Forensic Science, Medicine and Pathology (2019) 15:474–480
https://doi.org/10.1007/s12024-019-00122-5

CASE REPORT

Massive intracranial bleeding due to the rupture of a rare spontaneous pseudoaneurysm of the middle cerebral artery in a pediatric patient: case report with clinical, radiological, and pathologic findings

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Accepted: 2 May 2019 / Published online: 19 June 2019

Abstract

Intracranial pseudoaneurysm (IPA) is a rare but likely underdiagnosed cause of intracranial hemorrhage, which accounts for just 1–6% of all intracranial aneurysms. Spontaneous IPAs are exceptionally rare, and their etiology and features are not well defined. Herein, we report a case of a pediatric patient who died from massive intracranial bleeding due to the rupture of a spontaneous IPA after undergoing multiple radiological studies and neurosurgical operations. At the postmortem examination of the brain, a giant size pseudoaneurysm of the right middle cerebral artery was observed. Microscopic examination demonstrated variable wall thickness and dense fibrosis focally in the vessel wall with disruption of the media structure together with a loss and fragmentation of the elastic laminae, loss of organization of smooth muscle cells in the media, and multifocal areas of hemorrhage throughout the vessel wall, as well as direct evidence of wall dissection. Since IPAs without any traumatic or infective history are extremely uncommon, further pathologic studies should be performed to clarify spontaneous pseudoaneurysm etiology.

Keywords Forensic pathology · Neurosurgery · Neuropathology · Pseudoaneurysm · Pediatric patient · Intracranial bleeding

Introduction

Intracranial aneurysms occur rarely in children and adolescents. The prevalence of saccular aneurysms is higher in adolescents older than 15 years; conversely, in those 2–5 years old the incidence of dissecting aneurysms (or pseudoaneurysm) is higher [1]. Pseudoaneurysms are arterial dilatations with complete disruption of the arterial wall. They usually show a rent in the intima with dissecting hemorrhage into the tunica intima or media, with fusiform enlargement of the vessel wall. Sometimes called "false" aneurysm, they lack all three normal elements of the arterial wall, distinguishing it from a "true" aneurysm. Intracranial pseudoaneurysms (IPAs) are a rare but likely underdiagnosed cause of intracranial hemorrhage, which accounts for just 1–6% of all intracranial aneurysms [2]. Despite their rarity, IPAs are observed more frequently in the pediatric population. The affected vessels are commonly the larger intracranial vessels, especially the internal carotid arteries, the middle cerebral arteries and the vertebrobasilar system. The etiologies of the dissections have been reported to include severe infections (i.e. syphilis), cerebral or cervical trauma, congenital defect of the vessels, hereditary connective tissue disorders (i.e. Marfan's syndrome), and allergic arteritis [3, 4]. We present a case of a pediatric patient who died from

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massive intracranial bleeding due to the rupture of a spontaneous IPA of the right middle cerebral artery. Radiological and pathological findings will be discussed.

Case report

A 14-year-old Caucasian female was brought to the hospital after losing consciousness while attending her morning school session. She had no pertinent familial history. According to her recent medical history, she had heavy menstrual bleeding, with a mild headache and lack of appetite that started the night before. On arrival at the emergency department, the neurological examination showed she was drowsy but easily arousable; the Glasgow Coma Scale (GCS) score was 13 (E3V4M6). Physical and neurological examinations were unremarkable: the pupils were bilaterally isochoric, isocyclic, and reactive to light, and there was no papilledema, cranial nerve deficits, or sensory or motor deficits. An EKG was performed, which showed no cardiac rhythm alterations. A pregnancy test was negative. Laboratory blood tests showed no specific alterations, with an unremarkable complete blood count and glucose concentration within normal limits.

A non-contrast computed tomography (CT) of the brain showed a right intra-cerebral hemorrhage (ICH) of the temporal-insular region (maximum diameter = 6 cm), with peripheral cerebral edema, a subarachnoid hemorrhage (SAH) within the right sulci and basal cisterns, and an intraventricular hemorrhage (IVH) of the fourth ventricle. There was no midline shift, but obliteration of the frontal horn of the right lateral ventricle was evident (Fig. 1).

After the neuroradiological study, the GCS score decreased to 10 (E2V3M5).

