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Autoimmune Thrombocytopenia on Imatinib Mesylate About Two Cases of Chronic Myeloid Leukemia in Abidjan

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Abstract

Context: *Cytopenias are very common during the treatment of chronic myelogenous leukemia by Imatinib mesylate (IM). They are linked either to direct cytotoxicity related to IM or to progression. Thrombocytopenia related to autoimmune mechanism induced by IM have not been described in the Marketing Authorization for Glivec and is poorly described in the literature. We report two cases.*

Observation: *The thirst case was about, a 38-year-old woman(AA), trader with no particular background, with whom we noted type III splenomegaly, hyperleukocytosis (64 G/L), anemia (6 g/dl) and normal number of platelets (287G/L). she was treatedby IM 400. The second case (KK), is that of a 39-year-old man, police officer, without comorbidity, who presented type III splenomegaly, hyperleukocytosis (154 G/L), hyperplaquetosis(800 G/L) and anemia (9.8 g/dl)treated by IM 400.*

These two patients developed anti-GPIIbIIIa antiplatelet antibodies at 4 months and 9 months for AA and KK, respectively.

Thrombocytopenia was initially considered iatrogenic before immunological mechanism was determined. We thought about, in view of the persistence of cytopenia, despite the IM discontinuation for the first case and its recurrence upon IM resumption and especially the persistence of CML in the chronic phase in both cases.

Keywords: *CML; Imatinib mesylate; Autoimmune thrombocytopenia*

1. Introduction

Cytopenias are very common during the treatment of chronic myelogenous leukemia (CML) with Imatinib mesylate (IM), which has revolutionized its treatment. They are related to either a Direct cytotoxicity associated with IM or a progression of CML. According to Sneed T B **[1]**, more than 45% of patients present myelosuppression greater than grade ≥3 under treatment with IM. Thrombocytopenia induced by IM associated with an autoimmune mechanism has not been described in the Marketing Authorization (MA) for Glivec as an adverse reaction and it's very little described in the literature. A case of autoimmune thrombocytopenia was reported under IM in 2007 by Senthil Rajappa et al **[2]**

Our article reports two cases of patients with CML who developed severe autoimmune thrombocytopenia during IM treatment.

2. Observation

The thirst case was about, a 38-year-old woman (AA), trader with no particular background, living in Abidjan, whom the diagnosis of chronic phase CML was made in 2017. We noted type III splenomegaly according to Hackett, about 6 cm on the left costal edge,. Biology analyzing found hyperleukocytosis at 64 G / L, anemia at 6 g/dl and normal platelet count at 287 G/L without additional chromosomal abnormality. The EUTOS score placed him in the low risk category at 49,5. Mr A.A. was put under IM 400 mg/day allowing us to obtain hematological remission at 2 months with complete regression of the splenomegaly and normalization of the complete blood count (CBC).

We noted on the 4th month check-up (M4) a decrease in the number of platelets to 147 G / L confirmed on a citrate tube. The downward

trend continued to 72 G /L at M5 associated to absence of any other acceleration criteria.

The antiplatelet antibody test came back positive from the 4th and 5th month. Under immunosuppressive therapy, we noted a correction of the thrombocytopenia after 1 month so we kept the patient on Azathioprine in addition to MI.

The second case is that of KK, a 39-year-old man, police officer, without any comorbidity, in whom we noted, in November 2018, Hackett's III splenomegaly 4 to 6 cm, hyperleukocytosis at 154 G / L, hyperplaquetosis at 800 G/L and anemia at 9.8 g / dl without additional chromosomal abnormality and an EUTOS score within the low risk limit of 77. The patient was treated with IM 400 mg, this resulting in a hematological response at 3 months, followed by 'poor therapeutic compliance. In fact, treatment was stopped twice for cytopenias: the first interruption from M5 with resumption at 4 weeks later at 300 mg after hematological recovery and the second treatment interruption occurred in the 7th month (M7) followed by a resumption of treatment six weeks later after blood recovery at 200 mg of IM. This cytopenia which is corrected when the treatment is stopped, reappeared after 8 days despite the dose reduction to 300 and after 4 days under 200 mg. From M9 we noted a persistence of thrombocytopenia at 58 G / L despite discontinuation of treatment and a marked improvement in anemia 11.6 g / dl and leukocytosis at 4.6 G / L. there was no clinical and biological acceleration criteria. The antiplatelet antibody test done at M9 came back positive. We obtained a correction of the thrombocytopenia with corticosteroid therapy to 1 mg / kg after 20 days followed by a rapid decrease and the patient resumed his treatment but with a 2nd generation TKI, iedasatinib 100 mg / day.

