Review

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Review

Refractory Immune Thrombocytopenia or Myelodysplastic Syndrome Presenting with Isolated Thrombocytopenia? A Review of Literature and a Case Report

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Abstract: Immune thrombocytopenia (ITP) is an autoimmune disorder characterized by isolated thrombocytopenia caused by both immune-mediated platelet destruction and impaired platelet production in the bone marrow, in the absence of any other identifiable cause of low platelets count. ITP in adult patients is a disease that frequently relapses and/or becomes refractory to multiple treatments during its course, with only a small minority of adult patients attaining a sustained complete remission off-therapy. Treatment of refractory ITP can be challenging, due to the unlikeliness of attaining complete response over time. On the other hand, isolated thrombocytopenia may be due to a misdiagnosed clonal myeloid disorder, such as myelodysplastic syndrome (MDS) or chronic myelomonocytic leukemia (CMML), thus mimicking ITP. We here perform a narrative review on the association between ITP and MDS/CMML and the possibility of overlap and misdiagnosis between these conditions, while we report also the case a patient treated for a severe refractory thrombocytopenia which bone marrow examination led to suspect an overlap of MDS and ITP. Our clinical case describes ITP which is refractory to glucocorticoids, high-dose immunoglobulins, Rituximab, splenectomy, thrombopoietin receptor agonists and Fostamatinib, that ultimately attained a short-lived response to a hypometylating agent that was initiated due to bone marrow examination that aroused the suspect of MDS.

Keywords: immune thrombocytopenia; chronic ITP; myelodysplastic syndrome; chronic myelomonocytic leukemia; refractory thrombocytopenia

1. Introduction

Immune thrombocytopenia (ITP) remains a diagnosis of exclusion despite several efforts to find a unique pathogenetic model or trustable biomarkers [1]. Basic evaluation of patients with seemingly ITP includes in fact history, physical examination to assess muco-cutaneous and superficial bleeding, and repeating the full blood count with citrated blood to rule out pseudo-thrombocytopenia. If ITP is suspected, secondary thrombocytopenia must be ruled out by further assays including immunoglobulin levels, helicobacter pylori (urea breath test, stool antigen), and serological screening

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for hepatitis viruses B (HBV) and C (HCV), and human immunodeficiency virus (HIV) [2]. Even if considered a rare disease, ITP is the most common cause of acquired isolated thrombocytopenia. Several studies report that a vast majority of misdiagnosed ITP are actually myelodysplastic syndromes (MDS) or thrombocytopenia secondary to autoimmune diseases, immunodeficiency or drug reaction [3-8]. Due to the possibility of a misdiagnosis, it is important to rule out an underlying disease especially in older adult patients (at higher risk of MDS) or in women in childbearing age (at higher risk of systemic lupus erythematosus (SLE) and other autoimmune diseases) [9]. Bone marrow examination is not compulsory according to current guidelines on ITP management but it is recommended if clonal disease is suspected. Autoimmunity screening including antinuclear antibodies (ANAs), anti-phospholipid antibodies (APLAs), and anti-thyroid antibodies is not routinely performed without a reasonable suspect of an underlying or associated autoimmune disease [10]. In this review, we will focus on the risk of an underlying clonal myeloid disorder in patients with persistently isolated thrombocytopenia. An accurate differential diagnosis between ITP and myeloid malignancies can be reached by conventional cytogenetics, immunophenotyping, and morphology. Additionally, new molecular biology techniques like Next Generation Sequencing (NGS), conducted on bone marrow samples, are emerging. These assays have a high sensitivity and specificity towards MDS [11]. However, bone marrow examination is an invasive procedure and NGS is a highly expensive test. Furthermore, a diagnosis of MDS within an isolated thrombocytopenia is not so common to routinely support this diagnostic process [12]. Aim of the present study is to review the criteria currently adopted to define the concept of refractoriness in ITP, available drug classes and the sequence of treatment lines preferred to manage refractory ITP. Furthermore, this study reports on the available data on the not so uncommon association between ITP and MDS/CMML, by focusing on the gray zone that exists between these diseases. We also present a case report managed at our Institution that encompasses this dramatic diagnostic and therapeutic challenge. This narrative review with a case report aims to give an immediate snapshot of the actual landscape of chronic ITP and the unmet needs that clinicians face when treating this challenging condition.

