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a nationwide discovery cohort

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by Johanne M. Holst, Trine L. Plesner, Martin B. Pedersen, Henrik Frederiksen, Michael B. Møller, Michael R. Clausen, Marcus C. Hansen, Stephen Jacques Hamilton-Dutoit, Peter Nørgaard, Preben Johansen, Tobias Ramm Eberlein, Bo K. Mortensen, Gustav Mathiasen, Andreas Øvlisen, Rui Wang, Chao Wang, Weiwei Zhang, Hans Beier Ommen, Jesper Stentoft, Maja Ludvigsen, Wayne Tam, Wing C. Chan, Giorgio Inghirami, and Francesco d'Amore

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Myeloproliferative and lymphoproliferative malignancies occurring in the same patient: a nationwide discovery cohort

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Running heads: Myeloid and lymphoid neoplasms in the same patient

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Abstract

Myeloid and lymphoid malignancies are postulated to have distinct pathogenetic mechanisms. The recent observation that patients with a myeloproliferative neoplasm have an increased risk of developing lymphoproliferative malignancy has challenged this assumption. We collected a nationwide cohort of patients with both malignancies. Patients diagnosed in 1990-2015 were identified through the national Danish Pathology Registry. We identified 599 patients with myeloproliferative neoplasm and a concomitant or subsequent diagnosis of lymphoma. Histopathological review of the diagnostic samples from each patient led to a final cohort of 97 individuals with confirmed dual diagnoses of myeloproliferative neoplasm and lymphoma. The age range at diagnosis was 19-94 years (median: 71 years). To avoid the inclusion of cases of therapy-induced myeloproliferative neoplasm occurring in patients previously treated for lymphoma, only patients with myeloproliferative neoplasm diagnosed unequivocally before the development of lymphoma were included. The average time interval between the diagnoses of the two malignancies was 1.5 years. In the majority of patients (90%) both diagnoses were established within 5 years from each other. Among the lymphoma entities, the frequency of peripheral T-cell lymphomas was markedly increased. Interestingly, all but one of the T-cell lymphomas were of angioimmunoblastic type.

These findings suggest that myeloproliferative neoplasm and lymphoproliferative malignancy developing in the same patient may have common pathogenetic events, possibly already at progenitor level. We believe that the molecular characterization of the newly developed biorepository will help to highlight the mechanisms driving the genesis and clonal evolution of these hematopoietic malignancies.
Introduction

The diagnosis of multiple clonal hematological neoplasms in the same patient is considered to be rare. Furthermore, when it does occur, it is unclear whether the individual disorders are pathogenetically related, e.g. sharing common driver mutations, or whether they simply reflect independently developed random events.

Studies of tumoral DNA from patients with angioimmunoblastic T-cell lymphoma (AITL) have identified genomic changes which can be detected in the early hematopoietic stem cell precursors. These alterations include IDH2, TET2, and DNMT3A, and are commonly seen in myeloid malignancies. Acquired somatic mutation in the Janus kinase 2 (JAK2) gene plays an essential role in the development of myeloproliferative neoplasms (MPN). Notably, this mutation has also been detected in some lymphoid malignancies (LM). These findings have prompted the hypothesis that some genomic changes in the early hematopoietic stem cell precursors may predispose to and could drive the development of both MPN and LM.

MPN are clonal hematopoietic stem cell disorders characterized by proliferation of one or more of the myeloid derived cell lineages. They include essential thrombocythemia (ET), polycythemia vera (PV), primary myelofibrosis (PMF), chronic myeloid leukemia (CML) and MPN-unclassifiable (MPN-U). According to the database of cancer statistics for the Nordic countries (NORDCAN; www-dep.iarc.fr/NORDCAN/English/frame.asp), the age-adjusted incidence rate of CML in Denmark is 0.95/100,000 and for the other chronic myeloproliferative entities (PV, ET, PMF, MPN-U; taken as one group) 4.05/100,000. In general, MPN are slowly progressing diseases which are, however, capable of transformation to severe bone marrow failure or acute leukemia. Recent epidemiological studies have reported an increased risk of developing other types of malignancy in
patients with MPN.\textsuperscript{9,10} In particular, the risk of also developing LM is significantly increased compared with a sex- and age-matched background population.

