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CASE REPORT

Pulmonary arteriovenous malformation causing sudden death due to spontaneous hemothorax

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Abstract A sudden death due to hemothorax caused by spontaneous rupture of a congenital pulmonary arteriovenous malformation (AVM) is reported. A 44-year-old woman died unexpectedly with chest pain and dyspnea. The post-mortem examination revealed a massive right-sided hemothorax arising from a subpleural AVM of the upper lobe. There were multiple telangiectases in the tongue and the tonsils, as typically associated with Osler–Weber–Rendu disease (hereditary hemorrhagic telangiectasia, HHT). The post-mortem molecular genetic analysis proved the presence of a disease-causing mutation in the endoglin gene constituting a predisposition for pulmonary AVMs. According to the literature, almost half of the AVMs in the lung are seen in HHT patients. Based on the presented case and the relevant literature, the article addresses the forensic aspects of fatal hemothorax and the importance of detecting the source of bleeding.

Keywords Hemothorax · Pulmonary arteriovenous malformation · Osler–Rendu–Weber disease · Telangiectasia · Sudden unexpected death

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Introduction

Hemothorax is caused by chest trauma [1], iatrogenic bleeding due to medical intervention with insertion of a central venous line [2], thoracentesis [3], pleural biopsy [4], catheterization [5], anti-coagulant treatment [6], spontaneous bleeding due to aortic dissection or aneurysm [7], malignancies [8], endometriosis [9], ruptured bleb in pulmonary emphysema, hematological disorders such as hemophilia [10], and pulmonary infarction [11]. In very rare instances, arteriovenous malfomations (AVMs) as seen in Osler–Weber–Rendu syndrome (hereditary hemorrhagic telangiectasia, HHT) may constitute the source of bleeding. A review of the international literature covering the past 30 years yielded 13 articles on "massive hemothorax" due to a rupture of pulmonary AVMs [12–24], but no report on a sudden death with medicolegal implications was found. The case presented in the following deals with an unexpected sudden death due to a hemothorax caused by the spontaneous rupture of a pulmonary AVM with post-mortem proof of HHT1 by genetic analysis.

Case report

Case history

A 44-year-old saleswoman (Caucasian) had gone to bed the evening before her death around 10:30 p.m. According to her husband, she had not suffered from any health problems up to then. Around 5:45 a.m., he woke up because of loud cries from his wife who complained of dyspnea and pain in the back. While he was calling the emergency doctor, his wife became unconscious. Resuscitation efforts were unsuccessful.

As the family doctor told the police, the deceased's father had been diagnosed with HHT. The daughter had occasionally experienced spontaneous nosebleeds, but no serious symptoms. Since the post-mortem examination did not provide clear hints as to the cause of death, the prosecutor ordered a forensic autopsy.

Autopsy findings

With a body weight of 88 kg and a height of 165 cm the body mass index was 32.3. Post-mortem lividity was conspicuously sparse. There were no skin telangiectases on the face, lips, and hands. External examination of the chest did not show any traumatic or iatrogenic findings. On internal inspection, no thoracic injuries were detected either.

Internal examination demonstrated a massive right-sided hemothorax containing about 2,200 ml of blood. The right half of the diaphragm was protruding towards the abdominal cavity. As the source of bleeding, a ruptured subpleural bleb (2 cm×3 cm) of the upper pulmonary lobe was ascertained (Fig. 1). Beneath the bleb, an AVM of 2 cm×2 cm in size was located with blood infiltrations; a branch of the right pulmonary artery was identified as the feeder vessel (Fig. 2). The right lung (220 g) was remarkably pale and almost bloodless. The left lung (240 g) did not show any abnormalities apart from moderate bronchitis. Under the surface of the tongue, the tonsils and the pharynx multiple telangiectases were seen. The lips and the hard palate were not affected. The liver, the central nervous system, and the digestive tract did not show any AVMs. The inner organs were very pale due to exsanguination. There was no gravidity.

