Agranulocytosis and puerperal sepsis in woman after the use of ceftriaxone

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A 34-year old woman was admitted at the obstetric ward in the 34th week of gestation, complaining of progressive dyspnea, until it occurred, two days ago, in supine position, and edema in lower limbs.

The patient's obstetric history included one miscarriage four years ago and childbirth two years ago. The patient was under prepartum care at Basic Health Unit, using vitamin supplementation. The patient knew she had heart murmur. Three days ago, the patient received ceftriaxone intramuscularly for treatment of pyelonephritis.

The physical examination revealed that the patient presented normal color, was hydrated, dyspneic, weighed 56 kg, was 1.70 m high, had a heart rate of 116 beats per minute, blood pressure of 110/70 mm Hg. The lung examination revealed bilateral vesicular murmur and no adventitious sounds. The heart examination revealed rhythmic sounds, systolic murmur ++/6 and diastolic rumble in the mitral area. There was edema in lower limbs ++/4.

Obstetric tests revealed fetal tachycardia (170 bpm) and reduction of amniotic fluid (oligohydramnios).

Serologic tests for diagnosis of HIV, hepatitis and Chagas disease infection were negative. The blood count revealed leukocytosis of 18,360 cells/mm^3.

The electrocardiogram revealed sinus rhythm, rate of 70 beats per minute, QRS electrical axis at+120º, the final component of negative P wave in V1, and carved and divided in II, deep S wave inV_1, V_2 and V_3, changes of ST segment and T wave in V_2, V_3 and V_4. (Figure 1)

The chest radiography showed an enlarged cardiac area ++/4 and signs of pulmonary congestion in both lungs (Figure 2).

The echocardiogram showed a 26 mm aorta, 56 mm left atrium, 44 mm (diastole) and 33 mm (systole) left ventricle, and left ventricular ejection fraction at 63%. The mitral valve was thickened with commissural fusion. The maximum transvalvular gradient was estimated at 32 mm Hg, and the mean gradient was estimated at 19 mm Hg. The valve area was estimated at 1.05 cm^2. There was no mitral regurgitation. The aortic and tricuspid valve showed discreet regurgitation. The pulmonary artery systolic pressure was estimated at 93 mm Hg.

Ultrasound test of the urinary tract was normal.

The patient was treated with 40 mg propranolol and 40 mg furosemide, both twice daily, with improvement of symptoms. After 15 days of treatment, ceftriaxone was suspended, and the administration of Macrodantin has begun in prophylactic character.

At that time, with 37 weeks of gestational age and obstetric tests confirming that the oligohydramnios and intrauterine growth restriction, delivery by cesarean section was indicated.

On this day, the patient had cough with light-colored sputum, which got worse when lying down, with intercostal retraction and suprasternal notch. On lung auscultation, there were diffuse inspiratory wheezes, which were lessened with inhalation of beta-2 agonist.

After the childbirth, the patient received oxytocin (15 u) and nitric oxide (20 ppm). Ceftriaxone 2g/day was administered again, due to tracheobronchitis. There was an uneventful obstetric evolution. The newborn weighed 2070 g, was considered small for gestational age and had uneventful progress.

On the fourth day after delivery, the patient developed severe dyspnea, cough, odynophagia, skin pallor and fever. Lung auscultation revealed rales in the lower two-thirds of both hemithoraxes, more pronounced on the left side, and wheezing.

On the following day, the patient presented blood pressure of 57/29 mm Hg, which did not rise with administration of 0.9% saline solution. Treatment with norepinephrine was started and, as a result, dobutamine. There was progress with oliguria and a non-invasive ventilation (BIPAP) has been performed.

Oral lesions appeared compatible with oral thrush, and the blood count revealed leukopenia (340 cells/mm ^{3}).

A chest radiography showed homogenous opacity in the upper third of the left hemithorax.

Ceftriaxone and dipyrone were suspended, and the treatment with imipenem, ganciclovir, oral nystatin and human factor stimulating recombinant granulocyte colony formation has begun.

The obstetric test revealed no bleeding, normal loquia flow and the surgical wound was in good condition.

On the subsequent days (6th postoperative day), the patient underwent a worsening of the general condition, intermittent

Keywords

Agranulocytosis; leukopenia; shock, septic; opportunistic infections.

