Articles

Splenomegaly in 2,505 Patients at a Large University Medical Center From 1913 to 1995

1963 to 1995: 449 Patients

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Splenomegaly was studied retrospectively at the University of California, San Francisco (UCSF), School of Medicine in 301 patients from 1963 to 1995 and compared with the UCSF service of the San Francisco General Hospital Medical Center (SFGH) in 148 patients from 1979 to 1994. The combined 449 patients were classified into several diagnostic groups and were studied by means of several clinical and laboratory associations. Hepatic disease in the percentage of patients at UCSF (with those at SFGH given in parentheses) was associated with splenomegaly in 29% (41%), hematologic disease, 32% (16%); infectious diseases, 16% (36%); congestive or inflammatory diseases, 10% (4%); primary splenic disease, 6% (1%); other, 5% (1%); and cause unknown, 2% (1%). Massive splenomegaly occurred in 27% of the patients of the combined series, particularly in patients with hematologic diseases. The acquired immunodeficiency syndrome (AIDS) occurred in more than half of the patients with infectious diseases at SFGH and was four times more frequent than in the patients at UCSF. The commonest diseases associated with splenomegaly were hematologic (lymphoma), hepatic (chronic liver disease), infectious diseases (AIDS and endocarditis), congestive (congestive heart failure), primary splenic (splenic vein thrombosis), and other (malignancy not metastatic to the spleen). In 11 patients with AIDS and massive splenomegaly, *Mycobacterium avium* complex occurred in 8 (73%). Splenectomy was performed in 117 patients (26%), primarily for hematologic amelioration. I conclude that for splenomegaly of unknown origin, the invasive procedure of choice for patients with hematologic associations may be a bone marrow biopsy; for hepatic associations, a liver biopsy; and for infectious disease associations, a lymph node biopsy, before any consideration of a diagnostic splenectomy.

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Splenomegaly presents a diagnostic challenge because nearly always it is due to another primary disorder.[1] The only analyses from a developed country on splenomegaly in general were two office-based studies performed decades ago in which no diagnosis was established in more than 25% of the patients.[2,3] Only a single study of hospital-based patients in the United States has been reported.[4] Now, a second municipal hospital has been studied, San Francisco General Hospital Medical Center (SFGH), which has been compared with and contrasted to a university medical center at the University of California, San Francisco (UCSF), School of Medicine for about the same period. Infections with the human immunodeficiency virus (HIV) and with diseases related to the acquired immunodeficiency syndrome (AIDS) are prevalent in the young male homosexual community of northern California. The centering of AIDS patients at the SFGH and to a lesser extent at UCSF allowed the assessment of the development of AIDS on the diagnostic evaluation of splenomegaly and massive splenomegaly.

Patients and Methods

Patient Demographics

All hospital records at SFGH for patients of any age diagnostically coded as splenomegaly from 1979 through 1994 were reviewed retrospectively. Splenomegaly was defined as an enlarged spleen determined by one of the following: palpable by at least two clinicians or noted on two written observations, greater than 12 cm in length on radiologic imaging study, or more than 250 grams wet weight on an

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ABBREVIATIONS USED IN TEXT

AIDS = acquired immunodeficiency syndrome
CLL = chronic lymphocytic leukemia
CML = chronic myelocytic leukemia
HIV = human immunodeficiency virus
ITP = idiopathic thrombocytopenic purpura
PVT = portal vein thrombosis
SFGH = San Francisco General Hospital Medical Center
SVT = splenic vein thrombosis
UCSF = University of California, San Francisco

excised spleen from a surgical procedure or autopsy. A total of 331 patients were coded as having splenomegaly at UCSF for the years 1963 to 1995; 30 medical records (9%) could not be found. Therefore, the study was based on the remaining 301 patients. A total of 193 patients at SFGH were coded as having splenomegaly; 45 medical records (23%) could not be found. Therefore, the study was based on the remaining 148 patients. The incidence of splenomegaly for these years at UCSF was 301 patients from about 90,000 admissions, or 0.3%.