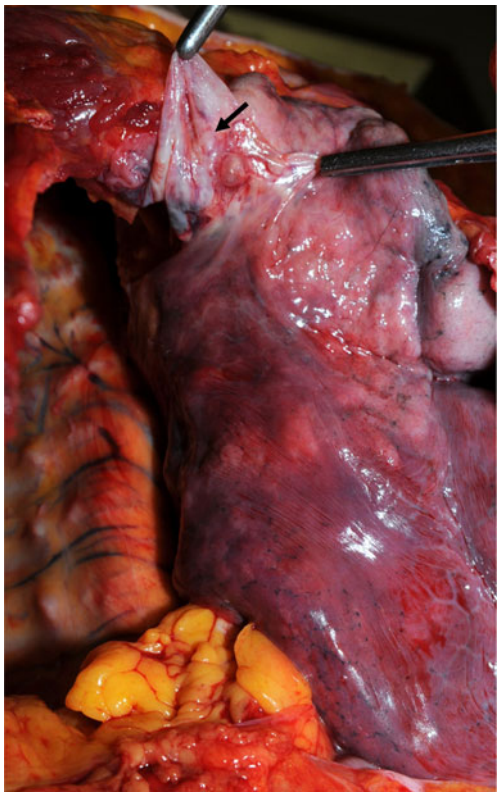

Fig. 1 Ruptured bleb of the right upper lobe (*arrow*)

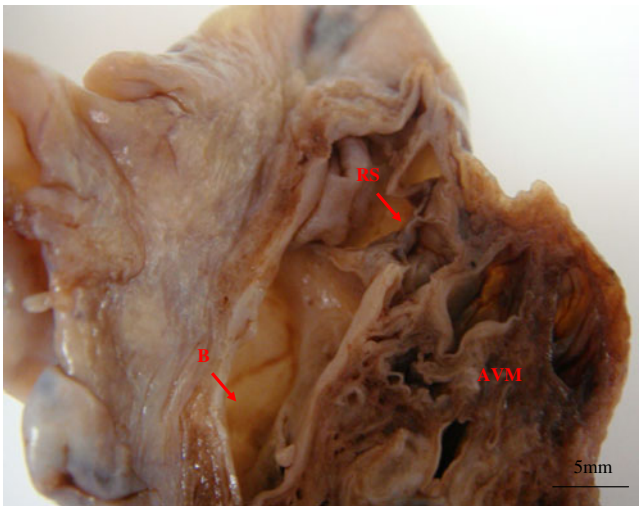

Fig. 2 Subpleural arteriovenous malformation (*AVM*) beneath a bleb (*B*) of the right upper lobe after formalin fixation. The *red arrow* shows the rupture site (*RS*)

Microscopic findings

Histological examination with hematoxylin and eosin staining showed that the pulmonary AVM consisted of ectatic blood vessels with variable wall thickness (Fig. 3). Elastica van Gieson staining revealed direct junctions of

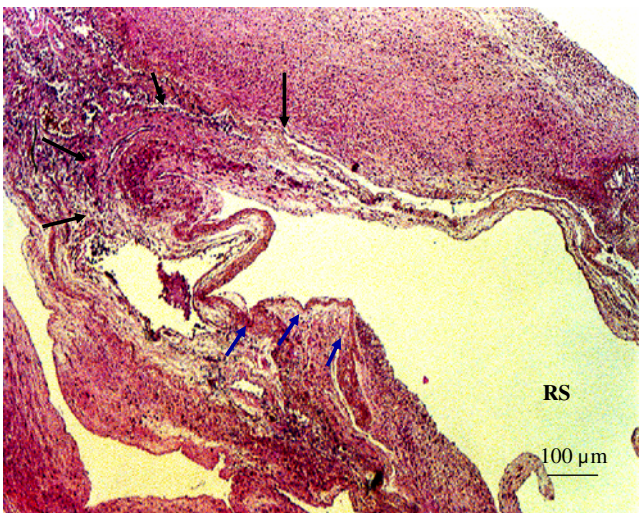

Fig. 3 Histology of the pulmonary arteriovenous malformation with a vessel transition from the arterial side (*black arrows*) to the venous side (*blue arrowheads*) H.E. staining, magnification×200. *RS* rupture site

arterial vessels (characterized by an internal elastic lamina) and venous branches without interposition of a capillary bed. There was no vascular necrosis within the AVM, but massive extravasation of blood associated with local detachment of the visceral pleura, especially in the area of the ruptured bleb. No malignancy, inflammatory disease, or other pathological changes were found in the lung tissue apart from the AVM. Histopathologic examination of the tongue and the tonsils demonstrated the presence of multiple thin-walled vessels immediately below the surface epithelium. Located deeper in the submucosa were numerous large dilated vessels surrounded by thickened muscular layers (Fig. 4). The histology of the other organs turned out to be normal.

