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Case Report

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AU1 ▶

Pulmonary Embolism Masquerading as High Altitude Pulmonary Edema at High Altitude

AU1 No change

AU2 ▶

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AU2 No change

Abstract

Pandey, Prativa, Benu Lohani, and Holly Murphy. Pulmonary embolism masquerading as high altitude pulmonary edema at high altitude. *High Alt Med Biol.* 16:000–000, 2016.—Pulmonary embolism (PE) at high altitude is a rare entity that masquerades as or presents in conjunction with high altitude pulmonary edema (HAPE) complicating the diagnosis and management. When HAPE cases do not improve rapidly with descent, other diagnoses, including PE, are considered. From 2013 to 2015, we identified eight cases of PE among 303 patients with initial diagnosis of HAPE. Upon further evaluation, five had deep vein thrombosis. One woman had a contraceptive ring and seven patients had no known thrombotic risk. PE can coexist with or mimic HAPE and should be considered in patients presenting with shortness of breath from high altitude regardless of thrombotic risk.

Keywords: extreme altitude; high altitude pulmonary edema; pulmonary embolism; thrombosis

AU4 ▶

Introduction

ACUTE MOUNTAIN SICKNESS (AMS), high altitude cerebral edema (HACE), and high altitude pulmonary edema (HAPE) occur with frequency of 40%–50%, 1%–2%, and 0.2%–6% at altitudes greater than 4000 m (Hackett et al., 1976; Maggiorini, 2010). Pulmonary embolism (PE) at high altitude is a rare occurrence that is described only in case reports in the high altitude medicine literature (Nakagawa et al., 1993; Shlim and Papenfus, 1995; Ashraf et al., 2006). While AMS, HAPE, and HACE resolve with the oxygen-rich environment of lower altitudes following descent (Hackett and Roach, 2001; Murdoch, 2004; Imray et al., 2010; Luks et al., 2014), PE diagnosis requires definitive treatment and, if missed, may result in death. Severe pulmonary arterial thrombosis and pulmonary infarcts were noted during autopsy in four of seven trekker deaths in the Himalayas (Dickinson et al., 1983) (the remaining three were noted to have cerebral edema; two with brain herniation). Before death, all patients had history and/or findings suggestive of severe altitude illness and PE was not suspected despite one patient being anticoagulated after diagnosis of deep vein thrombosis (DVT). Reported death among trekkers from presumed altitude illness in Nepal ranges from 3.6 (Shlim and Gallie, 1992) to 7.7 per 100,000 trekkers (Leshem et al., 2008). It is possible that PE was responsible for some of these deaths.

Approximately 100,000 foreigners trek in Nepal annually (Nepal Tourism statistics 2014). From 2013 to 2015, more than 1000 persons were seen at CIWEC clinic with altitude illness diagnosis, including 217 with HACE and 303 with HAPE. Among 303 persons diagnosed with HAPE at initial presentation, 8 tested positive for PE by computed tomography pulmonary angiography (CTPA) and an equal number (8) with suspect PE had negative CTPA; pneumonia was suspected in 22 patients coexisting with HAPE, whereas 3 persons were confirmed to have pneumonia as the primary diagnosis. We did not identify any patients in this cohort with congestive heart failure as the primary diagnosis although two persons with suspected HAPE had a final diagnosis of myocardial infarction based on ischemic changes on electrocardiogram (ECG) with positive troponin. Among all travelers seen at CIWEC during the same period (24,000 for 3 years), PE was diagnosed in three cases without altitude exposure.

We describe and discuss eight cases with PE diagnoses from altitude in this study. An evaluation of these cases may provide clues to PE diagnosis in the altitude traveler.

