Clinical Study

Coexistence of Myeloid and Lymphoid Neoplasms: A Single-Center Experience

Anthi Bouchla, Thomas Thomopoulos, Sotirios Papageorgiou, Panagiotis Tsirigotis, Efthymia Bazani, Konstantinos Gkirkas, Diamantina Vasilatou, Eirini Glezou, Georgia Stavroulaki, Konstantinos Gkontopoulos, George Dimitriadis, and Vasiliki Pappa

Second Department of Internal Medicine and Research Unit, Hematology Unit, University General Hospital "Attikon", 1 Rimini St. Haidari, 12462 Athens, Greece

Correspondence should be addressed to Vasiliki Pappa; vas_pappa@yahoo.com

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The coexistence of a myeloid and a lymphoid neoplasm in the same patient is a rare finding. We retrospectively searched the records of the Hematology Division of the Second Department of Internal Medicine and Research Institute at Attikon University General Hospital of Athens from 2003 to 2018. Nine cases have been identified in a total of 244 BCR-/ABL1-negative MPN and 25 MDS/MPN patients and 1062 LPD patients referred to our institution between 2003 and 2018. Each case is distinct in the diversity of myeloid and lymphoid entities, the chronological occurrence of the two neoplasms, and the patient clinical course. All of them exhibit myeloproliferative (6 JAK2 V617F-positive cases) and lymphoproliferative features, with 1 monoclonal B-cell lymphocytosis (MBL), 3 B-chronic lymphocytic leukemias (B-CLL), 3 B-non-Hodgkin lymphomas (B-NHL), 1 multiple myeloma (MM), and 1 light and heavy deposition disease (LHCDD), while in three cases myelodysplasia is also present. The challenges in identifying and dealing with these rare situations in everyday clinical practice are depicted in this article.

1. Introduction

The annual incidence of BCR-/ABL1-negative myeloproliferative neoplasms (MPN), namely polycythemia vera (PV), essential thrombocytopenia (ET), and primary myelofibrosis (PMF) in the western world, is estimated to be maximum 2.8, 2.3, and 1.5 cases per 100,000 population, respectively [1, 2]. On the other hand, the cumulative incidence of lymphoproliferative disorders (LPD) is difficult to be estimated as they comprise a highly heterogenous group; however, that of a major representative of this group, B-chronic lymphocytic leukemia (B-CLL) seems to be around 5.5 cases per 100,000 population per year [3]. Based on the notion that the concomitance of MPN and LPD in the same patient should be the product of the individual incidence rates, an extremely low incidence of cases with both MPN and LPD would be expected. However, it has been shown that the presence of an MPN increases the probability of an LPD in the same individual. In a study by Vannucchi et al., which included 820 BCR-/ABL1-negative MPN patients in a period from 1980 to 2008, 11 concomitant LPD cases were reported, with a 3.44-fold increase in the risk of developing LPD in the MPN group compared with the general population [4]. In addition, Rumi et al. reported 22 concomitant LPD cases in a cohort of 1915 BCR-/ABL1-negative MPN patients followed up from 1970 to 2009, with a 2.79-fold increased risk, respectively [5].

Despite these observations, the coexistence of MPN and LPD remains rather rare; in fact, scarce case reports and limited cases series have been reported [6–11]. A recent systematic review of single patient clinical data by Marchetti et al. has identified 214 individuals harboring both diseases [12], while a Danish registry reported 97 new LPD cases in patients previously diagnosed with MPN [13].

Herein, we present our institution's experience with patients harboring both MPN and LPD, focusing on the peculiarities of their management. Furthermore, we suggest...
pathophysiological mechanisms that might explain the afore-
mentioned coexistence.

2. Materials and Methods

A thorough search of the records of the Hematology Division of
the Second Department of Internal Medicine and Research
Institute at Attikon University General Hospital of Athens,
Greece, was performed. The search included the records of all
patients referred to our institution in the time period from
2003 to 2018. Clinical notes were used to identify patients
harboring both diseases. Patient demographics, medical his-
tory, initial disorder at presentation, treatment for both dis-
esases, and response to treatment were obtained from patient
records. An informed consent was obtained from every
subject.

3. Results

The search yielded nine cases of coexistent MPN and LPD out
of a total of 269 patients diagnosed with BCR-/ABL1-negative
MPN (244) or an MDS/MPN (myelodysplastic syndrome/
myeloproliferative neoplasms (25)) and 1062 patients diag-
nosed with an LPD. Patient characteristics are depicted in
Table 1.

