Neurofibromatosis 1 and massive hemothorax: a fatal combination

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Abstract
Type 1 neurofibromatosis (NF 1), a rare genetic disease with autosomal dominant transmission, has typical dermatologic manifestations with pathognomonic Lisch nodules, and is rarely known for vascular alterations. Among these, aneurysmal dilatation is the most common form. We report a fatal case of massive hemothorax due to a spontaneous rupture of the left pulmonary artery branch micro-aneurysm in a NF 1 patient. Indeed, spontaneous rupture of these pathologic vessels is very rare in clinical practice and the literature, but, for its potentially life-threatening complications, there is the need for it to be taken into account in differential diagnosis. The origin of bleeding was first confirmed by computed tomography angiography (CTA). The patient's condition worsened suddenly leading to pulmonary hemorrhage and death. A clinical autopsy was required to assess the definitive cause of death.

Keywords Spontaneous hemothorax · von Recklinghausen's disease · Neurofibromatosis type 1 · Autopsy · Pulmonary artery · Micro-aneurysm

Introduction

Also known as Von Recklinghausen's disease, type 1 neurofibromatosis (NF 1) is a genetic disease with autosomal dominant transmission and a very low incidence rate of approximately1 in 2500 to 1 in 3000 [1]. No differences in incidence between different races and genders are reported in the literature; it has a high grade of phenotypic variability. Usually NF 1, developing from childhood to adulthood, is not easily diagnosed. It is due to mutations in the neurofibromin gene that is located on chromosome 17q11.2 with characteristic variable penetration. This pathology affects several organs and systems; its typical manifestations are observed at the level of connective tissue, affecting nervous and vascular structures, as well as skin neoplasms (neuromas) and abnormal pigmentation of the skin. The latter, also known as café-au-lait spots, are the most common signs of NF 1. Numbers of variable and uncertain complications should be considered when assessing for NF 1, due to its phenotypic heterogeneity. Moreover, numerous vascular manifestations, which include stenosis, aneurysms, and arteriovenous malformations, have been reported, among which, with an incidence of about 3.6%, the most important vascular lesions are well-defined alterations of small and large vessel layers [2]. Spontaneous hemothorax is one of the uncommon complications of NF-1 and it is potentially fatal with a mortality rate as high as 36%. Characteristically the causes that need to be considered are: neoplasm, hemorrhage due to vascular syndrome, endometriosis and/or hematologic abnormalities such as hemophilia [3].

Case report

A 52-year-old woman, affected by NF-1, with a "visible" low penetrating phenotype and without other significant comorbidities, was admitted to the Emergency Department with syncope, previously anticipated by a sudden onset of acute and severe right back pain. The patient, before loss of consciousness, had neither dyspnea, thoracic pain, neurovegetative manifestation, nor other relevant symptoms. No history of recent trauma was reported in her anamnesis.

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On physical examination, she was unconscious, with a blood pressure of 114/69 mmHg, a heart rate (HR) of 120 beats per minute, 94% oxygen saturation, and 8.6 g/dL of hemoglobin. An ECG was performed and no pathological anomalies were detected except for sinus tachycardia.

An emergency thoracic and abdominal computed tomography with contrast agent was performed, with tetraphasic study, including basal acquisition and arterial, portal and late phase with multiplanar (MPR) and 3D reconstructions to obtain an angio-vascular map.

The main relevant finding was a massive left pleural effusion with passive atelectasis of the adjacent pulmonary parenchyma. CT acquisition without contrast showed a mediastinal adipose tissue thickening with high density of the fluid, an aspect suggesting the possible presence of blood (Fig. 1a). CT with radiocontrast, confirmed the diagnostic hypothesis, and identified, above all by means of MPR and 3-D reconstructions, the presence of a micro-aneurysm of the left pulmonary artery, affecting the apical segmental branch, with recognizable signs of rupture and acute bleeding and irregular enhancement of the mediastinal fat, compatible with hematoma (Figs. 1b and 2). CT scan also showed a micro-aneurysmatic dilatation of the left internal mammary artery.

Even though endovascular embolization was considered, a thoracic surgery consultation was immediately arranged. Unfortunately, the patient's condition worsened and a pulseless electrical activity was recorded. The ALS guidelines for cardiopulmonary resuscitation were immediately applied, but without success.