AU3 ▶

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AU3 No change

Case 1

A 64-year-old British traveler was helicopter evacuated from the Everest region with symptoms of dyspnea and cough in October 2013. She reported a relatively slow rate of ascent to Dingboche (4400 m) when she developed severe headache and nausea. She noted chest pain and dyspnea with SpO_2 73% on room air. She descended slowly by foot to Tengboche (3800 m) and then to Namche (3440 m) without symptom improvement. She noted fatigue and dyspnea on exertion (DOE) with a few steps. She denied any significant past medical history and was not taking any medication. Upon arrival to CIWEC, SpO_2 was 99% on room air although she remained dyspneic with respiratory rate (RR) of 26 breaths per minute. Lungs were clear to auscultation, and chest X-ray was negative for pathology. She was thought to have residual HAPE and was administered O_2. Echocardiogram showed mild mitral regurgitation (MR), mild tricuspid regurgitation (TR), and mild pulmonary artery hypertension (PAH) with no dilatation of right atrium (RA) or right ventricle (RV). In light of persistent dyspnea, 24 hours after admission, CTPA was done that documented thrombi in the right pulmonary artery and segmental branches of bilateral lower lobe pulmonary arteries (Fig. 1). Patchy consolidation was noted in the right middle lobe. Doppler studies showed normal deep venous system in both lower limbs. She was treated with oxygen and anticoagulation and discharged with a therapeutic INR.

F1 ▶

AU5 ▶

Case 2

A 62-year-old male climbing in the Manaslu region of Nepal in October 2013 developed pain and heaviness in the left calf 18 days into the trip at 6100 m. Four days later, he developed chest pains and shortness of breath (SOB) upon further ascent. He was evacuated by helicopter to CIWEC where mild improvement in respiratory symptoms was noted by patient. He had no significant past medical history and was not taking any medication. His SpO_2 on room air was 89%; lungs were clear and leg swelling was noted. ECG showed nonspecific changes in the inferior leads with normal troponin and creatinine kinase MB (CK-MB) isoenzyme. Polycythemia was noted with hematocrit at 54.8%; other laboratory studies were unremarkable. Doppler ultrasound confirmed DVT in the left popliteal and posterior tibial veins. CTPA revealed thrombus in superior and inferior segments of right main pulmonary artery and bilateral lower lobe arteries (Fig. 2). Cardiac ultrasound showed mitral valve prolapse, mild MR, and trivial TR. RV and RA were not dilated. There was no obvious thrombus visualized at the PA bifurcation. He was treated with oxygen and anticoagulation and discharged after 5 days.

◀ F2

Case 3

A 53-year-old American male was evacuated by helicopter from the Everest region in October 2013. He had history of hypertension, high cholesterol, and bilateral hip surgeries (2 and 6 years prior). He had a relatively slow ascent after a flight to Lukla (2800 m) and with appropriate acclimatization before trekking to Khumjung and the Kongde Ridge (4250 m). He noted severe hip pain and cold from a drafty room, thus sleeping on an electric mattress intermittently for 16 hours. By morning, he noted dizziness and a fall without known trauma with brief loss of consciousness and DOE. He received oxygen and oral hydration before evacuation to Kathmandu by helicopter. Upon arrival, he was diaphoretic, tachycardic, and hypotensive (pulse 120/min, blood pressure [BP] 90/80 mm Hg, and RR 24/min) with SpO_2 77% on room air and experienced symptomatic improvement with descent. Lungs were clear, and cardiac examination was normal. There was no leg swelling or tenderness.

AU5 international normalized ratio

Laboratory evaluation revealed leukocytosis, renal insufficiency, and hyponatremia (WBC count 17,800/mm^3, hematocrit 43.2%, BUN 20.4 mg/dL, serum creatinine 1.6 mg/dL, sodium 129 meq/L, potassium 3.4 meq/L, and glucose 186 mg/dL). Chest radiograph was unremarkable. ECG showed T wave inversions in leads III, v3–v5. Troponin and CK-MB were within normal limits. CTPA done on the same day confirmed thrombi in the right main pulmonary artery and segmental branches of left pulmonary artery (Fig. 3). He received oxygen 10 L by nonrebreather mask. Echocardiogram showed mildly dilated RV with mildly elevated PA pressures. Doppler revealed acute DVT in the left popliteal vein. He was treated with oxygen and anticoagulation and was discharged after 5 days.

