

Pulmonary arterial hypertension emerged in a patient with acute myeloid leukemia. The role of transfusions.

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Abstract

Due to the fact that human albumin is expensive, for the treatment of hypoproteinemic edema in patient with poor nutrition (anorexia, vomiting, etc) there is a tendency to use fresh frozen plasma. Fresh frozen plasma and plasma from platelets concentrates help restore protein levels, but they can produce side effects due to the fact that they contain clotting factors. One of these side effects is thrombosis, including in the pulmonary blood circulation, generating pulmonary arterial hypertension. In this article we present the clinical case of a female patient with acute myelogenous leukemia, which in the complete remission state presented a severe edematous syndrome - until anasarca - for which she received transfusions with human albumin, plasma and platelet concentrates (she was in post-chemotherapy aplasia). With the increase of serum protein levels we also observed an increase of the edema, which led to further investigations and to ultrasound diagnosis of major pulmonary hypertension, together with a high peak of thrombin generation. While reducing the peak of thrombin generation, we noticed the decrease of the pulmonary blood pressure. In this article we discussed the role of plasma transfusions and other predisposing factors in the occurrence of this episode.

Keywords: Acute leukemia, plasma, pulmonary arterial hypertension, thrombin generation, thrombosis

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Introduction

We know that pulmonary hypertension occurs in patients with myeloproliferative diseases, including in those with acute leukemia [1]. But if this complication develops while the patient is in complete remission, the pulmonary hypertension is not induced by leukemia, so other risk factors must be analyzed. We present the case of a patient with acute myeloid leukemia type 2, FLT3-ITD positive, who presented an episode of pulmonary hypertension after transfusions.

Case Report

A 27 years old patient, mother of three children, was admitted for weight loss (7.5kg in 2 months), fever (39.5°C), asthenia and headache. Physical examination showed severe skin pallor and multiple dental caries. She had 55kg in weight and 1.70 m in height. Blood test showed a serum hemoglobin of 4.5g/dl, platelets count – 187,000/mm³, white cells 14,200/mm³ with 67% blasts, no evidence of disseminated intravascular coagulation, with normal immunological tests and uninfected with HIV, syphilis, hepatitis B or C virus. Myelogram showed

the presence of peroxidase-positive blasts (70%), with non-segmented nuclei, some of them bilobar, with fine chromatin and nucleoli, with basophilic cytoplasm, with grit and Auer rods. Immunophenotyping of the bone marrow aspirate established that blasts are CD61-, CD41-, CD34+/- (39%), CD33+ (100%), CD38+/- (35%), HLA-DR+/- (37%), CD64+/- (10%), intracellular MPO+ (50%). Molecular testing detected the presence of FLT3-ITD mutation (45%), with negative AML-ETO [t(8;21)] and NPM. Cytogenetic examination showed a normal karyotype (46XX).

An electrocardiogram showed sinus tachycardia. The echocardiography showed a left ventricular ejection fraction of 55%, with normal valves and no pericardial fluid. The abdominal ultrasound found the presence of a right ovarian cyst with a diameter of 8 cm and a sterile – which was extracted. Orthodontic drainage and lavage with hydrogen peroxide was performed.

After a port was implanted she received the first course of polychemotherapy with cytosine arabinoside (1700 mg divided in seven daily doses) and epirubicin (75 mg/day, 3 days) under intestinal decontamination and treatment

with meropenem and vancomycin for her dental outbreaks. During the bone marrow aplasia state she received 8 units of packed red blood cells and 50 units of platelet concentrates. After the aplasia, the myelogram showed the presence of 4-5% blasts (complete remission). At 17 days after discharge the patient returned for the extraction of four teeth.

Further she received the first course of polychemotherapy for consolidation with high dose of cytosine arabinoside (2g every 12 hours, for 3 days) and epirubicin (70mg/day, for 3 days). During the post-chemotherapy bone marrow aplasia, the patient presented fever and the chest radiography reveals bilateral alveolar condensations, with a tendency to confluence in the right lower lobe and minimal pleural reaction, interpreted and treated as bronchopneumonia and parapneumonic pleural effusion. Before the second polychemotherapy consolidation course (with the same treatments and doses) 6 more rotten teeth were extracted.