Six out of the nine patients presented with a BCR-/ABL1-
negative MPN. More specifically, one patient was diagnosed
with PV, one patient with post-ET MF; two patients with
primary myelofibrosis (PMF), and the remaining two with
pre-fibrotic PMF; all of them were positive for the mutation
JAK2 V617F. Of these patients, four required treatment with
a cytoxic agent, namely hydroxychloroquine (two of
whom also required occasional bloodlettings), whereas one
patient (Patient 8) received a JAK2 inhibitor (ruxolitinib) for
7 months. All MPN-treated patients had good control of their
symptoms and blood counts.

Three out of the nine patients (patients 3, 6, and 7) were
initially diagnosed as MDS-RS-T and were later found to fulfill
criteria for MDS/MPN-RS-T according to the 2016 WHO
revision [1]. None of them harbored the JAK2 V617F muta-
tion; calreticulin (CALR) and MPL W515 mutation studies
were negative in Patient 6 but were not performed for patients
3 and 7 due to reimbursement issues. All of them were sup-
ported with an erythropoietin analogue and red blood cell
transfusions.

Regarding the specific LPD phenotype, variability was
noted as three patients were diagnosed with B-CLL and one
patient with monoclonal B-cell lymphocytosis (MBL), three
patients with lymphoma (two marginal zone lymphomas
(MZL) and a plasmablastic lymphoma), and two patients with
plasmacytic neoplasms (one with multiple myeloma and one
with light and heavy chain deposition disease). All but two of
the patients required treatment and were managed appropri-
ately. The exact treatment approach for each patient is depicted
in Table 1. Response was defined using the Cheson criteria [14]
for patients 4 and 6. These criteria could not be applied for
Patient 8 because even though lymphocytosis subsided with
treatment, splenomegaly remained due to the underlying MPN.

The International Workshop on Chronic Lymphocytic
Leukemia (iwCLL) criteria [15] were used for patients 2 and 7.
For Patient 9, the response was evaluated based on clinical cri-
teria as discussed below.

All but one patient had significant comorbidities (Table 1).
In the two patients with treatment intolerance, exacerbation
of anemia was the main cause for stopping treatment. Both
patients were old and frail. Patient 7 had been supported with
RBC transfusions and erythropoiesis-stimulating agents for
her MDS/MPN-RS-T. She only received 2 cycles of obinutu-
zumab/chlorambucil due to a dramatic increase in her trans-
fusion needs. Her lymphocytosis has been in regression ever
since. Patient 5 initially received hydroxycarbamide to control
her thrombocytosis, but after 2 years, she developed anemia
attributed to myeloma. A trial of lenalidomide was performed,
which resulted in transfusion dependency, so treatment was
stopped prematurely after a few days. On the other hand, the
underlying MDS/MPN-RS-T did not seem to adversely affect
treatment outcome of Patient 6, a fitter patient, who received
6 cycles of bortezomib/CHOP, resulting in an astonishing
relapse-free survival, as previously reported [16].

It should be noted that the diagnosis of the MPN preceded
that of LPD in all patients with the exception of Patient 4.
Regarding this patient, a splenic MZL was diagnosed in
another institution based on spleen pathology, and at this time
point, bone marrow biopsy was reported to be normal and no
further information was available in his records. Ten years
later, the patient was referred to our institution for a massive
abdominal lymphoid block which proved to be a relapse of
the original low-grade LPD and for which he was treated with
8 cycles of rituximab. Myelofibrosis and JAK2 V627 mutation
were discovered during restaging of the patient. A few months
later, a steady hemoglobin increase was observed and the
patient was treated with hydroxychloroquine and phlebotomies.
Whether this was a manifestation of his MPN is not known,
as the patient (a heavy smoker) was also diagnosed with lung
cancer shortly thereafter.

Patient 8 had suffered from ankylosing spondylitis the past
20 years and had received tumor necrosis factors (anti-TNF)
to control her symptoms. She also received ruxolitinib for 7
months due to symptomatic splenomegaly. Baseline clonal
immunoglobulin gene rearrangements and flow cytometry
were not available for this patient before the initiation of rux-
olitinib. She gradually developed anemia and clonal B-cell
lymphocytosis. After 6 cycles of RChOP, both these findings
have subsided. Ruxolitinib was not reintroduced for fear of
LPD reoccurrence, as discussed below. Patient 2 received 6
cycles of obinutuzumab/chlorambucil and is currently on CR
for his LPD.

