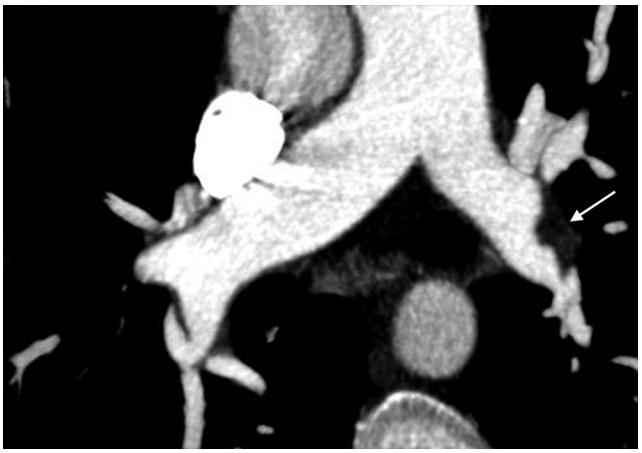

FIG. 2. Computed tomography pulmonary angiography showing thrombus in the left lower lobe pulmonary artery (*arrow*).

Discussion

Hypobaric hypoxia is associated with an increased thrombotic risk (Wheatley et al., 2011). Earlier studies have suggested that prolonged stay at high altitude is associated with a significantly higher risk of spontaneous vascular thrombosis in lowlanders (Anand et al., 2001). In highlanders, high hematocrit levels and polycythemia increase blood viscosity and impair blood flow, thus predisposing them to thrombosis. In addition, elevated platelet counts and enhanced platelet adhesiveness were found in permanent high-altitude residents in India (Sharma et al., 1980; Sharma, 1981). Furthermore, shortening of clotting time was reported in high-altitude natives in Peruvian Andes (Hurtado, 1932). In contrast, in our patient, erythrocyte counts, hematocrit values, and platelet counts were not elevated compared with those in sea level residents, and blood coagulation tests were normal. The reasons for this discrepancy are not clear, but might be related to differences in ethnicity, conditions, and duration of high-altitude residence between various populations. According to some sources, the Kyrgyz people are relatively recent immigrants to high-altitude areas and they started populating the Tian-Shan and Pamir-Alai Mountains during the 14–15th centuries (Dani and Masson, 2003).

Recently, cases of pulmonary embolism after prolonged stay at extreme altitude were reported in high-altitude natives (Singhal et al., 2016). Furthermore, pulmonary hypertension due to thrombotic occlusive vascular disease was described in acclimatized lowlanders residing at high altitude for the duration of up to 2 years (Singh and Chohan, 1972). To date, there have been no reports of CTEPH in high-altitude residents. To the best of our knowledge, this is the first documented clinical case of CTEPH in a high-altitude dweller.

A significant proportion of CTEPH patients present with a history of deep venous thrombosis and acute pulmonary embolism (Lang et al., 2013). In addition, several risk factors that predispose patients to CTEPH have been identified, including elevated circulating levels of factor VIII and antiphospholipid antibodies, intrinsic abnormalities in fibrinogen, and non-O blood groups (Lang et al., 2013; Delcroix et al., 2016). Moreover, some medical conditions are associated with an increased risk of CTEPH, including a history of splenectomy, malignancy, presence of a ventriculoatrial shunt, chronic inflammatory diseases, and thyroid substitution therapy (Lang et al., 2013; Delcroix et al., 2016). Interestingly, our patient became symptomatic 4 years after emergency postpartum hysterectomy, an independent risk factor for venous thromboembolism. Furthermore, other risk factors of CTEPH such as a history of deep vein thrombosis and non-O blood group were also present in our patient.

Echocardiographic study revealed signs of severe pulmonary hypertension in our patient. A detailed history and examination raised a suspicion of CTEPH, which was later confirmed by right heart catheterization and computed tomography pulmonary angiography. It has been shown that some patients with complete unilateral obstruction may display normal pulmonary hemodynamics at rest (McCabe et al., 2014). However, CTEPH is a disease with a concomitant pathology of small pulmonary vessels as evidenced by a lack of a linear correlation between the severity of pulmonary hypertension and the extent of vascular obstruction, progressive pulmonary hypertension in the absence of recurrent thromboembolic events, and persistent pulmonary hypertension despite successful surgical desobliteration in some patients (Galie and Kim, 2006). In addition, high-altitude hypoxia could contribute to the remodeling of small pulmonary vessels, thus aggravating hemodynamic alterations in our patient.

This case illustrates that causes other than hypoxia may underlie and/or contribute to severe pulmonary hypertension in high-altitude residents. It is, therefore, very important to keep this in mind and to consider all the potential causes of pulmonary hypertension using the classic diagnostic tools, including careful clinical history taking and physical examination complemented by modern imaging studies.

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Author Disclosure Statement

No competing financial interests exist.

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