Pulmonary Thromboembolism at Extreme High Altitude: A Study of 7 Cases

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Abstract

Backgrounds: The high incidence of venous thromboembolic disease (VTE) in plateau area has aroused widespread concern. Through the collection and analysis of pulmonary thromboembolism (PTE) cases in extreme high altitude, to explore the epidemiological characteristics and possible risk factors of PTE in extreme plateau region.

Methods: Seven cases of pulmonary thromboembolism occurring in extreme plateau region were prospectively collected in a high altitude hospital at 3800 m from May to November 2020. All patients were serving at 5000 m above sea level, and diagnosed with PTE by using computed tomography pulmonary angigraphy (CTPA).

Results: Seven patients with an average age of 24±3.6 yr, the mean altitude is 5200±200 m at the onset of symptoms. And the time of them stay at high altitude between 8-210 days (99.29±77.31). Cough, expectoration, chest tightness, fever, short of breath, chest pain were the commonest symptom. 6 of 7 patients were initially diagnosed with pulmonary inflammation and 4 with HAPE by CT or X-ray. Most patients had an increase in inflammatory cells and all of them showed a high level of D-dimer in initial hematologic test during the course of the disease.

Conclusions: Pulmonary thromboembolism has a high incidence in plateau areas and shows a younger age trend. Prodromal infection and high altitude pulmonary edema (HAPE) were the potential risk factors for its occurrence.

Background

Pulmonary thromboembolism (PTE), the most common clinical type of pulmonary embolism (PE), is a disease characterized by circulation and respiratory dysfunction which caused by thrombus from the venous system or the right heart blocks the pulmonary artery or its branches. Progressive dyspnea, tachycardia, pleuritic chest pain and hemoptysis are the cardinal symptoms of PTE [1]. PTE and deep venous thrombosis (DVT) represent the distinct phase of venous thromboembolism (VTE) [2]. Because of the unhealthy prognosis and high mortality, much attention has been paid on PTE in the recent several decades. Certain acquired factors (major surgery, cancer, trauma, spinal cord injury, advanced age, pregnancy and postpartum and so on) and hereditary factors (protein C/S deficiency, factor V Leiden, antithrombin deficiency, plasminogen deficiency and so on) increase the feasibility of DVT and PTE [1, 3]. Accompany with a number of case reports and small studies, prolonged stay and travel to high altitude (HA) also be considered as the risk factor of PTE [4–6].

Although definitions controversy, height above 2500 m is a widely accepted definition in the main trend of high altitude medicine. Attendant the hypobaric hypoxia and cold conditions at HA area, many diseases in which emerged distinct from low altitude. In HA area, VTE showed a high morbidity and mortality. Kumar S et al. reported 28 DVT cases of the Indian soldiers located at 11800 feet, compared with the data from the hospital in plains, the results showed a significant higher DVT incidence in HA hospital (0.7/1000 population VS 0.028/1000 population). Soldiers at HA had 24.5 times relative risk for DVT than that in the plains (95% CI: 8.59 < RR < 69.84) [6]. Another prospectively research showed an 30.5 odds ratio for vascular thrombosis in HA Indian soldiers when compared non-HA soldiers (< 3000 m), Significantly, ischemic stroke was included in this study [7]. According to these study, HA was a general risk for VTE. In addition, Dutta et al. reported 53 Indian soldiers prolonged stay at HA area more than 4 months and were diagnosed with PE, 17% of them had hereditary risk

factors of thrombophilia (3 with protein C/S deficiency, 3 with hyperhomcystinemia, 2 with antithrombin III deficiency, 1 with factor V Leiden), the rest of 83% patients without disease burden were related with HA probably [8]. Khalil et al. described HA was the only risk factor for the 50% of the 50 PE cases in Pakistani soldiers at HA [9]. At present, the limited number of studies mentioned that HA is the potential risk factor for PTE and DVT, but more forceful researches need to support this topic yet.

