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Case Report

Sudden death due to rupture of the right internal carotid artery in neurofibromatosis type 1: A case report

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ABSTRACT

Vascular involvement is a well-recognized manifestation of neurofibromatosis type 1 (NF1) which has the potential to be fatal when disrupted. We here present a case of sudden death due to the fatal arterial rupture resulted from infiltration of the neurofibromas. A 42-year-old man who suffered from NF1 presented a 1-h history of sudden onset of pain in his right cervical region. His condition worsened and became unconscious on his way to the emergency room. Despite resuscitation efforts, he died 30 min later without regaining consciousness. Autopsy examination showed that a neurofibroma located around the right internal carotid artery, confirmed immunohistochemically with S-100, vimentin and CD34. Furthermore, proliferation of spindle cells positive for S-100 was seen in the wall of right internal carotid artery, which was disrupted and resulted in a hemorrhage. These findings suggest that the artery was disrupted by neurofibromas in the vascular wall, which led to fragility of the vessel. On the basis of these findings, we concluded that the cause of death was asphyxia resulting from airway obstruction compressed by the hematoma due to the arterial rupture. As the locality of the neurofibroma and hemorrhage were closed to the carotid baroreflex, we considered another possible mechanism of his sudden death, which could be cardiac inhibition induced by vagal stimulation. We hope this case will increase recognition of NF-1 vasculopathy when encountering any sudden death in NF1 patients.

1. Introduction

Neurofibromatosis type 1 (NF1), previously known as Von Recklinghausen's neurofibromatosis, one of the most common autosomic-dominant disorders of the nervous system, affects one in 2500–3000 persons worldwide, and shows no gender or ethnic preferences [1]. The responsible gene, located on the chromosome 17q11.2, encodes for the protein neurofibromin and mutation of it result in cell proliferation and inhibited apoptosis throughout the body, which manifests the characteristic neurofibromas [2,3]. In addition, vasculopathy represent another important manifestation which has the potential to be fatal when disrupted [4,5].

Sudden death caused by vasculopathy in NF1 is extremely uncommon and very few cases have been reported in the literature. In this paper, we will present a case of sudden death in a man with NF1 due to the rupture of fragile right internal carotid artery (RICA). An extensive cervical haematoma was formed, causing significant airway compression.

2. Case report

2.1. Clinical data

The decedent, a 42-year-old man, presented with a 1-h history of sudden onset of swelling of the right-side neck with progressive tightness. He experienced severe dyspnea and aggravation of his cervical swelling on his way to the emergency room (ER). Approximately 30 min later, his condition worsened and loss of consciousness subsequently occurred. Several attempts at endotracheal intubation failed as the soft tissues of the neck were swollen and obstructing the larynx. Despite resuscitation efforts, he never regained a cardiac rhythm and he expired. A review of his past medical history was a five-year of multiple neurofibromas and, there was no history of trauma. Suspicious of his death due to malpractice, his relatives asked for medicolegal autopsy to be performed.

2.2. Autopsy findings

Forensic necropsy was performed 48 h after death. Upon external examination, there were no findings of trauma. The most significant finding was limited to the neck, which showed

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right-sided swelling. We also found asphyxial signs including cyanosis and petechial conjunctival hemorrhages. Freckles could be seen diffusely over the axillary and inguinal region. At least 10 typical café-au-lait spots were observed on the trunk and upper legs, which were flat and brown. A large number of both cutaneous and subcutaneous nodules of different sizes ranging in size from 0.2 to 4.0 cm were unevenly distributed over the entire skin (Fig. 1). The nodules were soft, fleshy, sessile and showed no sign of inflammation. Layer dissection of the neck revealed subcutaneous bleeding at the right side (Fig. 2A), which had spread to the right retropharyngeal wall and the thyrohyal. A large hematoma ($10.0 \times 7.5 \times 6.5$ cm) was found adjacent to right carotid bifurcation. Moreover, an oval, off white, fleshy mass measuring $2.5 \times 2.0 \times 1.3$ cm that caused the RICA compressed and displaced was located within this perivascular hematoma (Fig. 2B). The RICA had a tiny defect in its extracranial segment adjacent to the mass, approximately 2 cm distal to the carotid bifurcation, which was the predominant source of the hemorrhage. No aneurysmal dilatation of the artery was noted. Edema of the retropharyngeal wall was remarkable. The swelling within the larynx had caused significant obstruction of the airway and was associated with mucosal edema that involved the epiglottis, especially on the left side. The right side of the esophageal adventitia showed sheet hemorrhage.

Additional internal examination findings included cerebral edema and sporadic hemorrhagic spots of the lungs. The subsequent toxicology screening was negative.

2.3. Histological findings

The mass surrounding the wall of RICA revealed an irregular pattern of proliferative elongated spindle cells with wary or comma-shaped nuclei embedded in a stroma composed of wire-like collagen fibers and amorphous mucoid substances. There was no evidence of malignancy, such as cellularity, cellular pleomorphism, or mitoses. Immunohistochemistry (IHC) of the mass revealed positivity for S-100 protein of the nuclei and cytoplasm of the spindle cells and most cells within the fibrous connective tissue were vimentin and CD34 positive.

