PATHOLOGY OF HIGH ALTITUDE PULMONARY OEDEMA

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ABSTRACT

Objective: To describe autopsy findings in fatal cases of high altitude pulmonary oedema.

Study Design: Descriptive study.

Place and Duration of Study: The study was carried out between 1999 and 2002 at an army field medical unit in Baltistan, Armed Forces Institute of Pathology, Rawalpindi and Army Medical College, Rawalpindi, Pakistan.

Patients and Methods: Autopsies were performed in 17 fatal cases of High Altitude Pulmonary Edema (HAPE) occurring among soldiers serving in Siachen.

Results: All cases were males with a mean age of 26.8 years (19-35). The mean altitude at which HAPE occurred was 5192 meters (2895-6492), and the mean duration of stay at these altitudes was 15.3 days (1-30). Eleven individuals had undergone proper acclimatization. The commonest clinical findings were cough (70%), dyspnoea (53%), nausea (47%), headache (41%), vomiting (35%), chest pain (35%) and tightness in chest (24%). Cyanosis and frothy secretions in the nostrils and mouth were present in all but one case. Mean combined weight of lungs was 1470 grams (1070-1810). There was marked congestion of outer and cut surfaces. Interstitial oedema was present in all cases. RBCs and leukocyte infiltrates were seen in 13 and alveolar hyaline membranes in 9 cases. Thrombi were seen in 2 cases. Cerebral oedema was present in 9 cases.

Conclusion: HAPE can occur after more than two weeks of stay at high altitudes despite proper acclimatization. Concomitant cerebral oedema is frequently present. Our autopsy findings are consistent with what has been reported previously.

Keywords: Autopsy study, Cerebral oedema, High altitude pulmonary oedema.

INTRODUCTION

The effects of high altitude range from frost bite to acute mountain sickness and potentially fatal pulmonary and cerebral edema. They are a result of body's response to hypoxia and cold. High Altitude Pulmonary Edema (HAPE) is a severe and often fatal disease which develops in individuals exposed to high altitude above 2500 meters (8200 feet)[1]. High altitude is defined as 1500-3500 meters (5000-11,500 feet), very high altitude as 3500-5500 meters (11500-18000 feet), while extreme altitude is above 5500 meters (18000 feet)[2]. The symptoms typically develop 2 to 5 days after reaching high altitude. These include shortness of breath, which increases progressively, tightness and pain in chest, and cough. Cough is usually dry in the beginning and later becomes productive, often with frothy blood-stained sputum. These symptoms gradually increase in intensity and may be accompanied by progressive deterioration of consciousness, headache and vomiting[1-4].

Hypoxia at high altitude results in exaggerated pulmonary vasoconstriction and raised pulmonary artery and capillary pressure, leading to increased filtration of fluid and proteins into the alveoli. The raised hydrostatic pressure can also lead to disruption of alveolar microvasculature, which may trigger a secondary inflammatory response; further increasing capillary permeability[1,5,6]. The increased permeability of alveolar capillaries results in collection of protein-rich fluid in the alveoli. It is believed that pulmonary vasoconstriction in HAPE is uneven, causing varying blood flow in different parts of lungs[5]. This probably explains the patchy nature of oedema observed in cases of HAPE[4]. Although there are no definite predictors of a person's susceptibility to HAPE; factors such

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as altitude, rate of ascent, acclimatization and individual susceptibility can all have a direct relationship with its development[3,7].

Pakistan is home to the world's highest mountain ranges, with more than a hundred peaks over 7000 meters (23,000 feet). A large number of people, including the local population and mountaineers visiting these areas are at risk of high altitude illnesses. Of particular concern is the health of thousands of troops, who are serving in the Siachen area, where the average height of deployment is above 5500 meters (18000 feet). Exposure to such extreme altitudes over prolonged periods of time has resulted in serious morbidity and mortality among the troops; a significant number of them due to HAPE[8,9]. Despite this large disease burden, little has been published on autopsy findings in cases of HAPE. In this study, we present clinical and autopsy findings in seventeen fatal cases of HAPE.