In this study, we describe 7 cases with PTE diagnosis at HA area and discuss in detail. We found that infection and high altitude pulmonary edema in the HA may increase the risk of PTE, it as a precursor process before PTE was diagnosed explicitly need more attention to avert misdiagnose and ineffective treatment.

Methods

All clinical data for this prospective study were collected at a medical station, which provides medical services to less than 10,000 residents in the surrounding area, located at Pishan county, Xinjiang autonumous region of China (3800 m above the sea level) from May to November 2020. Further treatment for patients were performed at the People's Liberation Army 950th hospital and General Hospital of Xinjiang Military Command which located in Kashgar and Urumqi, Xinjiang autonumous region of China respectively. Altitude > 2500 m was the definition of HA, while extreme altitude was defined as altitude > 5000 m above sea level [7].

All patients were diagnosed with PTE by computed tomography pulmonary angigraphy (CTPA) explicitly. Thromboembolus of lower extremity vein, iliac vein, inferior vena cava and the heart chamber were confirmed by color Doppler Ultrasonography. High altitude pulmonary edema (HAPE), high altitude cerebral edema (HACE) and pulmonary inflammation were determined by X-ray or computed tomography (CT). The intracranial venous sinus thrombosis was diagnosed by magnetic resonance venogram (MRV). The data of blood routine, coagulation function in this study were obtained from the patient's initial hematologic test since this illness.

In addition to the clinical examination data, patient’s own and family history of embolic disease was included. The special note were made of alcohol consumption, smoking history, previous HA exposure history, total time stay at HA, symptoms, and weight lose and so on. All of these items were included in the risk factor assessment.

Results

Patient’s characteristics

7 male patients with PTE who hospitalized the medical station from May to December 2020 were enrolled in this study. All of them fell ill at altitude above 5000 m and were send down to the medical station for further treatment. The basic diagnostic information and characteristics of patients were showed in Table 1 and 2, respectively. Patients ranged in age from 20 to 31, with an average age of 24±3.6. They are all residents from low altitude area, the altitude of their settlements is above 5000 meters after entering HA area.

Patient’ s basic diagnostic information

The timing of their migration varies, with symptoms appearing in as few as 8 days and up to 210 days. 6 of 7 patients were initially diagnosed with pulmonary inflammation and 4/7 with HAPE by CT or X-ray, and empirical treated with antibiotic drugs, dehydrant, oxygen supply and other symptomatic support therapy (SST). The

further examinations were performed due to poor therapeutic effect. Finally, PTE was definitely diagnosed by CTPA. Only one patient sought medical attention due to lower extremity pain and was diagnosed as DVT of lower extremity by color Doppler Ultrasonography. The existence of PTE was confirmed by further examination. Notably, in addition to PTE in patient 2, cerebral venous sinus thrombosis (CVST) and right ventricular thrombosis were also clearly diagnosed. In patient No. 3, the time from symptom onset to definite diagnosis was so long that the effective treatment was relatively delayed, leading to aggravation of the disease and subsequent failure of respiratory and circulatory system. Furthermore, thrombosis in the right renal vein system was also present in patient No. 7, which resulted in severe acute kidney injury. Subsequent follow-up revealed marked atrophy of the right kidney and a significant decrease in the glomerular filtration rate.

Clear history of catching cold prior to the onset of symptoms and developed pneumonia displayed in six patients, and four of them developed HAPE (Table 2). Smoking and alcohol consumption were present in the minority of them, but weight lost occurs in majority patients, and the weight lost was positively correlated with residence time in HA.

Patient's clinical features and clinical examination profiles

Abnormal manifestations in respiratory tract were the main symptoms, especially respiratory infection-related symptoms (Table 3). Majority of them with cough, expectoration, chest tightness, shortness of breath as the primary performance. In the course of exacerbation, chest pain, cough pink bubbling sputum appeared in a small proportion of the population. Two of the three patients with definite diagnosis of DVT presented with lower extremity pain, and only one had DVT related symptoms as the first manifestation. Similarly, abnormal signs of the respiratory system, including tachypnea and abnormal breath sounds, were observed in most patients. Others, such as tachycardia, cyanosis, engorgement of the neck vein, and percussion tenderness over kidney region were present in faction.

