INVASIVE ASPERGILLOSIS IN AN ELBW PREMATURE

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Abstract

Invasive aspergillosis represents a severe condition, with extremely rare incidence in the neonatal period, but it is a major cause of morbidity and mortality, especially among patients with compromised immunity: extreme prematurity newborn from a mother with HIV, immune deficiency syndromes. We present the case of a ELBW premature newborn, with gestational age of 26 weeks and weight at birth of 850 grams, from a pregnancy not taken into evidence, with severe intrapartum asphyxia, APGAR index 1 on 1 minute, with severe neonatal respiratory distress and neonatal sepsis, who was transferred into the Prematures Department of the "Louis Turcanu" Emergency Clinical Children's Hospital in Timisoara in the first day of life, from a 1st degree maternity in Romania. The newborn required mechanical respiratory support throughout the entire period of hospitalization and the evolution was fulminant, towards death in the 15th day of life. Necropsy was performed, and the histopathological examination detected Aspergillus at the level of the pulmonary, hepatic, renal and intestinal parenchyma.

Keywords: Aspergillus, invasive aspergillosis, premature, sepsis.

Introduction

Aspergillus sp. continues to be an important cause of life-threatening infections in the immunocompromised patients. Patients with severe and prolonged neutropenia, severe immunodeficiency, prematures, patients with HIV or stem cells transplant have an increased susceptibility to fungal infections.

Aspergillus sp. are conditionally pathogenic fungi present in the air, water, soil or decomposing plants. Outbreaks of disease among immunocompromised persons may appear in renovation or construction works within hospitals or around them [1, 2], through inhalation of spores (conidia) in the air [1]. These colonize the superior and inferior respiratory tract and then hematologically disseminate, later determining the invasive form of disease (invasive pulmonary aspergillosis, Aspergillus sinusitis, disseminate aspergillosis).

There are known approximately 180 species of Aspergillus, of which 34 have been associated with human disease [3]. In the pediatric area most illnesses are caused by Aspergillus fumigatus (90%), followed by A. flavus, A. niger and A. nidulans [1].

Premature neonates, due to cortisone therapy and wide-spectrum antibiotic therapy, of damaging the barrier function of the skin, or the very immaturity of the immune system, may develop primary cutaneous aspergillosis or even invasive aspergillosis, with multiple organs involvement.

Case Report

We present the case of a male newborn, born prematurely at gestational age of 26 weeks, with a weight of 850g. The newborn comes from a pregnancy not taken into evidence, with imminence of abortion at 11 weeks of pregnancy, the mother 32 years old, with intrapartum anemia (Hb=7g/dl), G IX P III (we do not have data on the number of abortions requested versus pregnancies interrupted in evolution). He was born naturally, membranes broken in expulsion and clear amniotic fluid, in a 1st degree maternity in our country. APGAR score was 1 at 1' and 3 at 5'; he was ventilated with positive pressure with 100% O_2 through mask in the delivery room, then CPAP ventilation was instituted nasally, maintaining SaO_2 of 87-92%.

General condition was severe from the first day of live, and the newborn was transferred to our ward with the following diagnoses: Extreme prematurity, Neonatal respiratory distress, severe asphyxia.

On admission he presents an influenced general condition, erythematous thin skin, white-pearly umbilical stump, purulent conjunctival secretions in both eyes, cold extremities, anterior fontanelle of 2/1.5cm normotensive; functional respiratory syndrome – Silverman score=7; SaO_2=86-92% with oxygen therapy 8 l/min under cephalic tent; AV=122b/min; BP=49/31mmHg; meconium stool; diuresis present.

Cardiopulmonary X-ray was performed: discrete alveolar opacities at the base of the left lung, enhanced right infrahilar interstitial tissue, normal heart.

Laboratory tests on admission indicate: leukocytosis (Le =44.370/mm^3 on admission, increasing up to 72.680/mm^3 in evolution), reactive C protein positive, elevated Procalcitonin (1,3ng/ml) (Figure 1.), hypoglycemia, hypoproteinemia, dyselectrolytemias, mixed acidosis.

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3 hours after admission, the general condition of the premature aggravates, the respiratory functional syndrome enhances (Silverman score = 8), ASTRUP indicates severe respiratory acidosis and requires orotracheal intubation (OTI) and mechanical ventilation (MV) SIMV mode (subsequently IPPV). At 15 hours of life Surfactant was administered. Wide spectrum antibiotic therapy was also instituted, from admission into our Clinic, plus hydration and hydroelectrolytic and acid-alkaline balancing perfusion, inotropic support, gastric protector, antihemorrhagic drugs. (table 1).