◀ F3

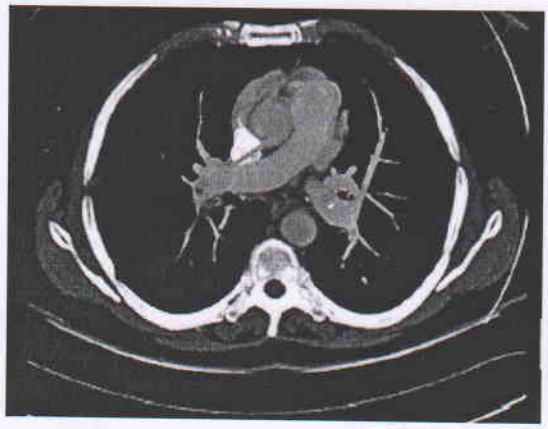

FIG. 1. Patient 1: Axial image of computed tomography (CT) pulmonary angiogram with filling defect in right pulmonary artery (*arrow*) indicating thrombus.

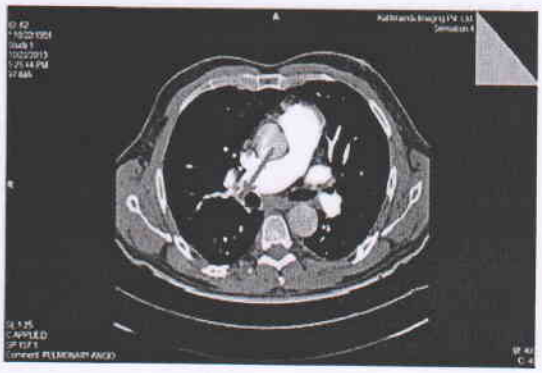

FIG. 2. Patient 2: Axial image of CT pulmonary angiogram showing thrombi as filling defects in distal right pulmonary artery (*arrow*) with extension into right lower lobe branches.

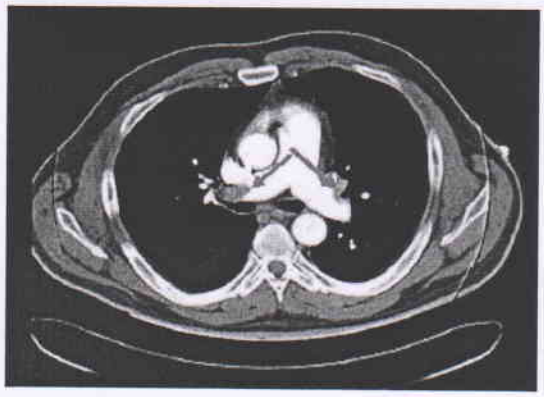

FIG. 3. Patient 3: Axial image of CT pulmonary angiogram showing thrombi as filling defects in right main pulmonary artery (*right arrow*) extending into its branch and in distal left pulmonary artery (*left arrow*) with extension into its superior branch.

Case 4

A 37-year-old German tourist presented in November 2013 with right leg pain for 3 days upon completion of a trek to the Everest region. She reported SOB and dry cough at 4900 m. She was evacuated by horse to 2800 m with subsequent helicopter evacuation to Kathmandu. She had a combined contraceptive vaginal ring (NuvaRing). She denied cigarette smoking. Presenting vital signs at CIWEC were unremarkable (temperature 37.5°C, pulse 97/min, BP 110/80 mm, and SpO_2 98% on room air) as were lung and cardiac examinations. Edema and tenderness were noted in the right calf. She reported a slightly larger right calf at baseline due to a congenital large vascular nevus. Doppler ultrasound demonstrated acute DVT extending along the mid one-third of the femoral vein proximally. ECG and echocardiogram were unremarkable. CTPA showed nonocclusive hypodense thrombus in left lower lobe pulmonary artery. She was treated with oxygen and anticoagulation, and contraceptive vaginal ring was removed.

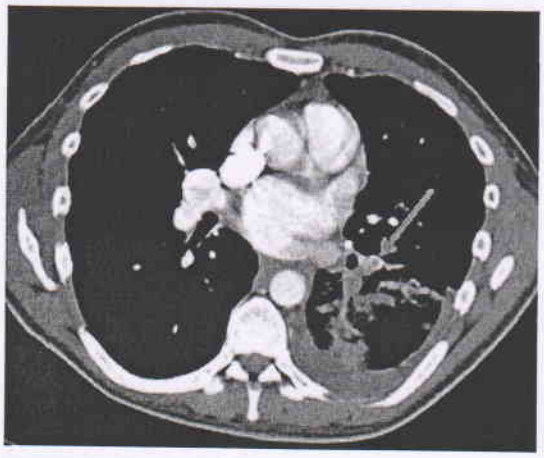

FIG. 4. Patient 6: Axial image of CT pulmonary angiogram showing thrombus as central hypodense focus with ring enhancement in lower branch of left pulmonary artery (*arrow*). Also seen in the image is consolidation of left lower lobe with pleural effusion.