The patient was referred to the neurosurgery department of a tertiary health care provider. A second CT scan showed an interval increase in size of the right ICH, with a 5 mm midline shift (Fig. 2). A CT-angiography with 3D rendering showed a pseudoaneurysm of the M3 segment of the right middle cerebral artery (MCA) (Fig. 3).

The patient was immediately brought to the operative room, where a decompressive craniectomy and external ventricular drainage were performed, followed by cerebral

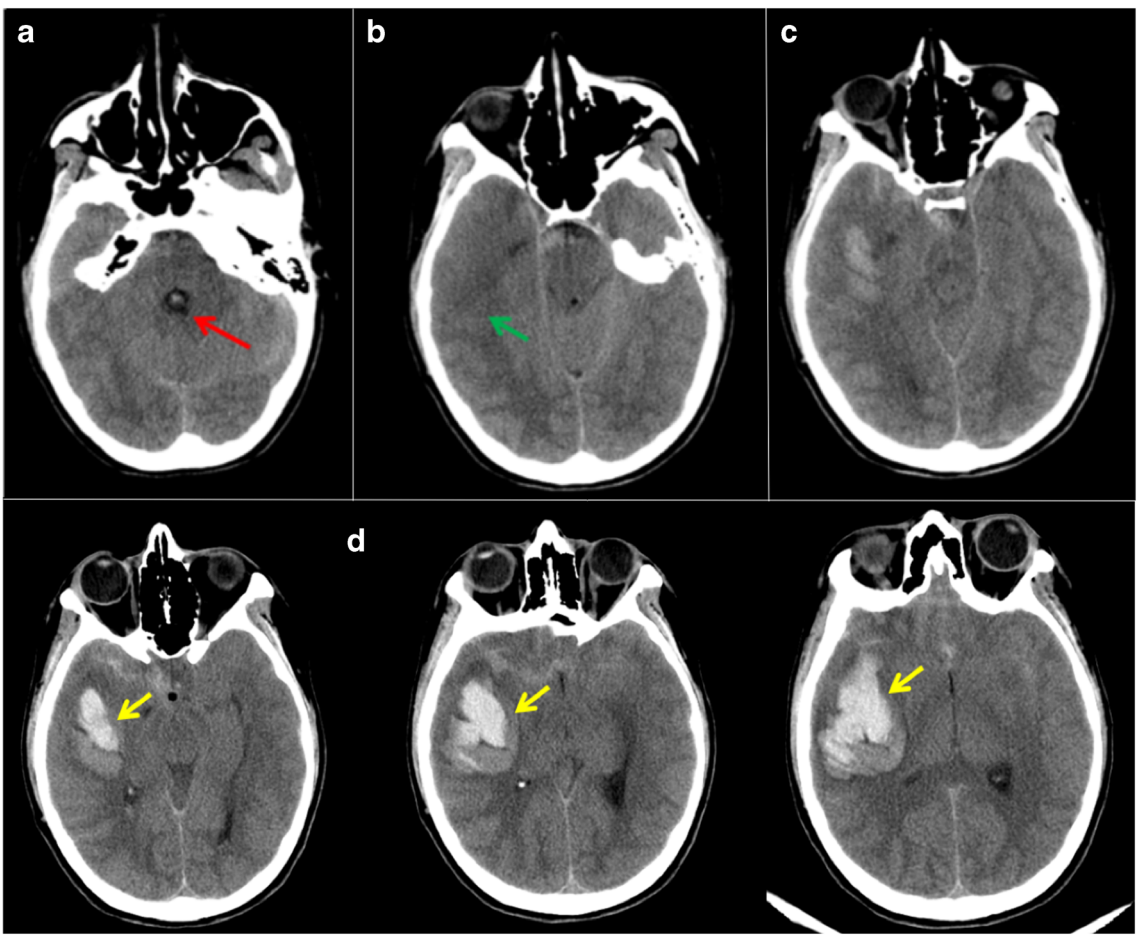

Fig. 1 CT of the head without contrast. **(A)** Mild intraventricular hemorrhage of the IV ventricle. **(B)** Mild perilesional edema. **(C)** Subarachnoid hemorrhage on the right temporal-parietal regions. **(D)** Intraparenchymal hemorrhage in the right temporo-insular region

