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CASE REPORT

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Amniotic fluid embolism with involvement of the brain, lungs, adrenal glands, and heart

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Abstract The case of a healthy 31-year-old woman in the 40th week of second pregnancy is presented. During preparation for an emergency caesarean section, she developed an amniotic fluid embolism (AFE) with unusual and unique features. The acute onset of disease with cardiorespiratory failure with hypotension, tachycardia, cyanosis, respiratory disturbances and loss of consciousness, suggested at first a pulmonary thromboembolism, but the appearance of convulsions led to the diagnosis of AFE. The patient died after 5 days due to an untreatable brain edema. At autopsy, AFE with the usually associated disseminated intravascular coagulation was found in the lungs, brain, left adrenal gland, kidneys, liver and heart. Eosinophilic inflammatory infiltrates were found in the lungs, hepatic portal fields and especially in the heart, suggesting a specific hypersensitivity reaction to fetal antigens. Moreover, intravascular accumulation of macrophages in the lungs also favored a non-specific immune reaction to amniotic fluid constituents.

Keywords Amniotic fluid embolism · Anaphylactoid syndrome of pregnancy · Systemic amniotic fluid embolisms · Interstitial eosinophilic myocarditis

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Introduction

Amniotic fluid embolism (AFE) is a rare complication in pregnancy, but it is a significant cause of maternal death. The aim of this report is the presentation of the case of a patient with rare systemic AFE affecting the brain, lungs, adrenal glands, kidneys, liver, and heart.

Case history

Patient history

A healthy 31-year-old woman was admitted to the obstetrics department for delivery after a normal 40th week second pregnancy. The patient had already given birth to a healthy girl 7 years before. The medical history revealed an allergy to poplar pollen, mites, dog hairs, organic solvents and penicillin. During preparation for an emergency caesarean section because of child bradycardia she suddenly collapsed, lost consciousness, and had convulsions. She became hypotensive with tachycardia, cyanosis and shallow and agitated respiration. She was intubated and immediately moved to an operating room where she gave birth by caesarean section to a normal baby girl weighing 2830 g and 48 cm in length. The placenta did not disclose any abnormality. After surgery the mother did not wake up and began to bleed from the surgical wound and from the uterus. She was administered an uterotonic drug and ice was put on the abdomen, which was also treated by massage but the blood did not coagulate. AFE with disseminated intravascular coagulation (DIC) was suspected. Laboratory tests at the end of surgery and after 12 h confirmed anaemia and disturbances in coagulation. She was given Capramol (epsilon-aminocaproic acid) and transfusions of concentrated erythrocytes, fresh frozen plasma, cristalloids, and 6% HAES (colloidal plasma expander, hydroxylethyl starch) and 2 h after surgery the bleeding stopped. Her respiration was spontaneous and adequate but she began to suffer from myoclonic seizures and was tranquilized using Dormicum (midazolam) and Diprivan (propofol). Unconsciousness and convulsions with developing lateralization indicated the involvement of the central nervous system. Computer tomography revealed a thrombosis in the right medial artery with a large ischemic lesion in the corresponding area that became haemorrhagic in the next 24 h. She died 5 days after delivery with clinically untreatable brain edema.

An autopsy was performed and formalin-fixed paraplast-embedded tissue specimens were stained with hematoxylin and eosin and immunohistologic markers for cytokeratin, macrophages (CD68), choriogonadotropine, and epithelial membrane antigen (EMA).