General condition remained severe all throughout the admission in our Clinic (table 1). He required continuous mechanical respiratory support, transfusion of erythrocyte mass isogroup isoRh, repeated transfusions of freshly frozen plasma, Cryoprecipitate, he also received human albumin and immunoglobulin. He develops multiorgan failure, digestive hemorrhage, subsequently also pulmonary hemorrhage and death occurs in the 15th day of life.

Necropsy was performed and the macroscopic morphopathological diagnosis was: thrombosis of choroid plexuses, bronchopneumonia, hepatic and renal abscesses, suprarenal hemorrhage.

Organ fragments were also taken for the histopathological exam. On microscopic examination of samples taken specific modifications were observed, of a chronic inflammatory type, specific for *the Aspergillus type* at the level of the pulmonary parenchyma, renal parenchyma, of the liver and the intestine (Fig. 2-11).

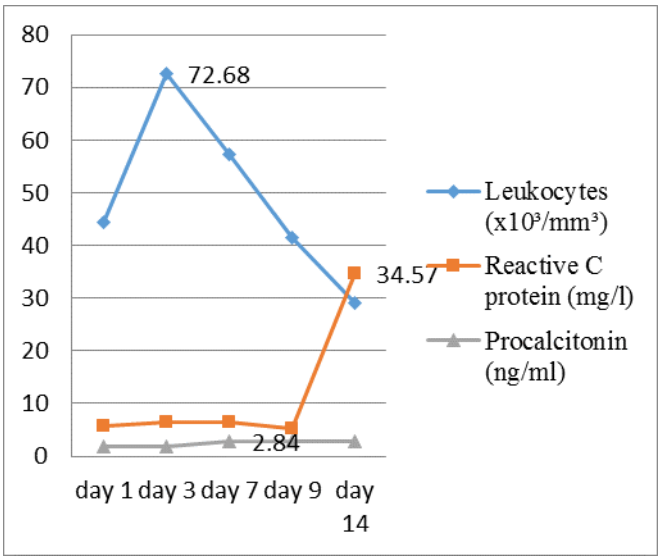

Fig. 1. Evolution of inflammatory markers

Medical problems	***Day's onset (no. of days of life)***	***Treatment***
Extreme prematurity (GA=26 weeks, WB=850g)		
Neonatal sepsis with Enterobacter aerogenes	d1	Wide spectrum antibiotic therapy, human Immunoglobulin
Neonatal respiratory distress. Acute respiratory failure, severe form	d1	Surfactant, mechanical ventilation
Arterial hypotension	d1	Dopamine, boluses with saline solution
Metabolic conditions (hypo/hyperglycemia, hyproteinemia, hyperkalemia, hypocalcemia)	d1	Hydroelectrolytic & acid-alkaline rebalancing, human albumin
Acute renal failure	d2	Dopamine, Furosemide
Thrombocytopenia	d4	Plasma
Mixed anemia (of prematurity, intrainfectious)		Transfusion of erythrocyte mass isogroup isoRh in d14
Hemorrhagic syndrome (digestive, pulmonary hemorrhage)	d12-14	Plasma, Cryoprecipitate, Etamsylate, Fitomenadione

Table 1. Medical problems and consecutive treatment.

Discussion

Early detection of infection with Aspergillus is extremely important in the premature newborn, due to the immaturity of their defense system, immune system, due to the complex and severe pathology of prematures, of complications that may occur and that are associated with high neonatal morbidity and mortality. Early diagnosis may be easier in cutaneous forms, when biopsy performed from a skin lesion with initial aspect of erythematous or purple papula, which progresses rapidly (24 hrs) towards ulceration and bedsores [4], uncovers the fungal infection and it is difficult in the invasive forms, when many times the diagnosis is established post-mortem. Diagnosis is based on a combination of clinical risks, symptoms and signs, culture, histopathology, and detection of the fungal components such as the antigen galactomannan [3].

