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Increased Risk of Lymphoid Neoplasms in Patients with Philadelphia Chromosome–Negative Myeloproliferative Neoplasms

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Abstract

Association of myeloproliferative neoplasm (MPN) with lymphoproliferative neoplasm (LPN) has been occasionally reported. The aim of this study, which included 353 patients with polycythemia vera and 467 with essential thrombocythemia, was to assess whether the risk of developing LPN is increased in MPN patients. Expected numbers of LPN incident cases were calculated based on 5-year age group, gender, and calendar time–specific cancer incidence rates in the general population of the same area. Standardized incidence ratios were computed to estimate the relative risk of developing LPN. Analyses were carried out for the whole series and then separately for essential thrombocythemia and polycythemia vera, gender, and *JAK2*V617F genotype. With 4,421 person-years, we found 11 patients developing LPN, including four chronic lymphocytic leukemias, five non–Hodgkin's lymphomas, and two plasma cell disorders, after a median interval time of 68 months from MPN diagnosis. Cumulative risk to develop LPN at 5 and 10 years was 0.93% (95% confidence interval, 0.39-2.22) and 2.96% (95% confidence interval, 1.52-5.72), respectively. There was a 3.44-fold increased risk of LPN compared with the general population, ranging from 2.86 for plasma cell disorder to 12.42 for chronic lymphocytic leukemia; the risk was significantly increased in *JAK2*V617F mutated patients (5.46-fold) and in males (4.52-fold). The *JAK2*V617F mutation was found in lymphoid tumor cells in two of three cases evaluated, indicating that, in some patients, LPN originated in a *JAK2*V617F mutated common lymphoid-myeloid hematopoietic progenitor cell. We conclude that the risk of developing LPN is significantly increased in MPN patients compared with the general population. (Cancer Epidemiol Biomarkers Prev 2009;18(7):2068–73)

Introduction

The Philadelphia chromosome–negative myeloproliferative neoplasms (MPN), according to the 2008 WHO classification of tumors of hematopoietic and lymphoid tissues, include the ''classic'' clinical entities polycythemia vera (PV) and essential thrombocythemia (ET), in addition to other entities (1). These are relatively indolent neoplastic disorders, resulting in a modest reduction of life span compared with the general population (2); however, most patients ultimately suffer from one or more severe, potentially fatal complications directly attributable to the disease. These disorders have common features that include their origin in a multipotent hematopoietic stem cell; a relatively normal cellular maturation; a striking overlap in clinical presentation; the propensity to evolve into postpolycythemic or postthrombocythemic myelofibrosis, or less frequently each into the other; and the possibility to transform to acute myeloid leukemia (3).

The molecular mechanisms at the basis of MPN have remained largely unclear until the discovery in 2005 of a single point mutation in the gene encoding the tyrosine kinase Janus-activated kinase 2 (JAK2); the JAK2V617F mutation, located in exon 14, is found in almost all patients with PV and in ~60% of those with ET or primary myelofibrosis (4-7). The JAK2V617F mutation is located in the JH2 pseudokinase domain of JAK2 and results in the loss of autoinhibitory control and in cytokine-induced hyperactivation of JAK2 (8). More recently, mutations in *MPL* at codon 515 in ET or primary myelofibrosis (9) and in exon 12 of JAK2 in PV (10) have been reported. These mutations are considered integral to the myeloproliferative process, but whether they represent the original molecular lesion or a secondary genetic event (11-14) and how one single mutation can associate with different clinical phenotypes (15) are still under investigation.

The MPNs are among the most frequent hematologic neoplasms; according to a survey (16) based on the North

Received 4/14/09; accepted 5/6/09; published OnlineFirst 6/16/09.

Grant support: Ministero della Università e Ricerca (PRIN projects), Istituto Toscano Tumori, EC project no. LSHB-CT-2005-518167 (INNOCHEM, FP6), Associazione Italiana per la Ricerca sul Cancro, Ente Cassa di Risparmio di Firenze, and Università di Firenze institutional funds (ex-60%).

