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CASE REPORT

C. H. Rickert · C. Greiner · G. Rellensmann · H. G. Kehl
H. H. Scheld · W. Paulus · G. Fechner

Mycotic cerebral vasculitis in a paediatric cardiac transplant patient excludes misadventure

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Abstract We present the case of a 10-year-old girl with cardiomyopathy who received a heart transplant. Due to organ rejection, the dosage of immunosuppressive agents was increased postoperatively. The patient complained of intermittent headaches in the following days and developed a haemorrhagic necrosis of the left thalamus. A week later, an oral dose of cyclosporin A was accidentally given intravenously, and 2 weeks later a recurrent subarachnoid haemorrhage of unknown origin was diagnosed. The clinical course was then characterised by progressive deterioration resulting in coma, fluctuating brain stem symptoms and the development of a massive cerebral oedema with subsequent brain death. A coroner's autopsy was instigated to investigate a claim of medical misadventure. Neuropathological investigations found a focal infiltration of fungal hyphae in the left posterior cerebral artery resulting in necrosis of the vascular wall and thus explaining the source of the recurrent subarachnoid haemorrhage which eventually resulted in the girl's death. Medical misadventure due to the administration of cyclosporin was not directly responsible for the death of this patient. This case illustrates that it is of paramount importance to copiously sample and investigate the basal cerebral arteries in cases of subarachnoid haemorrhage of unknown origin, in particular in a medico-legal context.

Keywords Accidental drug administration · Medical misadventure · Immunosuppression · Cyclosporin A · Mycotic vasculitis

C.H. Rickert (✉) · W. Paulus
Institute of Neuropathology, University Hospital Münster,
Domagkstrasse 19, 48129 Münster, Germany
e-mail: rickchr@uni-muenster.de,
Tel.: +49-251-8356969, Fax: +49-251-8356971

C. Greiner
Department of Neurosurgery, University Hospital Münster,
Albert-Schweitzer-Strasse 33, 48129 Münster, Germany

G. Rellensmann · H.G. Kehl
Department of Paediatric Cardiology,
University Hospital Münster,
Albert-Schweitzer-Strasse 33, 48129 Münster, Germany

H.H. Scheld
Department of Cardio-thoracic Surgery,
University Hospital Münster,
Albert-Schweitzer-Strasse 33, 48129 Münster, Germany

G. Fechner
Institute of Legal Medicine, University Hospital Münster,
Roentgenstrasse 23, 48149 Münster, Germany

Introduction

Medical or therapeutic misadventure refers to deaths that result from unexpected complications of medical procedures, although it does not always or necessarily imply a degree of medical negligence (Murphy 1986). Such cases must be brought to the attention of the coroner for thorough investigation and documentation to ensure that in the public interest, procedures and protocols are rectified as required and sufficent evidence collected on behalf of the next of kin to enable claims for compensation.

We report the case of a 10-year-old girl with cardiomyopathy who, after a heart transplant operation accidentally received an intravenous dose of the immunosuppressive drug cyclosporin A actually meant to be given orally. In the course of the following 3 weeks, the patient developed a thalamic necrosis, a recurrent subarachnoid haemorrhage of unknown origin, and progressive clinical deterioration resulting in massive cerebral oedema and brain death. A coroner's autopsy was ordered to investigate the possibility of medical misadventure.

Case report

Clinical history

The 10-year-old female patient suffering from dilatated cardiomyopathy of unknown origin (New York Heart Association grade IV) underwent heart transplantation on 20.09.2000. Postoperatively, the girl received immunosuppressive therapy consisting of prednisolone, azathioprine and cyclosporin A. After signs of organ rejection the dosage of these drugs was increased. The patient developed severe hypertension for which she also received medication.