2. Materials and Methods

We performed a non-systematic search of literature aimed to describe the current treatments available for relapsed-refractory ITP, the correlation between ITP and MDS/CMML and the management of refractory ITP which in some cases can be a misdiagnosed bone marrow malignancy, in order to introduce a case report in which the two diagnoses seem to overlap. Additionally, our case presents the use of many agents which are usually effective in ITP and MDS as well, and the possibility that ITP may at some point evolve into MDS. The whole research paper collection was conducted within the following time-frame: September 2022 - April 2023, by searching the following online libraries and respective bibliography during the last ten years (from June 2013 to June 2023):

- PubMed: association between ITP and clonal myeloid disorders;
- Google Scholar: unmet needs in chronic ITP;
- UpToDate: response criteria of ITP, definition of refractoriness, definition of chronic ITP, most common therapies in second or further line;
- Guidelines: SIE (2021), IWG (2019).

The following inclusion criteria were adopted in the selection of material:

- Search keywords: ITP, MDS, CMML, refractory;
- Publication date: last 10 years (2013 - 2023), except for cornerstone papers on the subject.

The following exclusion criteria were adopted in the selection of material:

- Secondary thrombocytopenia, if not correlated to clonal myeloid disorders;
- Thrombocytopenia in children (congenital or acquired).

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Paper review for inclusion in this study was conducted within May 2023. A total of 130 papers were selected from initial search. After review process, a total of 92 papers were included, while 38 were discarded due to low relevance on the subject.

3. Results

3.1. Relapsed and refractory ITP

Patients diagnosed with ITP are promptly treated with corticosteroids and often high dose immunoglobulins when platelets count is lower than 10000 /microliter or if they show any hemorrhagic manifestation. However, around 80% of frontline successfully treated patients will eventually experience a relapse [13]. When facing a relapse of ITP, it is necessary to confirm again the diagnosis before starting a second-line treatment, in particular ruling out MDS should be taken into account in older patients and before splenectomy [2]. We refer to relapsed ITP when a patient who previously attained a response experiences a significant drop in platelets count and/or a clinically relevant bleeding directly related to ITP [14]. Refractoriness is defined by the failure to attain a safe platelet count after multiple therapies [14]. When facing one of these scenarios, confirmation of diagnosis is highly recommended in order to rule out another possible cause of chronic thrombocytopenia, notably MDS [9]. This often includes a bone marrow examination, especially in patients older than 50 years. Furthermore, as thrombopoietin-receptor agonists (TPO-RAs) are currently the cornerstone of treatment of persistent and chronic ITP, exclusion of a clonal myeloid disorder of the bone marrow is even more important [15]. The association between MDS and ITP has been suspected but not yet confirmed, as demonstrated in low-grade myeloid disorders in MDS with low IPSS/low and very low R-IPSS risk [16-17], where supportive therapy with TPO-RAs is able to reduce thrombocytopenia-related morbidity. Where supportive therapy with TPO-RAs is able to reduce the morbidity related to thrombocytopenia. This is due to the fact that progression to acute myeloid leukemia has not been significantly reported in these subset of patients [16,17]. On the other hand, the administration of TPO-RAs is not recommended in intermediate and high-risk IPSS MDS, in the absence of a life-threatening bleeding risk, because of the negative impact on the overall response rate to specific treatments [18]. Appropriate evaluation of response is crucial to pose a reasonable suspect of refractoriness.

Criteria for assessment of response to ITP treatments are listed below [19]:

- Complete response (CR): platelet count >/= 100.000/microliter and absence of bleeding symptoms;
- Response (R): platelet count >/= 30.000/microliter and at least a two-fold increase from baseline platelet count and absence of bleeding symptoms;
- No response (NR): platelet count <30.000/microliter or less than two-fold increase from baseline platelet count and presence of bleeding.

Response obtained during treatment may persist after treatment discontinuation, however, it is common for the disease to relapse, especially in presence of triggers like pregnancy, traumas, infections, tumors and any condition that may cause production of auto-antibodies and/or platelet consumption.

This “loss of response” is defined by one of the following scenarios [19]:

- For a patient previously in CR: platelet count < 100.000/microliter;
- For a patient previously in R: platelet count < 30.000/microliter or less than two-fold increase from baseline platelet count.

