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Immune thrombocytopenia in myeloid and lymphoid clonal disorders: an intriguing association

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doi:10.3324/haematol.2020.275933

In this issue of *Haematologica*, Jachiet *et al.*[1] present the first systematic study on the association of severe immune thrombocytopenia (ITP) with preleukemic clonal myeloid disorders. Patients from 16 French Departments of Hematology and Internal Medicine were accrued between January 1999 and July 2019, under the coordination of the French Network of Dysimmune Disorders Associated with Hemopathies. A total of 41 cases, 17 with myelodysplastic syndrome (MDS) and 24 with chronic monomyelocytic leukemia (CMML), meeting the 2016 World Health Organization classification[2] and a maximum period of 10 years between the diagnosis of ITP and MDS/CMML were retained for the final retrospective analysis. The majority of cases (73%) were scored as low-risk with a median Revised International Prognostic Scoring System score of 3.[3] ITP, mainly of chronic type, was diagnosed with *bona fide* criteria and could be anterior, concomitant or posterior to the diagnosis of the myeloid disorder. These patients were compared to 200 MDS/CMML patients without ITP and to a control group of 75 patients with primary ITP without MDS/CMML.

Patients with MDS/CMML with associated ITP had more severe bleeding and a multirefractory profile to firstline treatments for ITP compared to those with primary ITP alone and showed a moderate response to thrombopoietin-receptor agonists. They had a lower rate of progression toward acute myeloid leukemia than MDS/CMML patients without ITP but, disappointingly, the overall survival was similar. Limited cytogenetic and molecular studies did not contribute to differentiate MDS/CMML with or without ITP, apart from a higher prevalence of 20q deletion in cases with ITP, but high-throughput next-generation sequencing was not used to describe genetic profiles.

In addition to these interesting clinical findings, the study by Jachiet *et al.* poses a preliminary question: is the "association" of ITP with low-grade myelodysplastic disorders (whichever comes first) just casual or is it indeed related to a shared pathogenic mechanism? In other words, is the prevalence of this association beyond what could be expected by chance alone?

Unfortunately, Jachiet *et al.*[1] did not report the number of patients with MDS/CMML from which the ITP cases were identified, thus hampering any estimation of the prevalence of ITP associated with MDS/CMML, unlike another French study reporting 61 low-risk MDS patients in nine of whom (15%) ITP was identified as the cause of thrombocytopenia (platelet count <70x10^9/L) on the basis of a greater reduction in platelet lifespan and low bone marrow blast infiltration (<10%) not justifying the severity of the thrombocytopenia. Indeed, splenectomy was successful in three of these cases.[4] A much lower percentage (3%) of thrombocytopenia of putative autoimmune nature was identified among 1,408 MDS patients included in the Moffitt Cancer Center database and at King's College Hospital.[5]

Conversely, limited investigations have tackled the problem from the other side, by reporting the incidence of co-occurrence or subsequent development of MDS in patients first presenting with ITP. The only large study on this issue is based on the identification of 2,885 adults with incident ITP requiring healthcare and accessing the French health insurance national database over a 3-year period.[6] Among these patients, 2.3% were concomitantly affected by MDS. Interestingly, some reports of "primary" ITP later developing into MDS are also available and it is noteworthy that in the study by Jachiet *et al.*[1] ITP preceded the diagnosis of MDS/CMML in 36% of cases by several months to years. In another retrospective French series of 516 patients with ITP, the diagnosis of CMML was unveiled by the finding of thrombocytopenia in eight cases (1.4%) and 13 additional cases were identified through a systematic literature review of patients in whom the diagnosis of CMML was associated with or heralded by (in some cases several years before) isolated

Table 1. **Main clonal myeloid disorders in which a low platelet count may occasionally hide immune thrombocytopenia.[§]* Some lymphoid clonal disorders are also included as illustrative examples.**

PRELEUKEMIC CLONAL MYELOID DISORDERS[14,15]
Clonal hematopoiesis of indeterminate potential (CHIP) At least one somatic mutation otherwise found in myelodysplastic syndromes (MDS). Peripheral cytopenias absent but increased risk of developing MDS heralded by the development of persistent thrombocytopenia/other cytopenia(s). Increased overall mortality and increased risk of cardiovascular disease.
Idiopathic cytopenia of undetermined significance (ICUS) Persistent thrombocytopenia or other cytopenia(s) for at least 6 months, which cannot be explained by any other etiology and do not fulfill the formal diagnostic criteria for a myeloid disorder.
Clonal cytopenia of undetermined significance (CCUS) One or more somatic mutations otherwise found in patients with myeloid neoplasms in bone marrow or peripheral blood with an allele burden of ≥2%. Persistent thrombocytopenia or other cytopenia(s) for at least 4 months that cannot be explained by any other etiology and do not fulfill the formal diagnostic criteria for a myeloid disorder.
Myelodysplastic syndrome of lower risk (IPSS-R <3.5)[2,3] Presence of single or multilineage dysplasia involving at least 10% of cells of each lineage at bone marrow examination and <10% and <5% of blast cells in bone marrow and peripheral blood cells. Cytogenetic and/or somatic mutation associated with myeloid neoplasm invariably found and relevant for prognosis.
Chronic myelomonocytic leukemia (CMML) of lower risk[2] CMML-0 (<2% peripheral blood blasts including promonocytes and <5% bone marrow blasts) and CMML-1 (2%-4% peripheral blood blasts including promonocytes and 5%-9% bone marrow blasts). Due to overlapping features of both MDS and myeloproliferative neoplasms, the two entities are currently included among myelodysplastic/myeloproliferative neoplasms (MDS/MPN). Splenomegaly may be a confounding factor for the diagnosis of immune thrombocytopenia. Cytogenetic and/or somatic mutations associated with myeloid neoplasms are invariably found and are relevant for prognosis.
CLONAL LYMPHOID DISORDERS
B-cell monoclonal lymphocytosis[10]
Monoclonal gammopathy of uncertain significance (MGUS)[12]