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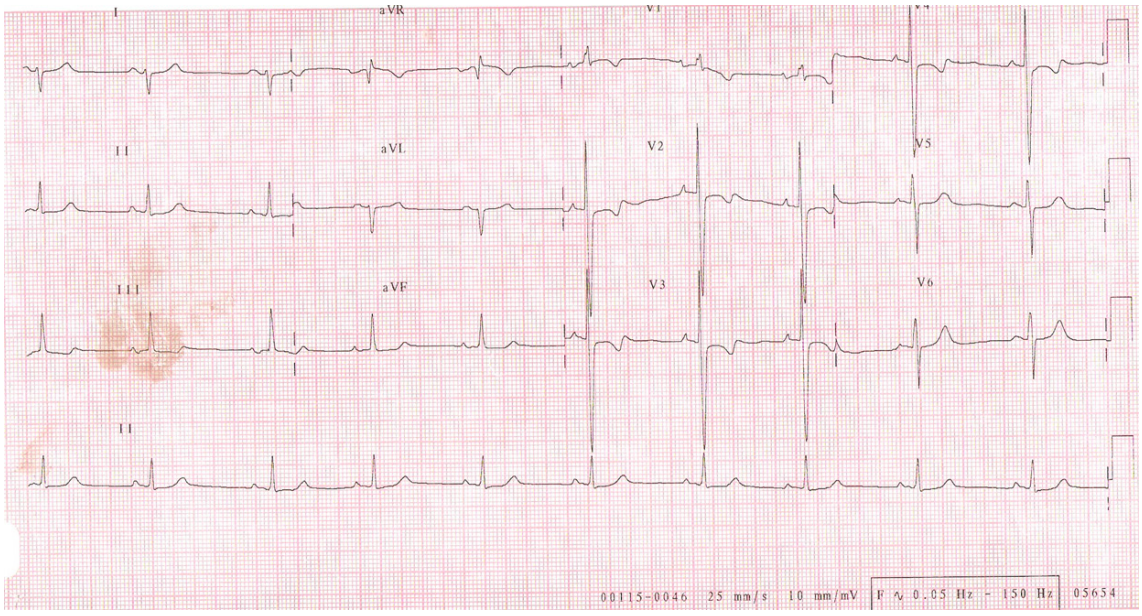

Figure 1 - *ECG: left atrial overload and probable left ventricular overload.*

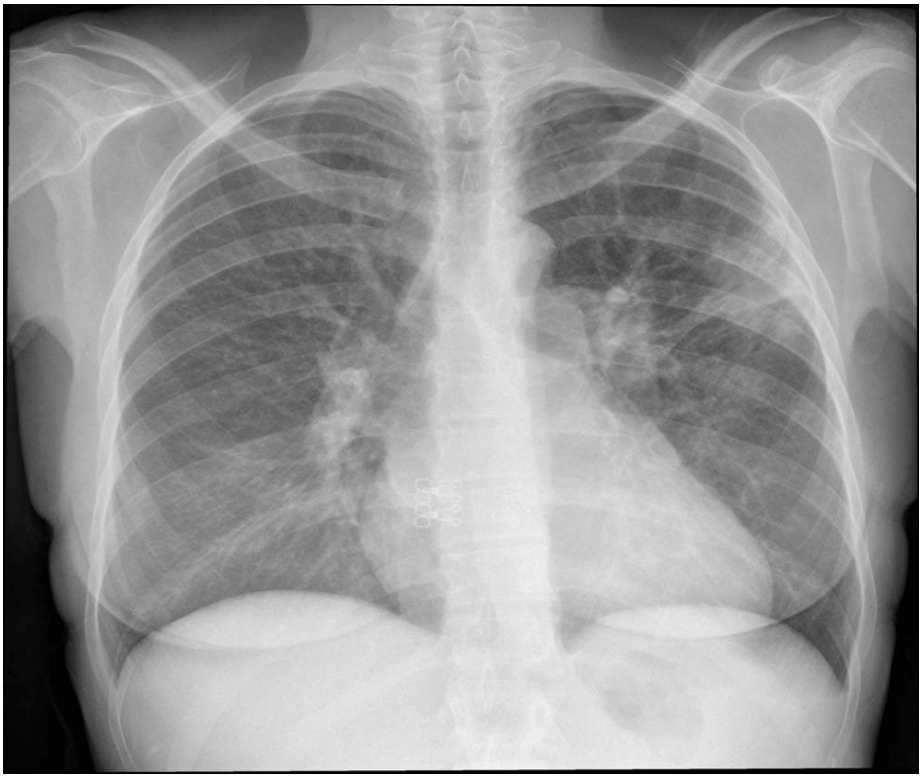

Figure 2 - *Chest radiography in posteroanterior: cardiomegaly ++/4+ and pulmonary congestion.*

fever up to 39 °C, heart rate of 130 bpm and blood pressure of 100/70 mm Hg.

In evolution, the patient had periods of agitation, respiratory distress and drop in oxygen desaturation. This was followed by seizure, with lowered level of consciousness. Orotracheal intubation and assisted mechanical ventilation were necessary for respiratory support.

The evaluation by cranial tomography revealed normal brain parenchyma, preserved cisterns and sulci, without deviation of the midline structures.

The thorax tomography revealed areas of condensation in the left upper lobe, lingula and left lower lobe with air bronchogram. There were signs indicative of mosaic perfusion of the pulmonary parenchyma bilaterally and focal pleural thickening in the left apex.