The latest guidelines from ASH (2019) [14] introduce new, more practical, clinically-oriented definitions to better identify different response patterns in order to guide patient’s management:

- Early response: Platelet count ≥30.000/microliter and at least doubling baseline at 1 week;

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- Initial response: Platelet count ≥30.000/microliter and at least doubling baseline at 1 months;
- Durable response: Platelet count ≥ 30.000/microliter and at least doubling of the baseline count at 6 months;
- Remission: Platelet count >100.000/microliter at 12 months;
- Corticosteroid-dependent: Ongoing need for continuous prednisone >5 mg/day (or corticosteroid equivalent) or frequent courses of corticosteroids to maintain a platelet count ≥30.000/microliter and/or to avoid bleeding.

3.2. ITP and clonal myeloid disorders

ITP is considered a primary disorder in most cases. However, in a small subset of ITP cases, an association with clonal myeloid disorders has been observed. In some cases, MDS can present with isolated thrombocytopenia, mimicking ITP, making a differential diagnosis between the two conditions difficult, based solely on clinical presentation. CMML is a clonal myeloid disorder that has both myelodysplastic and myeloproliferative features. Similarly to MDS, CMML can also present with isolated thrombocytopenia, leading to potential diagnostic confusion with ITP. Distinguishing between primary ITP and clonal myeloid disorders with thrombocytopenia is crucial for appropriate management and treatment decisions. It often requires a thorough evaluation, including bone marrow biopsy and genetic testing, to differentiate between the two conditions. It is important to note that while an association exists, the majority of ITP cases are not related to clonal myeloid disorders. The coexistence of ITP with MDS or CMML is relatively rare, but it highlights the importance of careful evaluation and consideration of underlying conditions, especially in patients with atypical or refractory ITP.

Autoimmune complications are not a rare finding in the course of hematological malignancies, especially chronic lymphoproliferative disorders. Among these manifestations, autoimmune cytopenias (AICs) are of particular interest because of their severity and difficulty to treat, mainly autoimmune hemolytic anemia and immune thrombocytopenia [20-21]. In the context of lymphoid malignancies the mechanism of autoimmunity could find its explanation in a dysregulation of the negative selection that occurs during the maturation process of B-cells and T-cells, that leads to impairment of tolerance development towards self-antigens [22]. In this review, we will focus mainly on the occurrence of ITP as an autoimmune complication of myeloid malignancies, a setting that is still vastly unknown being this association fairly rare. On the other hand, ITP can also occur before the malignant clone is fully emerged [23]. This is particularly true in the case of CMML, which onset in many cases is of an isolated and seemingly idiopathic thrombocytopenia [24].

The first systematic study on the association between ITP and clonal myeloid disorders was conducted in France and published in 2021. This retrospective analysis of 41 cases of ITP, of which 17 were diagnosed with concurrent MDS and 24 with concurrent CMML, demonstrated that these patients had a worse bleeding tendency than “pure” MDS/CMML patients and thrombocytopenia was more prone to relapse than in “pure” ITP patients [25]. A large case series from another French group revealed that the main alteration that led to diagnosis of CMML for some of these patients was indeed thrombocytopenia, that was sometimes present from several years before diagnosis [16]. When both diseases are present, it appears that ITP is the main reason for bleeding, as suggested by a French retrospective study on a population of 61 patients with MDS and low platelet counts [26]. This association does not appear to be a chance, as suggested from the reports of the SEER Cancer Statistics Review of 2017, where the annual incidence of both ITP and MDS/CMML were almost identical [27]. If this is true, then a shared pathogenetic mechanism must be taken into account [23]. It is known in fact that clonal myeloid disorders are often associated with autoimmune disorders, thus making immune dysregulation a potential cause for secondary ITP in these patients. At the same time, immune dysregulation can promote the selection of a malignant clone in the bone marrow [28]. However, available data from the largest studies are not enough to determine the timing of development of one disease in the context of the other one [29].