As mentioned before, majority had pre-infection history, so the first blood routine examination suggested that 5 of them had increased white blood cell and neutrophil counts (Table 4). This result mentioned that infection may plays an important role in the pathogenesis of PTE. With the increase of residence time at HA, hemoglobin and hematocrit also presents an upward trend, but whether there is a correlation with PTE remains to be determined. Abnormalities in coagulation function were observed in all patients, with a definite increase in D-dimer and changes in fibrinogen (FIB) and thrombin time (TT). Imaging results showed that all patients had pulmonary artery branch thrombosis, and 3 patients with pulmonary trunk thrombosis. Renal vein, right ventricle and superior sagittal sinus thrombosis were reported in 1 case, respectively (Table 5).

Treatment and prognosis of all patients

Because of the different classification conditions of medical institutions, each patient goes through the process from the local health center to the medical station and then to the hospital. Anticoagulant therapy is applied to every patient after diagnosis, including oral and anticoagulant subcutaneous injection anticoagulant (Table 6). Two patients were given inferior vena cava filter implantation after consultation with multidisciplinary doctors due to their medical conditions. Because of compliance with the surgical guidelines, patient No. 3 underwent thrombectomy and pulmonary artery catheter directed thrombolysis therapy under general anesthesia. However, the patient experienced progressive deterioration of the respiratory and circulatory system, he had to use

extracorporeal membrane oxygenation (ECMO) for life support, but the final outcome is regrettable. Except for patient No. 3, other patients improved gradually after comprehensive treatment and followed up regularly.

Discussion

Previous studies have reported that HA may be the risk factor for PTE [7, 10], but the strong evidence studies still lack to confirm this view. Some studies have indeed indicated that the viscosity of blood will increase at high altitude. However, there is no clear definition of plateau-related blood hypercoagulability. Chohan et al. mentioned an immediate increase of factor X, XII, platelet count, impairment of clot retraction and shortening on prothrombin time [11]. Stimulation of HA environment reduced the plasma fibrinogen hemolysis time and resulted in a compensatory increased for fibrinolytic activity [12]. When individual stay in HA area, the plasma fibrin activity increases, which leads to a persistent hypercoagulable state, and reaches a peak over 5 months then continues until the patient stays in HA [13]. Furthermore, adaptive changes generated when long-term migration to HA can result in gradual increase of red blood cells, and high altitude polycythemia (HAPC) was induced under the uncontrolled compensatory mechanism [14]. Previous studies revealed that the aggregation of red blood cells significantly when hemoglobin concentration increases to 220–250 g/L, causing the separation of red blood cells from plasma and changes in hemodynamics [15]. Eventually, the blood cells accumulate in blood vessels and even stagnate, leading to thrombosis. People with HAPC have a 1.5–2.4 times greater risk of VTE than that in general population [16].

7 patients with PTE who developed at extreme HA were enrolled in this study, the incidence of this population which less than 10,000 residents in the surrounding of the medical station is high only during in seven months. The average age is lower than previous report in HA area and plain [7, 8], after all advanced age is a unambiguous risk factor for PTE [1]. These basic clinical data indicated PTE in HA showed a unusual epidemiology. Anand et al. summarized a 30 times higher risk of vascular thrombosis for long term stay (mean 10.2 months) in HA area when compered with non-HA, the odds ratios of pulmonary thromboembolism was 65.91 (95% CI: 7.95-1453.48) [7]. For this point, some researches advocated that HAPC may dominant the formation of VTE and PTE in HA long stay individuals [16]. Our data showed patients had been high altitude for a time ranging from 8-210 days (mean 96.3 days), only one patients attain to the criteria of HAPC (HGB $\geq$ 21 g/dL for male) [17]. So early stage enter into HA also obtain the risk for PTE.