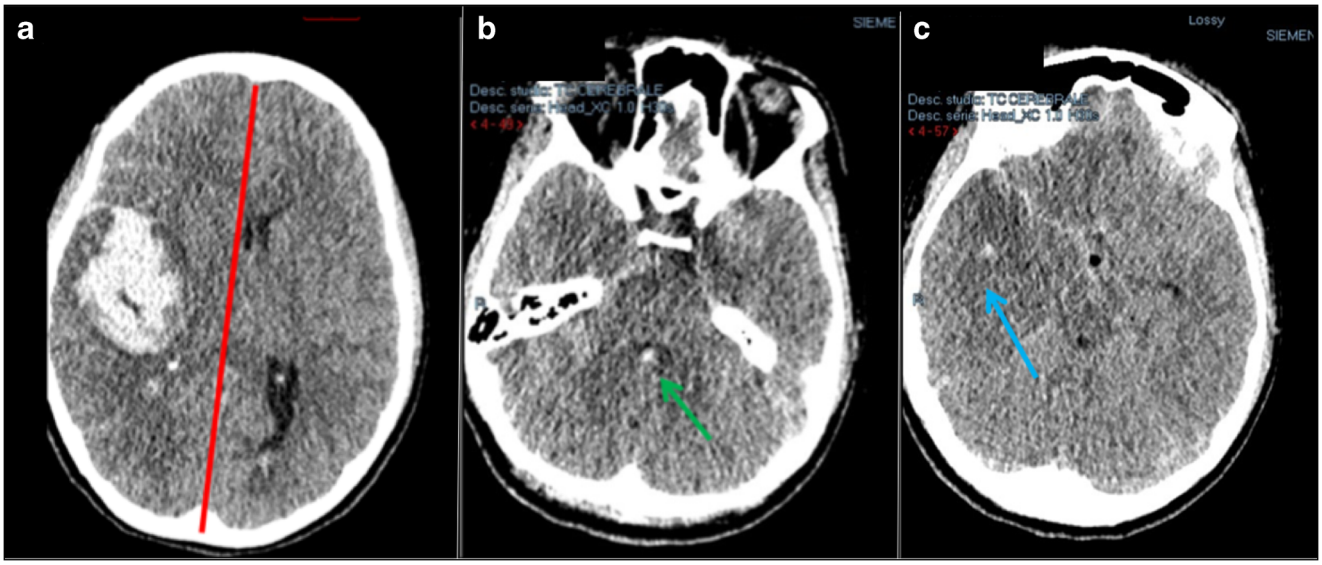

Fig. 2 CT of the head. **(A)** Right intracerebral hemorrhage increased in size, with a 5 mm midline shift. **(B)** Increased intraventricular hemorrhage of the IV ventricle. **(C)** Increased perilesional edema and restriction of the brain vascular function

angiography (Fig. 4). The digital subtracted angiography (DSA) confirmed the finding: a pseudoaneurysm at the level of the frontal-parietal branch of the right MCA. A partial inflow with contrast staining was evident. For this reason, endovascular treatment was performed, injecting glue in the pathological arterial branch. Unfortunately, final control runs with injection in both right and left internal carotid arteries showed the almost total lack of intracerebral blood flow.

Despite multiple neurosurgical operations, the patient died after three days of coma. Death was due to irreversible cerebral damage as a consequence of the massive intracranial bleeding.

At postmortem examination there was evidence of a post organ donation status. The whole brain was saved in formalin for a neuropathology consultation.

Analysis of the fixed brain showed a massive subarachnoid hemorrhage on the right cerebral hemisphere. An extensive right temporal lobectomy was seen as a result of the neurosurgical cortectomy. Following the branches of the circle of Willis, the right middle cerebral artery was filled with glue and showed the presence of a fusiform vessel dilatation, 2.5 × 1.0cms in size (Figs. 5 and 6).

