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

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

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In this issue of Haematologica, Jachiet et al\(^1\) present the first systematic study on the association of severe 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 MDS and 24 CMML, meeting the 2016 World Health Organization classification\(^2\) and a maximum period of 10 years between ITP and MDS/CMML diagnosis were retained for final retrospective analysis. The majority of cases (73%) were scored as low-risk with a median IPSS-R 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 versus 200 MDS/CMML patients without ITP and versus a control group of 75 patients with primary ITP without MDS/CMML.

Patients with MDS/CMML with associated ITP had more severe bleeding and multirefractory profile to first line treatments for ITP than those with primary ITP alone and showed a moderate response to thrombopoietin-receptor agonists (TPO-RA). They resulted in a lower progression toward acute myeloid leukemia than MDS/CMML 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, this study poses a preliminary question: is the “association” of ITP with low-grade myelodysplastic disorders (whichever comes first) just casual or indeed related to a common 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 ITP cases were identified, thus hampering any prevalence estimation of ITP associated to MDS/CMML, at variance with another French study reporting 61 low risk MDS patients in 9 of whom (15%) ITP was identified as the cause of thrombocytopenia (<70,000/μL) on the basis of a major platelet lifespan reduction and a low bone marrow blast infiltration (<10%) not justifying the severity of thrombocytopenia. Indeed, splenectomy was successful in 3 of these cases\(^4\). A much lower percentage (3%) of thrombocytopenia of putative autoimmune nature was identified among 1408 MDS patients included in the Moffitt Cancer Center database and at King’s College Hospital\(^5\).

Conversely, limited investigations tackle 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 2885 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 of 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 8 cases (1.4%) and 13 additional cases were identified through a systematic literature review in whom the diagnosis of CMML was associated or heralded (in some cases several years before) by isolated 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 in around 2/100,000/year and that of MDS/CMML in around 5/100,000/year. Clearly any by chance association can be immediately excluded, since if so, we would expect 10 new cases of ITP associated to MDS/CMML every 10^10 people, several orders of magnitude below any clinical observable phenomenon, even accumulating cases occurring over 2-3 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. Noteworthy, not only ITP, but a variety of other autoimmune disorders, are consistently reported as associated to myeloid pre-leukemic disorder, in a percentage up to 30% or more of cases. Also in these series, as in Jachiet at al, ITP could be found to occur prior to, in concomitance of, or after the diagnosis of these disorders, in keeping with current terminology. For these two latter instances, the term “secondary”, instead of “associate” 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 correctly point to a common background in a 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, like monoclonal B-cell lymphocytosis preceding chronic lymphocytic leukemia or indolent lymphomas, monoclonal gammopathy of uncertain significance (MGUS) and in patients with congenital or acquired immunodeficiencies such as common variable immunodeficiency.

But, which comes first? Is the clonal expansion of an aberrant myeloid or lymphoid clone causing immune disregulation or vice versa is a primary immune disregulation promoting 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, due to the complex interaction between heamatopoiensis, immune system, genetic background, epigenetic features and environmental factors as illustrated in some reviews.

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 develop into overt malignancy.

From a practical standpoint, patients presenting with unexplained thrombocytopenia, associated or not to other cytopenias revealed by routine peripheral blood analysis, particularly in the elderly, should raise the suspect of one of the various clonal myeloid and lymphoid disorders synthetically described in Table 1. In these disorders, disentangling secondary or associated ITP as the cause of thrombocytopenia may impact on prognostication, management and follow up. Indeed, thrombocytopenia may be inherent to the severity of the myeloid or lymphoid disease itself and be indicative of a worsening bone marrow infiltration by aberrant cells and consequent megakaryocyte hypoplasia and/or dysplasia or be indicative of a dysregulated immunity leading to ITP, thus not necessarily indicating a worse prognosis, as shown in the study of Jachiet at al. 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 paper of Jachiet et al 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 demand the collection of large prospective series of patients with either or both disorders and their investigation with extensive next-generation sequencing (NGS) technology and better immunophenotyping of the involved cellular components. 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.

REFERENCES


Table 1. Main clonal myeloid disorders in which thrombocytopenia may occasionally hide ITP\(^*\). Some lymphoid clonal disorders are also included as illustrative examples.

<table>
<thead>
<tr>
<th>PRELEUKEMIC CLONAL MYELOID DISORDERS(^{14, 15})</th>
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<tr>
<td><strong>Clonal hematopoiesis of indeterminate potential (CHIP)</strong></td>
<td>At least one somatic mutation otherwise found in MDS. Peripheral cytopenias absent but increased risk of developing MDS heralded by development of persistent thrombocytopenia/other cytopenia(s). Increased overall mortality and increased risk of cardiovascular disease</td>
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<tr>
<td><strong>Idiopathic cytopenia of undetermined significance (ICUS)</strong></td>
<td>Persistent thrombocytopenia or other cytopenia(s) for at least 6 months that cannot be explained by any other etiology and lacking fulfillment of the formal diagnostic criteria for myeloid disorder.</td>
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<tr>
<td><strong>Clonal cytopenia of undetermined significance (CCUS)</strong></td>
<td>One or more somatic mutations otherwise found in patients with myeloid neoplasms in bone marrow or peripheral blood (PB) with an allele burden of (\geq 2%). Persistent thrombocytopenia or other cytopenia(s) for at least 4 months that cannot be explained by any other etiology and lacking fulfillment of the formal diagnostic criteria for myeloid disorder.</td>
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<tr>
<td><strong>Myelodisplastic syndrome (MDS) of lower risk (IPSS-R &lt; 3.5)(^{2, 3})</strong></td>
<td>Presence of single or multilineage dysplasia involving at least 10% for each lineage at bone marrow (BM) examination and &lt; 10% and &lt; 5% of blast cell in BM and PB cells. Cytogenetic and/or somatic mutation associated to myeloid neoplasm invariably found and relevant for prognosis.</td>
</tr>
<tr>
<td><strong>Chronic Myelomonocytic Leukemia (CMML) of lower risk(^2)</strong></td>
<td>CMML-0 (&lt;2% PB blasts including promonocytes and &lt;5% BM blasts) and CMML-1 (2%-4% PB blasts including promonocytes and 5%-9% BM blasts). Due to overlapping features of both, myelodysplastic syndromes (MDS) and myeloproliferative neoplasms (MPN), the two entities are currently included among Myelodysplastic/Myeloproliferative neoplasms (MDS/MPN). Splenomegaly may be a confounding factor for ITP diagnosis. Cytogenetic and/or somatic mutation associated to myeloid neoplasm are invariably found and are relevant for prognosis.</td>
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CLONAL LYMPHOID DISORDERS

| **B-cell monoclonal lymphocytosis\(^{20}\)** |  |
| **Monoclonal Gammopathy of Uncertain Significance (MGUS)\(^{12}\)** |  |

\(^6\) Cytopenias defined as: hemoglobin, 10 g/dL; platelet count 100 x 10\(^9\)/L; and absolute neutrophil count, 1.8 x 10\(^9\)/L.

\(^*\) Only lower risk MDS and CMML are mentioned, since in higher risk it would be difficult to make a bona fide diagnosis of ITP in patients with thrombocytopenia due to the expected greater infiltration of BM by blast cells and/or major dysplasia/hypoplasia of megakaryocytes that could by itself cause non immune thrombocytopenia.