The ultrasound test of the abdomen revealed no biliary changes and preserved kidney size, with discreet bilateral hyperechogenicity. The uterus showed enlarged size, finely heterogeneous texture and small amount of anechoic content in the endometrial cavity. The spleen and pancreas showed no changes. There was small amount of free fluid in the abdominal cavity, wall thickening and distended loops of jejunum.

The myelogram revealed unchanged bony consistency and mild hemodilution, and the granulocytes/erythrocytes ratio was 1.6/1.0 (normal, from 2/1 to 4/1).

The granulocytic series test revealed absolute and relative hypocellularity, with staggered ripening and maturation arrest in promyelocytes. There were 85% of eosinophils (normal up to 5.5%) and presence of granulocytes with dysplastic changes.

The red series test revealed relative hypercellularity and preserved staggered ripening. The lymphocytic series test revealed 35% of lymphocytes (normal up to 17%) and 2% of plasma cells, preserved monocytic and megakaryocytic series (platelet production). There were increased numbers of macrophages. There were no foreign elements to the bone marrow.

The search for cytomegalovirus and parvovirus in DNA by polymerase chain reaction was positive; the search for Mycobacterium tuberculosis was negative.

Culture (via aerobic and anaerobic media) was negative, as well as culture for fungi and mycobacteria.

Cerebrospinal fluid test was normal.

Antibiotic therapy was expanded with the administration of vancomycin and clarithromycin.

On the eighth day after surgery, the patient underwent shock with metabolic acidosis, acute renal failure and need for progressively higher concentrations of vasoactive drugs. The intra-aortic balloon pump was indicated and an antifungal (amphotericin) was introduced. However, the patient underwent a cardiac arrest in refractory asystole and was subject to resuscitation maneuvers, and eventually died.

Clinical Aspects

Considering the potential for complications in pregnant women with heart disease, peripartum period should be divided into three distinct stages: (1) pregnancy, which includes the initial three quarters, (2) delivery, and (3) immediate postpartum period (first 48 hours postpartum) and late postpartum period (up to six weeks)[1,2].

This case happened in the third moment, immediate postpartum, and refers to a woman with severe mitral stenosis, admitted to the intensive care unit of InCor in shock. In this situation, considering whether the shock is hypovolemic, obstructive, cardiogenic or septic is mandatory.

Hypovolemic shock arising out of hemorrhage represents around 25% of maternal deaths (60% out of these occur in the postpartum period, 45% in the first 24 hours postpartum). The most common causes include uterine atony, present in approximately 80% of cases, retained placental fragments and lacerations of the birth canal, complications which were not undergone by the patient of this case[3]. In postpartum, obstructive shock is a hypothesis which always be considered, as, during gestation, coagulation factors are activated as of the second quarter, culminating, progressively, in the immediate postpartum[4]. Besides this, in this time, there was vessel stasis of uterine plexus and lower limbs and vessel changes in placental insertion place, factors which predispose to thrombosis. The incidence of venous thromboembolism is 5 to 50 times higher in pregnant women, when compared to non-pregnant women[2]. Over the last decades, pulmonary thromboembolism represented 15 to 20% of maternal deaths, surpassed only by hemorrhage. Most of these deaths occurred due to lack of diagnosis. Symptoms of pregnancy and puerperium, such as dyspnoea, chest pain and hypotension contribute to confuse the clinical diagnosis of pulmonary thromboembolism. In any case, cesarean delivery, prematurity, and mitral valve disease were present in this case, therefore stressing the possibility of pulmonary thromboembolism as a cause of maternal death[5].

The amniotic fluid embolism must also be regarded as a cause of obstructive shock in this time of pregnancy and peripartum period[6]. Having an incidence from one to 8,000 at 80,000 births and pathophysiology still not completely understood, this obstruction was first reported in 1926 by Meyer, head of the Pathology Lab of the Medicine School of University of São Paulo (USP).

In most cases, complementary tests for the diagnosis of pulmonary thromboembolism have shown low sensitivity and specificity[5]. Arterial blood gas measurements, the dosage of D-dimer, electrocardiogram and transthoracic echocardiogram have low sensitivity in the puerperium period. It is estimated that 50% of the cases of pulmonary embolism have a definite diagnosis by angiography. In this case, there was no change between the echocardiograms on admission and during the clinical worsening of the patient. In addition to this, the tomography showed areas of condensation in the left upper lobe, lingula and left lower lobe, identifying air bronchogram, highly indicative of bronchopneumonia.

The cardiogenic shock in this case must be considered due to maternal postpartum decompensation caused by mitral stenosis. In this time of the peripartum period, there is an increase from 30 to 50% in cardiac output, compared to the pre-partum period, hindering uterine contractions and autotransfusion of uteroplacental blood to the intravascular compartment, chiefly in the first 24 hours postpartum. In general, obstructive valve lesions

such as mitral stenosis have a worse clinical outcome compared to regurgitant lesions. Through stenotic valve, the increased volemia causes sudden increase of flow, pressure gradient and pulmonary venocapillary pressure.