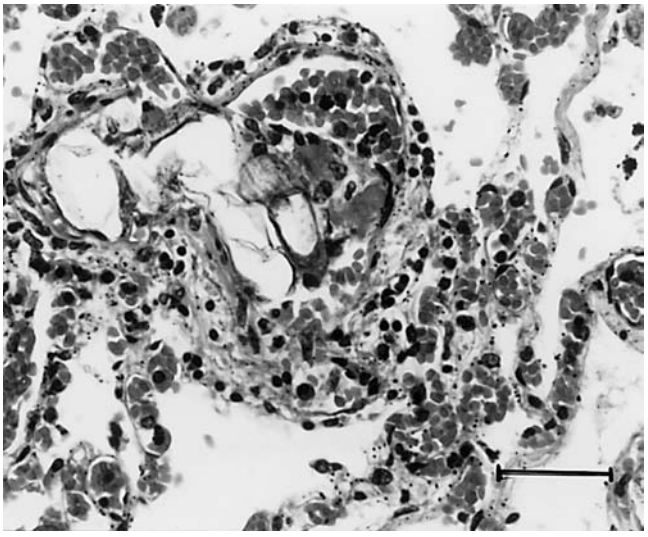

Fig. 1 Amniotic fluid embolism in a lung vessel (HE, original magnification 190×, *bar* 50 µm)

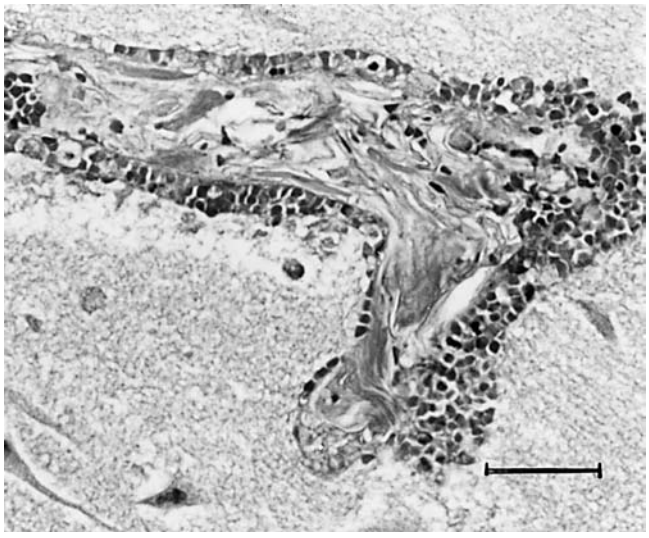

Fig. 3 Cerebral vessel packed with filamentous structures (HE, original magnification 190×, *bar* 50 µm)

Autopsy findings

Both lungs were moderately congested and edematous: the weight of the left lung was 460 g, and the right 540 g. Multiple AFEs were found in numerous lung vessels (Fig. 1). Cytokeratin-positive structures and even epithelial cells were disclosed in fibrin thrombi. Scattered interstitial inflammatory infiltrates rich in eosinophilic granulocytes were widespread in the lung tissue. Clusters of macrophages, but no choriogonadotropine-positive cells were found in the lung vessels.

Abundant fetal squame debris with cytokeratin-positive filamentous structures was also packed in the capsular vessel of the left adrenal gland (Fig. 2).

The autopsy confirmed haemorrhagic infarction in the region of the right medial and posterior cerebral arteries. Infratentorial herniation of both parahippocampal gyruses, and herniation of the right cerebellar tonsilla into the great occipital aperture were caused by severe brain edema. The weight of the brain was 1,370 g. Histologically, a diffuse hypoxic brain lesion was accompanied by numerous fibrin thrombi and AFE in small cerebral arteries with perivascular and intracerebral haemorrhages. Immunohistological staining for cytokeratin revealed numerous filamentous structures of deformated epithelial cells, focally mixed with fibrin thrombi (Fig. 3).

