Table 1. Splenectomy in thrombotic thrombocytopenic purpura. Patients' main characteristics.

UPN	Sex/Age	Platelet count at diagnosis (x10⁹/L)	No. of PE#	Before splenectomy Platelet count (x10⁹/L)	Status	Response Follow-up (months)	Status
1	M/42	3	20	94	Refractory	CR	Alive (26)
2	M/35	25*	5	120	Relapse	CR	Alive (24)
3	M/35	10*	28	61	Refractory	Relapse	Alive (4)
4	M/57	5	28	50	Refractory	CR	Alive (11)

**Platelet count at relapse; #represents the number of days with PE before splenectomy; PE: plasma exchange; CR: complete response.*

as well as those reported by others[6] show that splenectomy can be safely performed with good results even in patients who do not respond to PE. Other authors have done splenectomy to prevent relapses in TTP, confirming a reduction of the relapse rate with minimal morbidity.[5,7] Overall, these findings suggest that splenectomy reduces the frequency of relapses and can induce prolonged remissions in refractory patients. The reason for clinical improvement after splenectomy remains elusive. Recently, the body of evidence supporting an autoimmune mechanism as the primary cause of endothelial damage in TTP has increased.[9] If the preliminary reports suggesting an autoimmune basis for TTP are confirmed,[10] these findings could contribute to a better understanding of the role that the spleen plays in the pathogenesis of this disease.

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Delay of onset of candidemia and emergence of *Candida krusei* fungemia in hematologic patients receiving prophylactic fluconazole

Invasive fungal infections are an important cause of morbidity and mortality in hematologic patients. In spite of newer antifungal approaches candidemia remains a severe condition associated with a high mortality. Since the introduction of fluconazole prophylaxis we registered an increasing prevalence of *C. krusei* fungemia as well as a significant reduction of early-onset candidemia.

Sir,

Fungal infections have increased substantially over the past two decades in patients with hematologic malignancies. Since the introduction of fluconazole prophylaxis in the early 1990s, changes in the epidemiology of candidemia have been reported[1-3] with an increase of infections caused by species other than *C. albicans*, mainly *C. krusei*. However, a causal relationship between prior use of fluconazole and increasing number of infections due to *C. krusei* remains controversial.[5-9]

We report a retrospective evaluation of 39 candidemia episodes which occurred in patients with

Table 1. General characteristics and overall outcome of patients with candidemia.

	No. of cases	*1986/ 1991*	*1992/ 1997*	*p*
Patients	39	21	18	
Gender				
Male	24	12	12	NS
Female	15	9	6	
Age (years)				
≤ 50	18	13	5	0.03
> 50	21	8	13	
Underlying disease				
AML	27	18	9	0.04
ALL	6	2	4	
Other	6	1	5	
Neutropenia	37	20	17	NS
Central venous catheter	36	18	18	NS
Parenteral nutrition	15	8	7	NS
Previous bacteremia	12	6	6	NS
Primary candidemia	23	11	12	NS
Infection source	16	10	6	NS
Lung	9	5	4	
Catheter	3	1	2	
Gastrointestinal tract	3	2	0	
Skin/soft tissue	1	1	0	
Central nervous system	1	1	0	
Early-onset candidemia	12	10	2	0.01
C. krusei fungemia	14	3	11	0.002
Breakthrough candidemia	8	4	4	NS
Overall mortality	22	10	12	NS
Mortality attributed to candidemia	15	7	8	NS

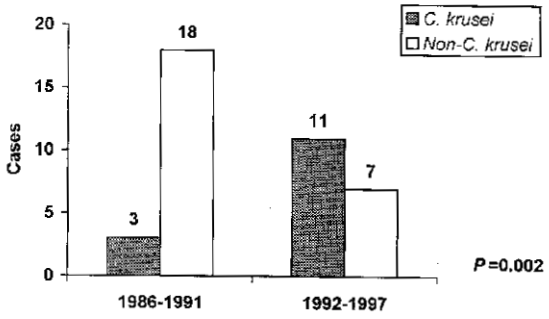

Figure 1. Incidence of *C. krusei* vs. *non-C. krusei* fungemia in the period without (1986-1991) and with (1992-1997) fluconazole prophylaxis.

hematologic malignancies between January 1986 and December 1997 treated in our Unit. There were 21 cases diagnosed in the period 1986-1991, before using fluconazole prophylaxis, and 18 cases in the period 1992-1997, when prophylactic fluconazole (100 mg/day po) was routinely used.