Molecular analysis

In order to amplify exons 2–10 and 1–14 of the activin receptor-like kinase 1 (*ALK-1*; HHT2) and the endoglin gene (*ENG*; HHT1) previously published primers were used [25–28]. After performing the sequencing reaction (Big Dye Terminator V1.1 Cycle Sequencing Kit, Applied Biosystems, Darmstadt, Germany) with the same primers and purification with the Dye Ex 2.0 Spin kit (Qiagen, Hilden, Germany), the sequencing products were separated by means of capillary electrophoresis either on an ABI 3130xl or 3100 automated DNA sequencer (Applied Biosystems, Darmstadt, Germany). As a result, one mutation in exon 9A of the endoglin gene was found. In detail, a heterocygous deletion of an adenin was detected (c. 1195_1196 del A). This mutation results in a frame shift of the amino acid translation code and causes a premature stop codon at amino acid position 420 (p. Arg399fsX420). These findings were confirmed by cloning the polymerase chain reaction products with the TOPO TA Cloning Kit and subsequent sequencing of the clones (Fig. 5).

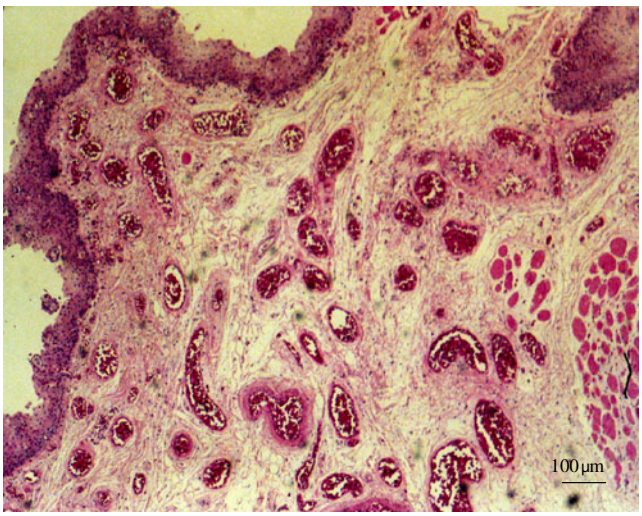

Fig. 4 Histology of the tongue showing vascular hyperplasia (H.E. staining, magnification ×100)

Toxicological findings

Using liquid chromatography tandem mass spectrometry (LC-MS/MS) in a multi-target-screening, no pharmaceuticals could be detected [29]. The blood was free from alcohol.

Discussion

In the present case, a hemothorax due to the spontaneous rupture of a subpleural AVM in the upper lobe of the right lung was determined as the cause of death. There was no traumatic or iatrogenic cause of the hemothorax. AVMs in the lung belong to the classical manifestations of HHT (Osler–Weber–Rendu disease) [30].

HHT is a well-known autosomal dominant hereditary disease characterized by heterogenous multisystemic dysplasia of the vascular tissue. The so-called Curaçao criteria are as follows: (1) spontaneous recurrent epistaxis, (2) multiple skin and mucosal telangiectases in typical locations (tongue, mouth/throat, lips, conjunctivae, ears, hands/fingers, and gastrointerstinal tract), (3) visceral AVMs (lung, liver, brain, and spine), and (4) family history (first-degree family member with HHT) [31].

HHT is a genetic disorder with both locus and allelic heterogeneity. Its overall incidence in North America is estimated at about 1:5,000. HHT1 is caused by mutations in the endoglin gene on chromosome 9 predisposing for pulmonary AVMs and early nosebleeds. In type 2 HHT, the activin receptor-like kinase 1 (*ALK-1*) gene on chromosome 12 is affected; these patients often develop liver disease [28]. Endoglin and *ALK 1* are receptors of transforming growth factor beta 1 (TGF-ß1). Defects in TGF-ß signaling are thought to adversely affect connective tissue and matrix production during angiogenesis.