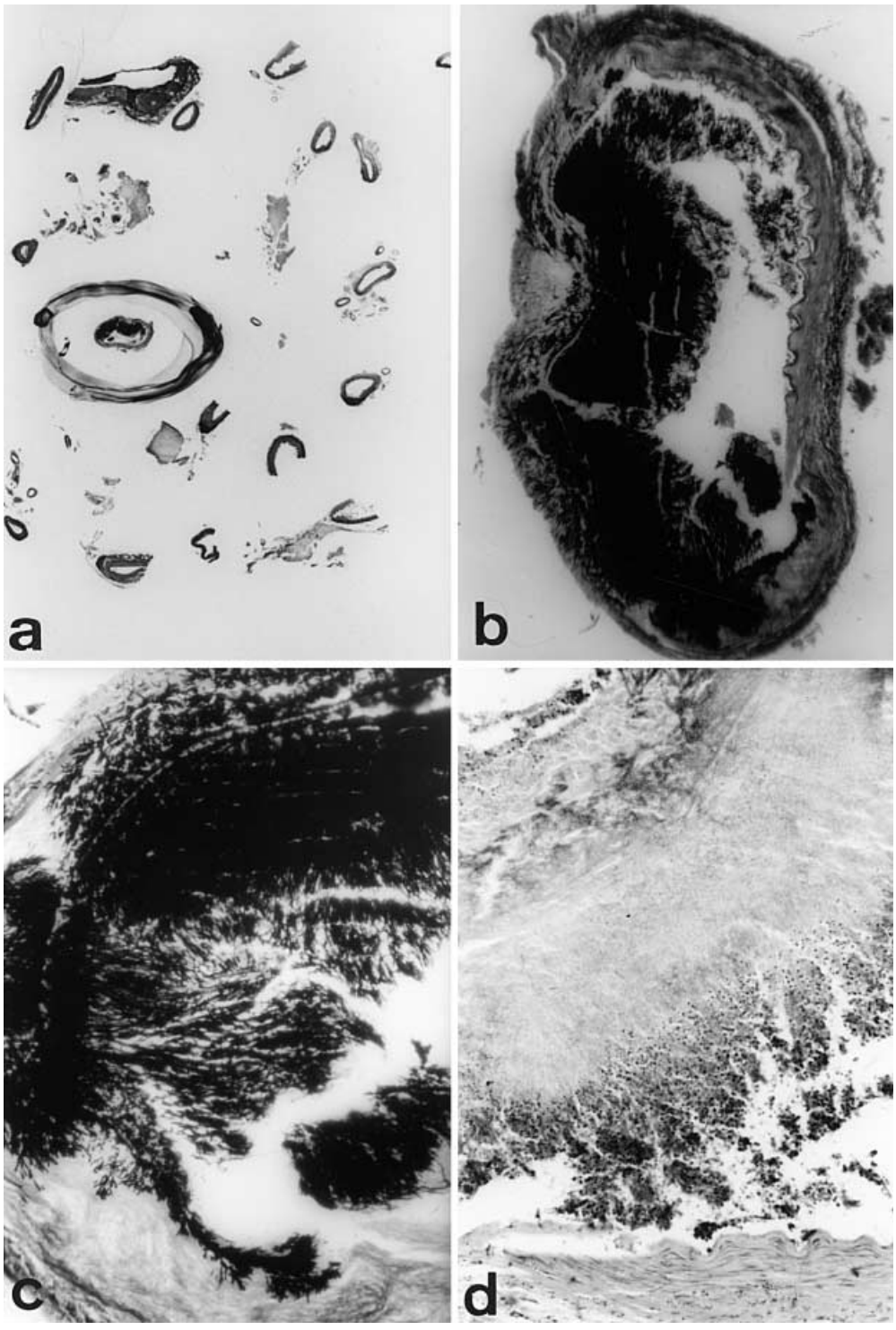

Fig. 1 **a** Macroscopical aspect of histological slide showing segments of the left posterior cerebral artery. Segment affected by mycotic vasculitis is circled and **b** close-up of circled vascular segment. Note massive infiltration of fungi *(bottom and left)* from the vascular lumen into the blood vessel wall. Part of the vessel wall shows an intact internal elastic lamina (*top and right*; Grocott, original magnification: ×8). **c** At higher magnification, penetration of the vessel wall by fungal hyphae with morphological characteristics of aspergilli can be identified (Grocott, original magnification ×32) and **d** the vessel wall is completely necrotic with loss of distinct layers (HE, original magnification ×32)

The clinical course was characterised by intermittent headaches and meningism with CSF pleocytosis. A cytomegalovirus infection was detected in the CSF which was resolved under anti-viral therapy. On 01.11.2000 a left-sided thalamus infarction was diagnosed without establishment of an embolic source. On 09.11.2000 a dose of cyclosporin A meant for oral consumption was accidentally applied intravenously, however, no immediate impact on clinical or laboratory parameters was noticed. On 26.11.2000, the girl developed a subarachnoid haemorrhage. Angiographically, no source of bleeding could be established and an intraventricular drainage was inserted which continuously drained blood-tinged CSF. On 29.11.2000, the clinical state of the patient deteriorated and the girl fell into a coma characterised by fluctuating brain stem symptoms with extensor spasms. A cranial CT scan showed subarachnoid haemorrhaging and a thalamic infarction. On 01.12.2000, Doppler sonography of the cerebral blood vessels revealed increased blood flow velocities indicative of cerebral vasospasm secondary to the subarachnoid haemorrhage. On 02.12.2000, no pupillary light reflexes were demonstrable and a cranial CT scan showed a massive cerebral oedema. A subsequent Doppler sonography of the cere-

bral blood vessels established cessation of cerebral perfusion. On 03.12.2000, the patient was declared brain dead.

