cation. In contrast, a few cases have been reported of HPS as an early and prominent manifestation of an underlying cell lymphoma.[4,5] Differentiation from other causes of HPS is difficult and lack of histologic proof of malignancy in the initial stage often delays definitive diagnosis and treatment. Demonstration of clonal TCR gene rearrangements has been useful for the diagnosis of clonality in peripheral T-cell lymphomas.[6] However, monoclonality can be demonstrated using PCR in only 50-73% of peripheral T-cell lymphomas.[7] For the present, there are no reliable treatment strategies for malignancy-associated HPS. When HPS occurs at the time of initial diagnosis of a malignancy, patients should receive aggressive therapy including chemotherapy and supportive care. Furthermore, initial therapy with steroids and etoposide for rapidly progressing HPS has been suggested to control the cytokine storm during the acute phase of the disease preventing acute death.[3]

Esperanza Real, Alvaro Gomez,° Maria J. Alcaraz,# Ana I. Saez,@ Emilio Pastor,* Enric Grau**

**Department of Hematology. Hospital Lluís Alcanyís, Xàtiva, °Department of Pathology, Hospital Lluís Alcanyís, Xativa; #Department of Microbiology, Hospital Dr. Peset, Valencia; @Department of Pathology, Hospital Virgen de la Salud, Toledo, Spain*

Key words

Hemophagocytic syndrome, Epstein-Barr virus, T-cell lymphoma

Correspondence

Enric Grau, M.D., Dept. Hematology, Hospital Lluis Alcanyis, Ctra. Xativa-Silla, km 2, 46800 Xativa, Spain. Phone: international +34-96-2289595 – Fax: international +34-96-2289572 – E-mail: grau_enr@gva.es

References

1. Risdall RJ, Mckenna RW, Nesbit ME, et al. Virus-associated hemophagocytic syndrome: a benign histiocytic proliferation distinct from malignant histiocytosis. Cancer 1979; 44:993-1002.
2. Henter JI, Elinder G, Öst A. Diagnostic guidelines for hemophagocytic lymphohistiocytosis. The FHL Study Group of the Histiocyte Society. Semin Oncol 1991; 18:29-33.
3. Janka G, Imashuku S, Elinder G, Schneider M, Henter JI. Infection- and malignancy-associated hemophagocytic syndromes. Secondary hemophagocytic lymphohistiocytosis. Hematol Oncol Clin N 1998; 12: 435-44.
4. Falini B, Pileri S, De Solas I, et al. Peripheral T-cell lymphoma associated with hemophagocytic syndrome. Blood 1990; 75:434-44.
5. Su IJ, Hsu YH, Lin MT, Cheng AL, Wang CH, Weiss LM. Epstein-Barr virus-containing T-cell lymphoma presents with hemophagocytic syndrome mimicking malignant histiocytosis. Cancer 1993; 72:2019-27.
6. Theodorou I, Bigorgne C, Delfau MH, et al. VJ rearrangements of the TCR gamma locus in peripheral T-cell lymphomas: analysis by polymerase chain reaction and denaturing gradient gel electrophoresis. J Pathol 1996; 178:303-10.
7. Ashton-Key M, Diss TC, Du MQ, Kirkham N, Wotherspoon A, Isaacson PG. The value of the polymerase chain reaction in the diagnosis of cutaneous T-cell infiltrates. Am J Surg Pathol 1997; 21:743-7.

Splenectomy in patients with refractory or relapsing thrombotic thrombocytopenic purpura

Thrombotic thrombocytopenic purpura (TTP) is managed with plasma exchange. Rarely, patients do not respond or develop refractory disease. In these cases, treatment options are limited. Splenectomy has been associated with achievement of complete remission. We present the case histories of four patients undergoing splenectomy for refractory or relapsing TTP, three of whom achieved complete remission.

Sir,

Thrombotic thrombocytopenic purpura (TTP) is a syndrome characterized by thrombocytopenia, microangiopathic hemolytic anemia and, less commonly, neurologic and renal impairment and fever.[1,2] Currently, the use of plasma exchange, alone or combined with other agents, has resulted in a survival rate of over 80%.[2,3] However, 20-40% of patients undergo recurrent episodes of TTP, with an estimated 10-year risk of relapse of 36% in some series.[4] Splenectomy has been occasionally reported to achieve permanent control of the disease in this setting, although its definitive role is still unknown.[5-7] We describe the results of splenectomy in four patients with refractory or relapsing TTP.