D-dimer is an important indicator for the diagnosis of patients with VTE, and its increase has important significance for the differential diagnosis of symptomatic PTE patients. Le Roux et al. measured D-dimer increased significantly at 6542m after 1 week (with a mean value of 700 ng/mL) and 3 weeks (900 ng/mL) compared with at sea level (300 ng/mL) in 7 climbers on the summit of Nevado Sajama in Bolivia [18]. Analogously, Pichler Hefti et al. found D-dimer levels increased with increasing altitude on Muztagh Ata in China, 34 climbers with a median of 620 ng/mL D-dimer at 4497 m and increasing to 810 ng/mL at 6865 m (reference range < 500 ng/mL) [19]. The non-pathological increase of D-dimer in the plateau area seems to be a consensus, and it has also been reported that there is no positive (< 800 ng/mL) increase of D-dimer in the asymptomatic population [20]. This is not inconsistent with our study. Our data showed that serum D-dimer levels in patients with PTE at high altitude were all higher than normal (referring to the cut off in the plain area), although the definition of D-dimer range was different in the respective studies. This suggests that D-dimer, as an important differential index for PTE diagnosis, still has diagnostic efficacy in the plateau region.

A transcriptomic and proteomic analysis of platelets mentioned that HA was associated with up-regulation of proteins with thrombosis and platelet activation form HA-residing without thrombosis subjects when compared with low altitude residing subjects [21]. Moreover, a novel genome wide expression analysis performed by Jha et al. showed a genes associated with the coagulation cascade and platelets activation were up-regulation significantly in the patients with DVT at HA [5]. The activation of platelets may induce the generation of thrombosis was encouraged in these studies, but the platelet counts in our research were in the normal level. More parameters about platelets activation need us to detect in the further study .

Activation of inflammatory signaling pathway is involved in the formation of venous thrombosis by promoting the activation and aggregation of platelets and endothelial cells, as well as increasing the expression of tissue factors (TFs) [22]. Neha et al. demonstrated that activation of inflammasome in hypoxia condition promotes venous thrombosis via ligating the inferior veins in rats [23]. They revealed that HIF-1α induced by hypoxia stimulation can increase nucleotide binding oligomerization domain like receptors 3 (NLRP3) expression and promote the assembly of NLPR3 and pro-caspase 1 protein complexes. Subsequently, pro-caspase1 is self-splicing into an activated form, further promoting the transformation of pro-IL-1β to IL-1β and release into extracellular cells, ultimately mediate the formation of thrombus. Notable, NLRP3 promoted thrombosis in this study is in the non-inflammatory state of hypoxia, while NLPR3 expression did not increase in the pure hypoxia state without thrombosis. Therefore, NLRP3 mediated thrombosis is more about the differential expression after thrombosis, whether the pre-inflammatory state can mediate the expression of NLPR3 and promote thrombosis is not clear. Of interest, 6 of 7 patients had a prodromal infection history and were initially diagnosed with pulmonary inflammation in this prospective research. From this, we can speculate that the pre-inflammatory state may promote venous thrombosis under hypoxic conditions. It will bring new breakthrough point and direction for further research in the future. By identifying the key targets of inflammatory pathway mediated thrombosis under hypoxia conditions, then search for targeted prevention and treatment drugs.

It has been recognized that advanced age is an acquired factor for VTE, the risk for people suffering from VTE increases dramatically with after the age of 40 years[1]. In this study, 7 patients were all young adults, with an average age of 24 ± 3.6 years. This is a unexpected result, which makes it necessary to pay more attention to the disease in stripling at highland, and even to reduce misdiagnosis. There are also some limitations in this paper. Firstly, the number of cases is small, we need more cases to confirm the perspective in future. Secondly, the lack of detection of patients with genetic predisposing factors of PTE, such as protien S/C, antithrombin, plasminogen deficiency, and variations in related genes[24, 25], so that we can't distinguish the interference of endogenous factors.