Pulmonary hypertension and mitral valve area of 1.0 cm^2, data obtained by echocardiography in this case, are parameters of poor prognosis in patients with lowly symptomatic mitral stenosis before pregnancy. In fact, the patient developed functional class III (New York Heart Association – NYHA) over the 34th week of gestation, stage of greater increase in cardiac output. Nonetheless, the patient had clinical improvement when treated with low doses of propranolol and furosemide, remaining stable until delivery. Due to the good response to medication, a percutaneous or surgical intervention in stenotic valve was not regarded[7].

Septic shock due to puerperal infection is the third largest obstetric cause of maternal death. A fever which occurs in the first 24 hours after birth and continues for two consecutive days, within ten days after delivery, is usually caused by endometritis, the predisposing factors of which are: premature rupture of membranes, birth canal laceration, prolonged labor and vaginal infection[8]. None of these diagnoses were made, as well as surgical trauma, hematoma on the suture line and a foreign body (suture thread) in the post-operative period of cesarean surgery. The abdominal ultrasound excluded potential sources of infection: retention of products of childbirth, intracavitary abscess and hematoma. Urine and blood cultures and CSF analysis were negative for aerobic and anaerobic bacteria, fungi and mycobacteria.

The patient developed systemic inflammatory response, defined by the presence of two or more of the following criteria: hyperthermia (> 38 °C) or hypothermia (< 36 °C), tachycardia (> 90 bpm), tachypnea (RR > 20 ipm or $PaCO_2$ < 32 mm Hg or mechanical ventilation), leukocytosis (> 12,000 cells/mm^3) or leukopenia (< 4000 cells/mm^3 or > 10% of young forms, rods) Swiftly, the patient developed systemic shock[7].

In this case, the sequence of clinical events underscored the hypothesis of septic shock infecting the lung, rendering invalid the hypotheses of hemorrhagic and cardiogenic shock (although the latter happened in the final outcome). The severe leukopenia was an important datum, with very low white blood cell count (340 cells/mm^3).

Agranulocytosis was confirmed by myelogram, which revealed a neutrophil count lower than 1000/mm3, and which was associated with fever and infection. Agranulocytosis may be secondary to severe sepsis, myelodysplastic syndromes, and to hypersplenism and, in 70 to 90% of cases, exposure to drugs or chemicals. There is evidence that toxic, immunological, and allergic mechanisms are related to its pathogenesis.

The criteria for the diagnosis of drug-induced agranulocytosis include: sharp drop in neutrophils during treatment or within seven days of prior exposure to the same drug; complete recovery, with more than 1500/mm^3 of neutrophils after one month of suspension of the drug; recurrence during exposure[9,10].

The chemicals related to agranulocytosis include: analgesics, NSAIDs, medicines for cardiovascular action (amiodarone, captopril, digoxin, nifedipine, furosemide, propranolol), antibiotics, cephalosporins and nitrofurantoin. The conducts in this case are: hospitalization, immediate suspension of any potentially harmful agents, prevention of secondary infections, aggressive treatment of sepsis with broad-spectrum antibiotic therapy, culture collection, antifungal therapy, if the fever is persistent, and administration of haemopoietic growth factors[11,12]. **(Dr. Haliana Muzio Candido)**

Hypothetical diagnosis

The most probable hypothesis for this case was agranulocytosis caused by the use of ceftriaxone, since its reintroduction in the treatment of tracheobronchitis coincided with leukopenia, pulmonary infection, septic shocks and cardiogenic shock and multiple organ failure. **(Dr. Haliana Muzio Candido)**

Comment of Obstetrics Department

The patient was admitted to the obstetrics clinic at the 34th week of gestation, with congestive heart failure of unknown etiology, during treatment of pyelonephritis. In the previous pregnancy, the patient presented dyspnea with suspected cardiac disease, but a proper investigation was not performed. The diagnosis of heart disease at an advanced stage of pregnancy, mainly in clinical decompensation is related to poor prognosis in both maternal and perinatal periods. After the definite diagnosis and appropriate therapy, there was improvement in maternal clinical conditions, but the fetus had already been impacted (fetal growth restriction). The worsening of functional class during pregnancy is associated with a higher frequency of perinatal complications, such as growth restriction, prematurity and fetal distress. As the other evidence in the assessment of fetal vitality was preserved, the delivery was scheduled for after the 37th week, thus avoiding prematurity. Nonetheless, the delivery was anticipated some days when the presence of oligo-hidramnia was evident and the cesarean surgery was indicated due to abnormal fetal presentation (pelvic). The indication of the time and delivery section were obstetrical. General anesthesia was indicated due to severe mitral stenosis associated with pulmonary hypertension.