Arteriovenous malformations may remain asymptomatic for a long time. Approximately 30-50% of people with HHT have AVMs in the lungs, which are at risk of rupture particularly during pregnancy and may lead to life-threatening bleeding (hemoptysis or hemothorax). Therefore, pulmonary AVMs can be regarded as “hidden time bombs”. Other serious problems may result from the impaired filter function due to the lack of intervening capillaries in arteriovenous malformations: if blood clots and clumps of bacteria pass into the venous vessels of the lung, there is a high risk of neurological complications such as stroke or brain abscess. These complications are mainly seen in patients with multiple and diffuse AVMs involving several segments or more than one lobe [32–34], whereas in our case, only a single and rather small lung segment was

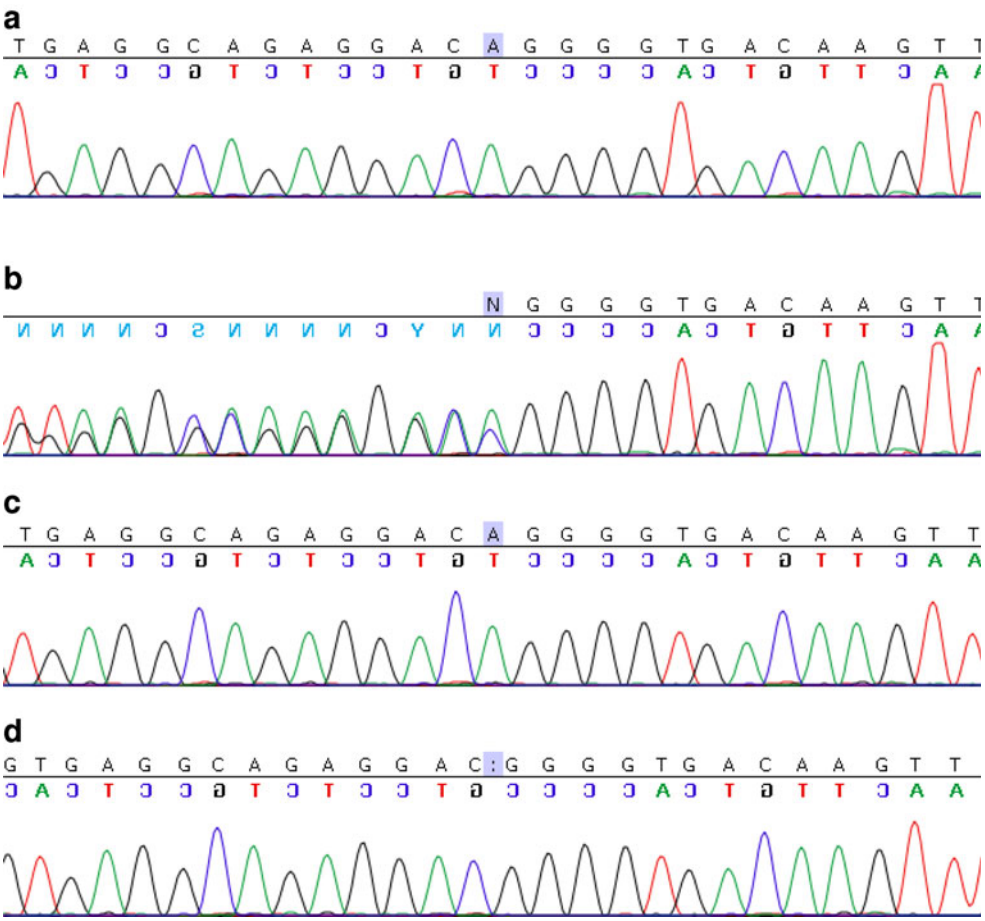

Fig. 5 In all electropherograms, the DNA sequence of exon ENG 9A is shown. Position c1195 is marked. **a** Wild-type DNA sequence with an adenin at position c1195. **b** DNA sequence of the deceased showing a heterocygous deletion of an adenin at c1195 resulting in a base shift. **c** and **d** DNA sequences of the deceased after cloning the ENG 9A exon PCR-product with the lower one showing the mutation

affected. For the above-mentioned reasons, screening for lung AVMs is recommended by HHT centers.