Dual diagnoses of MPN and LM in the same patient have previously been described in either individual case reports or small case series.\textsuperscript{11} However, a more substantial, population-based evaluation of this phenomenon, together with a biorepository of tumor specimens from such patients, has not yet been reported. The aim of our study was to identify and characterize a nationwide cohort of Danish patients with dual diagnoses of myeloproliferative and lymphoproliferative malignancies. We describe what we believe to be the largest series of patients with diagnoses of both MPN and LM, with particular emphasis on the establishment of the cohort, the histopathological classification of the malignancies, and description of the clinical characteristics of the patients.
Methods

Cohort identification

Patients diagnosed with both MPN and LM within the period 1977-2015 were identified through the national Danish Pathology Registry (DPR). The DPR is a nationwide register that records data on all pathology specimens from patients in Denmark. The registry and its associated database are updated daily. Since essentially all pathology investigations in Denmark are performed within the tax-funded public health system, the coverage of the DPR is close to 100%. The registry includes detailed variables related to patients, specimens and workload. All Danish citizens and residents are assigned a unique identifier, the civil personal registration (CPR) number, at birth or immigration. Using the CPR number system, patient data in the DPR can be linked to the many other Danish clinical databases. In addition, each specimen identified via the DPR can be linked to the available formalin-fixed, paraffin-embedded (FFPE) tissue biopsies stored in the diagnostic archives of the Danish pathology departments, allowing identification, location and retrieval of relevant primary diagnostic tissue specimens from the cohort patients.

The MPN diagnoses include PV, ET, PMF, CML, and MPN-U. In order to exclude secondary myelodysplasias/MPN occurring as a result of previous treatment for LM, only patients diagnosed with either both diseases concomitantly (i.e. diagnosed no more than six month apart) or with MPN first and LM subsequently, were selected for further histopathological revision. Because of the low number of samples available for the period 1977 to 1990 and the poor tissue quality of the older samples, only specimens from patients diagnosed in 1990 or later were included in the final cohort.

The study was approved by The Central Denmark Region Committees on Health Research Ethics (record no. 1-10-72-161-15) and the Danish Data Protection Agency (record no. 1-16-02-420-15),
and it was conducted in compliance with the principles of the Helsinki Declaration.

**Data sources**

All data sources were linked using the unique patient-specific CPR number. Clinical data were obtained from the population-based Danish National Lymphoma Registry (LYFO) and supplemented by medical records.

For comparison of overall survival (OS), a diffuse large B-cell lymphoma (DLBCL) reference cohort matched for age, sex, and the International Prognostic Index (IPI) was identified and randomly selected from LYFO (n=100). For AITL patients, a reference cohort previously described by Pedersen et al was used (n=25).

**Tissue collection and histological revision**

All specimens were pre-therapeutic biopsies from patients diagnosed with both MPN and LM. FFPE tissue specimens were collected from the archives at 15 different Danish pathology departments. After careful evaluation of the original pathology reports, new hematoxylin and eosin stained sections were cut from the study paraffin blocks and the histopathological diagnoses were reviewed. If necessary, supplementary immunohistochemical stains were assessed, in addition to those originally performed. Samples were reviewed by an experienced hematopathologist (TLP) at a tertiary referral center according to the 2017 revision of the 2008 WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. AITL tumors were specifically tested for well-known recurrent mutations in \textit{IDH2}, \textit{TET2}, \textit{DNMT3A}, and \textit{RHOA} genes.
**Statistical methods**

Outcomes were described by OS, defined as the time interval from LM diagnosis to last follow-up or death from any cause. OS estimates were calculated according to the Kaplan-Meier method and compared using the log-rank test. All statistical analyses were performed using STATA version 14.1 (StataCorp, College Station, TX, USA).
Results

Establishment of the cohort

The algorithm leading to the establishment of the cohort is shown in Figure 1. In total, 26,736 patients with MPN were identified. Of these, 1,524 had an additional registered diagnosis of concomitant or subsequent LM. If multiple biopsies from the MPN and/or LM diagnosis of a given patient were taken at different times the patient would end up with multiple registrations in the DPR. These redundant registrations were omitted (n=925). Patients with diagnoses of MPN and/or LM, which were unconfirmed after histopathological review (n=344), were excluded. A group of 67 patients diagnosed with LM prior to the MPN were also excluded, as were 18 patients diagnosed before 1990. Thus, diagnostic tissue specimens from 170 patients were retrieved for histopathological validation. Of these, 97 patients were confirmed to have both MPN and LM and represent the final cohort of the study.

Demographic and clinico-pathological features

Table 1 summarizes demographic characteristics of the patients. No major differences in sex distribution were observed, either overall or at subtype-specific level. The age at MPN diagnosis was for most patients within the 6th and 7th decade of life with the exception of lymphoblastic lymphoma (LBL), where patients were significantly younger (median 33 years, interquartile range 22-57 years). The overall average time between the diagnosis of MPN and LM was 1.5 years and in the majority of the patients (90%) both diagnoses were established within 5 years from each other.
Table 2 shows a cross tabulation between MPN and LM diagnoses. The most frequent LM diagnoses were chronic lymphocytic leukemia (CLL, 32%) and DLBCL (21%), in line with these being two of the more common LM entities in the general population.