On histologic examination (Fig. 7 A-G), the artery demonstrated variable wall thickness (Fig. 7 A-C) and fibrosis focally in the vessel wall with disruption of the media structure (Fig. 7

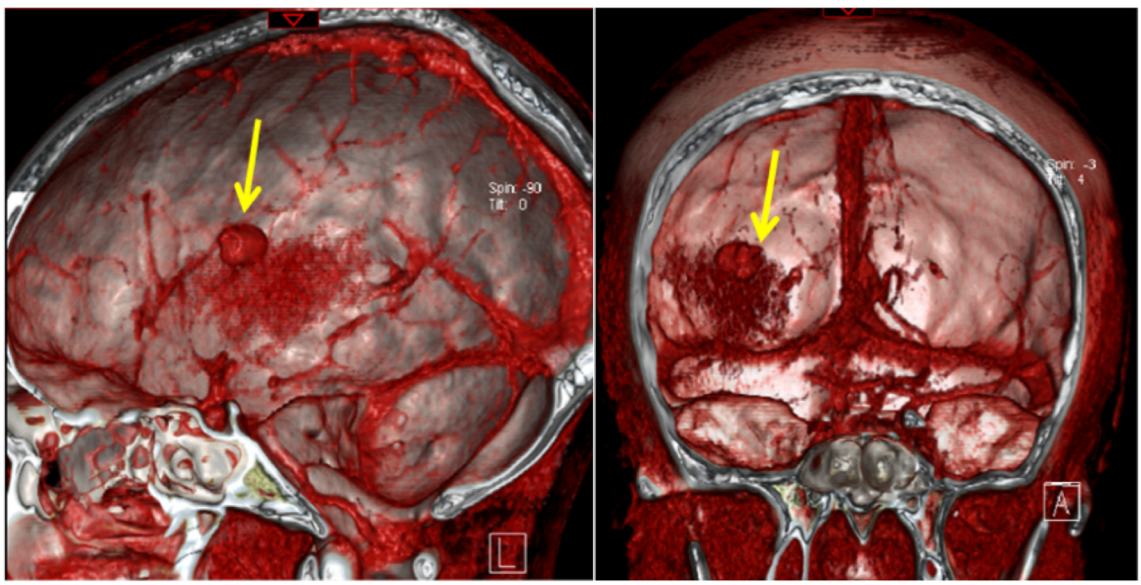

Fig. 3 CT angiography with 3D rendering. The arrows show the location and the morphology of the intracranial pseudoaneurysm

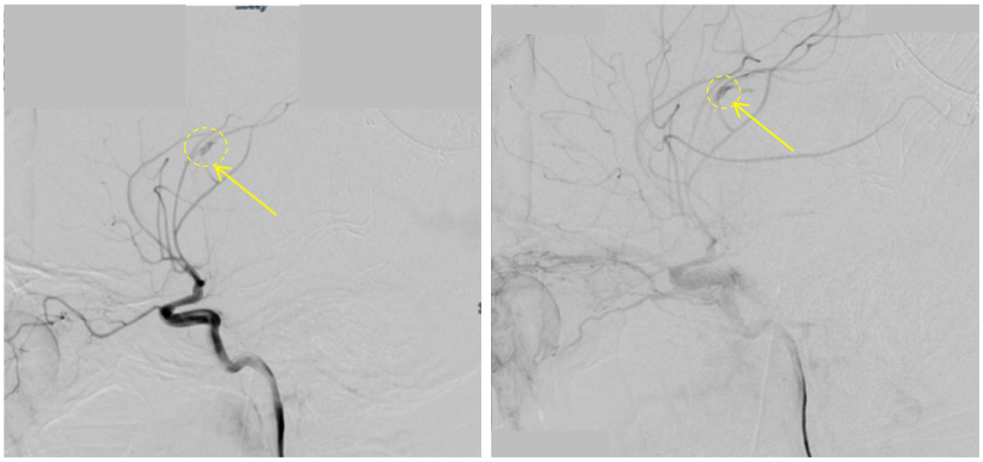

Fig. 4 Cerebral arteriography. The arrows show the location and the morphology of the intracranial pseudoaneurysm

B, D, and E). There was apparent loss and fragmentation of the elastic lamina (Fig. 7 C and F) compared to an uninvolved neighboring artery (Fig. 7 G), and multiple foci of hemorrhage throughout the vessel wall (Fig. 7 A-C), in some areas showing fusiform expansion and direct dissection into the vessel wall. Smooth muscle actin (SMA) immunohistochemical staining demonstrated a loss of organization of smooth muscle cells in the media compared to an adjacent, uninvolved artery.