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doi:10.1158/1055-9965.EPI-09-0353

Table 1. Characteristics of the MPN patients considered in the study

	PV	ET
n	353	467
Males/females	237/116	154/313
Age (y), median (range)	61 (16-89)	57 (14-97)
Individual follow-up duration (y), median (range)	3.4 (0.1-26.2)	3.2 (0.1-23.9)
Total follow-up (PY)	1,882	2,539
Leukocyte count ($\times 10^9$/L)	9.63 (3.8-13.2)	9.0 (4.1-26.0)
Hemoglobin (g/L)	176 (148-24)*	140 (71-174)
Platelet count ($\times 10^9$/L)	414 (125-1, 250)	800 (529-3, 125)
*JAK2*V617F positive, *n* (%)†	169/172 (98.2)	215/336 (64.0)

Abbreviation: PY, person-years.
*Some patients had been already phlebotomized before a diagnosis of PV could be firmly established.
†Data refer to 508* patients genotyped (61.9% of total).

American Association of Central Cancer Registries, they summed up to an average 2001 to 2003 annual age-adjusted incidence rate of 2.1 per 100,000. It is known that familial clustering of these disorders also occurs, leading to the suggestion of predisposition allele(s) (17-19). This hypothesis is supported by results of a large Swedish study (20) that pointed to a 5.7 relative risk of having PV, a 7.4 relative risk of having ET, and a 7.5 relative risk of having unclassified forms of MPN in the relatives of patients with MPN. The coexistence of different clinical entities and of *JAK2*V617F-positive and *JAK2*V617F-negative disorders in the same family is noteworthy (18, 21, 22).

It is commonly held that the incidence of secondary neoplasia or of another tumor of the hematopoietic system is increased in MPN, but no large epidemiologic study exists at this regard. In particular, the association of MPN and a disorder of lymphoid system has been sporadically reported in the literature. The aim of this study was to evaluate the risk of developing lymphoproliferative neoplasms (LPN) in a large cohort of patients affected by ET and PV. We also had the opportunity to genotype lymphoid cancer cells in three *JAK2*V617F mutated patients, aiming at ascertaining whether the two diseases originated from a common, *JAK2*V617F mutated lymphoid-myeloid progenitor cell.

Results of this study indicate that patients with MPN carry a statistically significant increased risk of developing LPN compared with the general population and that, although in some cases lymphoid cancer cells harbor the V617F allele, the presence of mutation is not a prerequisite for LPN to develop.

Patients and Methods

All consecutive patients with MPN newly diagnosed at the Haematology Department of University of Florence in the period 1980 to 2008 were identified and included in the study. All patients were offered an active clinical follow-up protocol. Information on individual demographics (sex, date of birth, age at diagnosis, area of residence), baseline clinical characteristics, and *JAK2*V617F mutational status was retrieved from medical records and computerized, together with information on newly diagnosed LPN during follow-up and on vital status.

A total of 877 patients with MPN were retrieved from the archive. According to residence, ~85% of them were residing in the provinces of Florence and Prato, an area covered since 1984 by the Tuscany Cancer Registry. The remainders were mostly residing in neighboring areas.

The diagnosis was reevaluated in all instances using the original clinical records and bone marrow biopsy when available; overall, there were 532 patients (61%) who had a diagnosis fulfilling the WHO criteria (1) and 345 (39%) in whom the diagnosis fulfilled the Polycythemia Vera Study Group criteria (23). Clinical history was reviewed with special attention to the diagnosis of LPN based on chart records. Diagnosis of LPN was made according to the WHO criteria (1), and in all cases, the original diagnosis was critically reviewed using chart records, laboratory records (routine tests, immunophenotyping, conventional or molecular cytogenetics when available), bone marrow biopsy, or lymph node biopsy. This retrospective analysis was approved by the local ethical committee of Azienda Ospedaliera-Universitaria Careggi, according to the principles of the Helsinki Declaration.