The delivery was performed at InCor, without intraoperative complications. The newborn was small for gestational age, but had a good neonatal evolution. The patient remained at the intensive care unit in the early postpartum period, until the circulatory stabilization, and was subsequently transferred to a maternity hospital. There was improvement of dyspnea, but cough persisted (with hypothetical diagnosis of tracheobronchitis), which is reason why she was treated with ceftriaxone. The discharge was postponed for completion of antibiotic therapy and stabilization of heart disease. On the fourth postoperative day, the patient returned to the intensive care unit due to worsening of clinical status (worsening of dyspnoea, tachycardia, hypotension and shock). Neutropenia was observed on this day.

It should be noted that the puerperium is the stage in which most maternal deaths related to heart disease occur, not only by due to deep hemodynamic changes over this period, but also because the other morbidity conditions encountered at this phase (obstetric hemorrhage, anemia, puerperal infection and pulmonary embolism) may alter the fragile cardiac and circulatory balance of patients. In this case, there was no bleeding during or after birth, and no clinical sign of puerperal

infection was observed. Neutropenia and sepsis have evolved swiftly with shock, unresponsive to therapeutic measures. **(Dr. Maria Rita Bortolotto)**

Comment of Infection Department

Before delivery, the patient was treated for acute pyelonephritis with ceftriaxone over 15 days, the etiological agent was identified, showing good response. Currently, third-generation cephalosporins are the drugs of choice for empirical treatment of this infection, as the enterobacteria, most common etiologic agents[13], have shown increasing resistance to this class of antibiotics (40-60%).

Over the evolution, the patient was referred to caesarean delivery, and ceftriaxone was reintroduced. Then, the patient progressed to pulmonary infection and leukopenia with progressive neutropenia. In the discussion of the causes of leukopenia, the drug reaction was regarded as one of the hypothesis, and ceftriaxone was the most probable drug to be reintroduced after prolonged use and owing to the fact that there was temporal relationship with the onset of neutropenia. The class of cephalosporin is one antibacterial antibiotic with well-established risk for progression to neutropenia, despite the low frequency (< 1%) due to hipersensitivity[11].

Severe infections by Gram negative bacteria and some viral infections (cytomegalovirus, for instance) may also lead to leukopenia. They are less probable causes in this case, although the choice due to empirical coverage was ganciclovir, owing to the severity, despite the potential risk of worsening of neutropenia, upon the myelosuppressive effect of this anAt necropsy, pneumonia was confirmed by a fungus (*Aspergillus sp* and haloficomicose), agents found in immunocompromised hosts.

This case illustrates the severity of patients with febrile neutropenia, in spite of the triggering factor and the risk of adverse drug events, underscoring the importance of periodic laboratory tests during use. **(Dr. Tânia Mara Varejão Strabelli)**

Necropsy

The heart weighed 436 g. The left ventricle was normal and the right ventricle was hypertrophic and large in volume. There was rheumatic mitral stenosis with fibrous thickening of the cuspid valves and fusion of the commissures, associated with fibrous thickening, fusion and retraction of the tendinous cords (Figure 3). The aortic valve presented fibrous thickening of semilunar valves, without commissural fusion, There was no calcification of the mitral or aortic valves, and tricuspid and pulmonary valves showed no abnormalities.

The lungs weighed 1570 g together. They presented chronic passive congestion, with deposition of alveolar macrophages containing hemosiderotic pigment. There was multifocal necrotizing bronchopneumonia, with very minimal inflammatory component, given the extensive area of coagulation necrosis in the upper lobe of the left lung, together with vascular thrombosis (Figure 4). Amidst the necrotic areas, there were countless, small and thin fungal hyphae, with morphology indicative of hyalohyphomycosis (Figure 5). The histological section of the lung found fungal infection on a bronchus wall and adjacent pulmonary parenchyma, with no inflammatory reaction, presence of fungal hyphae with morphology indicative of *Aspergillus* (Figure 6). The uterus was enlarged in volume, weighed 704 g and presented surgical suture at the colon level, without abnormalities. The uterine cavity was covered with hemorrhagic material, which, on histological examination, showed traces of decidual endometrium (postpartum uterus). The kidneys had irregular scars, affecting the cortical and medullary layers, with distortion of the pielocalicial system. Histologically, there was fibrosis of the cortical and medullary layers, tubular atrophy and dilatation and mild mononuclear cell infiltration. Histological test of bone marrow showed marked congestion, edema, foci of hemorrhage and fibrin deposition, and marked global hypocellularity (25-30% of marrow space occupied by hematopoietic elements), delayed maturation and presence of micromegakaryocytes (Figure 7). The immunohistochemistry research of parvovirus and cytomegalovirus in bone marrow was negative. **(Dr. Luiz Alberto Benvenuti)**