From the onset of the disease the patient lost 5 kg in weight, but the leukemia remained in complete remission. During the post-chemotherapy bone marrow aplasia the patient presented an episode of septic shock with *E. coli* and *Enterobacter*, which was treated, but due to hypoproteinemia soft edema progressively occurred, until anasarca, patient complaining of shortness of breath and fatigue. In addition, it appeared an extensive cellulitis of the abdominal skin, with inguinal lymphadenopathy with Celsus signs of inflammation, of 2.4-3.8 cm diameter. In these conditions she received antibiotics – imipenem and vancomycin, diuretics, human albumin (10 vials) and transfusions with fresh frozen plasma (28 units), platelet concentrate (85 units) and packed red blood cells (13 units). As proteinemia was corrected, edema were growing. Although the electrocardiogram was normal, the patient had a second ecocardiografic exam, during which it was found the presence of severe pulmonary hypertension (60 mmHg), tricuspid insufficiency grade III/IV, significant dilatation of the inferior vena cava (23 mm) and suprahepatic veins, and also the formation of a cardiomyopathy by dilatation (left ventricle 62/52 mm, mitral insufficiency grade II/III, left atrium 43mm, enlarged right cavities), with global hypokinesia of the left ventricular wall, decreased left ventricular ejection fraction (34%), a shortening fraction of 16%, interventricular septum 9/12mm, posterior wall of the left ventricle 10/12mm. Pulmonary hypertension was not measured by catheter because the patient was in bone marrow aplasia at that time. The peak of thrombin generation was 233.7 nM. We continued the diuretic and verapamil therapy, to reduce the pulmonary hypertension, but without plasma transfusions. After one week we repeated the echocardiography, and this time there was an increase of the left ventricular ejection fraction (50%) and shortening fraction (26%), but with the same pulmonary

hypertension. During this treatment, the edema, dyspnea and the abdominal cellulite gradually disappeared.

After the platelets have increased over 100,000/mm³, the ovarian cyst which measured 10 cm in diameter was laparoscopic operated. A third course of consolidation polychemotherapy was performed with a high dose of cytosine arabinoside (2g every 12 hours for 3 days), without epirubicin (due to persistent deterioration of left ventricular function). At this time, the arterial pulmonary pressure was 25 mmHg and the peak of thrombin generation decreased to 172.3 nM. An episode of septic shock with *E. coli*, from a urinary tract infection (absent on admission, but appeared after a week) was treated empirically with imipenem/cilastatin and vancomycin (for possible associated gram-positive bacteria), then only with imipenem (after identifying the germ). The patient is in complete remission and we are now looking for a HLA-compatible hematopoietic stem cell donor.

Discussion

When the patient was admitted, she had 10 rotten teeth. Due to the fact that acute leukemia is an emergency, we couldn't delay the treatment until all dental problems were solved. We decided to do an orthodontic drainage, followed by hydrogen peroxide lavage and we started chemotherapy under antibiotic protection. The acute leukemia responded promptly to treatment and complete remission has been maintained for six months (to the present day), but there is a risk of relapse due to the presence of FLT3-ITD mutations. Therefore, an allogeneic peripheral blood stem cell transplantation is indicated, but we haven't found a compatible donor. From our experience, we know that the most frequent compatible donors for Romanians come from Romania and Bulgaria. We are searching for donors from other countries through the international register, but the chances of finding them are smaller.

Stomatological problems were resolved after the patient came out of the bone marrow aplasia and under antibiotic protection. We have also considered necessary to operate the ovarian cyst, due to the fact that the operation would be more difficult to perform after the allogeneic transplantation.