***JAK2*V617F Genotyping.** Genotyping was done in peripheral blood granulocytes collected by density gradient centrifugation to >95% purity. B and T lymphocytes were purified from peripheral blood at the diagnosis of

Table 2. Clinical and individual characteristics of the 11 patients with MPN who developed LPN during the follow-up

Case no.	Gender	MPN	Age at diagnosis of MPN (y)	Cytoreductive treatment	LPN	Interval between MPN and LPD diagnosis (mo)	*JAK2*V617F
01	M	PV	66	Yes	MM IgAλ	79	+
02	M	PV	59	Yes	CLL	77	NA
03	M	PV	74	Yes	CLL	23	NA
04	F	PV	64	Yes	DLBC-NHL	68	+
05	M	PV	64	No	MC-NHL	20	+
06	M	PV	43	No	WD	112	NA
07	M	PV	69	No	NHL	131	NA
08	F	ET	65	Yes	CLL	71	+
09	M	ET	64	No	CLL	25	+
10	M	ET	65	Yes	T-NHL	28	+
11	F	ET	70	No	MC-NHL	7	NA

Abbreviations: MM, multiple myeloma; CLL, chronic lymphocytic leukemia; DLBC, diffuse large B cell; NHL, non–Hodgkin's lymphoma; MC, mantle cell; WD, Waldenstrom disease; T-NHL, T-cell NHL; NA, not available.

Table 3. Distribution of LPN in the series of MPN patients, overall and by specific subtype; number of observed and expected cases and relative risks as estimated by SIRs and 95% CIs

	No. observed*	No. expected†	SIR (95% CI)
All MPN patients			
LPN (all types)	11	3.20	3.44 (1.90-6.20)
NHL	5	1.45	3.44 (1.43-8.27)
CLL	4	0.32	12.42 (4.66-33.09)
PCD	2	0.70	2.86 (0.72-11.43)
PV			
LPN (all types)	7	1.57	4.45 (2.12-9.34)
NHL	3	0.71	4.25 (1.37-13.17)
CLL	2	0.16	12.35 (3.09-49.38)
PCD	2	0.35	5.77 (1.44-23.08)
ET			
LPN (all types)	4	1.63	2.45 (0.92-6.54)
NHL	2	0.75	2.68 (0.67-10.71)
CLL	2	0.16	12.49 (3.12-49.94)
*JAK2*V617F positive			
LPN (all types)	6	1.10	5.46 (2.45-12.15)
NHL	3	0.53	5.71 (1.84-17.72)
CLL	2	0.10	19.14 (4.79-76.52)
Latency			
≤5 y‡	5	1.72	2.90 (1.21-6.97)
>5 y‡	6	1.48	4.06 (1.82-9.03)

Abbreviation: PCD, plasma cell disorder.
* LPN cases newly diagnosed in MPD patients (only LPN subtypes with at least two observed cases are included in the table).
† Expected cases of LPN according to incidence rates in the general population of the area applied to the number of person-years in the study follow-up.
‡ After the original MPD diagnosis.

MPN using immunomagnetic beads, as reported previously (24). In a patient with chronic lymphocytic leukemia, neoplastic cells ($CD19^+CD5^+CD20^+$) were sorted from peripheral blood mononuclear cells with a FACSAria flow cytometer (Becton Dickinson) using fluorochrome-conjugated anti-CD19, anti-CD5, and anti-CD20 monoclonal antibodies. DNA was obtained from granulocytes or sorted lymphoid cells using the QIAmp DNA blood kit (Qiagen GmbH) and quantified with the NanoDrop technology. QIAmp DNA micro kit (Qiagen) was used to isolate genomic DNA from paraffin-embedded biopsies of lymph nodes or other tissues. Genotyping for *JAK2*V617F mutation (5) was done with a quantitative real-time PCR assay (25).

Statistical Analysis. For each subject, the period at risk was defined from the date of diagnosis of MPN to the date of incidence of LPN, date of death, or date of the more recent clinical examination, whichever came first, and person-years were calculated. The expected number of incident cases of LPN in our series was calculated on the basis of 5-y age group, gender, and calendar time–specific cancer incidence rates in the general population of the same area applied to the person-years at risk in each 5-y age group, gender, and period-specific category of patients during the follow-up period. The specific cancer incidence rates were provided by the Tuscany Cancer Registry, which is active in the provinces of Florence and Prato since 1984 and provides routinely cancer incidence data for the area (~1,161,000 inhabitants). The degree to which incidence of LPN in this series of patients differed from the general population was measured by the ratio of observed to expected cases. This ratio, known as standardized incidence ratio (SIR), is a reliable estimate of the relative risk of developing LPN in the series of MPN patients in comparison with the general population of the area. Briefly, when a SIR results significantly higher than unit, then LPN risk among patients is significantly increased in comparison with the general population of the area. SIRs were estimated for LPN both as a whole and for specific histologic types, together with 95% confidence intervals (95% CI), calculated under the assumption of a Poisson distribution for cancer cases observed in the follow-up period. Analyses were first carried out for the whole series and then separately for ET and PV, gender, *JAK2*V617F mutational status, and by latency from diagnosis of MPN (0-5 and >5 y). SIR estimates are presented only for specific histologic types with at least two cases diagnosed. Cumulative risks at 5 and 10 y were also calculated.

