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Severe Persistent Primary Immune Thrombocytopenia, Refractory to Multiple Drugs, including Eltrombopag

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Abstract: Severe forms of primary immune thrombocytopenia may endanger patients' lives. Since there is no ideal treatment for all patients, the range of drugs available has expanded, especially after recognizing the pathogenetic role of deficient production of platelets and improper level of thrombopoietin. We present the case of a female patient aged 61, symptomatic, with multiple associated diseases, which presented a severe form of persistent primary immune thrombocytopenia, refractory to multiple drugs, including eltrombopag, in which platelet count reached 0/mm^3, but who responded to intravenous human immunoglobulins. Subsequently, we performed splenectomy. In this case, platelet destruction dominated the pathogenesis of the disease, not their poor production. The treatment of primary immune thrombocytopenia has to be personalized depending on the particularities of each clinical course.
Keywords: eltrombopag, immunoglobulins, melatonin, methylprednisolone, splenectomy, primary immune thrombocytopenia.

INTRODUCTION

Persistent primary immune thrombocytopenia (ITP) has often tendency to evolve towards chronicization. It is estimated that the incidence of chronic ITP is between 5.8 and 6.6/100000 in adult population [1]. Lately there have been realized advances in understanding the pathophysiology of this disease, which have been reflected in the treatment plan. It is accepted that in ITP thrombocytopenia is not only the consequence of the development of antiplatelet and antimegakaryocytic antibodies, especially due to the fact that at about 30% of patients these autoantibodies can not be emphasized [2]; the effect of CD8+ cytotoxic lymphocytes enter into discussion to them; in addition, there is a poor maturation and release of platelets from abnormal megakaryocytes [3] and a relative deficit of thrombopoietin [4]. So the thrombopoietin receptor agonist it came to placing in treatment, but even they are not effective in all patients. We are still during searches made in order to enhancing therapeutic response. We present the case of a symptomatic female patient with persistent ITP, refractory to usual medications, including eltrombopag, who developed adverse effects of this medication and whose platelets reached 0/mm^3.

CASE REPORT

The ethical committee permission to publish this hematological case was obtained. A female patient, aged 61, was admitted to the hematology service of Emergency County Clinical Hospital Sibiu for investigation and treatment of purpura which appeared a week ago, and that proved to be thrombocytopenic, according to blood count performed ambulatory. She was known by her family physician with diabetes type 2, balanced by diet, degree I obesity, essential hypertension with very high risk, and hypercholesterolemia. She was being under long treatment with valsartan, indapamide, and nebivolol.

From biological point of view, she had 6000 platelets/mm^3 (8000/mm^3 in blood collected on citrate), without anemia and with normal number of leukocytes; leukocytes formula was normal; immunoelectrophoresis - normal; antinuclear antibodies, rheumatoid factor, lupus cells - absent; complement (C3, C4) - normal; hepatitis C virus antibodies, HBs antigen, venereal disease research laboratory (VDRL) test, human immunodeficiency virus (HIV) test, helicobacter pylori antigen in stool, and inflammatory tests - negative; no signs of disseminated intravascular coagulation or thrombotic thrombocytopenic purpura; glucose 120 mg/dL, with the rest of the usual biochemical tests normal; in myelogram blasts or atypical lymphocytic infiltrate were not observed and mature megakaryocytes were frequent, appearance suggestive for thrombocytopenia of peripheral cause. Abdominal ultrasound revealed a hyperechoic liver, and chest radiography - an aortic diameter of 4 cm.

The patient was treated with methylprednisolonum 125 mg/day, iv, 4 days, under temporary insulin treatment after which platelets reached 111000/mm^3. At the discharge hypolipidic, hyposodic, ulcer, and diabetic diet with 200 g carbohydrate, 92 g protein/day, treatment with

prednisone (1 mg/kg/day with dose reduction with 10 mg/week), omeprazole, potassium supplement, cinnarizine, glycerine suppositories (if necessary) and continue antihypertensive therapy were recommended to her; in addition - dispensarization by diabetes center, endocrinology consult, and the repeat of the blood tests after a month, with subsequent hematologic consultation.

The patient returned 2 months later for epistaxis, fatigue and tremors. She had bruising on the abdomen and thighs, and 4000 platelets/mm^3. Endocrinological consultation established that the patient had only a neurogenic hyperkinetic syndrome (thyrotropic hormone and free tetraiodothyronine were normal and antithyreoperoxidase antibodies were absent). Intravenous methylprednisolone was resumed, but it was neither effective in higher dose; in addition, there were side effects: insomnia, depressive reaction, hyperglycaemia, hypertension, cushingoid type of obesity, which required treatment. The treatment with vincristine (2 infusion i.v. every 7 days) or melatonin (9 mg/day) has also been found to be ineffective. She started therapy with eltrombopag (50 mg/day, 3 weeks, then 75 mg/day) and without the corticosteroids, but without result. After a month platelets reached 0/mm^3. At such a value of platelets bleeding risk was high even spontaneously. Splenectomy could not practiced for this reason. Then, it was decided to give her human immunoglobulins (1 mg/kg/day, 2 days, i.v.), followed by rapid normalization of platelets (248000/mm^3). If thrombocytopenia had relapsed, retreatment with immunoglobulins would have been unlikely because it is extremely expensive. Therefore, in agreement with the patient, splenectomy was performed under general anesthesia, after pneumococcal vaccination and under protection of amoxicillin + clavulanic acid. Postoperative evolution was favorable. Platelet counts increased to 1139000/mm^3, and then decreased gradually up to 481000/mm^3 after one month. During the reactive thrombocytosis she received treatment with acetylsalicylic acid - 75 mg/day and did not require insulin therapy.