Autopsy results

The post-mortem examination revealed moderate hypertrophy of both cardiac ventricles with the transplanted heart weighing 290 g. Macroscopically, there were adhesions between epi- and pericardium. Microscopically, the heart showed a moderate interstitial oedema, however, no histological signs of organ rejection could be found. Addional autopsy findings consisted of bronchitis, tonsillitis, and mild immobilisation-induced atrophy of the skeletal muscles. Neither a source for the *Aspergilli* infection nor any other sites of vasculitis or embolism could be found.

Neuropathology findings

Macroscopically, the brain tissue was soft and showed an extensive cerebral oedema (brain weight after fixation 1430 g) resulting in bilateral prominent uncal grooves, compressed oculomotor nerves and herniation of both cerebellar tonsils into the foramen magnum. A CSF drain was found in a correct position in the right frontal lobe. The main macroscopical finding was a subarachnoid haematoma in the basal and prepontine cisterns, affecting the left side more than the right. The basal cerebral arteries (circle of Willis), however, were unremarkable macroscopically and in particular, there was no evidence of an aneurysm or other source of the haemorrhage. Furthermore, a haemorrhagic necrosis (1.5×1.0× 0.5 cm) in the left thalamus as well as fresh, partially petechial congestive haemorrhages in the central mesencephalon and pons could be found. All basal cerebral arteries were sampled separately, cut into segments of 0.3 cm length and paraffin wax-embedded.

Microscopically, all arteries of the circle of Willis were normal except for a single segment of the left posterior cerebral artery (Fig. 1a) which showed a focal infiltration of fungal hyphae (morphologically characteristic for *Aspergilli*) into the necrotic blood vessel wall without occlusion of the artery (Fig. 1b–d). However, no (mycotic) aneurysm could be demonstrated. Furthermore, partly necrotic, Prussian blue positive and partly fresh blood could be found in the basal subarachnoid space. Additional findings consisted of fresh haematomas in the brainstem, multiple fresh incomplete necroses with numerous hypereosinophilic neurons and a subacute haemorrhagic necrosis of the left thalamus (stage II) with numerous macrophages, capillary activation and mild perifocal reactive astrogliosis. Furthermore, a lymphocytic meningoencephalitis of the brainstem could be diagnosed which was characterised by lymphocytic infiltrates in the pontine and medullar leptomeninges as well as within the parenchyma.

In conclusion, the cause of death was a massive cerebral oedema with signs of herniation and multiple fresh infarcts secondary to recurrent subarachnoid haemorrhage due to focal mycotic vasculitis of the left posterior cerebral artery.

Discussion

Cyclosporin A is commonly used for immunosuppression following solid organ and bone marrow transplantation and for the treatment of autoimmune disorders. Administration of cyclosporin A is known to be associated with a wide range of systemic complications: neurotoxicity is noted in approximately 20% of patients and symptoms such as tremors, paraesthesias, headaches, confusion, seizures and coma have been recorded (Koide et al. 2000). The cyclosporin A encephalopathy is usually associated with white matter hypoattenuation on cranial CT scans, but is generally reversible after discontinuation of the drug (Hughes 1990). One of the proposed mechanisms is vasoconstriction induced by cyclosporin A and this was demonstrated experimentally in the coronary artery (Khalil et al. 1996). Furthermore, it was shown to cause direct toxic damage to brain cells, particularly to oligodendrocytes and neurons (McDonald et al. 1996), as well as mild cerebral cell loss (Nassbaum et al. 1995). Several fatal cyclosporin A-associated deaths have been presented in the literature (Nassbaum et al. 1995; de Perrot et al. 2000; Koide et al. 2000), one of them in a medico-legal setting after accidental administration of the drug in a 10-fold concentration via a central line: the patient subsequently developed a massive cerebral oedema with brainstem compression resulting in death (de Perrot et al. 2000). The non-accidental cases were also characterised by substantial cerebral oedema resulting in brain stem compression (Nassbaum et al. 1995; Koide et al. 2000), of which the more recent case showed a unique angiopathy with segmental narrowing of the basilar artery with intimal dissection resulting in multiple necrotic CNS lesions (Koide et al. 2000). Our case, however, presented normal cerebral blood vessels except for the focal mycotic vasculitis.

Accidental drug insertion into a wrong body cavity or into a blood vessel when the preparation is not meant for parenteral use as well as adverse drug reactions, may have profound immediate, delayed and/or long-term implications (Uchigasaki et al. 1998). Children are known to suffer a different range of adverse drug reactions which are not comparable with the experience in adults (Gupta and Waldhauser 1997). The incidence of such therapeutic misadventures was found to be 0.46% during an 11-year period in a metropolitan coroner's office in the USA and the largest category consisted of surgical complications followed by complications during anaesthesia, diagnostic procedures and drug reactions (Murphy 1986). Another study found the annual rate of fatal therapeutic misadventures to be 2.2 per 100,000 hospital admissions of which 60% died within the first 24 h; interestingly, with 118.2 vs. 53.9 cases per 100,000 beds per year, University-related hospitals had double the rate of misadventure fatalities compared to community-based hospitals (Perper et al. 1993), possibly reflecting the more hectic and busier wards, the higher percentage of inexperienced junior staff as well as the generally more serious condition of patients in a University Hospital environment which may require the administration of a more toxic range of drugs with increased risk of side-effects.