In our case, all diagnostic criteria of HHT (nosebleeds, telangiectases, visceral AVM, and family history) were present, and the sequencing analysis demonstrated that the causative mutation was in the endoglin gene (type 1 HHT) [35–37]. However, the deceased had never been screened for HHT during her lifetime. As far as the medical history could be clarified retrospectively, the family doctor was aware of the father's HHT but did not insist on appropriate diagnostic measures regarding the daughter, probably because there were only minor clinical symptoms (sporadic episodes of epistaxis).

The international literature contains 13 reports of "massive hemothorax" due to rupture of a pulmonary AVM during the past 30 years as shown in Table 1 [12–24]. In eight cases (five females and three males), the diagnosis of HHT had been established before death; three out of the eight females in our survey of the literature were pregnant [16, 17, 19]. In this respect, it was mentioned that pulmonary AVMs may become larger during pregnancy due to an increased cardiac output in combination with the relaxation of smooth muscle tissue [38]. Patient age at the time of the pleural hemorrhage ranged from 3 weeks to 71 years with a highest incidence in the fourth decade. This shows that the rupture may occur at any age and there is no evidence that vascular degeneration due to aging is of importance.

According to previous reports in the literature, the majority of ruptured pulmonary AVMs are located in the lower lobes of the lungs [15, 20, 21], whereas in the present case, the AVM was found in the right upper lobe just beneath the surface. As a consequence of this special site, the subpleural bleeding led to the formation of a bulla with secondary rupture of the visceral pleura and consecutive hemothorax. To the best of our knowledge, no similar finding has ever been described in the relevant literature concerning pulmonary AVM in HHT patients. Therefore, the superficial location may have contributed to the fatal hemothorax regardless of whether an upper or lower lobe was affected. For this reason, a subpleural localization of an AVM can be considered as a potential risk factor for spontaneous bleeding into the thoracic cavity.

The risk of bleeding does not depend on the size of the malformation either [14, 20, 24]. Two mechanisms have been suggested for the rupture of pulmonary AVMs: first, increased pulmonary arterial pressure (for instance in patients with congenital heart disease), and second, ischemic

Table 1 Review of the international medical literature (1975–2008): cases of massive hemothorax due to a ruptured pulmonary arteriovenous malformation

Case	Age (y)/sex	Symptoms	Amount of hemothorax	Rupture site	Size of AVM	Other findings	Treatment	Osler–Weber–Rendu disease	Year of publication, authors
1	71/F	Chest pain	Unknown	Right lower lobe	2 cm×2 cm×1.5 cm	Bronchogenic carcinoma	Lobectomy (middle and lower lobe)	−	1975 Spear BS [12]
2	37/M	Dyspnea Cough Chest pain	1,950 ml	Left lung (details unknown)	Small size (details unknown)	Telangiectases (lip, tongue, palate)	Application of ethinyloestradiol, methyltestosterone	+	1983 Karnik AM [13]
3	53/M	Anemia Chest pain	600 ml	Left lung (details unknown)	1 cm×1 cm	−	Pulmonary embolization	+	1985 Shashy SS [14]
4	0 (3 weeks)/F	Dyspnea	Unknown	Left lower lobe	Multiple (details unknown)	−	Lobectomy (lower lobe)	−	1989 Milović I [15]
5	27/F	Chest pain	Unknown	Right lower lobe	Unknown	Pregnancy (24 weeks)	Coil spring embolotherapy	+	1990 Gammon RB [16]
6	37/F	Dyspnea Cough Chest pain	Unknown	Right lower lobe	Unknown	Pregnancy (29 weeks)	Lobectomy (lower lobe)	−	1992 Laroche CM [17]
7	21/M	Chest pain	1,200 ml	Right lower lobe	Big size (details unknown)	Telangiectases (lip, tongue)	Segmentectomy	+	1993 Iwabuchi S [18]
8	24/F	Dyspnea	300 ml	Left lower lobe	Big size (details unknown)	Pregnancy (27 weeks)	Clamp and lobectomy	+	1995 Freixinet J [19]
9	46/F	Nose bleed	1,400 ml+ 790 g clots	Left lower lobe	4 cm×4 cm×3 cm	Biventricular cardiac hypertrophy	−	+	1996 Adegboyage PA [20]
10	35/F	Chest pain	2,000 ml	Left lower lobe	Unknown	Telangiectases (lip)	Video assisted thoracoscopic procedure	+	2003 Litzler PY 21)
11	56/M	Chest pain Profuse perspiration	750 ml	Right middle lobe	Unknown	−	Transcatheter closure	−	2008 Bandyopadhyay SK [22]
12	51/F	Chest pain	Unknown	Left lung (details unknown)	3.5 cm×3 cm×3 cm (right middle lobe) 3.5 cm×2 cm×2 cm (left lower lobe) 3 cm×2 cm×2 cm (left lower lobe)	Telangiectases (around mouth and lip)	Coil spring embolotherapy	+	2008 Elmali M [23]
13	46/M	Dyspnea	Unknown	Left lung (details unknown)	Unknown	Renal disease arteriovenous fistula (left arm)	Ligation	−	2008 Salim S [24]
14	51/F	Dyspnea	2,000 ml	Right upper lobe	2 cm×2 cm×2 cm	Telangiectases (tongue)	−	+	2009 Ishikawa T