PATIENTS AND METHODS

The study was carried out in an Army field medical unit in Baltistan, in collaboration with Armed Forces Institute of Pathology (AFIP), Rawalpindi, and the Department of Pathology, Army Medical College, Rawalpindi. The study included seventeen fatal cases of HAPE received over a period of three years. All of them were soldiers serving in the Siachen area. Available clinical details and personal data of the deceased were documented. Autopsies were carried out in the field hospital by a single pathologist, trained in autopsy procedures. All autopsy findings were carefully documented. Weights of all organs were recorded and compared with average weights in an adult male[10]. Gross examination of the organs was carried out and findings were recorded on hospital's autopsy form. Heart, brain and both lungs in toto, and representative sections from other organs were preserved in 10% formalin. The histopathological examination was carried out at AFIP by two consultant histopathologists and slides were reviewed independently by one of the authors at Army Medical College. Descriptive statistics were utilized to analyze data.

RESULTS

The study included 17 fatal cases of HAPE. All were young males with a mean age of 26.8 years (range 19 to 35). The mean altitude at which they developed HAPE was 5192 meters; range 2895 to 6492 (17000 feet; range 9500 to 21300). The mean duration of stay after which HAPE developed was 15.3 days (range 1 to 30). The mean time between onset of symptoms and death was 30 hours (range 1 to 120 hours). The status of acclimatization was known in 14 out of 17 cases. All patients except one either died at their posts or during evacuation.

Clinical Findings: The commonest clinical presentations were cough (70%), shortness of breath (53%), nausea (47%), headache (41%), vomiting (41%), chest pain (35%) and tightness in chest (24%). Other findings included haemoptysis, altered consciousness, vertigo, and in one case, high grade fever. Clinical findings are summarized in table-1.

Autopsy Findings: The most consistent findings on external examination, seen in all but one case, were cyanosis and presence of frothy secretions in the nostrils and mouth. For internal examination, standard 'Y' incision was made and all organs were removed individually for gross examination.

Respiratory System: Internal examination of the respiratory system showed froth-like secretions in trachea and main bronchi of 16 out of 17 cases. Mean weight of right lung was 765 grams (range 580 to 970 grams). Mean weight of left lung was 705 grams (range 490 to 840 grams). Combined mean weight of the lungs was 1482 grams (range 1070 to 1810), against an average weight of 1060 grams in an adult male. There was marked congestion of outer and cut surfaces and exudation of froth-like secretions from the cut surface in all cases. Thrombi were seen in medium-sized vessels in 2 cases. Histological examination of the representative sections revealed congestion and oedema in all cases.

Lung oedema manifested as interstitial oedema and presence of proteinaceous fluid in the alveoli (figure-1) and was seen in all cases. Extravasation of red blood cells (RBCs) and inflammatory cells in perivascular spaces and alveoli were seen in 11 cases, while in two cases, there was widespread haemorrhage with inflammatory infiltration. Hemosiderin laden macrophages were seen in 11 cases. Hyaline membrane formation, visualized as pink-staining thin membranes lining the alveoli, was present in 9 cases (figure-2). Foci of bronchopneumonia were seen in two cases and

Table-1: Clinical presentations in soldiers suffering from HAPE.

Parameter	Present study	Hayat13	ID Khan14	DA Khan20	Ahmed10
Number of cases	17	21	31	31	25
Mean age (years)	26.8	29.6	28.1	19-37	18-48
Mean altitude in meters (feet)	5192 (17000)	5695 (18700)	>5800 (19000)	>3000 (>10000)	4900-7000 (16000-23000)
Mean duration of stay at the altitude (days)	15.3	13.3	39	2-5	< 7
Acclimatized (%)	78	ND	100	ND	100
Concomitant HACE	9 (53%)	3 (14%)	Nil	Nil	7 (24%)
Cough (%)	70	>50	65	68	88
Dyspnoea (%)	53	>50	97	83	80
Nausea (%)	47	ND	19	ND	12
Vomiting (%)	41	ND	10	13	12
Headache (%)	41	ND	45	16	28
Chest pain (%)	35	ND	65	52	16
Haemoptysis (%)	12	ND	10	16	12
Altered consciousness (%)	12	ND	ND	ND	ND
Vertigo (%)	6	ND	16	ND	Nil
Fever (%)	6	ND	Nil	19	ND

HAPE = High altitude pulmonary edema, HACE = High altitude cerebral, ND = Not described

Table-2: Autopsy findings in cases of high altitude pulmonary edema.