Of special consideration is also Patient 9. This patient, hav-
ing a 4-year history of JAK2-positive post-ET MF; developed
persistent diarrhea and acute renal failure. Her serum protein
electrophoresis and immunofixation were normal, and her
bone marrow exhibited no plasmacytic infiltration. However,
renal biopsy showed deposition of monoclonal immunoglob-
ulin (IgAk), establishing the diagnosis of light chain and heavy
chain deposition disease (LHCDD), also known as Randall
disease, an entity recently recognized in the latest WHO clas-
sification [1]. Both diarrhea and acute renal failure subsided
<table>
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<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
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<td>MDS/MPN-RS-T</td>
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<td>PMF</td>
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<td>Negative</td>
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<td>Epoetin alpha, RBC transfusions</td>
<td>Hydroxycarbamide, bloodlettings</td>
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<td>MZL</td>
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<td>B-CLL</td>
<td>Splenic MZL</td>
<td>LHCDD</td>
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<td>Intolerance</td>
<td>CR</td>
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</table>

**Table 1: Patient characteristics and response to treatment.**

JAK2 inhibitors are associated with an increased risk of lymphoma [19]. It should also be noted that whether this patient’s exposure to anti-TNF (tumor necrosis factor) plasmas [18]. In our cases series, a patient treated with JAK2 treatment in these patients.

Interestingly, when treated with JAK inhibitors, this subgroup coexisting B-cell clone was detected in 16.3% of myelofibrosis patients. Indeed, Pajor et al. [17] have shown that 5% of MPN patients harbor a clonal B-cell population as demonstrated with clonal immunoglobulin gene rearrangements. In addition, a coexisting B-cell clone was detected in 16.3% of myelofibrosis patients in a different study, in line with previous findings. Interestingly, when treated with JAK inhibitors, this subgroup of patients was at an increased risk of developing B-cell neoplasms [18]. In our cases series, a patient treated with JAK2 inhibitor, indeed, developed MZL; however, it should be noted that this patient’s exposure to anti-TNF (tumor necrosis factor) agents for her ankylosing spondylitis could have also contributed to her lymphoma [19]. It should also be noted that whether JAK2 inhibitors are associated with an increased risk of lymphomagenesis remains equivocal, as the observational studies by Pemmaraju et al. [20] and Rumi et al. [21] did not show an increased risk of lymphoma in patients treated with these agents compared to those alternatively treated.

There is growing evidence that abnormalities in certain genes can result either in myeloid or in lymphoid malignancies. This is particularly true for the BCR/ABL1 fusion gene and the PDGFRα, PDGFRβ, and FGFR1 genes [22] as well as for TET2 mutations, observed in MDS, CMML, and in B and mainly T LPDs [23], for SF3B1 mutations, associated with both the MDS-RS phenotype and B-CLL [24, 25].

Whether the two concomitant diseases originate in the same or in two different clones is difficult to postulate in the everyday clinical setting. In cases where both myeloid and lymphoid cells harbor the JAK2 mutation, a common JAK2 V617F-mutated progenitor probably exists [9]. On the other hand, when the mutation is not detected in the B cells, two separate clones are present at the same time [7, 8]. A possible explanation could be that a milieu of genomic instability exists, leading to the acquisition of a JAK2 V617F mutation in one clone and the development of a separate B-cell clone in the same patient [26].

The inflammatory bone marrow microenvironment could be the cause of such instability. In support of this notion, it has been shown that in PMF, clonal cells produce inflammatory cytokines, which in turn promote remodeling of the microenvironment in the abnormal niche [27]. Furthermore, in vivo experiments have demonstrated that tissues characterized by chronic inflammation promote specific B-cell tumorigenesis by providing an environment where neoplastic B cells escape normal regulatory mechanisms [28]. These two observations could explain two main findings of our study: the high prevalence of PMF in keeping with that observed by Porpaczy et al. [18] as well as the high rate of precedence of the MPN over the LPD.

There are several limitations in this study. Importantly, no extrapolation of the incidence of concomitant MPN and LPD in the entire Greek population can be made as this study includes a population from a single institution. Moreover, because of the retrospective nature of this study, some information regarding patient history and initial presentation is missing. Finally, a thorough molecular testing for these patients could not be done due to practical difficulties; certainly, the results of such testing would have shed light on the clonal association of the two neoplasms in these patients.

In conclusion, we have presented a relatively large number of patients with MPN and a concomitant LPD. Various difficulties pertain to the diagnosis and management of these patients. More research is needed to elucidate the underlying mechanisms predisposing for both MPN and LPD coexistence.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

The authors declare that they have no conflicts of interest.
References