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Auto-antibodies surely have a major role in platelet destruction in ITP, however several bone marrow histology findings of megakaryocyte hypoplasia suggest that thrombocytopenia may be associated with platelet underproduction [30], thus explaining difficulty in maintaining safe platelets counts in these patients. It is known from fairly recent studies that there is actually a significant binding of antibodies to megakaryocyte's surface in the bone marrow of MDS patients [31]. Could this finding support a mechanism of immune clearance of megakaryocytes? A comparative study conducted on bone marrow samples from both ITP and MDS patients, and a control group, revealed a high IgG-class antibody binding to megakaryocytes in the first two group of patients than the control group. Furthermore, there was no significant difference in the intensity of IgG stain of the samples between ITP and MDS patients [32]. On the other hand, a similar study reports of substantially equal intensity of IgG binding to megakaryocytes' surface in bone marrow samples from both ITP and MDS patients. However, this study reports a frank megakaryocytes hyperplasia, which is in line with the pattern most commonly found in ITP but it's unusual for MDS [33].

Another perspective on megakaryocyte hypoplasia can be depicted from data regarding Eltrombopag therapy. This drug is used in MDS and aplastic anemia (AA) other than ITP. Interestingly, the results are not as encouraging in the former two diseases than they are in the latter. This could be partially explained by the impairment of all the hematopoietic clones that characterizes MDS and AA but not ITP. However, ITP can also become refractory to maximum doses of Eltrombopag. This suggests that a shared mechanism can be suspected for these scenarios [34]. An interesting point of view to further explore the association between ITP and clonal myeloid disorders could be offered by particular conditions in which a dysregulation of the immune system directly impairs differentiation of megakaryocytes. This could be the case of 5q-deleted MDS, in which is known to be a hyperplasia of megakaryocytes and which is often successfully treated with the immunomodulatory agent lenalidomide [35]. There are several although scattered reports of immune-mediated platelet destruction following variable periods of treatment with lenalidomide, all of them characterized by an overall good response to corticosteroids [36-39]. Moreover, there are even reports of co-existent ITP and 5q-deleted MDS both successfully treated with single-agent lenalidomide [40]. One of the above mentioned studies, however, unexpectedly reports on steroid-resistance and subsequent findings of bone marrow aplasia (both red cells and megakaryocyte) in the bone marrow, with the newly discovered presence of a PNH clone. Salvage off-label treatment with Eltrombopag was attempted but the patient died before it could be possible to evaluate the response [41]. This last case report presents a very unusual association between ITP (which is characterized by peripheral platelet destruction and reactive megakaryocyte hyperplasia) and aplastic anemia (which is an immune-mediated disorder of the bone marrow). This case suggests that immune response pathways may differ from one case of secondary ITP to another and further strengthen the hypothesis of a common pathogenetic mechanism that favors the association between ITP and clonal myeloid disorders.

3.3. ITP and clonal myeloid disorders

The case we present here is a 41-year-old female patient diagnosed with primary ITP in 2020. At the time of diagnosis, the patient was 36 weeks pregnant and during pregnancy and delivery she did not require specific therapy because she maintained a platelet count suitable for delivery-related procedures. No bleeding manifestations were reported during pregnancy. After five months from delivery, the patient was admitted at the ER due to spontaneous mucocutaneous bleeding. Complete blood cells count (CBC) showed severe thrombocytopenia (PLT < 10.000/microliter). Initial therapy was administered with corticosteroids (methylprednisolone at a dosage of 1 mg/kg) and intravenous immunoglobulin (IVIG), 30 g/day for five days achieving a platelet count never higher than 30.000/microliter. The patient was then treated with Rituximab, at the dosage of 375 mg/kg weekly for four weeks, but a response was not attained. Romiplostim was than initiated promptly after Rituximab, but response was not obtained after two months of full dose therapy. In December 2021, due to the finding of severe thrombocytopenia and anemia at routinely full blood count, and unspecified hemorrhagic manifestations , the patient was admitted to the ER, she was again treated

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with platelet transfusion and prednisone at the dosage of 1mg/kg body weight (125 mg/day). She was discharged with indication to continue corticosteroid therapy , which the patient took for about five months, with progressively decreasing response (January 2022: PLT 8.000/microliter; February 2022: PLT 11.000/microliter; May 2022: PLT 0/microliter).