Finding	Present study	Ahmed10	Hultgren24	Dickson25	Droma27
Number of cases	17	25	10	7	3
Mean age (years)	26.8	18-48	37	46	22.3
Combined mean weight of lungs (grams)	1482	1647	1682	ND	1164
Alveolar edema (%)	17 (100)	25 (100)	10 (100)	7 (100)	3 (100)
Vascular congestion	17 (100)	ND	ND	ND	3 (100)
Alveolar haemorrhage (%)	13 (76)	ND	6/9 (67)	ND	3 (100)
Hyaline membranes (%)	9 (53)	2 (8)	1/10 (10)	ND	3 (100)
Inflammatory infiltrate (%)	13 (76)	ND	6/7 (85)	ND	3 (100)
Broncho-pneumonia (%)	2 (12)	ND	7/8 (87)	6 (86)	Nil
Pulmonary infarction (%)	Nil	ND	1/10 (10)	3 (43)	Nil
Pulmonary thrombosis (%)	2 (12)	3 (12)	6/9 (67)	5 (71)	2 (67)
Cerebral edema (%)	9 (53)	7 (28)	5/8 (62)	5 (71)	1 (33)

ND = Not described

thrombus formation identified on gross examination was also visualized on histological sections.

Heart: Mean weight of the heart was 325 grams (range 280 to 405). Coronary atherosclerosis was present in 7 cases. No evidence of myocardial infarction or any valvular abnormality was seen in any case.

Brain: Mean weight of brain was 1555 grams (range 1250 to 1900), against an average weight of 1300 grams in an adult male. On gross examination, congestion was seen in 7 cases, whereas on histological examination, it was present in all cases. Brain oedema, characterized by blunting of sulci and compression of gyri, was evident on gross examination in 6 cases. On histological examination, oedema was seen in 9 cases. It was mild and focal in 8, and moderate to marked in one case. Extravasation of RBCs in brain parenchyma was seen in 3 cases.

DISCUSSION

All the deceased in our study were healthy and physically fit young males with no previous history of heart or lung disease. Eleven out of 14 cases, whose acclimatization status was known, had undergone proper acclimatization prior to their ascent. The altitude at which they developed HAPE was above 5000 meters (16400 feet), except for one individual, who developed it at 2895 meters (9500 feet). Although HAPE can occur at such low altitudes[3], it is usually seen at higher altitudes. One possible explanation for this could be the individual's susceptibility for HAPE at relatively lower altitudes[7]. The susceptible individuals have a low ventilatory response to hypoxia at exercise[11], while the endothelial lining of some people may also be predisposed to greater vasoconstriction[12].

The most unusual finding in our study was the prolonged duration of stay (15 days) at high altitudes after which these cases developed HAPE. It is generally accepted that HAPE develops within 2 to 5 days of arrival at high altitude[1-5]. However, studies done by army doctors in both Pakistan and India have reported HAPE in acclimatized individuals after much longer periods of stay (13 and 39 days respectively, table-1)[13,14]. Factors like strenuous exercise, infection, sleep medications or excessive salt intake have been implicated in development of HAPE in such cases[15-18]. However, these alone do not explain the development of HAPE in many acclimatized individuals with no history of these antecedents[14]. Foci of bronchopneumonia were seen on autopsy in two of our cases and one of them had history of high grade fever. While physical activity in operational area is a matter of routine, no specific history of strenuous exercise or drug intake was available in our patients. Six individuals were deployed at extreme altitudes of over 5500 meters (18000 feet). Exposure to extreme altitudes over prolonged periods is unique to the soldiers deployed in Siachen, and its effects on human physiology have not been properly studied. It has been suggested that at such extreme altitudes, physiological adaptations can fail despite proper acclimatization, and it is not possible to either predict or prevent development of HAPE[14,19].

Table-1 compares the clinical presentation seen in our series with other studies on HAPE among soldiers in Siachen[10,13,14,20]. Cough was the commonest presenting symptom (70% cases). It generally started as dry cough and with time became productive with frothy, often blood stained, sputum. The second commonest symptom was shortness of breath, seen in more than half the cases. These two symptoms, together or separately, are the most common and important presentations of HAPE[1,4,5,9,18]. They are caused by rapidly accumulating fluid in the lung alveoli. Initially, when the quantity of accumulated fluid is less, the symptoms are mild in intensity and the cough is dry. As the fluid accumulation progresses, the cough becomes productive[4]. Chest pain, tightness in the chest and haemoptysis are also due to pulmonary congestion and oedema. Chest pain and tightness may also be seen as a direct effect of hypoxia, while haemoptysis is attributed to alveolar haemorrhages due to rupture of capillary bed[1,21].