To date, our two patients are doing well one (AA) on IM + a Azathioprine (maintenance) and the other (KK) on Dasatinib. We note that in both cases the viral cheeking as well as the routine autoimmune cheeking were negative and the outcome was favorable under immunosuppressive treatment. We also point out that Mrs. A.A. could not provide the 2nd generation TKI.

3. DISCUSSION

Thrombocytopenia was first considered to be iatrogenic, that is to say of myelosuppressive origin by direct cytotoxicity, and subsequently, the search of antiplatelet antibodies found an immunological mechanism. We thought about this given the persistence of cytopenia, despite the discontinuation of IM for the A.A. case and the recurrence of thrombocytopenia at each of the two treatment times as soon as he normalization of the number of platelets, even at reduced doses of IM for the KK case. The immunological character was all the more evoked as the resurgence of the thrombocytopenia occurred within increasingly short periods (8 days and 4 days), and especially we noted no clinical, cytological and cytogenetic acceleration's criteria of CML, the absence of inflammatory or viral pathology and finally the negativity of the Coombs test.

The MA for Glivec* does not mention cytopenia by an immunological mechanism, cytopenia according to Vidal is probably linked to the advanced stage of CML (accelerated phase and blast crisis) and also to direct cytotoxicity.

However, IM would cause myelosuppression in 45% of patients treated [1]; this could be the nest of a dysimmune disorder contributing to cellular auto-reactivity directed against platelets. In fact, in addition to its powerful inhibitory effect on Bcr / Abl, imatinib also inhibits c-kit, which is involved in early hematopoiesis, the consequence of which is myelosuppression, unwanted suppression of normal progenitors. Some observations suggest that imatinib may impair the colony-forming ability of CD34 positive stem cells. [3;4].

This very often dose-dependent myelosuppression is favored by the underlying disease because it is comparatively more severe in patients under IM compared to others pathologies such as GIST (gastrointestinal stromal tumors) which are also treated with imatinib [5]

The mechanisms of drug-induced thrombocytopenia (DITP) can be described by several synergistic actions which are: myelosuppression, immunosuppression and dysimmunity state causing immunization, platelet activation and aggregation. [6].

Drug-induced immune thrombocytopenia occurs: [7; 8]

- Either after exposure to a new drug for 1 to 2 weeks, little longer for our patient A.A (onset 2 months after obtaining hematological remission).

- Either after intermittent use of a drug for a long time, this was the case with K.K.

In these two mechanisms there follows isolated thrombocytopenia, recurrence of thrombocytopenia upon re-exposure Its pathogenesis is complex, at least six distinct pathological mechanisms having been identified in the annals of Aster RH [8], 4 of which may be involved in our case. The first three mechanisms may correspond to the A A case. and the fourth mechanism may correspond to the K. K. case.

- Drug (hapten) links covalently to membrane protein and induces a drug- specific immune response. (Hapten-dependent antibody)

- Drug induces antibody that binds to membrane protein only in the presence of soluble drug. (Drug-dependent antibody)

- Drug (ligand) reacts with membrane glycoprotein IIb/IIIa and induces a conformational change recognized by naturally-occurring antibody (Fiban-induced thrombocytopenia)

- Drug induces antibody that reacts with platelets in the absence of drug.(Autoantibody induction)

The first case in the literature seems to have been described by Senthil Rajappa [2] in 2007 in the Journal Leukemia & Lymphoma. In March 2006, a 20-year-old man treated for chronic phase CML with IM 400 mg/day followed by a complete hematologic response. After 45 days he presented thrombocytopenia at 10,000 / mm3 with bleeding, implicating IM. In factits stopping and corticosteroid therapy allowed platelet normalization.

This clinical case is in addition to ours and should help index thrombocytopenia of immunological origin linked to MI in the Hematox® database, in which heparin appears to be the undisputed leader of drugs likely to induce an immunological thrombocytopenia, followed quite far by the gold salts, penicillin, abciximab and quinine[9].

4. Conclusion

These cases demonstrate the delicate management of cytopenias during IM treatment.

Understanding and attempting to explain the immunological mechanism of the thrombocytopenia induced by imatinib mesylate should allow us to admit a DITP, which should be considered in the face of isolated, recurrent or persistent thrombocytopenia occurring in post hematological remission and the absence of acceleration criterion. The therapeutic alternative to IM is widely available today.

Data Availability

We declare that the data in this article are available and searchable without any restriction on our part.

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