In order to define the cause of death, a complete post mortem examination was performed the following day. At external examination several irregular cafè-au-lait spots were visible on the skin with a segmental distribution. Gross examination revealed severe lung compressive atelectasis of the left lung due to a massive hemothorax, with presence of a large hematoma of about 12 cm in the mediastinum, involving the main pulmonary artery up to the ipsilateral pulmonary hilum, as the CT-scan revealed (Fig. 3). Hematoxylin and eosin were applied as a routine stain for general microscopic study of the tissues; immunohistochemical staining with S100 and MIB-1 on left pulmonary artery samples was performed, excluding neurofibromas on the vascular wall. Definitive cause of death was identified as acute metahemorrhagic shock secondary to sudden rupture of the apical branch of the left pulmonary artery (Fig. 4a and b).

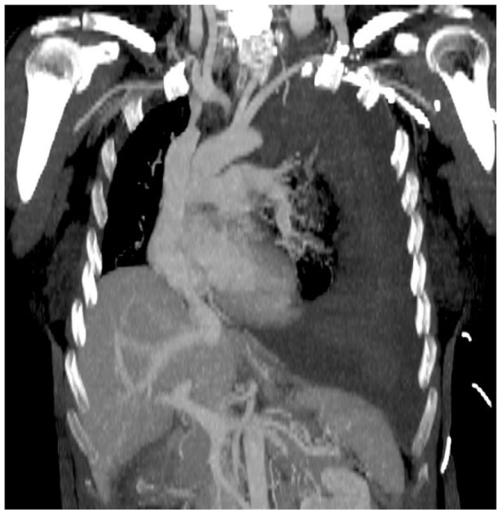

Fig. 2 Oblique-coronal MIP of arterial phase

Discussion

"NF 1 vasculopathy" is a term used in the literature to describe vascular alterations occurring in von Recklinghausen's disease. The first aspect that is important to underline is that even though several studies about vascular affections in NF 1 are reported in the literature, vessel alteration prevalence ranging from 0.4% up to 6.4% in large case series, do not demonstrate any evidence for the lack of routine screening studies. Most

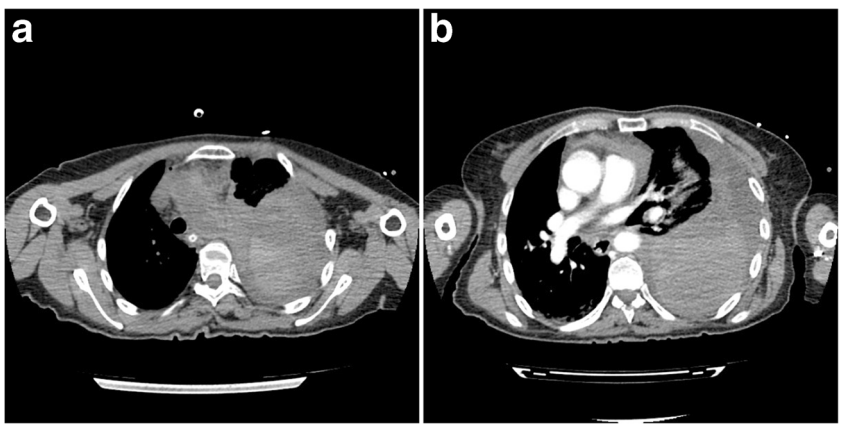

Fig. 1 **a** Axial CT-scan without contrast, showing a large pleural effusion of the left hemothorax. **b** Axial CT-scan, arterial phase

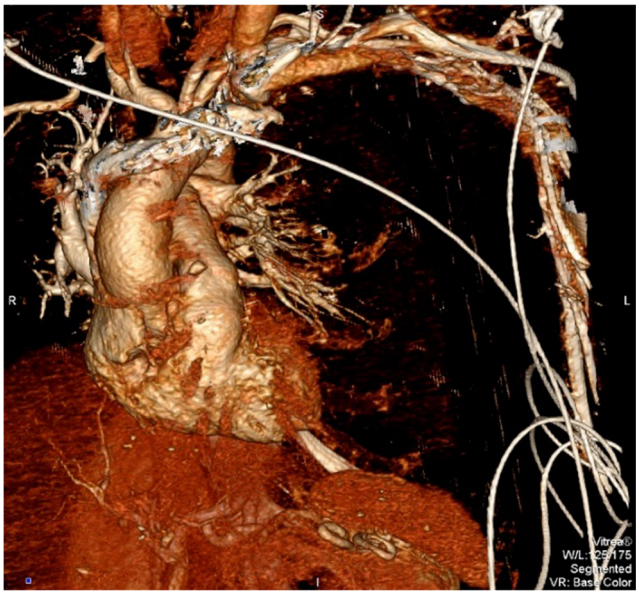

Fig. 3 3-Dimensional volume rendering

patients with NF-1 vascular abnormalities and involvement of multiple vessels are asymptomatic.