necrosis of the vascular wall in AVMs [39]. In the present case, there were no signs of vascular necrosis and no evidence of pulmonary hypertension. Therefore, the most probable explanation seems to be the general vulnerability of the arteriovenous junctions [22, 40], which are known to be susceptible to hemodynamic stress [41] resulting in an increased tendency towards spontaneous rupture even without an external trigger. This is consistent with the fact that, in our case, death occurred suddenly and unexpectedly.

Symptoms from AVMs may develop at any age, mainly caused by shunting, thrombosis, and embolization. The characteristic clinical manifestation of multiple and/or extensive pulmonary AVMs is respiratory failure with cyanosis, exercise intolerance, polycythemia, extracardiac bruits, paradoxical embolism, and clubbing [42, 43]. In such cases, imaging is mandatory. Although various screening tests are available for pulmonary AVMs, the literature does not specify which screening protocol is the optimal one. In clinical practice, computed tomography (CT), magnetic resonance imaging (MRI), and echocardiography are successfully used for detecting pulmonary AVMs. The diagnostic sensitivity of chest CT and MRI has been demonstrated to be higher than that of pulmonary angiography; chest CT and MRI may reveal small or thrombosed pulmonary AVMs missed by pulmonary angiography. Echocardiography is simple, safe, noninvasive, and widely available [44].

Until the late 1970s, the medical treatment for pulmonary AVMs was surgical resection or ligation of the AV fistula. Pulmonary lobectomy or pneumonectomy was performed in emergency cases or where multiple lesions were present [12, 18, 45]. However, transcatheter embolotherapy can prevent many of the debilitating and life-threatening complications; embolization is a reliable and efficient procedure for occluding pulmonary AVMs and is currently recommended for all pulmonary AVMs with a feeding artery ≥3 mm [46]. Nowadays, embolization is preferable to preserve pulmonary function and minimize surgical risks [16, 22, 23, 47]. This procedure may be useful to prevent life-threatening hemorrhage.

In conclusion, we reported an autopsy case of pulmonary AVM causing unexpected sudden death due to a spontaneous hemothorax. The diagnosis of HHT1 was confirmed by sequencing analysis revealing a mutation in the endoglin gene. A review of the literature suggests that AVM rupture can occur at any age with a slightly higher incidence in females, especially during pregnancy. In seemingly healthy individuals who die unexpectedly or under unclear circumstances, a criminal offense may be suspected so that a forensic autopsy is regarded as necessary. If death is found to have occurred due to a hemothorax, not only a traumatic source of bleeding but also a spontaneous rupture of an AVM must be taken into consideration, especially in patients with HHT.

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