In parallel with the increasing number of immunocompromised patients, be it through disease or, as in this case, due to therapeutic immunosuppression after organ transplant, the frequency of opportunistic infections also increases. Fungi with low pathogenicity are among the most common infectious agents found under such circumstances. Fungal emboli may lodge in the intracranial arteries and organisms may penetrate the wall and result in vasculitis which may weaken the wall to such an extent that haemorrhaging ensues. Septic foci may occlude an artery and cause an ischaemic infarct which undergoes secondary

haemorrhagic transformation. Among the most common fungi associated with cerebral vasculitides are *Aspergillus* and *Candida* of which particularly the former is known to cause cerebral infarction and haemorrhage (Somer and Finegold 1995). Occasionally, these vasculitides result in mycotic aneurysms from occlusion of the vasa vasorum which are caused by infected emboli usually stemming from the heart, lungs or paranasal sinuses, with *Aspergillus* once again being the most common species responsible (Kalimo et al. 1997). However, in our case no aneurysm was found as the source for the subarachnoid haemorrhage which is in accordance with the clinical observation that in about 15% of patients with subarachnoid haemorrhage no aneurysm can be detected by angiography (Rinkel et al. 1991). Although no extracerebral septic focus was found in our case and thus no microbiological culture was performed, the morphology of the hyphae is characteristic for *Aspergillus*. Whether the fungus was also responsible for the thalamic infarction remains speculative; however, after thorough examination of the brain parenchyma no other mycotic focus could be found leaving a cardiac embolus as the most likely source.

Among patients with subarachnoid haemorrhage, vasospasm of the cerebral arteries are found in approximately 46% of cases (Karhunen and Servo 1993) and the associated delayed cerebral ischaemia and infarction are currently the most important cause of morbidity and mortality (Findlay et al. 1991; Öhman et al. 1991) causing neurological deficits in 15–35% of patients (Kalimo et al. 1997). The clinical manifestations of delayed cerebral ischaemia do not usually begin before day 4 after the initial subarachnoid haemorrhage and reach a maximum around day 7 with 30% of patients dying and another 30% becoming permanently disabled due to brain infarction (Kalimo et al. 1997). A recent study showed that the pathogenesis of these delayed neurological deficits after subarachnoid haemorrhage may, at least in part, be due to products of haemolysis in the subarachnoid space, i.e. haemoglobin and potassium (Dreier et al. 2000). The site of these complicating lesions need not be related to the location of the maximum subarachnoid blood clot (Öhman et al. 1991), as is exemplified in our case where fresh necroses were found in the frontal and parietal lobes as well as in the nucleus lentiformis. The presence of blood in the cerebrospinal fluid seems to be the crucial initiating event, although the definite pathogenesis of arterial vasospasms still remains poorly understood (Kalimo et al. 1997). Regarding the increasing frequency of cardiac surgery and thus of potential cerebral complications, a recent publication in this journal recommended the use of cerebral post-mortem cast angiography in order to visualise intravascular pathology such as arterial stenoses and thromboses, and found a 92% sensitivity in showing new main cerebral artery thromboses (Saimanen et al. 2001). Quite correctly, the authors point out that this procedure would minimise or even prevent the likely distortion of the vascular anatomy by dissection; however, this method would probably not have solved the cause and source of the haemorrhage in the presented case.

In conclusion, neuropathological investigation found a focal infiltration of fungal hyphae in the left posterior cerebral artery resulting in necrosis of the blood vessel wall. Given that prior to embedding, each basal cerebral artery was cut into numerous sections of approximately 0.3 cm in length, the fact that only one vascular segment of the whole circle of Willis and its main branches was affected by mycotic vasculitis means that the vessel wall necrosis extended only a few millimeters. This minute defect, however, was enough to cause the recurrent subarachnoid haemorrhage which presented clinically as severe intermittent headaches and eventually resulted in the girl's death, thus ruling out that medical misadventure was directly responsible for the death of the patient. However, measures have been taken to investigate why this mishap took place in order to avoid its recurrence. Furthermore, the child's family still has the ability to resort to civil law; however, the relatives had not taken this step at the time of reporting. This case illustrates that it is of paramount importance to copiously sample and investigate the basal cerebral arteries in cases of subarachnoid haemorrhage of unknown origin, in particular in a medico-legal context.

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