The cause of death was massive intracranial bleeding following the rupture of a spontaneous pseudoaneurysm of the right middle cerebral artery.

Discussion

The English literature regarding pediatric IPAs is scarce and is mostly concerned with clinical and surgical features. These include a recent review of the literature, in which the authors describe 15 cases of pediatric IPAs, mostly from traumatic etiology [5]. Reports about spontaneous IPAs in the pediatric population are rare and limited to few clinical case reports [6–8]. To the best of our knowledge, no papers about *spontaneous* IPAs are published in the forensic literature, and this paper approaches the topic from a pathologist's point of view.

The wall of cerebral arteries consists of the following three concentric layers (from the inner to the outer): tunica intima, which contains a layer of endothelial cells and internal elastic lamina (the connective tissue layer that lies beneath the endothelium), the tunica media, which consists of smooth muscle cells arranged in layers, collagen and elastin fibers, and the tunica adventitia, made mostly by collagen fibers and fibroblasts. The structure of the cerebral arteries differs somewhat from the systemic arteries. Unlike systemic arteries, there are fewer elastic fibers in the medial layer in cerebral arteries, a thinner adventitia, and they lack a well-defined external elastic lamina [9].

Pseudoaneurysms are characterized by a complete subversion of the regular arterial wall. The typical gross appearance of IPAs is that of red to purple masses that show a thin and discontinuous tunica adventitia together with a large hematoma, usually containing clots of varying ages. At microscopic

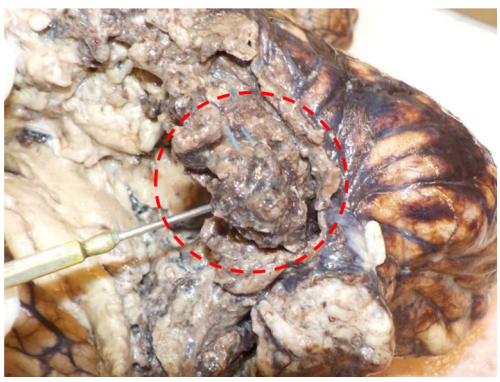

Fig. 5 Vascular lesion on the right temporal area

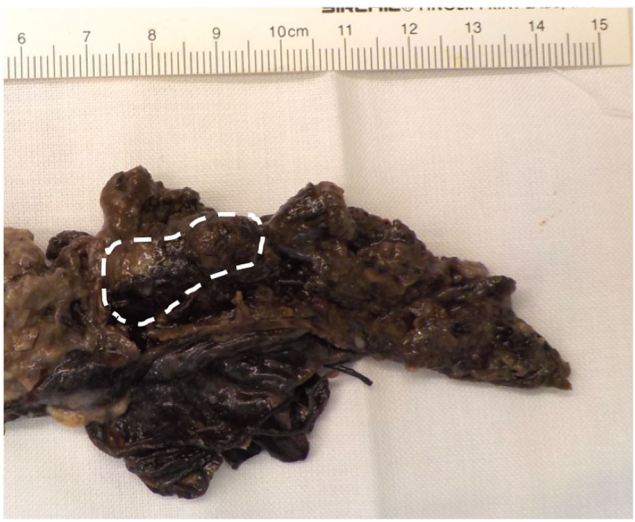

Fig. 6 Vascular lesion after dissection from the brain parenchyma. The dashed line shows the outline of the pseudoaneurysm