Peripheral T-cell lymphomas (PTCL) usually account for approximately 10% of all lymphomas, which is in line with the relative frequencies seen in our study. Interestingly, AITL patients accounted for 89% (8 out of 9) of the MPN-associated PTCLs, an unexpectedly high frequency (5-7 fold) for this specific entity. AITL tumors frequently harbored mutations of TET2 (60%), IDH2 (60%), DNM3A (60%), and RHOA (80%) genes. All five LBL patients (B-cell lineage (n=2), T-cell lineage (n=2), and unclassifiable (n=1)) were associated with a pre-existing CML, probably cases of lymphoid blast crises on a CML background.

Overall, 64% (n=62) of the MPN patients were diagnosed with a concurrent LM, while the remaining 36% (n=35) developed LM subsequently. Figure 2 illustrates the chronological occurrence of MPN and LM in each patient with PTCL, DLBCL, and CLL. The majority (n=23; 77%) of CLL patients were diagnosed with both malignancies concurrently. In contrast, most DLBCL (n=11; 55%) and, even more strikingly, most PTCL patients (n=6; 67%) were diagnosed at a mean time interval of between 1 to 3 years after the MPN diagnosis (1.5 years for DLBCL and 2.8 years for PTCL).

**Outcome in selected lymphoma subtypes**

In a survival analysis, patients with both MPN and DLBCL had an inferior outcome compared with an age, sex, and IPI matched DLBCL reference cohort (HR 1.9, 95% confidence interval (CI): 1.1-3.3, P<0.02; Figure 3A). The 5-years OS of the MPN+DLBCL patients was 19% (95% CI: 5-39%) as compared with 34% (95% CI: 24-43%) for the DLBCL patients of the matched reference cohort.
In contrast, no difference was found between outcomes for patients with both MPN and PTCL versus patients with ‘AITL only’ (Figure 3B).

5-years OS of the MPN+CLL patients was 65% (95% CI: 45-79%). Historical data from the Danish CLL group shows a corresponding value for ‘CLL only’ patients diagnosed in the period 2012-2017 of 79% (95% CI: 77-81%).

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Discussion

In establishing this population-based cohort, we identified a substantial number of patients diagnosed with myeloid malignancies, who were also diagnosed, either at the same time or later, with a lymphoid neoplasia. Among these lymphoid neoplasias, AITL were found at a much higher frequency than expected. We believe, that this represents the largest reported cohort of patients with dual MPN and LM diagnoses, and that the associated biorepository is unique for its potential to foster the recognition of driver pathogenetic aberrations as well as the hierarchical relationship within the clonal evolution of hematological malignancies.

Epidemiological studies have reported an increased standardized risk of developing LM in MPN patients.\textsuperscript{9,17–20} Recently, a Swedish population-based study confirmed an increased risk of second malignancies in MPN patients with a hazard ratio of 2.6 (2.0-3.3) for developing lymphoma.\textsuperscript{10} However, none of the published studies indicated the frequency of different LM subtypes. Our data revealed a diverse range of different lymphoma entities. In the general population, AITL is, along with PTCL-NOS, the most common PTCL entity, representing 20-35\% of all PTCL cases in Caucasian populations.\textsuperscript{21,22} Notably, in our cohort, 8 out of 9 PTCL cases were of angioimmunoblastic type, i.e. approximately 4-fold the expected number.

AITL has a complex clinical picture and is often diagnosed at advanced stage.\textsuperscript{23} Histopathologic examination of AITL tissue usually shows a microenvironment of nonmalignant bystander cells, together with a minor population of neoplastic follicular helper T-cells (TFH), that are believed to be the cell of origin of AITL.\textsuperscript{24} Recently, molecular alterations unique to AITL and to PTCL of TFH-origin have been described.\textsuperscript{4,25} Among the most frequent genomic alterations are recurrent mutations of \textit{RHOA}\textsuperscript{5,26} and epigenetic modifier genes such as \textit{DNMT3A}, \textit{TET2}, and \textit{IDH2}.\textsuperscript{1,3,27,28} The latter are well known genetic lesions and originally identified in myeloid malignancies including
MDS and MPN. *DNMT3A* and *TET2* mutations have been predominantly found in progenitors prior to T-cell and B-cell commitment, whereas *RHOA* and *IDH2* mutations are usually found more downstream in cells that have undergone lineage specification.\(^2^9\) *TET2* and *IDH2* mutations are mutually exclusive in myeloid malignancies, but often co-exist in AITL.\(^5^,^2^5^,^2^9\) Interestingly, the combination of *TET2* deletion together with *RHOA* mutation has been shown to lead to development of AITL in mice.\(^3^0^–^3^2\) In spite of an increasing number of anecdotal reports of MPN associated with the development of a variety of LMs, no definitive relationship between the conditions has been established.\(^3^3\) However, the relatively high frequency of mutations in epigenetic modifier genes, found in both myeloid and lymphoid malignancies, could suggest a possible pathogenetic relevance of these mutations for the dual malignant transformation. Moreover, they may represent evidence of shared pathogenetic mechanisms related to hierarchical mutation steps occurring as early events in the hematopoietic neoplastic process.