Clinical and Laboratory Features

The detailed criteria for the analysis of the clinical and laboratory features of the patients are all listed in the first part of this study.[5]

Results

Patients ranged in age from newborn to 88 years, with a median age of 45 years at UCSF and 41 years at SFGH. Nine percent of the patients were younger than 18 years, and 3% were older than 80 years. Of the 148 patients at SFGH, 121 (82%) were male; of the 301 patients at UCSF, 160 (53%) were male. The higher frequency of male patients and the younger age at SFGH probably reflected the young gay male population of San Francisco. More than 98% of the patients were admitted to a hospital at some time, which allowed the assignment to a diagnostic group of all but 8 patients (2%) for the combined series of patients at UCSF and SFGH. Splenomegaly was detected by physical examination alone in 288 (64%) of 449 patients and by additional objective methods in 161 patients (36%): physical examination and abdominal imaging in 131 patients (29%), imaging only in 22 patients (5%), and surgical procedure only in 8 patients (2%). Thus, abdominal imaging was used in this study to detect splenomegaly in 153 (34%) of 449 patients.

Table 1 shows all the patients at UCSF and SFGH with splenomegaly and massive splenomegaly by diagnostic group. The commonest disease group at UCSF associated with splenomegaly was hematologic disease, closely followed by hepatic disease. Contrarily, the commonest disease group at SFGH associated with splenomegaly was hepatic disease, closely followed by infectious disease. At UCSF, half the patients in the hematologic group had massive splenomegaly. The commonest disease groups at SFGH associated with massive splenomegaly were hepatic and hematologic diseases equally. Massive splenomegaly as a percentage of the total number of patients with splenomegaly for the combined series for all disease groups collectively occurred in 27%. The contribution from UCSF to the combined series was 67% (301 of 449 patients) of the splenomegaly and 75% (91 of 121 patients) of the massive splenomegaly. The absolute number of patients at UCSF with splenomegaly was 301 during 32 years, or about 9 per year. Similarly, the absolute number of patients at SFGH with splenomegaly was 148 during 15 years, or about 10 per year. For the first series at UCSF from 1913 to 1936, splenomegaly was found in 621 patients, or about 27 per year. For the second series at UCSF from 1937 to 1962, it occurred in 1,435 patients, or 57 per year.

TABLE 1.—*All Causes of Splenomegaly and Massive Splenomegaly by Diagnostic Group**

Diagnostic Group	Total Splenomegaly, %		Subtotal With Massive Splenomegaly, %		
	UCSF (n = 301)	SFGH (n = 148)	UCSF (n = 91)	SFGH (n = 30)	% of Each Diagnostic Group†
Hepatic	29	41	21	33	20
Hematologic	32	16	53	33	48
Infectious	16	36	9	30	18
Congestive or inflammatory	10	4	2	0	6
Primary splenic	6	1	9	3	45
Other	5	1	7	0	38
Cause unknown	2	1	0	0	0
Total	100	100	100	100	27

SFGH = San Francisco General Hospital Medical Center, UCSF = University of California, San Francisco, School of Medicine

*Data are given as the percentage of patients at UCSF and SFGH, 1963 to 1995. Other refers to malignant disease not metastatic to the spleen, storage diseases, and miscellaneous.
†% of Each Diagnostic Group indicates massive splenomegaly as a percentage of the total number of patients with splenomegaly.