Results

Patient Characteristics. Of the 877 subjects initially identified, 57 were excluded from the study because they had been lost to follow-up after the first visit. The clinical and laboratory features at diagnosis of the remaining 820 patients (353 PV and 467 ET) who remained in active follow-up are summarized in Table 1. There were 391 males (48%); median age at diagnosis of MPN was 59 years, and the median follow-up period was 3.3 years. During the follow-up, 20 patients (16 with ET and 4 with PV) died; there were 11 disease-related deaths (transformation to acute leukemia), one patient died of lung cancer whereas other causes were infections or multiorgan failure. A total of 4,421 person-years were available for analysis (2,450 person-years for females and 1,971 person-years for males); ET and PV provided 2,539 and 1,882 person-years, respectively.

*JAK2*V617F mutational status was available in 508 patients (61.9%), of whom 384 (75.6%) were mutated, 98.2% (169 of 172) and 64.0% (215 of 336) among PV and ET patients, respectively. Overall, 1,643 person-years were contributed by patients harboring the V617F mutation and 644 person-years by those who were JAK2 unmutated.

Table 4. Distribution of LPN in the series of MPN patients, overall and by specific subtype according to gender; number of observed and expected cases and relative risks as estimated by SIRs and 95% CIs

Gender	No. observed*	No. expected†	SIR (95% CI)
Male			
LPN (all types)	8	1.77	4.52 (2.26-9.03)
NHL	3	0.78	3.85 (1.24-11.95)
CLL	3	0.19	15.67 (5.05-48.58)
PCD	2	0.38	5.23 (1.31-20.90)
Female			
LPN (all types)	3	1.43	2.10 (0.68-6.50)
NHL	2	0.67	2.97 (0.74-11.86)

*LPN cases newly diagnosed in MPD patients (only LPN subtypes with at least two observed cases are included in the table).
†Expected cases of LPN according to incidence rates in the general population of the area applied to the number of person-years in the study follow-up.

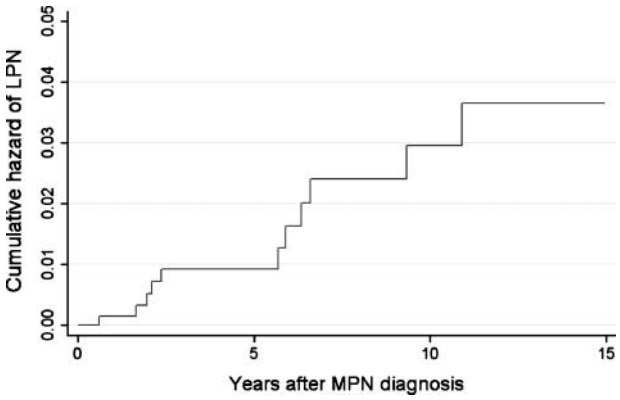

Figure 1. Kaplan-Meier's cumulative risk of developing LPN after MPN diagnosis.

Epidemiology of LPN in the Series of MPN Patients. The development of LPN was recorded during the follow-up in 37 patients (4.5%); of these, 14 had a diagnosis of ET and 23 of PV. Twenty-six patients, 10 with ET and 16 with PV, were diagnosed with a monoclonal gammopathy of undetermined significance; due to the high occurrence of this abnormality in the general population, its unclear neoplastic significance, and the lack of specific incidence rate in the general population, no estimate of SIR was done and patients were still considered in follow-up. Of the 11 LPN considered, there were four chronic lymphocytic leukemia, five non–Hodgkin's lymphomas, and two plasma cell disorders, represented by one multiple myeloma and one Waldenstrom disease. Seven cases occurred in patients with PV (7 of 11, 63.6%) and four in patients with ET (4 of 11, 36.4%; Table 2). The median age at diagnosis of LPN was 70 years, and the median follow-up after the diagnosis of LPN was 5.7 years. The median interval time from diagnosis of MPN to LPN was 68 months (range, 7-131). Six of the 11 patients (54.5%) were on cytoreductive treatment (hydroxyurea) from a mean time of 51 months (range, 12-84) when LPN was diagnosed.