From 1995, splenectomy has been performed at our institution in four patients with refractory (2 cases) or relapsing TTP (2 cases). Refractory patients had not responded to first-line therapy with a combination of daily plasma exchange (PE) and 200 mg/day of prednisone (or an equivalent dose of intravenous prednisolone).[8] Splenectomy was performed in one case after 20 PE and in the other case after 28 PE. The remaining two patients initially responded to PE and steroids. One of them relapsed 45 months after diagnosis. No response was obtained after 28 rounds of PE. It was considered a refractory relapse and splenectomy was subsequently performed. Finally, the remaining patient had five relapses at 8, 14, 36, 47, and 57 months after the initial diagnosis. In every case, he responded to PE and steroids. However, laparoscopic splenectomy was indicated after the fifth relapse while in remission. The patient's main characteristics are summarized in Table 1.

There were no major surgical complications or post-operative deaths. One patient required additional treatment with PE after splenectomy (four rounds), but no therapy was administered following surgery in the remaining cases. Patients were discharged a median of 14 days (range, 2-17) after surgery with normal platelet counts and LDH values. Three out of the four patients are still in remission at 11, 24 and 27 months after splenectomy. The patient who underwent splenectomy in refractory relapse suffered a new relapse five weeks later. He was then treated with cyclosporin A, and is currently alive and in remission.

Despite considerable controversy, splenectomy remains an important part of TTP treatment. Some groups have reported high mortality in patients not responding to medical therapy.[1] However, our results

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.

Javier de la Rubia, Inmaculada García, Isidro Jarque, Francisco Arriaga, Federico Gomis, Miguel A. Sanz

Department of Hematology, La Fe University Hospital, Valencia, Spain

Keywords

Thrombotic thrombocytopenic purpura, refractory, relapse, splenectomy.

Correspondence

Dr. Javier de la Rubia, M.D., Servicio de Hematología, Hospital Universitario La Fe, Avda. Campanar 21, 46009 Valencia, Spain. Phone: international +34-6-3862721 – Fax: international +34-6-3868757 – E-mail: delarubia-jav@gva.es

References

1. Amorosi EL, Ultmann JE. Thrombotic thrombocytopenic purpura. Report of 16 patients and review of the literature. Medicine (Baltimore) 1996; 139-59.
2. George JN, Gilcher RO, Smith JW, Chandler L, Duvall D, Ellis C. Thrombotic thrombocytopenic purpura-hemolytic uremic syndrome: diagnosis and management. J Clin Apheresis 1998; 13:120-5.
3. Rock GA, Shumak KH, Buskard NA, et al. Comparison of plasma exchange with plasma infusion in the treatment of thrombotic thrombocytopenic purpura. Canadian Apheresis Study Group. N Engl J Med 1991; 325:393-7.
4. Shumak KH, Rock GA, Nair RC. Late relapses in patients successfully treated for thrombotic thrombocytopenic purpura. Canadian Apheresis Group. Ann Intern Med 1995; 122:569-72.
5. Veltman GA, Brand A, Leeksma OC, ten Bosch GJ, van Krieken JH, Briët E. The role of splenectomy in the treatment of relapsing thrombotic thrombocytopenic purpura. Ann Hematol 1995; 70:231-6.
6. Winslow GA, Nelson EW. Thrombotic thrombocytopenic purpura: indications for and results of splenectomy. Am J Surg 1995; 170:558-63.
7. Crowther MA, Heddle N, Hayward CP, Warkentin T, Kelton JG. Splenectomy done during hematologic remission to prevent relapse in patients with thrombotic thrombocytopenic purpura. Ann Intern Med 1996; 125:294-6.
8. de la Rubia J, López A, Arriaga F, et al. Response to plasma exchange and steroids as combined therapy for patients with thrombotic thrombocytopenic purpura. Acta Haematol 1999; 102:12-6.
9. Porta C, Caporali R, Montecucco C. Thrombotic thrombocytopenic purpura and autoimmunity: a tale of shadows and suspects. Haematologica 1999; 84:260-9.
10. Tsai HM, Lian EC. Antibodies to von Willebrand factor-cleaving protease in acute thrombotic thrombocytopenic purpura. N Engl J Med 1998; 339:1585-94.

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