[§]Cytopenias defined as: hemoglobin <10 g/dL; platelet count <100x10^9/L; and absolute neutrophil count <1.8x10^9/L. *Only lower-risk myelodysplastic syndrome and chronic myelomonocytic leukemia are mentioned, since in higher risk cases it would be difficult to make a *bona fide* diagnosis of immune thrombocytopenia in patients with thrombocytopenia due to the expected greater infiltration of bone marrow by blast cells and/or major dysplasia/hypoplasia of megakaryocytes that could by itself cause non-immune thrombocytopenia. IPSS-R: Revised International Prognostic Scoring System.

thrombocytopenia classifiable as ITP.[7] Let's now compare these figures with what could be expected by a casual association of ITP and MDS/CMML.

The annual incidence of new cases of ITP can be estimated to be around two per 100,000 individuals/year and that of MDS/CMML around five per 100,000 individuals/year.[8] Clearly any association being simply by chance can be immediately excluded, since, on the basis of chance alone, we would expect ten new cases of ITP associated with MDS/CMML every 10^{10} people, a rate several orders of magnitude below any clinical observable phenomenon, even accumulating cases occurring over two or three decades.

From these data it could be concluded that there is a definite causal association between ITP and low-grade MDS or CMML. Quite surprisingly, so far MDS and allied disorders are not generally mentioned among the possible causes of secondary ITP. It is noteworthy that not only ITP, but a variety of other autoimmune disorders, are consistently reported as being associated with myeloid pre-leukemic disorders, in up to 30% or more of cases.[5,9] In these series, as in the one by Jachiet *et al.*,[1] ITP could be found to occur prior to, in concomitance with, or after the diagnosis of these disorders, in keeping with current terminology. For these two latter instances, the term "secondary", instead of "associated" ITP seems more appropriate and its use is recommended.

So what could be the pathogenic link between ITP and MDS/CMML or more in general with clonal myeloid disorders with a potential to evolve into leukemia? Jachiet *et al.*[1] correctly point to a common background of deregulated homeostasis of the immune system. This is a plausible hypothesis further strengthened by the sparse reports of ITP observed in other disorders with subverted immunity, such as monoclonal B-cell lymphocytosis preceding chronic lymphocytic leukemia or indolent lymphomas,[10,11] monoclonal gammopathy of uncertain significance[12] and in patients with congenital or acquired immunodeficiencies such as common variable immunodeficiency.[13]

But, which comes first? Is the clonal expansion of an aberrant myeloid or lymphoid clone causing immune dysregulation or *vice versa* does primary immune dysregulation promote a pre-malignant clonal expansion? So far this issue remains unsettled. As we have seen, the temporal succession of events is inconsistent and anyway not determinant to solve this conundrum, because of the complex interactions between hematopoiesisis, the immune system, genetic background, epigenetic features and environmental factors, as illustrated in some reviews.[5,9]

This study is an incentive to further investigate the pathogenic mechanisms at the basis of the intriguing association between ITP (and other autoimmune disorders) and the various pre-leukemic myeloid or lymphoid disorders with a potential to evolve into overt malignancy.

From a practical standpoint, patients presenting with unexplained thrombocytopenia, associated or not with other cytopenias revealed by routine peripheral blood analysis, particularly in the elderly, should raise the suspicion of one of the various clonal myeloid or lymphoid disorders succinctly described in Table 1. In these disorders, disentangling secondary or associated ITP as the cause of thrombocytopenia may affect prognostication, management and follow-up. Indeed, thrombocytopenia may be inherent to the severity of the myeloid or lym-

phoid disease itself and be indicative of worsening bone marrow infiltration by aberrant cells and consequent megakaryocyte hypoplasia and/or dysplasia or be indicative of dysregulated immunity leading to ITP, thus not necessarily indicating a worse prognosis, as shown in the study by Jachiet *et al.*[1] Hence, in these circumstances, separating ITP, diagnosed with *bona fide* criteria, from non-immune thrombocytopenia may be of clinical relevance for both the patient and the treating physician.

In conclusion, the report by Jachiet *et al.*[1] opens new perspectives for a deeper understanding of the pathobiological mechanisms linking ITP and some clonal myeloid/lymphoid disorders and of their temporal association. This will require the collection of large prospective series of patients with either or both disorders and their investigation with extensive next-generation sequencing technology and better immunophenotyping of the cellular components involved. In the meantime, the practicing hematologist should be aware of the difficulties and of the importance of separating ITP from the thrombocytopenia inherent to the defective megakaryopoiesis of these preleukemic disorders.

Disclosures

No conflicts of interest to disclose

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