AU11 ▶

Case 5

A 70-year-old American male was trekking in the Langtang region in April 2013, 4 days after arriving in Nepal. He reported fatigue, cough, and dyspnea 4 days into the trek. He was evacuated to Kathmandu by helicopter from Magin Goth (3285 m). On arrival, he was dyspneic with RR 30/min and SpO_2 70% on room air (afebrile, pulse 82/min, and BP 130/80 mm Hg). There were scattered crepitations in both lung bases. WBC count was within normal limit (echocardiogram showed mild TR, mild PAH, and mildly dilated RV). Chest X-ray showed nonhomogeneous opacities in the mid and lower zones of both lungs with PA enlargement interpreted as consistent with HAPE. He received oxygen, amoxicillin–clavulanic acid, and azithromycin. He remained dyspneic requiring oxygen for more than 24 hours. CTPA was done revealing thrombi in the segmental artery of right lower lobe. Doppler showed acute DVT involving the left popliteal vein. He was anticoagulated and discharged after 8 days.

Case 6

A 39-year-old traveler summited Everest and was evacuated from Camp 2 (6400 m) on Everest to Pheriche (4240 m) due to severe SOB. During descent from Camp 4 to Camp 2, he used supplemental oxygen and took nifedipine. He spent one night in Pheriche and was evacuated to Kathmandu on account of cough and left-sided pleuritic chest pain. On arrival, he was febrile (38.1°C) with pulse 82/min and BP 86/50 mm Hg with SpO_2 95% on room air. There were minimal crepitations in the lungs with good air entry. Cardiac examination was normal. There was no leg edema or calf tenderness. Leukocytosis and polycythemia were noted (WBC count 15,300/mm^3, Hct 52.6%). ECG revealed deep T wave inversions in V2–V3. Chest X-ray was unremarkable. Initial diagnosis was probable HAPE with possible pneumonia. He was treated with IV hydration and antibiotics. He developed worsening chest pain and mild hemoptysis within the first 24 hours of admission. CTPA showed hypodense nonocclusive thrombus in left lower lobe artery with an area of consolidation in left lower lobe along with air lucencies consistent with pulmonary infarction. He received anticoagulation and was discharged after 1 week.

AU11 (Fig. 4) ◀F4

Case 7

A previously healthy 71-year-old Austrian woman was evacuated from the Everest region from 4900 m on horseback to 4200 m due to severe respiratory distress and decreased responsiveness. Soon after arrival to the medical aid-post, she lost consciousness, lost pulses, and developed agonal breathing. She was treated with high flow oxygen, IV fluids, and dexamethasone with minimal improvement overnight, but remained somnolent with labored breathing at which point she was evacuated to Kathmandu. On arrival at CIWEC, she was conscious, but dyspneic with RR at 32/min, Pulse—100/min, Temp—37.9°C, and SpO_2 of 78%. Lungs were clear, and cardiac examination was normal. ECG showed T wave inversions in lead V1–V3. CXR was normal

and echocardiogram showed dilated RA/RV, mild TR, and mild PAH. CTPA confirmed thrombosis in the right and left pulmonary arteries and their inferior and superior branches. Doppler ultrasound of both legs showed normal deep venous system in both lower limbs with superficial acute thrombosis in muscular vein of the right calf. She was treated with anticoagulation, oxygen, and was discharged to home country.

Case 8

A 49-year-old German trekker was seen after helicopter evacuation from 4700 m 11 days into the trek. He developed SOB at altitude of 4100 m, but was able to continue and cross the Teri La pass in Mustang at 5600 m. He developed increasing SOB, fatigue, cough, and intermittent chest pain despite descent to 4700 m and was helicopter evacuated to Kathmandu. At CIWEC, he was tachypneic on arrival with other vital signs stable (RR was 28–30/min, SpO_2-96%, pulse 77/min, and temp of 37.1°C). There were bibasilar crepitations in the lungs, and cardiac examination was normal. ECG showed anterolateral T wave inversions and echocardiogram showed dilated RA and RV and trace TR with mild PAH. CTPA showed multiple thrombi in the subsegmental branches of right upper and both lower lobe pulmonary arteries. Doppler ultrasound of both lower extremities demonstrated acute thrombosis of muscular veins of left calf with extension into the deep venous system involving the posterior tibial veins. He improved with oxygen and anticoagulation.