The main characteristics of the 39 patients with documented candidemia are summarized in Table 1. All patients had received intensive chemotherapy, and eight of them had undergone hematopoietic stem cell transplantation. At the onset of candidemia, all but two had severe neutropenia. The median duration of neutropenia prior to candidemia documentation was 11 days (range, 2-32). Early-onset candidemia (within a week of the onset of a febrile episode) occurred in 12 patients (31%), and was more common before 1992 (48% vs 11%, p=0.01). As shown in Figure 1, of 14 episodes of *C. krusei* fungemia that occurred over the study period, 11 (79%) occurred during the period 1992-1997, when fluconazole was routinely employed. The incidence of candidemia due to *C. krusei* increased from 14% to 61% in the periods 1986-1991 and 1992-1997, respectively. Simultaneously, non-*C. krusei* candidemias declined from 86% to 39%, respectively (p=0.002). In contrast with our experience in hematologic patients, *C. krusei* caused only 1.5% of candidemias registered among non-hematologic hospitalized patients in the period 1991-1997 (p <0.0001).

Overall, 17 patients (44%) had a favorable outcome. Although crude mortality was 56% (22 patients), death was attributed to candidemia in 15 patients (38%). *C. krusei* fungemia had a higher mortality than the other candidemias (50% vs 32%), although the difference was not statistically significant. Likewise, no significant differences in mortality were found comparing both periods (44% vs 33%, p=0.47).

The increasing prevalence of *C. krusei* fungemia, which became the species of Candida most commonly isolated in blood cultures from patients with hematologic malignancies at our institution, along with the decline of other Candida species, seems related to the prophylactic use of fluconazole. With regard to mortality, we found a trend toward a higher death rate in our patients with *C. krusei* fungemia, but the sample size precluded a definitive conclusion. On the other hand, we have observed a significant reduction of early-onset candidemia beginning from the introduction of fluconazole prophylaxis. To the best of our knowledge, this has not been previously reported. However, we found that the delay of onset of candidemia did not significantly affect the outcome.

In summary, candidemia in patients with hematologic malignancies is still associated with a high mortality. Fluconazole prophylaxis is related to both a lower incidence of early-onset candidemia and a significant increase in the proportion of candidemias caused by *C. krusei*. These findings should be confirmed in prospective studies.

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β-thalassemia intermedia resulting from compound heterozygosity for an IVSI-1 (G-A) and a silent 5' UTR +33 (C-G) mutation

A Caucasian woman from Plasencia, Spain, was found to have a thalassemia intermedia phenotype due to a double heterozygosity for a IVSI-1 (G-A) mutation and a silent 5'UTR +33 (C-G) mutation. This silent mutation has been described previously, but with a different haplotype, in two unrelated Greek Cypriot families.

Sir,

A Caucasian woman from Plasencia, Spain was found to have a thalassemia intermedia phenotype.

Table 1. Hematologic data and Hb analysis.

Subject	Propositus		Father	Mother
	Pre S	Post S		
Hb (g/dL)	6.8	8.2	10.1	13
MCV (fL)	61.4	63	66	84
MCH (pg)	19.7	20	21	28
Ferritin (ng/mL)	237	614	n.d.	n.d.
Hb A2 (%)	5.8	4.1	5.0	3.0
Hb F (%)	n.d.	3.2	1.2	0.3
IEF	AA2F	AA2F	AA2	AA2

HbA_2 assayed by column chromatography and HbF by alkali denaturation. IEF using precasting gels (Pharmacia) of agarose pH 6–8. Pre-S – pre splenectomy; Post-S – post splenectomy.

Her father had β-thalassemia (β-thal) minor and her mother had normal hematologic indices. We found that the woman had inherited an IVSI-1 (G-A) mutation from her father and a silent 5'UTR +33 (C-G) mutation from her mother.

A few mutations have been described in the β-globin gene, most frequently in the promoter or in the 5' untranslated regions, leading to a slight decrease of β-globin chain synthesis.[1]

Carriers of these silent mutations show normal or slightly decreased hematologic parameters and a normal or slightly elevated Hb A_2 level; the co-inheritance of another β thalassemia mutation in *trans* gives rise to a thalassemia intermedia phenotype. Silent thalassemia mutations are most often identified among thalassemia intermedia patients who have one parent with a normal phenotype.[2]

The propositus was 49 years old. She had thalassemic facies, jaundice, hypochromic microcytic

Figure 1. Sequencing of the proband's DNA fragment showing the +33 C-G mutation.