On 30 May 2022, the patient was again she underwent transfusion of 1 EC and 1 unit of PLT. Steroids therapy was discontinued. In early June, due to refractoriness to PLT transfusions (PLT 2.000/microliter), the patient was transferred to the Hematology Department of our Institution. On admission, the CBC showed Hb of 7,1 g/dl, MCV 69,9 fl and PLT of 2.000/microliter. She was transfused with a total of 4 ECs and 1 unit of PLT. Moreover, she was treated daily with tranexamic acid at a dosage of 1 g every eight hours and high-dose IVIGs (30 g/day). Due to a severe refractoriness to this treatment (PLT after last IVIG infusion 1.000/microliter), and the history of a highly refractory disease, a combination therapy with both Fostamatinib 100 mg/day and Eltrombopag 75 mg/day was initiated, after obtaining Informed Consent from the patient. In June 2022, bone marrow examination was performed. Both immunophenotypic typing and histological examination showed no other disease and were therefore considered in line with ITP. However, molecular biology assay showed Wilms tumor-1 (WT1) expression of 3.400 copies (normal range 0-250 in bone marrow). The patient did not attain any response to the combination of Fostamitinib and Eltrombopag at maximum dose each.

On July 2022, a new course of therapy with Rituximab at a dose of 375 mg/mq weekly (total dose per week was 700 mg) for four weeks was carried out because she refused a continuative treatment with oral immunosuppressive agents and, at the same time, she refused vinca alkaloids. Due to persistent metrorrhagia, gynecological consultation was requested, which ruled out gynecological pathologies. The patient experienced an improvement of clinical conditions and performance status, despite persistently low platelet counts (last was 8.000/microliter), due to ameliorating conditions, she was thus discharged at home. She continued Rituximab administrations on an outpatient regimen, monitoring of platelet count values, that showed a rapid decrease followed by a sudden increase :

- PLT (07/07/2022): 27.000/microliter
- PLT (07/14/2022): 14.000/microliter
- PLT (03/08/2022): 3.000/microliter
- PLT (11/08/2022): 1.000/microliter
- PLT (07/09/2022): 50.000/microliter

In November 2022, the patient experienced a loss of response and was again admitted to our Department with PLT 6.000/microliter, Hb 10,1 g/dl, MCV 81,8 fl, and mucosal and cutaneous bleeding manifestations (petechiae and epistaxis). Due to a history of multiple refractory ITP to several lines of therapy, splenectomy was proposed. Splenectomy was performed at the end of November, after reaching an appropriate platelet count for the procedure through transfusion of 3 platelet pools. Duration of platelet response to transfusions was around 12 hours. Salvage therapy with Cyclosporine 200 mg/day was initiated, in association with Eltrombopag 150 mg/day. In December 2022, Eltrombopag was discontinued due to inefficacy and Avatrombopag was initiated at 20 mg every other day, in association with Cyclosporine. In the same month, the patient had a fever associated with leukocytosis (WBC 14.940/microliter of which 10.950/microliter) and high CRP, that was revealed to be caused by Corinebacterium striatum by blood culture. The sepsis was correlated with a deiscence of the surgical wound resulting from splenectomy, which was revealed to be infected with the same pathogen by wound swab. On the account of infectious complications and overall inefficacy, Cyclosporin was discontinued and the dosage of Avatrombopag was increased to 20 mg on even days and 40 mg on odd days. The patient did not attain any response, so the combination treatment was discontinued.

In December 2022, a new bone marrow evaluation with biopsy and aspiration was performed in which, despite the inclination toward a diagnosis of ITP, the hypothesis of a possible myelodysplastic

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syndrome was raised because of severe dysmegakaryopoiesis. This was further confirmed by observation of bone marrow smear. Due to absence of any improvement of the clinical conditions and platelet counts (PLT 1.000/microliter), and absolute refractoriness to PLT transfusions, hospital stay was deemed not indicated for the patient and she was then discharged home with an indication to perform close monitoring of the blood count. In January 2023, however, the patient was admitted again to the ER of a peripheral hospital, for metrorrhagia. CBC showed Hb 3,8 g/dL and PLT 3.000/microliter, thus the patient underwent erythrocyte and platelet transfusions. Due to absolute refractoriness to PLT transfusions, she was transferred to our Hematology Department.

On 16 January 2023, on the account of inefficacy of every previous line of therapy administered for ITP, and faced with a significantly poor clinical condition and performance status, a hypomethylating therapy with Azacitidine was started after acquisition of Informed Consent, at the dosage of 75 mg/mq daily for 7 days per month (total dose per day was 140,25 mg). During hospitalization, the patient suffered from a sudden intense headache in frontal and occipital regions for which urgent CT scan was performed, that showed the presence of a subarachnoid hemorrhage. Subsequent CT scans performed every 12 hours confirmed a stable hemorrhagic focus size. During hospitalization, the patient was transfused with ECs and PLT units and completed the first course of Azacitidine therapy achieving a platelet count of 62.000/microliter, which was confirmed at a second determination the next day. She was then discharged home in order to continue the courses of therapy as an outpatient.

