Table 1
Variation of allele frequencies at months 13 and 18.

Gene	Mutation	Allelle frequency at months	
		13	18
CSF3R	T618I	51%	10%
GATA2	R398W	44%	12%
RAD21	L53S	50%	12%
SRSF2	P95_R102del	+	+

Next generation sequencing of a myeloid panel in the bone marrow.

platelet count of 50 G/L. The patient developed grade II acute graft *vs.* host disease (GvHD) 1 month after allo-SCT, which was treated with a systemic tapering dose of corticosteroid. Two months after allo-SCT, cytomegalovirus reactivation was treated with valganciclovir for 1 month. At 3 months after allo-SCT, the patient was still in hematological remission, with a decrease of splenomegaly (4 cm under costal margin). We observed a normalization in the leucocytes at 3.9 G/L, an ANC at 3.3 G/L, normal eosinophil (0,5%) and basophil levels (0.3%), hemoglobin at 9.6 g/dl, and a platelet count of 91 G/L. Bone marrow aspiration detected the persistence of abnormal basophilia (5%), and the *CSF3R* T618, *GATA2*, *RAD21* and *SRSF2* mutations were still detected (Fig. 1, Table 1).

3. Discussion

This case illustrates the difficulty in the classification and treatment of some patients with atypical presentations of MPN. First, the absence of a hematological history, the clinical and biological presentation and the absence of classical mutations, such as *BCR-ABL*, *MPL*, *JAK2*, or *CALR*, ruled out some frequent subgroups of MPN, such as myelofibrosis and CML. Due to the presence of the *CSF3R* T618I mutation, an initial diagnosis of CNL was made. However, the clinical and biological presentation did not strictly fit the 2016 WHO criteria. Indeed, the presence of neutrophilia in association with eosinophilia, basophilia, monocytosis and bone marrow dysgranulopoiesis are more in line with unclassified MPN than CNL [1]. In addition, several observations have reported unexplained hemorrhagic tendencies, especially cerebral hemorrhage, in CNL patients, but this is not specific to this entity [4]. Hemorrhagic manifestations and platelet dysfunction may be shared features between some MPNs. However, the mechanism is still unclear. In this case, we did not find a hemostasis disorder, and thrombocytopenia could not explain the patient's bleeding. It would be interesting to evaluate the von Willebrand factor to eliminate an acquired von Willebrand disease. As explained by Dao et al., there is a continuum between CNL, aCML, myelomonocytic leukemia and other unclassified MPNs. Overlapping clinical and biological features should be taken into account in further classification to better define an atypical presentation that could not be strictly categorized [5].

The *CSF3R* T618I mutation is present in more than 80% of CNL and is very rare in aCML (<10%) [6,7]. This new druggable target allows a new approach in disease management [8]. The rationale for the use of ruxolitinib was clearly established due to the key role of the JAK-STAT pathway in the *CSF3R* T618I mutation since the truncation mutation in exon 17 that activates the SRC kinase pathway is sensitive to TKI [2,9]. Nevertheless, a recent report described relapse after several months of remission in a case of CNL with a *CSF3R* T618I mutation that was associated with the emergence of *RUNX1* or *GATA2* mutations at the time of relapse. These additional mutations appeared during drug administration, suggesting that clonal evolution conferred ruxolitinib resistance [10]. In the myeloid panel, our patient presented additional mutations, such as *SRSF2*, *GATA2* and *RAD21*. *SRSF2* is a spliceosome gene mutation associated with age-related clonal hematopoiesis that contributes to dysplasia. *GATA2* encodes a transcription factor implicated in several myeloid diseases, such as myelodysplasia or AML. *RAD21* is a cohesion complex component that is responsible for cohesinopathy and has not been described in CNL/aCML thus far. We hypothesize that the *CSF3R* T618I mutated clone evolved to acquire additional mutations, which enhanced the disease process and potentially contributed dysplastic features that conferred JAK2 inhibitor resistance. The reasons for the success of imatinib in this case remain unclear. According to the NGS results, our patient did not have an additional truncation mutation that could explain the sensitivity to imatinib [7]. A few studies have investigated the off-target effects of TKIs on immune cells *in vitro*, which may explain the partial hematological response in this case [11,12]. Further investigations on the effects of imatinib are necessary to identify the other potential mechanisms that are involved.

When a partial clinical and biological response is obtained, allo-SCT remains the only curative treatment in aCML and CNL [13]. The largest cohort that has been reported so far included 42 aCML patients who underwent allo-SCT in a retrospective study. With a median OS of 70 months, allo-SCT remained the best therapeutic option [14]. In addition, the pretransplant percentage of blasts in the peripheral blood appeared to be a prognostic factor for overall survival [15]. Here, we report the success of sequential allo-SCT after partial hematological response with the persistence of the

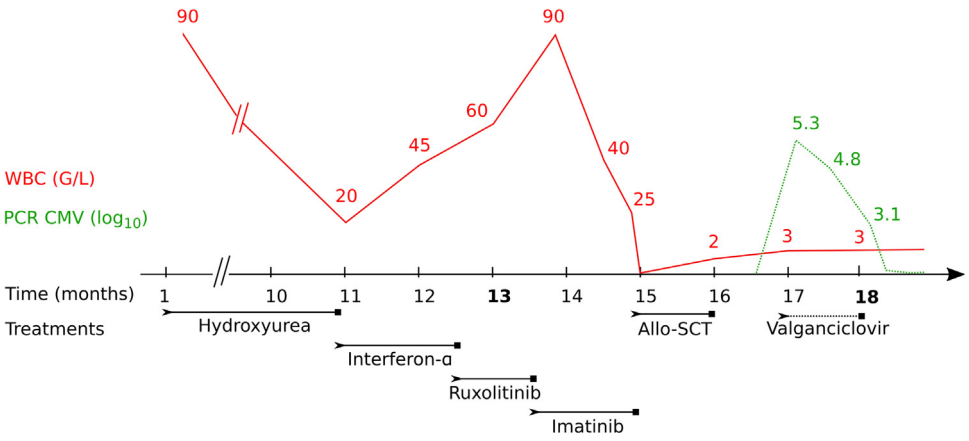

Fig. 1. Graphical analyses of the white blood count, cytomegalovirus replication and successive treatments. Imatinib caused a decrease in WBC from 90 G/L to 25 G/L. The *CSF3R* T618I status was monitored before imatinib introduction and 3 months after graft infusion. WBC: white blood count; VAF: variant allele frequency; PCR CMV: CMV replication; Allo-SCT: allogeneic stem cell transplantation.

CSF3R T618I mutation 3 months after allo-SCT (variant allele frequency = 10%). Although data regarding atypical MPN are lacking, posttransplant maintenance with imatinib should be considered owing to the potential high rate of relapse. This strategy, along with donor lymphocyte infusion, was explored in CML to limit the relapse rate without causing further toxicity [16–18]. In this case, the cytopenia induced by valganciclovir and acute GVHD did not allow the addition of imatinib earlier after transplantation.

4. Conclusion

NGS identified a druggable target, changing the approach for treating atypical MPN. Targeted therapy such as ruxolitinib has great promise for obtaining remission in *CSF3R* T618I-mutated patients, but additional mutations may confer drug resistance that lead clinicians to consider alternative therapies. Here, we report the anecdotal success of imatinib prior to undergoing transplantation. Further investigations on the action of imatinib are necessary to understand the mechanism involved in *CSF3R* T618I-mutated MPN.

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