The clinical findings in our cases are consistent with what has been reported in the literature[1,3,9,19,18,20,22].

Other symptoms like nausea, vomiting, headache, altered consciousness and vertigo are usually associated with cerebral oedema[1]. On autopsy, we observed cerebral oedema in 9 (53%) cases. High Altitude Cerebral Oedema (HACE) is a common accompaniment of HAPE and can be seen on autopsy in up to 50% fatal cases of HAPE. Its pathogenesis is the same as that of HAPE[23]. Hultgren et al have described concomitant HACE in 14% of 150 non-fatal cases of HAPE from the United States[22], while Hayat et al have also reported a 14% frequency of HACE in 21 non-fatal cases of HAPE in Siachen[13]. The higher frequency of HACE in our series could be because these were all fatal cases and concomitant HACE is more common in advanced cases of HAPE[3,23]. This is supported by the findings of Ahmed et al, who reported a frequency of 24% in an autopsy study of 25 fatal cases of HAPE from Siachen[10], and Hultgren et al, who in a review of autopsy studies reported a frequency of 62%[24]. The gross and histological features of brain seen in our cases were due to cerebral oedema and are consistent with what has been reported by other authors[10,24-26].

Cyanosis and frothy secretions in the mouth and nostrils are common autopsy findings in cases of HAPE[24,25]. It was present in 16 out of 17 of our cases. Cyanosis is a manifestation of decreased arterial oxygen saturation. In HAPE, it is caused by the direct effect of hypoxia and is exacerbated by decreased oxygenation of blood due to lung oedema. Leakage of this oedema fluid in the respiratory passages appears as frothy secretions.

Gross and microscopic findings in the respiratory system in cases of HAPE are mostly attributable to congestion and oedema. As mentioned earlier, hypoxia at high altitude leads to pulmonary vasoconstriction with increased hydrostatic pressure in pulmonary capillaries leading to increased filtration of fluid and consequent oedema[5]. On gross examination, these manifest as excessive bogginess and increased weight of the lungs, congestion of outer and cut surfaces, and presence of frothy fluid in respiratory passages. Histologically, congestion and oedema of varying degrees are present universally[5,18,24]. All of these features were seen in all of our cases. However, in one case, the mean combined weight of the lungs was 1070 grams, which is only slightly higher than the average weight of 1060 grams[10]. He was a fully acclimatized 29 years old soldier with

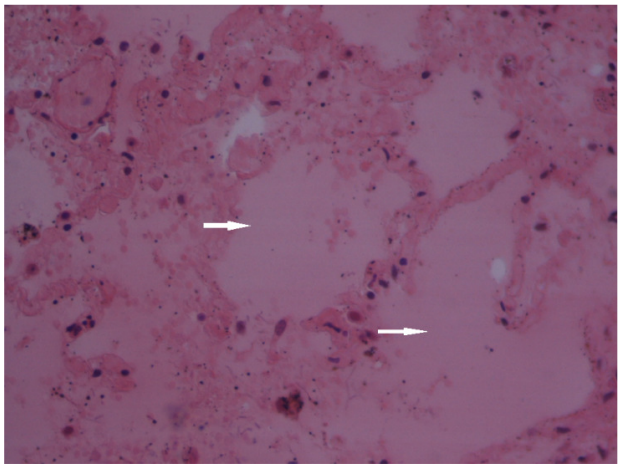

Figure 1: Histopathology of lung autopsy specimen showing proteinaceous edema fluid (arrows) in alveoli in cases of high altitude pulmonary oedema.