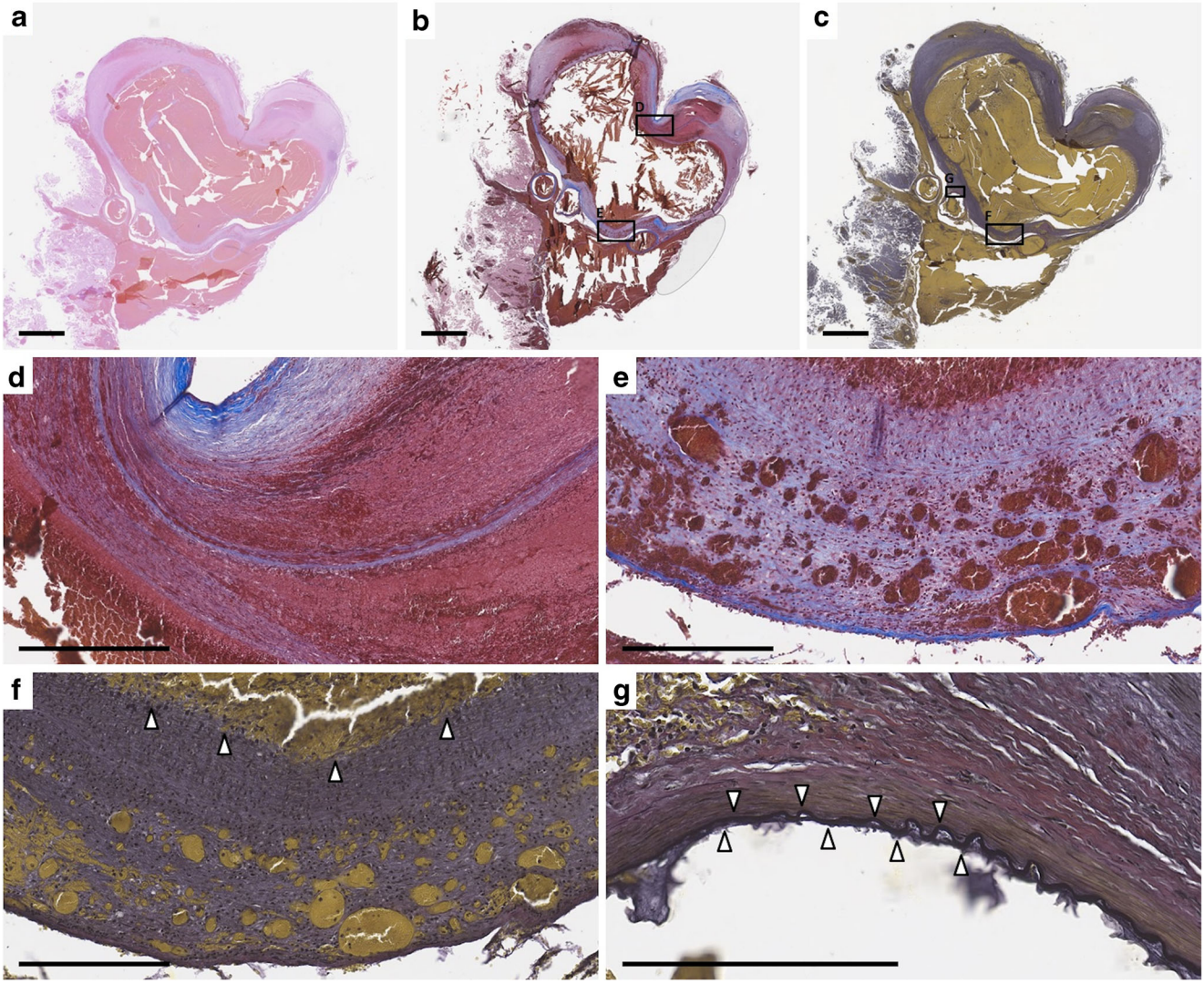

Fig. 7 Histologic images of the arterial pseudoaneurysm with H&E **(A)**, Masson's trichrome **(B)**, and elastic stains **(C)** (boxes represent areas examined with higher magnification). Higher power images of a segment of the artery with Masson's trichrome stain showing hemorrhage in the arterial wall and focal increase of collagen in the media (blue material) **(D-E)**, and elastic stain showing loss of the internal elastic lamina (arrowheads showing area of loss) **(F)** with elastic stain of control artery demonstrating retained internal elastic lamina (arrowheads) **(G)**. Images **A-C** are taken at a total magnification of 5x, scale bar = 2 mm. Images **D-F** are taken at a total magnification of 200x, scale bar = 200 μm. Image **G** is taken at a total magnification of 400x, scale bar = 200 μm

examination, IPA commonly shows a complete loss of normal arterial architecture, with wall disruption or necrosis, and aneurysmal dilation surrounded by many layers of fibrous tissue.

In the pediatric population, IPAs tend to be either large (10-24 mm in diameter) or giant size (diameter ≥ 25 mm) [10], and are most commonly located in the M2 segment of the middle cerebral artery [11].