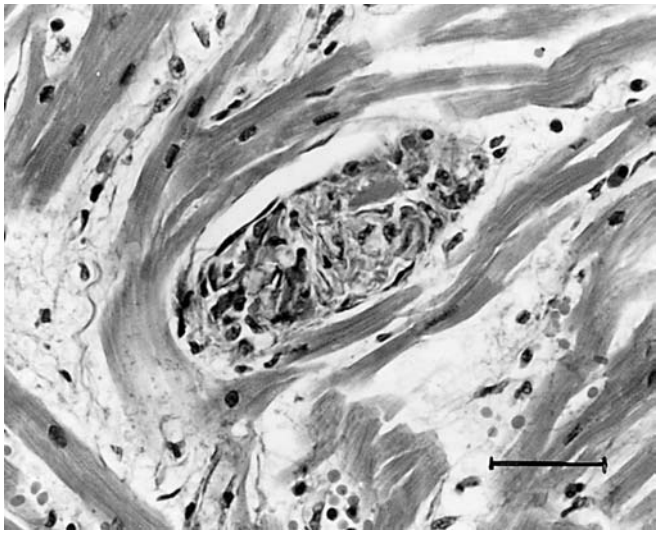

Fig. 4 Amniotic fluid embolism with squames in a small myocardial vessel (HE, original magnification 190×, *bar* 50 µm)

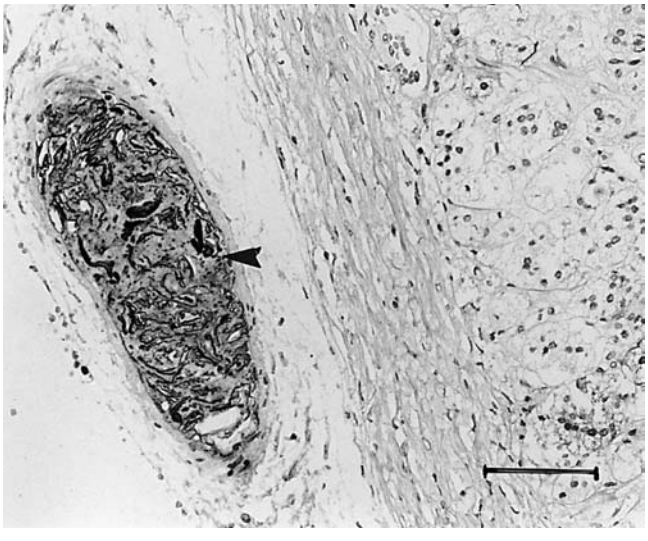

Fig. 2 Adrenal gland with abundant filamentous epithelial squames in the capsular vessel (*arrow*) (anti-cytokeratin, original magnification 95×, *bar* 100 µm)

There were some discrete punctate epicardial haemorrhages of the heart posterior wall, and the heart was moderately dilated with a weight of only 230 g. Intracardial shunt was not detected, the heart oval foramen was closed. AFE was accompanied by irregular, almost diffuse myocardial interstitial inflammatory infiltrates, rich in eosinophilic granulocytes, with sparse disseminated and isolated myocardial cell necroses. Cytokeratin-positive filamentous structures, not visible in hematoxylin-eosin staining, and even squamous cells were found in numerous myocardial capillaries (Figs. 4, 5 and 6).

In a small number of liver vessels, there were some large cytokeratin-positive epithelial cells with small nuclei and abundant cytoplasm and some filamentous structures also suggesting AFE.

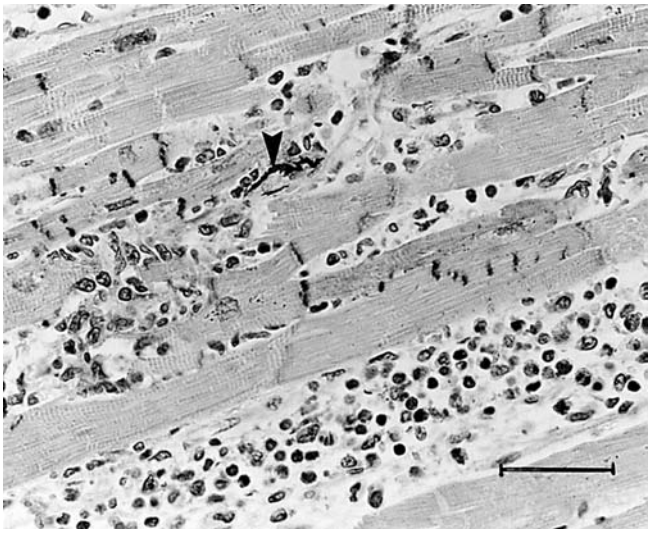

Fig. 5 Keratin squame (*arrow*) in a myocardial capillary with surrounding inflammatory infiltrate (anti-cytokeratin, original magnification 190×, *bar* 50 μm)