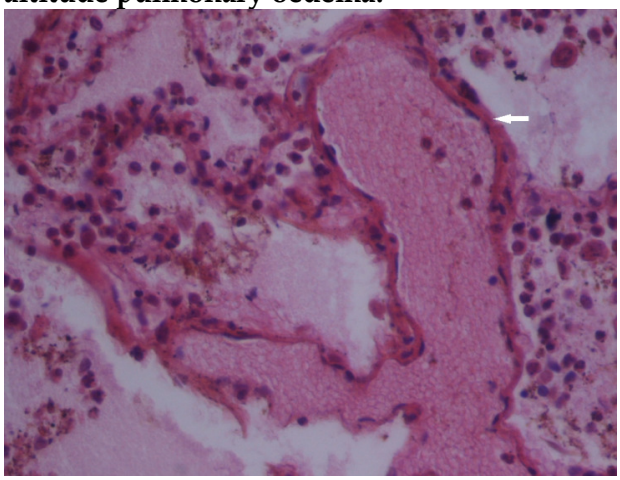

Figure 2: Histopathology of lung autopsy specimen showing hyaline membranes (arrow) lining the alveoli in cases of high altitude pulmonary oedema.

concomitant HACE, who had been deployed at a height of 6500 meters (21300 feet) for 5 days. He presented with disorientation and weakness in lower limbs but no respiratory symptoms. However, on chest examination, bilateral basal crepitations were heard. He died within 72 hours during evacuation. On autopsy, the weight of his brain was 1600 grams (average 1300 grams) with moderate blunting of gyri and compression of sulci. Microscopically, marked congestion of cerebrum along with oedema and foci of haemorrhages were seen. Lung oedema was mild. No thrombi were present. Heart was normal. The findings in this case were of well-developed HACE with early HAPE and it is possible that the cause of death in this case was HACE.

The fluid in alveoli is proteinaceous and stains pink with Haematoxylin & Eosin (H&E) stain[24,27]. Examination of this fluid has shown increased protein content[28]. The proteins in alveolar fluid are deposited on the alveolar walls and are evident on H&E stained sections on microscopy as hyaline membranes[24,28]. Pink-staining alveolar oedema fluid was seen in all of our cases, while alveolar hyaline membranes were seen in 9 (53%) cases. Extravasation of inflammatory and red blood cells was seen in a majority of our cases (65%). Inflammation in HAPE is considered to be a secondary phenomenon. It is believed that inflammatory cells leak into the oedema fluid because of disruption of the alveolar membrane due to increased hydrostatic pressure. Extravasation of RBCs and haemorrhages also occur due to alveolar damage[5]. Similar findings have been reported in other studies (Table-2)[10,24,25,27]. Hemosiderin laden macrophages were observed in the lungs of 11 (65%) cases. These have also been reported previously[21,25], and are usually seen 48 hours after the onset of alveolar haemorrhage[21].

Pulmonary thrombosis in cases of HAPE is a well-known, albeit an inconsistent finding[18]. It was observed in two of our cases. Although coagulation defects might play a role, the mechanism of thrombus formation at high altitudes is poorly understood. Singh and Chohan have reported an increased plasma fibrinogen level in Indian soldiers serving at high altitudes. Moreover, in soldiers who develop pulmonary hypertension at these altitudes, fibrinogen level decreases, presumably due to its conversion into fibrin. They have suggested that in cases of HAPE, the fibrinolytic system breaks down causing impairment of clot lysis. They also reported development of thrombotic occlusive vascular disease in these soldiers in the pulmonary, splenic, cerebral, coronary and mesenteric vasculature, after few weeks of arrival at high altitude[29]. No such widespread thrombosis was seen in our cases. Other authors however, have suggested that coagulation abnormalities in HAPE are pre-terminal phenomena in response to vascular injury rather than causative factors[18,24].

HAPE is a "non-cardiogenic" oedema, and heart is not involved in the pathogenesis of HAPE[5]. No cardiac abnormalities were observed in our cases. This is to be expected in a group of young soldiers, who had undergone repeated medical examinations prior to their induction to high altitude. Presence of atherosclerosis in the coronary arteries of 4 cases appears to be an incidental finding.

CONCLUSION

HAPE is a rapidly fatal disease that can occur after more than two weeks of stay at high altitudes despite proper acclimatization. Cough, dyspnoea, chest pain, headache and nausea are common clinical findings. On autopsy, severe interstitial oedema along with proteinaceous fluid in the alveoli is universally present. RBCs, leukocyte infiltrates and alveolar hyaline membranes are frequent histological findings, while concomitant cerebral oedema is frequently present.

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