Anatomical-pathological diagnoses

Mitral valve stenosis of rheumatic etiology, chronic pyelonephritis, bone marrow hypoplasia of probable toxic nature, localized pulmonary aspergillosis, fungal necrotizing bronchopneumonia, with morphology indicative of hyalohyphomycosis (cause of death). **(Dr. Luiz Alberto Benvenuti)**

Comments

34-year old woman of age with mitral valve stenosis of rheumatic etiology, presented, a few days after cesarean surgery, hematological picture characterized by agranulocytosis with hypocellularity and maturation arrest of granulocytic series in myelogram. The bone marrow examination, performed in the necropsy, confirmed a severe hypoplasia of the hematopoietic series, with hemorrhage, edema and interstitial fibrin deposition. These histological characteristics suggested that a direct toxic reaction or hypersensitivity to a drug therapy administered has occurred. In addition to the antineoplastic drugs, several other drugs may induce agranulocytosis as a side effect, such as antibiotics, anti-inflammatories, anticonvulsants etc. It should be noted that dipyrone, a drug widely used, even in this case, was among the drugs listed in ten or more cases of agranulocytosis induced by non-chemotherapy drugs, among 980 cases studied in previous report[11]. Indeed, frequent use of drugs in patients with heart diseases may induce agranulocytosis, such as diuretics, antiarrhythmic drugs and others[12]. Hence, in addition to dipyrone, the patient in point received several other drugs which may be associated with agranulocytosis, such as antibiotics and diuretics. As a result of immunosuppression secondary to agranulocytosis, the patient contracted an opportunistic fungal infection: initial localized pulmonary infection by *Aspergillus* and necrotizing bronchopneumonia by hyalohyphomycosis were detected, the latter leading to death. The best known representative of this last category is the fungi is *Fusarium sp*, which lead to the infection named fusariosis[14]. However, only the culture may definitely characterize the fungal species involved, which was not performed in this case. **(Dr. Luiz Alberto Benvenuti)**

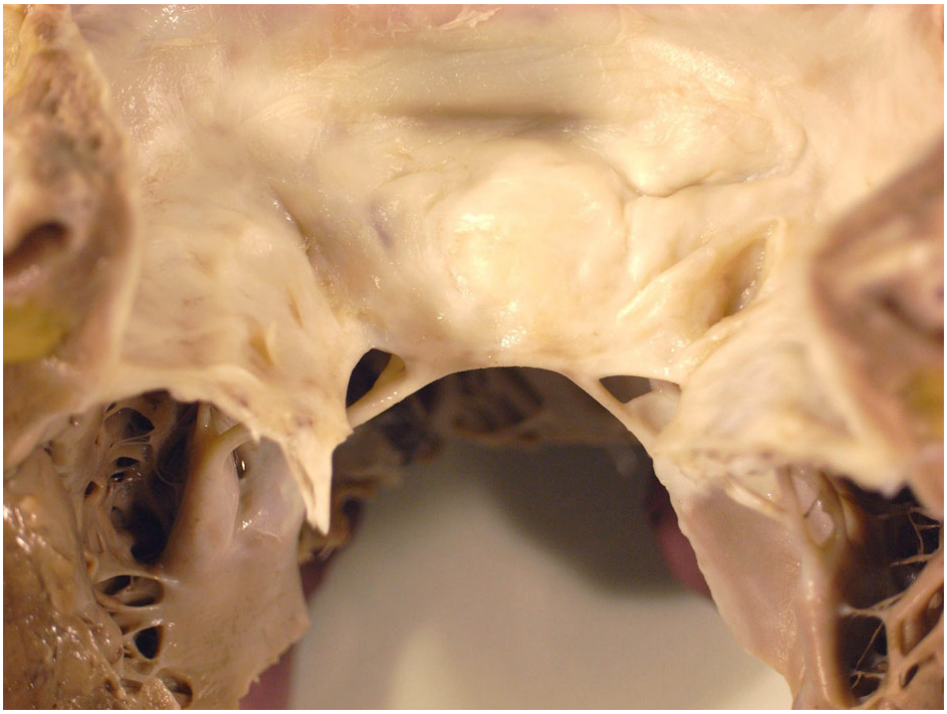

Figure 3 - *Macroscopic aspect of stenotic mitral valve with rheumatic etiology, characterized by fibrous thickening of the cuspid valves associated with fusion of commissures, thickening and retraction of the tendinous cords.*