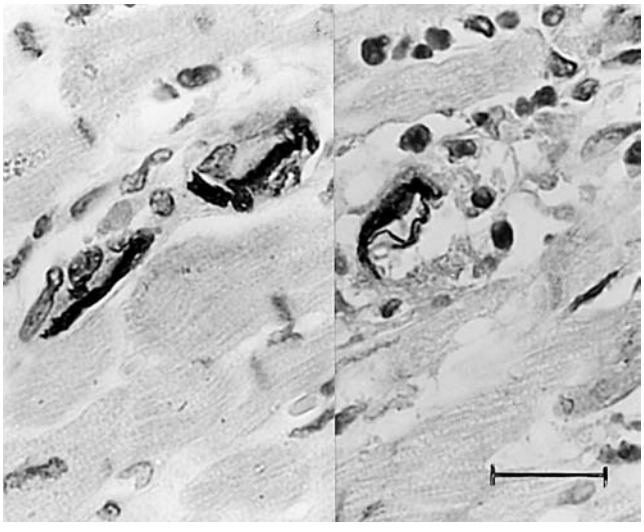

Fig. 6 Multiple keratin squames in myocardial capillaries (anti-cytokeratin, original magnification 380×, *bar* 25 μm)

Portal inflammatory infiltrates were rich in eosinophils. A few epithelial squames were found also in glomerular capillaries.

Only small haemorrhages were found on the uterus in the region of surgery without free blood in the abdominal space. The spleen was cyanotic and enlarged to 300 g.

Discussion

The pathogenesis and even the name of AFE, first described in 1926, are still controversial [1]. Besides less important hemodynamic changes due to mechanical obstruction by pulmonary emboli, an immune immunoglobulin E-mediated anaphylactic or non-immune anaphylactoid reaction to amniotic fluid, activation of complement, and direct influence of amniotic fluid constituents have been proposed [2, 3, 4]. The entrance of fetal antigens and potent bioactive substances (thromboplastin, plasmin activator, vasoconstrictor endothelin, platelet-activating factor) from the amniotic fluid into the maternal circulation, may cause a sudden onset of cardiovascular and respiratory failure, and may activate a coagulation cascade and thrombin generation [5, 6, 7, 8]. Our patient survived 5 days, developed eosinophilic myocarditis, focal eosinophilic pneumonitis and focal portal eosinophilic hepatitis, probably based on an allergic mechanism, a specific anaphylactic reaction to fetal antigens. Moreover, intravascular accumulation of macrophages suggested a non-specific immune mechanism to foreign material. The serious condition of the patient did not allow thorough immunologic examinations, and determination of serum tryptase was not available. This enzyme is a marker of mast cell degranulation, which may appear in both anaphylactic or anaphylactoid reactions [3, 9, 10].

The incidence of fatal AFE ranges from 1 in 8,000 to 1 in 120,000 deliveries [11, 12, 13, 14, 15, 16, 17] and although maternal death is rare, AFE is recognized as one of the most prominent causes, responsible for about 10% of all maternal deaths [4]. The real incidence of fatal and non-fatal AFE is difficult to ascertain. The only reliable histologic confirmation cannot be performed in survivors with only clinically suspected AFE. It occurs in most cases during labour (52.6–70%) or soon after delivery [4, 18], presenting as acute cardiopulmonary collapse with cardiac arrest or sudden profound shock, hypotension, respiratory failure with hypoxia, dyspnoe with cyanosis, haemorrhaging, coagulopathy, such as DIC (up to 85%) with or without clinically significant bleeding, and tonic-clonic seizures [19, 20]. In the first instance cardiovascular and respiratory disturbances suggested a pulmonary thromboembolism, but the appearance of seizures in our patient, which may be an initial sign of AFE in 10–50% of cases, was not compatible with such a diagnosis [21, 22].