Table 3 shows the observed and the expected number of LPN cases diagnosed in the whole series and the relative risks in comparison with the general population of the area estimated by SIRs. Overall, the incidence of LPN showed a significant 3.44-fold (95% CI, 1.90-6.20) increase in the entire series; the risk was significantly increased in PV (SIR, 4.45; 95% CI, 2.12-9.34) and, falling short of statistical significance, in ET (SIR, 2.45; 95% CI, 0.92-6.54). Among the different histologic subtypes, the risk of developing LLC was >12-fold increased in both PV and ET, based on two observed cases in each disease (Table 3). Considering non–Hodgkin's lymphoma, the risk was 4.25 (95% CI, 1.37-13.17) in PV and 2.68 (95% CI, 0.67-10.71) in ET, based on three and two cases, respectively. Finally, there was a significantly increased risk in patients harboring the *JAK2*V617F mutation ($n = 6$ cases; SIR, 5.46; 95% CI, 2.45-12.15) whereas no cases emerged among *JAK2* wild-type subjects. Overall, the risk to develop LPD increased with increasing latency from the original MPN diagnosis (SIR, 2.90 in the first 5 years of follow-up; SIR, 4.06 in the period after 5 years from diagnosis).

In Table 4, the distribution of LPN in relation to gender is shown. The risk of developing LPN was 4.52-fold (95% CI, 2.26-9.03) higher than expected in male patients, whereas among females, a nonsignificant increase of 2.10-fold (95% CI, 0.68-6.50) emerged.

Cumulative risks to develop LPN at 5 and 10 years after the original diagnosis of MPN were estimated as 0.93% (95% CI, 0.39-2.22) and 2.96% (95% CI, 1.52-5.72), respectively (Fig. 1).

***JAK2*V617F Genotype in Lymphoid Cancer Cells.** In three *JAK2*V617F mutated patients, one with PV and two with ET who developed LPN during the course of their MPN, we were able to genotype cancer lymphoid cells. There were one case of mediastinal diffuse large B-cell non–Hodgkin's lymphoma, one chronic lymphocytic leukemia, and one enteropathy-type T-cell ileal lymphoma ($CD3^+/CD56^+/BCL2^+/Mib1^+$ >90% of the cells; Table 5). In case of lymphomas, we extracted DNA from paraffin-embedded tumor biopsies, whereas in case of chronic lymphocytic leukemia, we sorted neoplastic B cells according to their CD19/CD5/CD20 phenotype to a purity of >97%. We found that, in the diffuse large B-cell non–Hodgkin's lymphoma and the chronic lymphocytic leukemia case, the lymphoid tumor cells harbored the V617F allele, whereas T cells from the ileal lymphoma were wild type (Table 5). In the two patients who developed a non–Hodgkin's lymphoma, we could also genotype B and T cells that had been purified from the peripheral blood at the time of MPN diagnosis; we found a concordance of the mutational status of tumor lymphoid cells and peripheral blood–derived T and B lymphocytes (Table 5).

Discussion

The association of a Philadelphia chromosome–negative MPN and LPN in the same patient is a relatively

Table 5. *JAK2*V617F mutational status of peripheral blood cells and neoplastic lymphoid cells in three cases of LPN that occurred during the follow-up of MPN patients

Case no.	LPN	MPN	*JAK2*V617F mutational status			
			GN*	CD3*,†	CD19*,†	Tumor cells†
04	DLBC-NHL	PV	V617F	V617F	V617F	V617F
08	CLL	ET	V617F	n.a.	n.a.	V617F
10	T-NHL	ET	V617F	WT	WT	WT

Abbreviations: WT, wild type.
*Genotyping was done on cells collected at diagnosis.
†DNA of tumor cells was extracted from tumor biopsies in case of NHL or from sorted clonal B cells in case of CLL.
n.a., not available

uncommon event, originally described in 1953 (26). After a revision of the literature (updated to December 2008), we identified at least 60 publications reporting single-case association of ET or PV with different types of LPN; these included chronic lymphocytic leukemia, which was the most represented, Hodgkin's disease, non–Hodgkin's lymphoma, and multiple myeloma.