Summary

We present eight cases with preliminary diagnosis of HAPE who did not improve with descent as expected and were diagnosed with PE. The average age of cases with PE was significantly older than that for HAPE in the same period: 58 years (range 37–71 years) versus 45 years (range 20–74 years). Seven of eight cases had been to altitudes >4000 m (Table 1). Six of eight patients developed symptoms after 10 or more days trekking at high altitude; one was an experienced mountaineer 45 days at altitude. Five of our PE cases were found to have DVT and one case had calf vein thrombosis on compression ultrasonography (Table 1). ◀T1

Discussion

While HAPE is a common problem at high altitude in Nepal with rates of 1%–6% reported in the Everest region alone (Hackett et al., 1976; Basnyat et al., 1999), PE has been uncommonly reported among trekkers and climbers to Nepal (Dickinson et al., 1983; Shlim and Papenfus, 1995). Despite the current knowledge of altitude and pulmonary disease and scattered case reports, there is no clear association between PE risk and altitude. There are some data suggesting an increased risk among individuals with underlying coagulopathy (Schreijer et al., 2006; Khalil and Saeed, 2010). There are larger retrospective studies suggesting that prolonged stay at altitude alone may be a risk for PE (Anand et al., 2001; Khalil and Saeed, 2010; Rathi et al., 2012), but these data do not conclude risks for shorter stays, for example, of the trekker/mountaineer. Considering the lack of clear association between altitude and PE and the prevalence of HAPE as a cause of respiratory distress from altitude, there is great difficulty in deciding which patients to evaluate for PE in this setting.

PE at altitude in our series is likely multifactorial—including modifiable and unanticipated factors—and may present in altitude travelers without prior risk factors. Despite the lack of evidence that short-term travel to altitude increases PE risk, there are aspects of altitude excursions that increase blood viscosity, for example, dehydration, hemo-

AU8 ▶ TABLE 1. TABLE SHOWING PATIENT DETAILS WITH MAXIMUM ALTITUDE REACHED, DAYS AT HIGH ALTITUDE, INITIAL DIAGNOSIS, TIME TO DIAGNOSIS OF PULMONARY EMBOLISM, FINDINGS ON COMPUTED TOMOGRAPHY PULMONARY ANGIOGRAPHY, AND DOPPLER ULTRASOUND OF LOWER EXTREMITIES

No.	*Age/sex*	*Preexisting*	*Max alt (m)*	*Days at high alt (days)*	*Initial diagnosis*	*Time to CTPA (hrs)*	*CTPA*	*Doppler U/S lower extremities*
1	64/F	None	4400 m	10	HACE, HAPE	24	Thrombus R PA branches	(–) DVT
AU9 ▶ 2	62/M	None	6100 m	20	? HAPE DVT LLE	22	Thrombus in R main PA	DVT L popliteal
3	53/M	HTN, both hips replaced	4250 m	10	R/O PE? HAPE	5	Thrombus R main, L, and R PA branches	DVT L popliteal
4	37/F	NuvaRing, vascular nevus	4900 m	14	? HAPE, R/O DVT? PE	26	Thrombus in LLL PA	DVT R Femoral
5	70/M	None	3285 m	5	HAPE	24	Thrombus in RLL segmental PA	DVT L popliteal
6	39/M	None	8848 m	45	Chest infection, resolving HAPE	24	Thrombus in LLL PA, LLL consolidation	Not done
7	71/F	None	4900 m	8	HAPE	8	Thrombus in R and L pulmonary arteries	Thrombus in muscular vein R calf
8	49/M	None	5600 m	11	HAPE	24	Thrombi in subsegmental branches of R upper and both lower lobes PA	DVT L popliteal