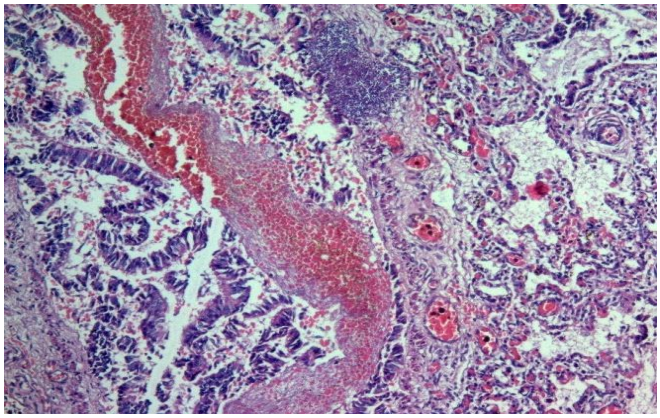

Fig. 2. Pulmonary parenchyma with specific chronic granulomatous inflammation of Aspergillosis type – hematoxylin-eosin stain

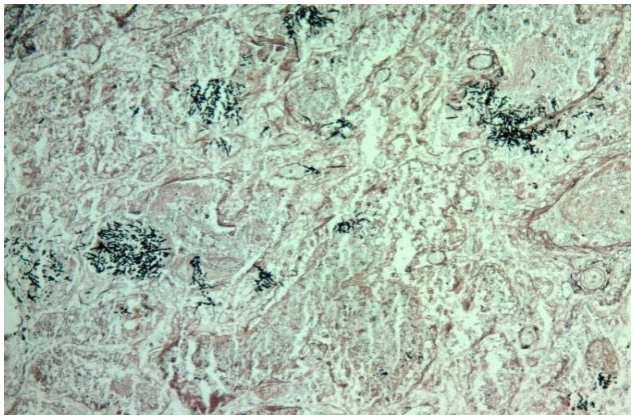

Fig. 3. Pulmonary Aspergillosis – Grocott stain

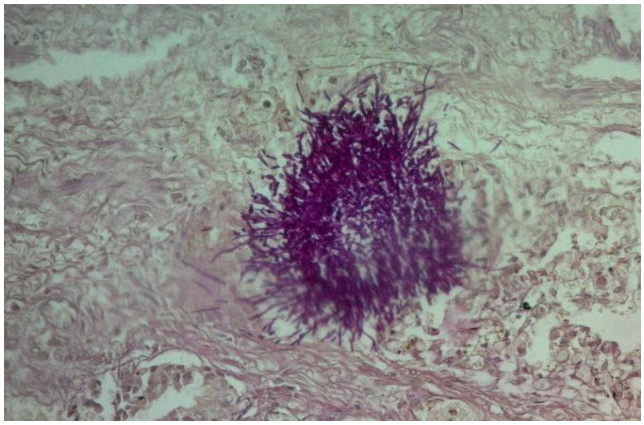

Fig. 4. Pulmonary Aspergillosis – PAS stain

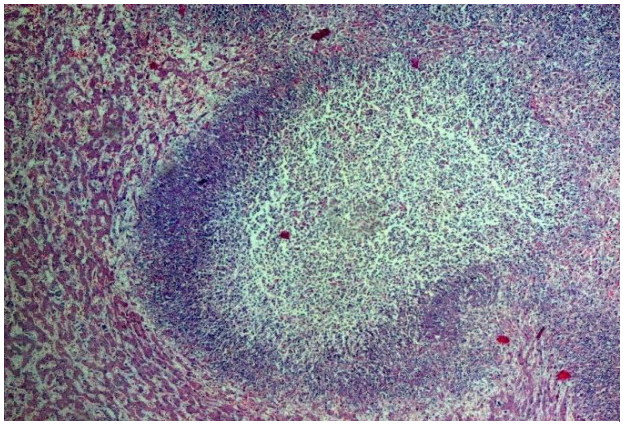

Fig. 5. Hepatic parenchyma with chronic granulomatous inflammation of Aspergillosis type – hematoxylin-eosin stain