The rupture site was identified on consecutive sections of RICA near the mass both in hematoxylin-eosin (HE) and Elastica–Masson's stains, which demonstrated focal loss of the internal elastic lamella and the media, and fragmentation or thinning of the adventitia with hemorrhage and collagen deposition in area of the adventitia. Concomitantly, a same lesion which showed diffuse proliferation of spindle cells with waxy nuclei and a mucoid change of the stroma widely infiltrated the wall of RICA. The lesion was S-100 positive, confirming the same origin with the surrounding mass (Fig. 3). On the other hand, a reduction of elastic fibers and focal loss of the muscularis were observed in the media near the disrupted site. And increased collagen deposition in areas of muscularis loss that is best appreciated with Elastica–Masson's stain, is observed (Fig. 4).

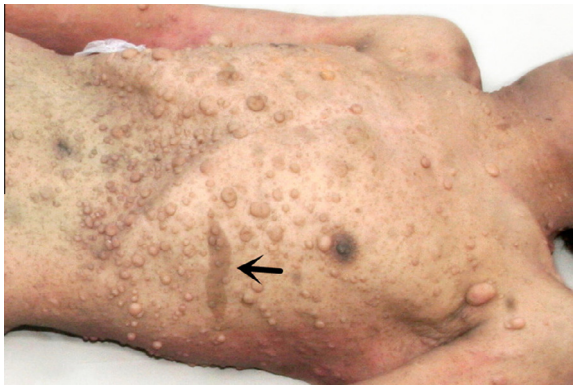

Fig. 1. A large number of nodules unevenly distributed over the skin, café-au-lait spots (arrow) were observed on the trunk and extremities.

Histological changes of cutaneous nodules were consistent with the mass, which was positive for S-100 protein. Examination of all other organs was unremarkable except for sporadic eosinophilic degeneration of neuronal cells in brain.

3. Discussion

NF1 is an autosomal dominant condition caused by heterozygous mutations of the NF1 gene. Most common characteristics include neurofibromas, café-au-lait spots, lisch nodules and axillary freckling. The neurofibromas, the hallmark feature of NF1, are benign tumors consisting of Schwann cells, perineurial cells, fibroblasts, mast cells, axons, and blood vessels and as well large amounts of intercellular material, including collagen and amorphous ground substances, for example, mucopolysaccharides and glycosaminoglycans [2,6,7]. They are positive for S-100 protein at IHC analysis, indicating their neural origin from Schwann cells [8]. Furthermore, positivity for vimentin and CD34 are also indicative of neurofibromas [9,10]. In this case, neurofibromas were demonstrated by macroscopic, histopathological and immunohistochemical characteristics. Consequently, according to the clinical diagnostic criteria [11], the patient who presented with more than six cafe-au-lait spots, axillary and inguinal freckling, multiple cutaneous and subcutaneous neurofibromas, was diagnosed with NF1.

Mortality associated with NF1 is about 0.92 per 1 million people and approximately a 15-year decrease in life expectancy of NF1 patients has been revealed in some studies. Fatal complications of NF1 resulting in death include malignant peripheral nerve sheath tumor, CNS tumors, spinal cord compression by neurofibromas, organ compression by neurofibromas and pheochromocytomas [12]. In addition, vasculopathy has been reported as an uncommon complication which is another cause of death in NF1 patients [4,5].

NF1 vasculopathy was first described in 1945 [13]. The prevalence is about 0.4% to 6.4% and it is often asymptomatic, though it has a potential for significant morbidity and mortality [14]. There are two distinct pathogenetic mechanisms of vasculopathy: smooth muscle dysplasia and direct vascular invasion by neurofibromatous tissue. Lesions manifest as stenosis, dissection, aneurysm formation, or rupture of the affected vessels [15]. Histopathological characteristics of the affected vessels are (1) surrounded by neurofibromatous tissue, (2) abnormal proliferation of spindle or epithelioid cells disturbing the integrity of the vessel, (3) thinning of the media and fragmentation of the muscularis and elastic layer, (4) intimal thickening with occlusion of the vascular lumen [16–18]. It is suggested that proliferation of spindle cells occurred within arterial walls leads to dysplasia of smooth muscle layers and destruction of the media and the elastic fibers. These pathological changes may increase fragility of the vessels gradually and are thought to be responsible for the associated arterial disruption [19]. In our case, this explanation is reasonable. In addition to the absent of intimal thickening, the most striking histological changes was the disintegration of the vascular structure by proliferation of spindle cells which were positively stained for S-100, suggesting their neural origin. On the other hand, other than a proliferation within the vessel microscopically**, a macroscopic neurofibroma was formed adjacent to the artery. These findings represent that the onset of vascular lesion is mainly due to direct tumor invasion which caused the arterial extreme fragility. Therefore, it is at increased risk of rupture which was spontaneous or