Differential diagnosis includes diseases with common features of acute onset of cardiorespiratory symptoms: thrombotic or air pulmonary emboli, septic shock, acute myocardial infarction, cardiomyopathy, anaphylaxis, aspiration, placental abruption, eclampsia, uterine rupture, transfusion reaction, and local anesthetic toxicity [1, 2, 3, 4, 7, 8]. The similarities of clinical and hemodynamic findings in AFE and in anaphylaxis or septic shock prompted Clark and colleagues to rename AFE as anaphylactoid syndrome of pregnancy, but the name was not generally accepted [2, 3, 4, 6].

Similar changes can be found with the HELLP (i.e. haemolysis, elevated liver enzymes low platelet count) syndrome, although in this case they are concentrated mainly in the liver and kidneys and are not described in the myocardium [23].

Symptoms of the special shock syndrome are important at the level of the lungs and brain because of hypoxia, which causes a clinical appearance similar to AFE [24].

Mortality is still high, 61–86%, in spite of all therapeutic measures [4, 7], among survivors only 15% were neurologically intact [4], 39% of patients die within 1 h after

onset, and half of the patients die in the first hours of the disease [18]. A peculiar feature in our patient was the relatively long period of survival.

Although AFE is more often associated with gemini/polydramnios, placental abruption, placenta praevia/accreta, rupture of the membranes, tumultuous labor/delivery with uterine hypercontractility, caused also by syntocinon or prostaglandin E therapy, rupture of the birth canal, macrosomia, pregnancy-induced hypertension, multiparous or older patients, fundal pressure, allergy or atopy, and caesarean section [6, 14, 18], no clear risk factors for development of AFE could be established [25]. Of the patients 41% had a medical history of allergy or atopy [4]. The history of allergy and more frequently than usual manual transvaginal inspections could be predisposing factors in our patient.

AFE is histologically usually demonstrated in the lungs with fragments of vernix caseosa, squamous cells and squames as filamentous structures, lanugo hair, mucin, meconium and trophoblastic cells. Systemic involvement with AFE is much more rare than only lung involvement [26, 27, 28]. Combined AFE and fibrin thrombi may also have affected and obstructed larger vessels, such as cerebral arteries in our case.

How can one explain systemic extrapulmonary AFE? Embolized particles of less than 10 µm can normally pass through pulmonary capillaries, but larger masses of amniotic material can pass through pulmonary arterial-venous anastomoses, especially during elevated right ventricular pressure due to massive pulmonary AFE with pulmonary hypertension.

The definite diagnosis is confirmed by histologic demonstration of AFE constituents in the vessels. Fetal squames in the central circulation are not enough for a definite diagnosis [29]. Serum tryptase could be helpful in confirmation of anaphylactic or anaphylactoid reactions, but the enzyme level is not always elevated [30]. The immunohistologic demonstration of amniotic fluid-derived mucin and a thorough examination of the resected cervix in cases of suspected AFE may be helpful [31, 32]. Antibodies to human keratin should be made to enhance detection of keratin squames [33]. This method was also helpful in our case revealing squames in many organs and especially in myocardial capillaries. Their appearance could explain the development of a not yet reported eosinophilic myocarditis due to fetal antigens. The squames are a discriminatory feature in the differential diagnosis of ischaemic, traumatic and toxic myocardial lesions with myocardial necroses and inflammatory infiltrates, and especially in the differential diagnosis of eosinophilic myocarditis due to infection or various immune-mediated reactions.

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