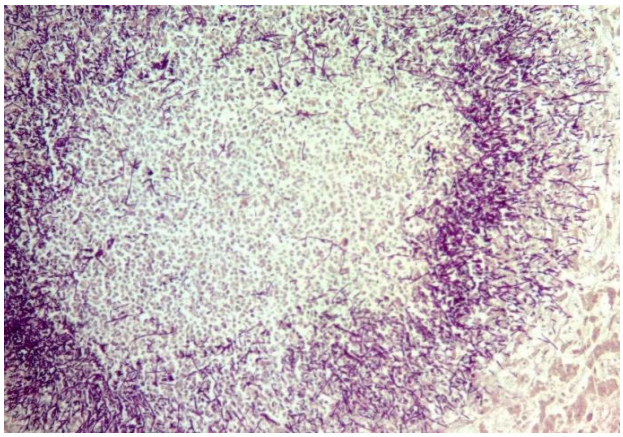

Fig. 6. Aspergillus sp. in the liver parenchyma – PAS stain

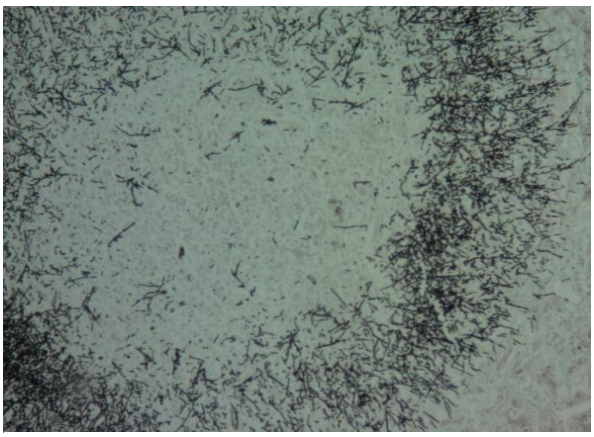

Fig. 7. Aspergillus sp. in the liver parenchyma – Grocott stain

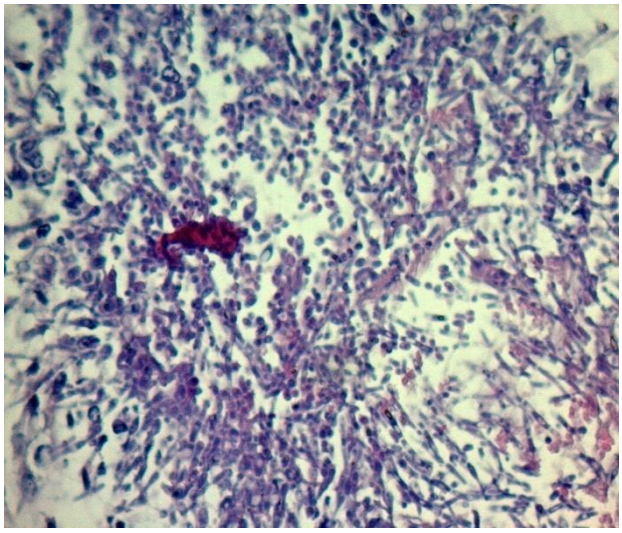

Fig. 8. Renal parenchyma with chronic granulomatous inflammation of Aspergillosis type (hematoxylin-eosin)

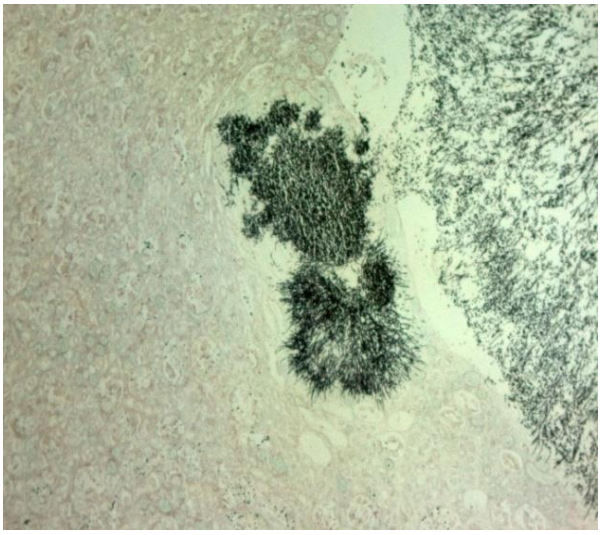

Fig. 9. Renal Aspergillosis (Grocott stain)