Development of second malignancies in MPN patients may influence survival.\(^3^4\) Our study indicates a worse prognosis in patients with both MPN and DLBCL compared with a reference DLBCL cohort matched for age, sex, and IPI. This observation cannot be readily explained, but may be due to added morbidity as a consequence of multiple treatment courses related to both the myeloid and lymphoid malignancy and/or added deleterious genomic alterations at both stem cell and committed lineage-specific cell level. Conversely, no significant outcome difference was seen between patients with both MPN and AITL and a reference cohort diagnosed with AITL alone. AITL is a rare disease with a poor prognosis and with frequent relapses. Hence, our outcome analysis was expectedly hampered by the limited size of the compared cohorts, and additional studies are needed to verify this observation.
Recently, an overrepresentation of B-cell lymphomas in PMF patients treated with JAK1/2 inhibitors has been observed. None of the MF patients in our cohort had received JAK inhibition therapy.

Observational studies based on archival material have inherent limitations regarding the completeness of available clinical information and the validity of the histopathologic diagnoses. Our study is a nationwide collaboration between departments of pathology and hematology in Denmark, one major aim being to provide specimens and clinico-pathological data from a population-based cohort of patients diagnosed with both a myeloid and a lymphoid malignancy. Furthermore, all cases underwent histopathologic validation including a diagnostic update according to the most recent revision of the WHO-classification. A biorepository of tissue specimens has been established and DNA extracted for genomic analysis from both the MPN and LM samples.

In conclusion, we here describe the frequency, demographics and epidemiology of the largest reported cohort of patients diagnosed with both MPN and LM. Patients with both MPN and DLBCL have poorer outcomes than those with DLBCL only. AITL is by far the lymphoma entity with the highest relative frequency of associated MPN. We hypothesize that shared genomic abnormalities may predispose to the combined or sequential development of MPN and LM in the same host. To further investigate this hypothesis, we have established a biorepository of all available specimens from this nationwide cohort. This unique material will be an invaluable resource for the performance of genomic studies to investigate the pathogenetic relationship between MPN and LM with possible novel therapeutic implications.
References


Table 1: Demographic features.

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<th>PTCL</th>
<th>WM</th>
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<td>2.8</td>
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CLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; DLBCL, diffuse large B-cell lymphoma; IQ, interquartile; LBL, lymphoblastic lymphoma; LM, lymphoproliferative malignancy; MPN, myeloproliferative neoplasms; PTCL, peripheral T-cell lymphoma; WM, Waldenström macroglobulinemia; y, year.
<table>
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<td><strong>14</strong></td>
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Abbreviations: PV, polycythemia vera; ET, essential thrombocythemia; PMF, primary myelofibrosis; CML, chronic myeloid leukemia; MPN-U, myeloproliferative neoplasms - unclassifiable.
Figure 1. Flowchart illustrating the establishment of the cohort.
DPR, the Danish pathology register; MPN, myeloproliferative neoplasms; LM, lymphoproliferative malignancy.

Figure 2. Swimmer plots showing, for each patient for three selected lymphoid diagnoses (PTCL, DLBCL, and CLL), the chronological occurrence of the myeloproliferative and lymphoproliferative malignancies.
Each bar represents one patient in the study. Dark grey parts of the bars represent time between the MPN diagnosis and the lymphoma diagnosis. Light grey parts of the bars represent time with both diagnoses to death or last follow up.
PTCL, peripheral T-cell lymphoma; DLBCL, Diffuse large B-cell lymphoma; CLL, Chronic lymphocytic leukemia/small lymphocytic lymphoma.

Figure 3. Survival analyses.
(A) Kaplan Meier estimates of overall survival in A) DLBCL patients with and without a previous diagnosis of a MPN.
(B) Kaplan Meier estimates of overall survival in B) PTCL patients with and without a previous diagnosis of a MPN.
DLBCL, diffuse large B-cell lymphoma; MPN, myeloproliferative neoplasms; PTCL, peripheral T-cell lymphoma.