Conclusions

Prodromal infection and high altitude pulmonary edema may be the potential risk factors for the development of PTE. The younger age of the affected population suggests that more attention should be paid to young individuals in the plateau region. The data show that D-dimer is still an important predictor of PTE diagnosis in plateau region, and more vigilant identification of similar symptoms of altitude sickness is also needed.

Abbreviations

PTE: pulmonary thromboembolism; VTE: venous thromboembolic; PE: pulmonary embolism; DVT: deep venous thrombosis; CTPA: computed tomography pulmonary angigraphy; HAPE: high altitude pulmonary edema; HA: high altitude; CT: computed tomography; CVST: cerebral venous sinus thrombosis; FIB: fibrinogen; TT: thrombin time; ECMO: extracorporeal membrane oxygenation

Declarations

Ethics approval and consent to participate

The protocol of this study was approved by the Committee for Ethical Affairs of the General Hospital of Xinjiang Military Command, Urumqi, China.

Consent for publication

Not applicable

Availability of data and materials

The datasets used during the current study are available from the corresponding author upon reasonable request.

Competing interests

No competing financial interests exist.

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Authors' Contributions

J.W., G.W. conceived the project, J.W., X.H., H.K., L.W., K.W., J.Z., J.T., W.Y. collected the data, J.W., X.H. wrote the paper with P.J, J.W., X.H. analysed the data.

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Tables

Table 1. Basic diagnostic information of patients

No.	Age (yrs)	Sex	Max altitude (m)	Time at HA (days)	Initial diagnosis	Final diagnosis
1	26	Male	5300	210	DVT of DLL	PTE, DVT of DLL
2	21	Male	5000	30	HAPE, PI	PTE, HAPE, PI, DVT of DLL, CVST, RVT
3	31	Male	5500	183	HAPE, PI	PTE, HAPE, HAPH, PI, ARF, AHF, DVT of BIV, SH
4	20	Male	5000	8	PI	PTE, HAPE, PI
5	26	Male	5300	61	HAPE, PI	PTE, HAPE, PI
6	25	Male	5300	60	PI	PTE, PI, DVT of IVC and DLL
7	23	Male	5000	122	PI	PTE, PI, TRRV, AKI

HAPE: high altitude pulmonary edema; DLL: double lower limbs; DVT: deep vein thrombosis; CVST: cerebral venous sinus thrombosis; RVT: right ventricle thrombosis; HAPH: high altitude pulmonary hypertension; PI: pulmonary inflammation; ARF: acute respiratory failure; AHF: acute heart failure; BIV: bilateral iliac vein; SH: subarachnoid hemorrhage; IVC: inferior vena cava; TRRV: thrombosis of the right renal vein; AKI: acute kidney injury.

Table 2. Basic characteristics of the patients

Variable	Mean or proportion
Age (yr)	24±3.6
Time at HA (days)	99.29±77.31
Altitude (m)	5200±200
Combined with HAPE	4/7
Combined with PI	6/7
Prodromal infection history	6/7
Smoking	2/7
Alcohol consumption	3/7
Total time stay at HA	96.3±77.3
Weight lose	5/7
HA exposure history	3/7
Family history of thrombotic disease	1/7

HA: high altitude; HAPE: high altitude pulmonary edema; PI: pulmonary inflammation.