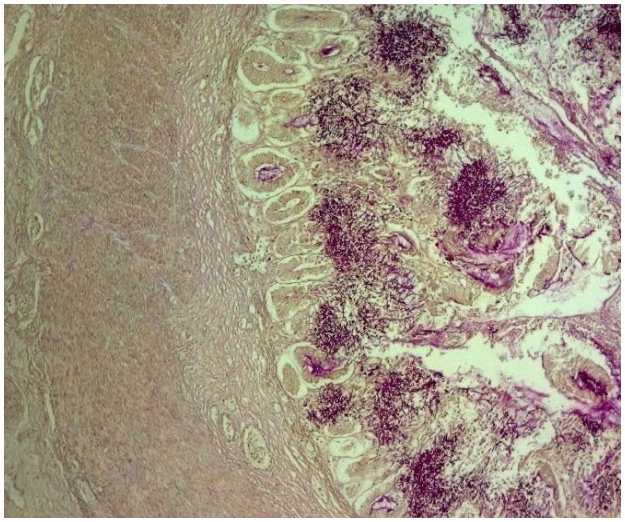

Fig. 10. Intestinal aspergillosis – PAS stain

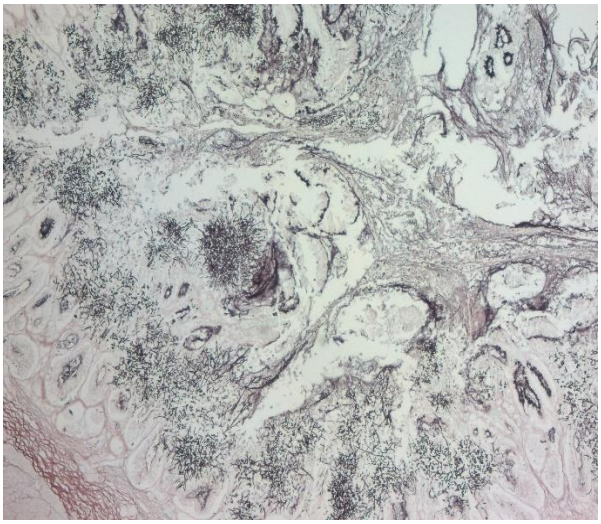

Fig. 11. Intestinal aspergillosis (Grocott stain)

The certainty diagnosis of aspergillosis is given by the histopathological or cytological exam and cultures from biopsy material (skin, lung), from secretions and blood.

In the case of suspicion of fungal infections (persistent fever in an immunocompromised patient, in spite of wide spectrum antibiotic treatment, acute pneumopathy with respiratory failure, radiologic modifications, neutropenia), detection of Aspergillus antigen through the galactomannan method is preferred to the PCR (polymerase chain reaction) technique for detecting the Aspergillus DNA, the latter not being routinely recommended anymore in medical practice. Serum and bronchoalveolar lavage galactomannan is recommended as an accurate marker for the diagnosis of invasive aspergillosis in pediatric patient [5].

In regard to the radiological diagnosis, it is difficult, the changes being non-specific (from focal or peripheral nodular lesions, to diffuse consolidations or cavities). Pulmonary computer tomography can be of greater help [6].

Isolating the Aspergillus from the sputum is a precise indicator of the invasive infection; however, according to specialty studies, only 25% of patients who were diagnosed tardy with aspergillosis had a positive sputum culture ante-mortem [7].

Bronchoalveolar lavage is also of great help in diagnosis, and nasal culture may be predictive for nosocomial aspergillosis from the renovation works.

In the case of our patient, several samples of tracheobronchial aspiration were taken, which did not detect Aspergillus or other germs at that level. Also, nasal culture was sterile. Cardiopulmonary X-ray performed on admission presents discrete alveolar opacities at the base of the left lung and enhanced right infrahilar interstitial tissue,

modifications that have been interpreted as being within the neonatal respiratory distress syndrome.

Hemoculture performed on admission detected Enterobacter aerogenes at 48 hours, the patient receiving treatment in accordance with the antibiogram. The culture from the tip of the endotracheal intubation tube (performed post-mortem) indicated Candida albicans.

The diagnosis of invasive aspergillosis was established following the necropsy and the microscopic exam (HE, PAS and Grocot stain). Chronic inflammatory modifications specific for the Aspergillus type were observed in the pulmonary, hepatic, renal and intestinal tissue. The distinction between the infection with Aspergillus discovered post-mortem and the severe pathology of the neonate – the sepsis, respiratory distress syndrome, complicated with pulmonary hemorrhage, multiorgan failure – is extremely difficult to make without identifying the specific pathogenic agent and the favoring factors that trigger the disease.

Conclusions

Pathology of the ELBW premature remains a challenge for the clinician, in the conditions in which the results of cultures taken are received late and many times are negative or sterile. Wide spectrum antibiotic therapy is initiated early, but the antifungal treatment begins only in the moment of a positive culture or in the case of a clinical suspicion of fungal infection.

A critical factor that influences the rate of infection with Aspergillus is the level of contamination of the environment. Specialty literature quotes the increase in incidence in units with ongoing adjacent building work, or whose systems of air filtration are defective [1,2]. During that period, in our unit or immediately close to the hospital no renovation works have been performed and no other cases of infections with Aspergillus were reported.

The septic state of the premature, the severe respiratory distress that required mechanical ventilation throughout the entire period of hospitalization, the necessity of administering wide spectrum antibiotic therapy and cortisone therapy, have created an ideal environment for the development of Aspergillus, whose source has not been detected. It is possible that the initial infection was on a respiratory or pulmonary level, with invasion of vascular structures and dissemination on the hepatic, renal and intestinal level.

It is very difficult to distinguish between the severe pathology of the newborns and the fungal infections that they may develop, while not being able to discover the specific pathogenic agent or certain trigger factors for the disease.

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