IPAs are highly unstable lesions due to their thin wall, and the absence of a normal wall structure makes them fragile with high risk of rupture. Growth and rupture of intracranial aneurysms are accompanied by vascular remodeling of the aneurysm wall in association with increased proteolytic activity, cell death, and inflammatory cell infiltration. Histological studies suggest that intracranial aneurysm walls rupture is a consequence of matrix degeneration and decellularization, which may due to direct vascular stress or injury or may correspond to defects in homeostatic maintenance or repair mechanisms [3].

Genetic and functional studies identified high-risk genetic variants which can lead to the loss or alteration of *THSD1* protein function: *THSD1* variants affect protein function, leading to disruption of normal endothelial cell adhesion to the extracellular matrix and significantly increasing the risk for intracranial aneurysm formation [12]. Other adhesion cell proteins may play an important role [13], but their activity is still under investigation.

When the rupture occurs, the blood penetrates inside the cerebral parenchyma causing necrosis, apoptosis, and infiltration by inflammatory cells [14]: the local destruction of neuronal and glial cells leads to the release of neurotransmitters, and to membrane and mitochondrial dysfunctions. The final stage is the development of cytotoxic edema with necrosis, followed by vasogenic edema and apoptosis.

In our case, most of the features of the IPAs described in the literature were detected. The subject was a pediatric patient who showed a giant size IPA (25 × 10 mm), which was located in the right middle cerebral tract, which confirms the previous observations.

During the examination of the formalin-fixed brain, the tissues surrounding the vascular anomaly were extremely fragile, and careful isolation of the pseudoaneurysm was performed. Microscopic examination showed fibrosis in the vessel wall with disruption of the media as well as loss and fragmentation of the elastic laminae. Smooth muscle actin immunohistochemical staining allowed us to detect a loss of organization of smooth muscle cells in the media of the affected vessel, while an adjacent uninvolved artery showed a regular wall architecture.

The peculiar characteristic of this case lies in the absence of any traumatic or infectious etiology of the IPA to explain the abnormalities found in the vessel wall architecture, and therefore it was classified as spontaneous or idiopathic. The patient's medical history was negative for any head trauma or previous head surgery, and the family history was negative for any connective tissue disorder.

In deaths due to intracranial bleeding in a pediatric patient, the pathologist should suspect and carefully search for an IPA, since the massive intracranial hemorrhage may hide the existence of this vascular lesion. In such cases, the brain should be saved for a later examination upon formalin fixation, and a neuropathological consultation is advisable to describe the microscopic features of the vascular lesion.

Specific histochemical and immunohistochemical stains (i.e. Masson's Trichrome, Elastic stains, SMA) are useful to demonstrate the main microscopic features of the IPA.

A thorough medical history of the subject, including family history about potential hereditary connective tissue disorders, infectious and autoimmune diseases, and previous head trauma, should always be investigated.

If the patient dies without hospitalization, but intracranial bleeding is suspected, a postmortem computed tomographic angiography can be useful to locate a vascular malformation, helping the pathologist to detect and locate it during the autopsy or the brain examination.

Since IPAs without any traumatic or infective history are incredibly uncommon, further studies in the pathology field should be done to clarify spontaneous pseudoaneurysm etiology.

Key points

1. The etiologies of intracranial pseudoaneurysms (IPAs) include severe infections, cerebral or cervical trauma, congenital defect of the vessels, hereditary connective tissue disorders, and autoimmune diseases. Spontaneous IPAs in the pediatric population are extremely rare.
2. IPA should be considered in deaths due to unexplained intracranial bleeding in a pediatric patient.
3. In cases with intracranial bleeding due to IPA rupture, the whole brain should be saved in formalin, and a neuropathological consultation should be requested.
4. Specific histochemical and immunohistochemical stains should be used to highlight the microscopic features of the pseudoaneurysm.
5. A thorough medical history of the subject, including family history about potential hereditary connective tissue disorders, infectious and autoimmune diseases, and previous head trauma, should always be investigated.

Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

Ethical approval Not applicable: only data collected in the process of a routine medico-legal investigation ordered by the legal authorities are described in this case report.

Informed consent As above.

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