Table 3. The detail of clinical features of patients

Variable	Number (n=7)	Percentage
Symptoms		
Cough and expectoration	5	71.4%
Fever	4	57.1%
Chest tightness	5	71.4%
Short of breath	5	71.4%
Chest pain	4	57.1%
Nausea and vomiting	2	28.6%
Extremity pain	2	28.6%
Pink frothy sputum	2	28.6%
Headache	2	28.6%
Waist pain	1	14.3%
Dyspnea	1	14.3%
Signs		
Tachycardia	3	42.9%
Cyanosis	3	42.9%
Tachypnea	4	57.1%
Engorgement of the neck veins	2	28.6%
Abnormal respiratory sounds	5	71.4%
Percussion tenderness over kidney region	1	14.3%

Table 4. Biochemical and coagulation profile of patients

No.	D-dimer (0-0.5mg/L)	FIB (2-4g/L)	TT （14-21sec）	WBC (3.97-9.15×10^9/L)	Neut. count (2-7×10^9/L)	Neut. % (50-70%)	Platelet count (85-303×10^9/L)	HGB (131-160g/L)	HCT (38-50.8%)
1	0.77	2.31	20.7	6.47	3.25	50.2	151	222	66.5
2	1.52	4.19	21	15.09	12.97	85.8	159	169	53.6
3	12.82	4.16	25	18.1	16.1	89.3	243	192	61
4	0.75	3.16	19.1	14.44	12.78	88.5	192	164	51.1
5	4.9	4.2	22.3	12.57	8.47	67.3	213	155	52
6	7.92	5.12	21.6	8.66	5.76	66.5	302	161	51.8
7	5.2	4.41	23	11.2	8.2	73	346	154	49

FIB: fibrinogen; TT: thrombin time; WBC:white blood cell; Neut: neutrophil; HGB: hemoglobin; HCT: hematocrit.

Table 5. Anatomical site of thrombosis, abnormal results of electrocardiogram and ultrasonography examination in patients with PTE

Variable	Number (Total No=7)
Location of thrombus	
Pulmonary trunk	3
Pulmonary artery branches	7
Lower extremity	3
Inferior vena cava	1
Renal vein	1
Iliac vein	1
Superior sagittal sinus	1
Right ventricle	1
Cerebral hemorrhage	1
Electrocardiogram	
Starboard electrical axis	3
T wave inversion	1
Cardiac color Doppler Ultrasonography	
Pericardial effusion	2
Right heart enlargement	2
Pulmonary hypertension	1

Table 6. Treatment program and prognosis of PTE patients

No.	Treatment program	Prognosis
1	Anticoagulant (Warfarin + LMWH) + SST	Improvement
2	Anticoagulant (Warfarin + LMWH) + Antibiotic (Vancomycin + CAZ) + GPT (MP) + DT (Mannitol) + SST	Improvement
3	IVCFI+PACDTT + Antibiotic (IPM) + Thrombectomy + Anticoagulant (LMWH) + GPT (MP) + AT (FAZ) + ECMO + DT (Furosemide) + Aminophylline + SST	Death
4	Anticoagulant (Warfarin + LMWH) + Antibiotic (AZM) + HBOT + Aminophylline + SST	Improvement
5	Anticoagulant (Warfarin) + Antibiotic (CRO) + Aminophylline + SST	Improvement
6	Anticoagulant (LMWH) + Antibiotic (LVFX) + IVCFI + Aminophylline + SST	Improvement
7	Anticoagulant (LMWH + Rivaroxaban) + Antibiotic + SST	Improvement

LMWH: low molecular weight heparin; CAZ: ceftazidime; GPT: Glucocortieoid pulse therapy; MP: methylprednisolone; DT: dehydration therapy; IVCFI: inferior vena cava filter implantation; PACDTT: pulmonary artery catheter directed thrombolysis therapy; IPM: imipenem; AT: antifungal therapy; FAZ: fluconazole; ECMO: extracorporeal membrane oxygenation; DT: diuretic therapy; HBOT: hyperbaric oxygen therapy; AZM: azithromycin; CRO: ceftriaxone; LVFX: levofloxacin; SST: symptomatic support therapy (Including oxygen therapy, gastric mucosa protection, anti-asthmatic, cough suppressant and expectorant, maintaining water, electrolyte acid-base balance and other conventional treatment).