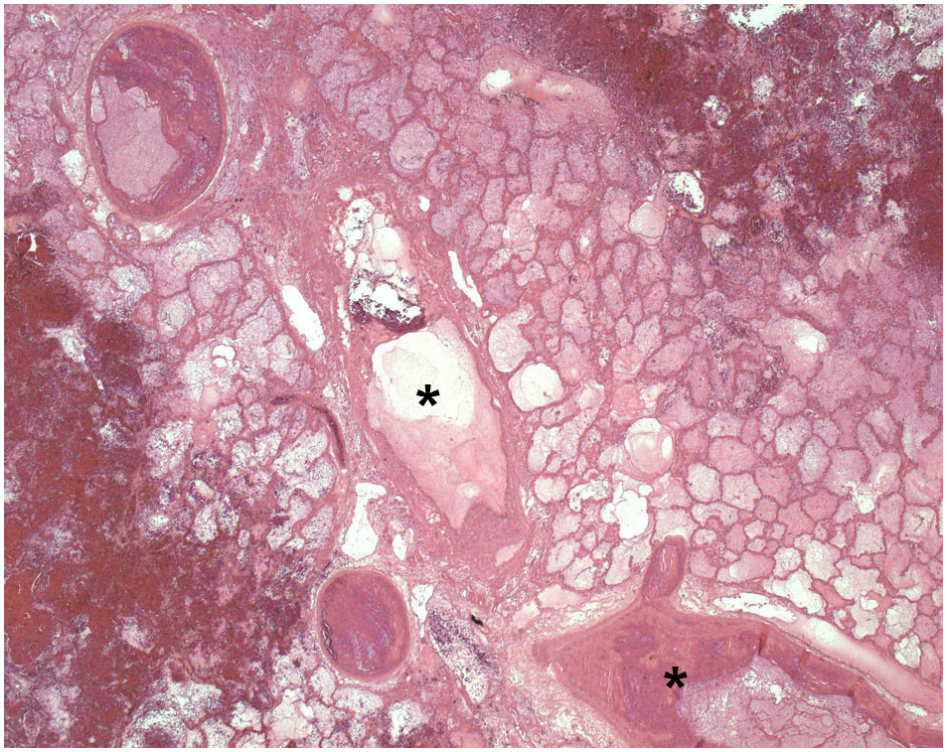

Figure 4 - *Photomicrograph of lung showing necrotizing bronchopneumonia. There is coagulative necrosis of lung parenchyma with areas of hemorrhage and vascular thrombosis surrounding necrotic bronchial lesion (asterisks). Note the virtual absence of inflammatory infiltrate. Coloration by hematoxylin-eosin, original magnification X 25.*

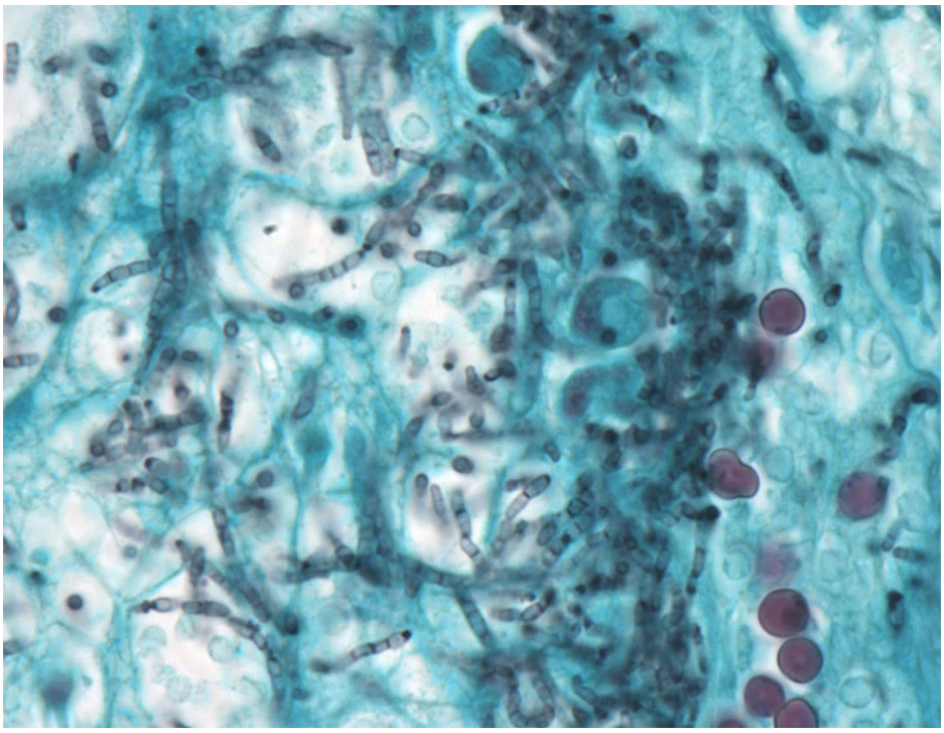

Figure 5 - *Photomicrograph which shows the presence of small, thin septate fungal hyphae, with morphology indicative of hyalohyphomycosis, among the areas of pulmonary necrosis, particularly close to the necrotic bronchial wall. Coloration by Grocott technique, original magnification X 1000.*