Septicemia is a common complication in immunosuppressed patients, including in those who are in post-chemotherapy bone marrow aplasia, especially if there are septic outbreaks which couldn't be drained in time. Sometimes, septic shock can be the clinical onset of the disease, which must be recognized and treated promptly with broad-spectrum antibiotics. If our patient had not responded to the empirical imipenem-vancomycin combination, we would have added to this polymixin or amikacin+metronidazole. If the fever would have been

persistent, the patient would have done a CT scan to find a possible septic outbreak (including a mycotic one), and if it were confirmed, we would have replaced fluconazole with voriconazole in infusion. Identification of gram-negative bacteria in blood cultures and in urine culture was useful to establish the etiology and management of sepsis.

The edema, that occurred after the second course of consolidation chemotherapy, and which progressed to anasarca, was not only due to hypoproteinemia, but also of the severe pulmonary hypertension (60mmHg). The fact that this situation occurred during the bone marrow aplasia, period in which the patient received fresh frozen plasma and platelets concentrates, raised the issue that the coagulation factors from these products, caused the pulmonary hypertension by the production of microthrombi in situ. The peak of thrombin generation level raised during this period (at 230), a level higher than the average level of a group of control subjects recently used in a study [2]. The fact that this level decreased one month after the transfusions had stopped (at 160), suggests that the transfusions with products containing plasma had played an important role in producing pulmonary hypertension. We have to mention that human albumin, ideal for treating hypoproteinemia, is not always available to us.

We were able to study the thrombin generation with an automated analyser – Technothrombin TGA Ceveron® alpha (Technoclone, Vienna, Austria), which is equipped with a fluorescence measurement module. Thrombin generation assays were made by us in pooled, citrated, platelet-poor plasma. Calibrated automated thrombography was used also by other researchers, who observed the presence of a hypercoagulable state at least in some patients with idiopathic pulmonary hypertension, reflected in all the studied parameters: lag time, peak thrombin and time to peak [3]. Antithrombotic mechanisms and the factors produced by endothelial cells are essential to ensure the free fluidity of blood in the pulmonary arterial circulation. This fluidity is disturbed in primary and secondary pulmonary hypertension [4], which explains the occurrence of vascular thrombosis involved in its pathogenesis [5]. It was observed an increase in the activity of thrombin in severe pulmonary hypertension, which favors thrombus formation, due to the disturbance of balance between tissue factor and thrombomodulin (secondary to endothelial damages) and the inefficiency of fibrinolysis. These findings were made in subjects with pulmonary hypertension and it is unknown whether they are the cause of pulmonary hypertension or they appear due to the hypertension [4].

The use of anticoagulants in the treatment of pulmonary hypertension is recommended by many experts in this field [5]. In long-term use, they increase the survival of

these patients [4]. A study made on a group of 58 patients with idiopathic pulmonary arterial hypertension, patients who received warfarin in stable dose, showed that maintaining an INR level between 1.5 and 2.5 is effective to suppress thrombin generation in these patients [6]. But due to the fact that today there are many drugs for reducing pulmonary arterial hypertension in use, for example continuous infusion of prostacyclin [4], bosentan, epoprostenol, sildenafil [5] and others, it is not appropriate to use anticoagulant therapy alone.

In the pulmonary vascular remodeling, involved in the pathogenesis of pulmonary hypertension, p21-activated kinase-1 and its upstream regulator Rac1 (a small G protein signaling) are implicated. They are activated by thrombin involving calcium and are involved in an increase of reactive oxygen species production in artery smooth muscle cells [7].

Another argument for the implication of thrombin in producing pulmonary arterial hypertension was obtained by administering melagatran - a selective thrombin inhibitor – in a model of pulmonary hypertension in rats; it diminished the right ventricular hypertrophy. Endothelial dysfunction may be involved in this process. In the short term, thrombin contributes to the increase of cyclic guanosine monophosphate (cGMP), but prolonged exposure of pulmonary endothelial cells to thrombin contributes to decreased levels of cGMP. Activated protease-activated receptor-1 can produce a similar effect. This depletion of cGMP in the lung endothelial cells may contribute to the development of pulmonary arterial hypertension[8].

Severe infection during the treatment of our patient could also contributed to enhanced thrombin generation with subsequent risk of thrombosis, as was showed in a recent study made in children with acute lymphoblastic leukemia [9].

Conflict of interest: The authors have no conflicts of interest that are directly relevant to the content of this article.

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