DISCUSSION

We excluded a possible pseudothrombocytopaenia, that sometimes occurs, even when blood is collected in ethylenediaminetetraacetic acid - to 0.1% of the general population [5] (our patient had severe thrombocytopenia also in blood collected on citrate, microscopically checked - without agglutinated platelets). The diagnosis of ITP is made by excluding all possible causes of thrombocytopenia. In our patients, we eliminated a possible haematological malignancies (acute leukemia, myelodysplasia, chronic lymphoproliferation, etc) based on the leukocyte formula and myelogram appearance. Disseminated intravascular coagulation and thrombotic thrombocytopenic purpura were excluded by normal coagulation tests, the absence of hemolysis and kidney failure. The latter condition may even be associated with ITP in 6.3% of cases compared to 0.02% to the general population [6]. There were no clinical or laboratory arguments for any collagenosis, a hepatitis virus, HIV or helicobacter pylori infection. Later thyroid function was also found to be normal. The patient had chronic antihypertensive treatment and she did not change her drugs or doses lately. The only case of immune thrombocytopenia induced by valsartan was published after our patient was splenectomized: a splenectomised man, who developed immune thrombocytopenia after doubling the dose of lostartan, answered to corticotherapy, but after valsartan entering immune thrombocytopenia relapsed [7]. We have no reasons to believe that valsartan induced thrombocytopenia in our patient, given the rarity of such possibility, and due to the fact that the patient had no prior modification of dose, the treatment was long and continuous, and she responded to immunoglobulins. It is known that angiotensin II receptor blockers and angiotensin converting enzyme inhibitors are the drugs of choice for treatment of hypertension in diabetics. Some cases of immune thrombocytopenia after angiotensin-converting enzyme inhibitors have also been reported [8]. Since hypertension of our patient could not be corrected only with β-bocker and diuretic drug, we considered it useful to continue valsartan, especially as she was under glucocorticoids. Many authors accept that the efficiency of the administration of steroids pulse therapy is controversial and, in general, does not lead to long-term responses [1]. Moreover, our patient's initial response to i.v.corticotherapy was not complete, so that it was chosed to continue her treatment, but orally, in decreasing doses.

The releapse occured after two months, which proved refractory to corticosteroid therapy, vincristine and melatonin. Melatonin has proved to be effective in some published cases of ITP [9], but it may increase the rate of platelet apoptosis [10], which may explain its ineffectiveness in all patients. Another therapeutical solution would be rituximab. After one year, rituximab administered for a month (weekly or every 2 weeks) may increase the response rate to 36-50% of patients with ITP [11]. The combination of dexamethasone (40 mg/day for 4 days) with rituximab (100 mg/week for one month) resulted in an overall response rate of 84% at 4 weeks, but it dropped to 6 and to 12 months [12]. Rituximab is expensive, reason for which we could not use it.

Because the patient had side effects of corticosteroid (hyperglycemia, hypertension, insomnia, depression, cushingoid obesity) and thrombocytopenia was severe, we opted for further treatment with eltrombopag. This thrombopoietin-mimetic nonpeptide product do not favor the appearance of autoantibodies, as opposed to recombinant thrombopoietin agonists (1). In a recent published study, 65% of patients with ITP

responded to eltrombopag +/- corticosteroids (platelets increased over 50000/mm^3 and bleeding events decreased or disappeared) [13]. An open-label study that included 299 patients with ITP treated with eltrombopag for 3 years showed that 80% of splenectomised and 88% of non-splenectomised patients obtained at least once over 50000/mm^3 platelets; for some patients the need for concomitant medication and the number of bleeding events decreased [14]. Our patient did neither respond to eltrombopag. Although ITP severity does not correlate with the risk of bleeding, when platelets reach 0/mm^3, as to our patient, there is no doubt that whenever bleeding can occur, even spontaneously or during an acute hypertensive spurt or after a minor injury. Some patients who do not respond to eltrombopag can get response to romiplostim and opposite. Here, romiplostim was not available. Although still uncertain, the main risks of long-term administration of thrombopoietin receptor analogues are myelofibrosis and thromboembolism [1, 15, 16] - the latter in a proportion of 4% in the EXTEND study [14].

She responded to human immunoglobulins administered i.v., fact which many authors argue that confirms the diagnosis of ITP in the absence of identifiable causes of thrombocytopenia [1]. Splenectomy was performed after pneumococcal vaccination and under antibiotic protection, as it is considered that the risk of sepsis in splenectomised ITP patients is 11.1% [17]. After surgery, the patient received antiplatelet therapy due to reactive thrombocytosis, in order to reduce the thrombotic risk. If thrombocytosis had increased more it would have come into question the possibility of trombocytapheresis [16]. It is estimated that splenectomy causes sustainable responses to 60-70% of patients [18]. Postsurgery platelet increasing over 1000000/mm^3 (as in our patient) is a predictor of favorable long-term response to splenectomy.

The fact that the patient did not respond to eltrombopag, but only to immunoglobulins is an argument for the predominant role of immune platelet damage and not for deficient platelet production in this case and calls for a personalized treatment of ITP, depending on the particularities of each patient.

CONCLUSION

Persistent ITP does not always respond to corticotherapy, even when it is administered in large doses, and it has frequently notable side effects, especially in diabetic patients. Other drugs (such as vincristin and melatonin) are not always effective, too, and rituximab is expensive. Eltrombopag is not a solution for all patients. Immunglobulins with intravenous administration may represent an alternative therapy, even in the era of thrombopoietin mimetic agents. Treatment must be individualized, depending on peculiarities of each patient.

Note: All authors contributed equally to drafting the article.

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