AU10 ▶ Alt, altitude; CTPA, computed tomography pulmonary angiography: DVT, deep vein thrombosis; F, female; HACE, high altitude cerebral edema; HAPE, high altitude pulmonary edema; M, male; Max, maximum; L, left; LLL, left lower lobe; PA, pulmonary artery; PE, pulmonary embolism; R, right; RLL, right lower lobe; R/O—

AU8 OK

AU9

② Remove? space between HAPE & DVT

③ Remove? R/O PE, HAPE

④ Remove? HAPE R/O DVT, R/O PE

AU10 rule out

concentration, and polycythemia, which are likely to increase PE risk. In our series, two patients were noted to have polycythemia. Although a prolonged journey before trekking poses an obvious risk, most of the patients presented in this study developed symptoms late in their trek suggesting that this was not a risk factor. Only one elderly traveler who developed respiratory symptoms at lower altitude (3200 m) had trekked within 7 days of an international flight, suggesting that time from flight may have been a risk in this case. Furthermore, we noted 3 × more PE cases from altitude than not in the last 3 years. The majority of these PE cases at altitude became ill above 4000 m, which may support prior work suggesting a role for increasing altitude in thrombosis (Gupta and Ashraf, 2012). Still, none of these factors distinguish PE from HAPE.

The average age of our PE cases was significantly higher than that for HAPE patients. The risk of phlebitis and PE has been shown to be higher for >age 60 versus younger travelers (Gautret et al., 2012). However, selecting patients for evaluation simply based on age would still result in missed PE diagnoses, considering three of eight patients in this series were <age 55. In this series, only one patient had a known thrombotic risk–a vaginal contraceptive ring, which has similar prothrombotic risk as combined oral contraceptives (Kolacki and Rocco, 2012; Nguyen and Jensen, 2014; Kenmuir et al., 2015; Paresi et al., 2015). Based on this and prior reports (Shlim and Papenfus, 1995; Schreijer et al., 2006; Khalil and Saeed, 2010), we conclude that any thrombotic risk factor should warrant a PE workup for hypoxia at altitude.

Initial clinical, laboratory, and radiographic presentation provided clues to PE diagnosis in the case of two patients with DVT symptoms (Cases 2 and 4) and for one patient (Case 3) who was hypotensive and hypoxemic on arrival with a negative cardiac workup and normal chest X-ray. Another five were persistently dyspneic after descent and, therefore, subjected to CTPA. Other data, including EKG, CXR, and echocardiogram findings, among these patients did not vary significantly from patients with "pure" HAPE. The clinical assessment tools, for example, the Wells criteria that take into account recent surgery, immobility, and presence of malignancy were not useful in identifying risk among these patients (Wells et al., 2000). We do not screen patients with HAPE with D-dimer testing despite the high sensitivity (Righini et al., 2014; Woller et al., 2014) due to the low specificity that can lead to unnecessary imaging studies that may also introduce further hazard to the hypoxic patient (Rathi et al., 2012; Bokobza et al., 2014). Furthermore, there is evidence that D-dimer levels increase with altitude (Pichler Hefti et al., 2010). We are not aware that we missed any cases of significant PE with this approach. We conclude that a thorough clinical evaluation remains our most sensitive diagnostic tool for PE in this setting.

Theoretically, systemic endothelial dysfunction, recently shown to occur in HAPE cases with finding of raised endothelin-1 levels (Droma et al., 1996; Charu et al., 2006; Barker et al., 2016), may also be confounded by PE. Efforts to identify rapid tests for HAPE will need to differentiate between these potentially overlapping and confounding diagnoses.

We conclude that PE, a diagnosis with significant mortality, may be missed among the traveler from altitude due to similar presentation with HAPE. Based on our experience, including the cases presented in this study, we propose CTPA when patients present from altitude with symptoms suggestive of HAPE who do not improve or get worse with descent within 24 hours, when there is DVT in addition, when symptoms develop during descent, and when significant chest pain is present and other etiologies like myocardial infarction are ruled out and for patients with any known or perceived thrombotic risk. Due to the high fatality of PE diagnosis and the overlap in clinical presentation with HAPE, a more aggressive approach to PE diagnosis is warranted among high altitude travelers with respiratory symptoms.

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Author Disclosure Statement

No competing financial interests exist.

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