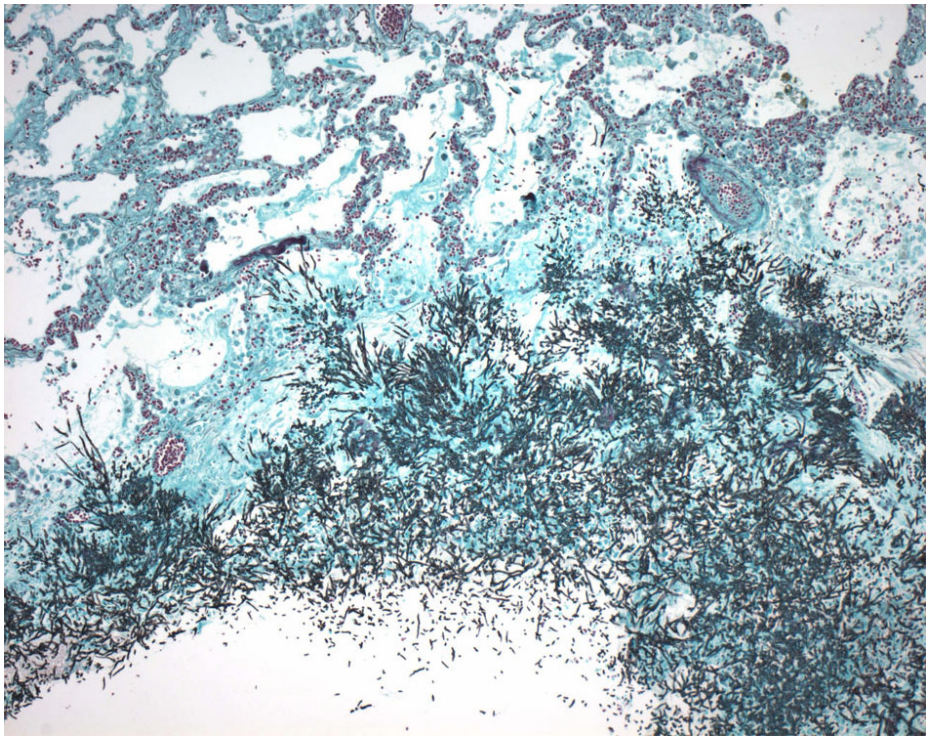

Figure 6 - *Photomicrograph of single and localized lung injury with invasion of the bronchial wall and lung parenchyma adjacent to fungal hyphae with morphology indicative of Aspergillus sp. Note the virtual absence of inflammatory infiltrate. Coloration by Grocott technique, original magnification X 100.*

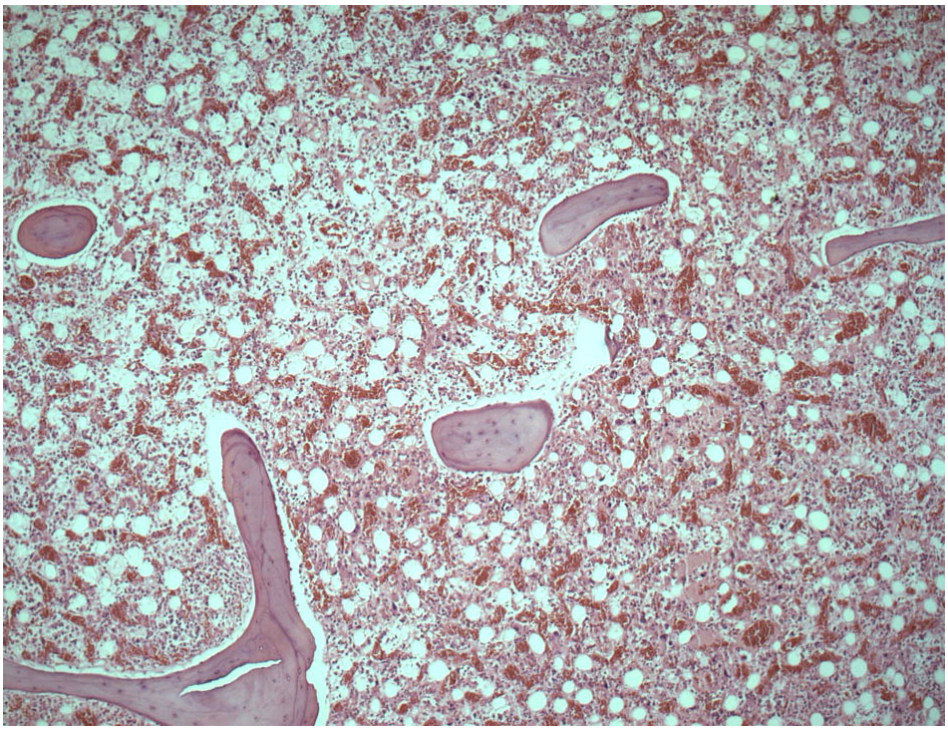

Figure 7 - *Histological section of bone marrow showing marked hypoplasia of the hematopoietic series, severe congestion and interstitial edema. Coloration by hematoxylin-eosin, original magnification X 50.*

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