The authors reported two main mechanisms to define vascular alterations according to vessel size and type in patients suffering from NF 1. In particular, Greene et al. suggested that the arterial wall integrity was lost due to the presence and development of invasive neurofibromatous tissue, called ganglioneuromas, consequently determining compression/dislocation of vasa vasorum. This pathophysiological damage determines ischemia and wall weakness, causing in its turn, the increase of aneurysm formation tendency. Instead, vascular disruption affecting small vessels seems not to be related to neural malformation/infiltration but could be considered subsequent to wall dysplasia with intima proliferation, muscularis layer hypertrophy, and loss of the media strength with fibrotic transformation of adventitia [4]. In addition, Griffiths et al. reported all these micro- and macro-structural modifications of the arterial wall begin the substrata for vessel stenosis, causing fragility and weakness and increasing rupture risk [5]. Moreover, not only fibroneural anomalies, but also mesenchymal disruption, is considered the basis of small vessel vasculopathy.

The clinical appearance of NF1 vasculopathy differs according to the type of damaged vessel and depends on the localization and dimension. Hypertension of renal origin and neurovascular syndromes are the most common manifestations as are signs and symptoms linked with either mass effect or ischemia respectively. While it is rare that the large artery is affected, its consequent rupture is even more rare [6]. Spontaneous hemothorax is a rare and often lethal complication of NF-1 with a reported incidence of 3.6% [3]. To the best of our knowledge, the first description of death due to pulmonary artery rupture aneurysm hemorrhage was described by von Recklinghausen in 1882, in a middle-aged female. Only 27 cases of spontaneous hemothorax are summarized in literature, while Miura et al. reported one of the most numerous case series counts of 12 patients in Japan, highlighting that the location prevalence for arterial bleeding lists first of all the subclavian and intercostal arteries, followed in frequency by the thyrocervical trunk, phrenic, internal thoracic and left vertebral arteries [7]. It is also known that hemothorax is a deadly complication, with a high mortality rate, estimated at about 36 and 33% in post-operative cases [8].

In our case bleeding was due to a rupture of an aneurysm of the apical segmental branch of the left pulmonary artery producing massive hemothorax with hemorrhagic shock. The histologic study of the pulmonary artery excluded involvement of the vascular wall by neurofibromas and the rupture was related to the aneurysm clearly documented with angio-CT study performed in-vivo.

Conclusion

Vascular anomalies are becoming more and more frequent in clinical practice, either due to an increase in the use of clinical imaging, and /or because of medical improvements. Their possibility must be taken into account when a patient with NF-1 is examined, above all if clinical signs and symptoms address us to a possible problem of vascular origin.

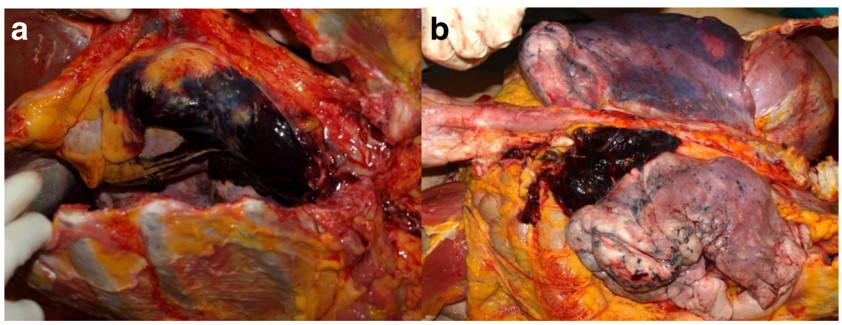

Fig. 4 **a–b** Evisceration of cervico-thoracic organs according to Ghon's technique. Large mediastinum hematoma involving left pericardium and left pulmonary artery extending to pulmonary hilum

Key points

1. Vascular complications in a patient with NF-1 should be taken into account.
2. Often vascular manifestations of NF-1 consists of stenosis, aneurysms, and arteriovenous malformations affecting either small or large vessel layers.
3. Angio-CT is essential to confirm correct diagnosis.
4. Hematoxylin and eosin with immunohistochemical staining with S100 and MIB-1 should be performed to confirm the presence of neurofibromas on the vascular wall.
5. The presence of micro-aneurysmatic dilatation of the left internal mammary artery supports the hypothesis of a causal role of NF-1 in systemic vascular damage.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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