To our knowledge, this is the largest series reported that included >800 patients with the two commonest MPNs (i.e., PV and ET). The single-center design of this analysis represents, in our opinion, an added value for the interpretation of data, in particular with regard to the epidemiologic design of the study. In fact, most patients were residing in a well-defined area in Tuscany where a Cancer Registry is collecting information since 25 years, allowing us to have a large and representative series of LPN incident cases to estimate stable incidence rates in the general population and, therefore, a reliable number of expected cases in this study series. Furthermore, the availability of incidence rates in the same population guaranteed that the role of environmental variables potentially influencing the risk of developing LPN was kept under control.

The results of this study indicate that the risk of developing LPN is significantly increased in patients with MPN compared with the general population, in particular in those with PV and in males. The overall frequency of LPN in this series was 1.34% of all MPN, comparable with the 1.6% reported in a recent series of 499 ET patients that enumerated eight cases of LPN (27). The cumulative risks of developing LPN at 5 and 10 years were between 1% and 3%. Furthermore, the risk was significantly higher in patients harboring the *JAK2*V617F mutation than in wild type. In addition, it is worthy to note that the risk was as high as 12-fold in case of chronic lymphocytic leukemia. Our results also suggest that the risk tends to increase with increasing duration of the MPN, with a SIR of >4 after 5 years of follow-up. Therefore, it is also likely that the true incidence of LPN is underestimated in this analysis if we take into account that the median time for LPN to develop after the diagnosis of MPN (72 months) was almost twice the median follow-up time (39 months) of the whole series.

The design of the study did not allow drawing of any conclusion about a possible causative or contributing role of cytotoxic therapy instituted for the control of MPN; however, it is of note that in most single cases reported in the literature, the two diseases were diagnosed simultaneously, in the absence of any treatment.

A large population-based case-control study in Sweden described a 5-fold to 7-fold elevated risk of developing MPN among first-degree relatives of MPN patients, supporting susceptibility genes predisposing to these disorders in the population (20). In addition, defined single-nucleotide polymorphisms in *JAK2* were found to associate with PV or ET, rather than primary myelofibrosis, and one single-nucleotide polymorphism in *EPOR* to significantly associate with PV only among the MPN (28). Data from current study would imply that similar predisposition allele(s) underlie the risk of developing LPN in patients affected by MPN. It is also of relevance that activation of JAK2 by the V617F mutation has been shown to favor a condition of genetic instability in cells forced to express the mutated gene, as well as in *ex vivo* isolated $CD34^+$ hematopoietic progenitor cells from PV or primary myelofibrosis patients; these cells showed an increased homologous recombination rate, spontaneous RAD51 foci formation, and high mutagenesis at different loci (29). Therefore, the finding in our series that increased risk of LPN was particularly associated with a *JAK2*V617F mutated status is intriguing. On the other hand, the fact that, in one of three cases examined, the lymphoid cancer cells were *JAK2* wild type suggested that the presence of *JAK2*V617F is not essential for LPN to develop in the course of MPN. There are at least two possible explanations: one is that the MPN and LPN originated from different progenitors and the other is that both disorders originated from a common lymphoid-myeloid progenitor cell, hinted by a first genetic insult followed first by the *JAK2*V617F mutation leading to the MPN phenotype and later by (an)other mutation(s) favoring the development of LPN.

In conclusion, we found a significantly increased risk of developing LPN in a large population of patients with PV or ET that ranged from 3-fold for any LPN up to 12-fold in case of chronic lymphocytic leukemia. Indirectly, these results are in support of the theory of a global genetic instability of pluripotent hematopoietic progenitors in the MPN as well as of generic susceptibility alleles. This information could also be of relevance for interpreting results of ongoing gene mapping and candidate gene studies in patients with MPN, which recently resulted in highlighting novel, still largely to be defined interactions between germ line haplotypes and acquired mutations at the *JAK2* locus (30).

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Acknowledgments

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