On February 2023, the patient accessed our outpatients clinic presenting with impaired walking ability, probably caused by prolonged bed stay at the hospital and then drastically reduced mobility at home. The full blood count performed reported Hb 8 g/dl, Hct 24%, MCV 76 fl, PLT 4.000/microliter, WBC 6.100/microliter, N 5.300/microliter, L 730/microliter, M 60/microliter. At the end of February 2023, the second course of therapy with Azacitidine was started. The third course was postponed due to hematologic toxicity. The third course of therapy was then carried out on an inpatient setting from March 2023. During this hospitalization, bone marrow study for cytofluorimetric evaluation, molecular biology and the NGS panel was performed, that showed no pathogenic variants. The patient moved to Northern Italy where she was taken in care by another Center. There, she initiated a new treatment line with mycophenolate mofetil with a response (PLT 75.000/microliter) after two weeks of treatment. However, she was ultimately lost at follow up.

4. Discussion

ITP is the most common cause of acquired thrombocytopenia. However, diagnosis is made in presence of platelet count less than 100.000/microliter only by ruling out other causes of isolated cytopenia. The vast majority of misdiagnosed ITP are actually MDS or secondary thrombocytopenia in the context of autoimmune diseases, immunodeficiency, or drug reactions. An accurate review of the patient medical history, physical examination, and confirmation with full blood counts are mandatory to guide further diagnostic measures. Evaluation of peripheral blood smear can help ruling out other hematological disorders, mainly MDS.

Evidences on the treatment of refractory ITP after the well-established induction with steroids and IVIGs are not well defined. Historically, splenectomy has been the most efficient option to obtain a durable response, however, new therapies developed in recent years, especially Rituximab and TPO-RAs, have reduced the use of splenectomy as second-line treatment. Current guidelines, both European and North American, recommend postponing splenectomy for at least one year in most cases for the possibility of achieving spontaneous remission in this time frame. In the case we presented, splenectomy was performed more than one year after ITP onset, due to the failure of previous treatments. For patients with refractory ITP and a disease duration of less than 12 months, available studies favor TPO-RAs over Rituximab because of the longer duration of response achievable with the former. Rituximab might be favored in patients who prefer to avoid treatment in the long term.

Bone marrow examination is not compulsory according to current guidelines on ITP management but it is recommended before splenectomy or second line therapy especially in patients

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older than 60 years in case a clonal disease is suspected. This differential diagnosis between ITP and myeloid malignancies can be reached by new molecular biology techniques like NGS, conducted on bone marrow samples. These assays have a great sensitivity and specificity towards MDS.

In our clinical case, the patient was refractory to all the available lines of therapy (Rituximab, TPO-RAs, immunosuppressive agents, and Fostamatinib), including splenectomy. Multiple bone marrow biopsies were performed, they all ruled out the diagnosis of MDS, except for the last one. Given the patient's critical condition and the confirmation of dysplasia at the last bone marrow histology and smear, Azacitidine therapy was started with an initial rise in platelet count (PLT>50.000/microliter) never reached during previous therapies while NGS report was pending. However, in the end, NGS showed no pathogenic variants. Additionally, the patient ultimately responded to treatment with an immunosuppressive agent before being lost at follow-up.

5. Conclusions

Although most patients respond to standard treatments for ITP, there are some multi-refractory patients who may pose a challenge both in diagnostic evaluation and clinical management. Clearly, more accurate diagnostic procedures are needed in these cases, and bone marrow sampling is useful to perform for histological, cytogenetics, and molecular studies in order to rule out clonal disorders. However, additional diagnostics do not always allow to identify an alternative diagnosis and to explain the refractoriness of the disease. Many multi-refractory ITP are treated with each available agent, sometimes with extreme difficulty in maintaining a safe platelet count able to prevent spontaneous bleeding.

Further, larger studies are needed to find trustable markers of the association between ITP and clonal myeloid disorders, in order to identify underlying conditions which management may relieve thrombocytopenia and disease burden of patients.

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