TABLE 2.—*Hepatic, Congestive or Inflammatory, Primary Splenic, and Other Diseases Associated With Splenomegaly and Massive Splenomegaly**

Diagnostic Group	Total Splenomegaly, %		Subtotal With Massive Splenomegaly, %		
	UCSF	SFGH	UCSF	SFGH	% of Each Disease†
Hepatic	(n = 87)	(n = 61)	(n = 19)	(n = 10)	
Chronic	49	38	53	50	23
Alcoholic	33	55	32	40	16
Viral hepatitis	9	3	0	10	10
PVT	7	2	16	0	43
Hepatoma	2	2	0	0	0
Total	100	100	100	100	20
Congestive or inflammatory	(n = 31)	(n = 6)	(n = 2)	(n = 0)	
CHF	48	33	0	0	0
Collagen or rheumatic	36	17	100	0	17
Other than‡	13	0	0	0	0
Pancreatitis	3	50	0	0	0
Total	100	100	100	100	5
Primary splenic	(n = 18)	(n = 2)	(n = 4)	(n = 1)	
SVT	44	0	50	0	25
Infarct or hematoma	16	100	0	100	20
Miscellaneous§	29	0	50	0	40
Abscess	11	0	0	0	0
Total	100	100	100	100	25
Other	(n = 22)	(n = 2)	(n = 6)	(n = 0)	
Malignancy‖	50	50	0	0	0
Storage disease	17	0	50	0	75
Cause unknown	17	50	0	0	0
Also#	16	0	50	0	75
Total	100	100	100	100	25

CHF = congestive heart failure, PVT = portal vein thrombosis, SFGH = San Francisco General Hospital Medical Center, SVT = splenic vein thrombosis, UCSF = University of California, San Francisco, School of Medicine

*Data are given as the percentage of patients at UCSF and SFGH for 1963 to 1995.

†% of Each Disease indicates massive splenomegaly as a percentage of the total number of patients with splenomegaly.

‡Other than indicates psoriasis, inflammatory bowel disease, amyloidosis, and Graves' disease (1 patient each).

§Miscellaneous indicates a congenital splenic cyst, splenic lymphopenia, lymphatic hyperplasia, uterine carcinoma metastatic to the spleen, and arteriovenous malformation of the splenic blood vessels (1 patient each).

‖Malignancy indicates cancer *not* metastatic to the spleen

#Also indicates histiocytosis X, splenic lymphopenia, hemophagocytic syndrome, and craniofacial syndrome

Table 2 shows that the commonest hepatic disease associated with splenomegaly at UCSF was chronic liver disease and at SFGH was alcoholic liver disease. The commonest disease with massive splenomegaly at both UCSF and SFGH was chronic liver disease. Portal vein thrombosis (PVT) occurred in seven patients, six of whom were at UCSF. Similarly, viral hepatitis occurred in ten patients, eight of whom were at UCSF. Contrarily, pancreatitis occurred in four patients, three of whom were at SFGH. In the congestive or inflammatory diseases group, the commonest disease associated with splenomegaly in the combined UCSF-SFGH series was congestive heart failure (45%), followed by collagen-rheumatic diseases (30%). In the primary splenic group, all eight patients with splenic vein thrombosis (SVT) were at UCSF. Three of four patients with storage disease had massive splenomegaly.

Table 3 shows that lymphoma was the commonest hematologic disease associated with both splenomegaly and massive splenomegaly. The chronic leukemias, chronic lymphocytic leukemia (CLL) and chronic myelocytic leukemia (CML), were twice as common as the acute leukemias for splenomegaly and six times more common for massive splenomegaly. In the combined SFGH-UCSF series, the commonest disease of erythrocytes associated with splenomegaly was hemoglobinopathy, and with massive splenomegaly was myelofibrosis. Hemoglobinopathy was found in 13 patients: 6 with thalassemia, 5 with hemoglobin SC disease, 1 with hemoglobin SS disease, and 1 with β^0-thalassemia–hemoglobin E. The highest incidence of massive splenomegaly for a disease was myelofibrosis (100%). Massive splenomegaly occurred in 58 (47%) of 124 patients of all the patients with hematologic disease.

TABLE 3.—*Hematologic Diseases Associated With Splenomegaly and Massive Splenomegaly**

Diseases	Total Splenomegaly, %		Subtotal With Massive Splenomegaly, %		
	UCSF (n = 100)	SFGH (n = 24)	UCSF (n = 48)	SFGH (n = 10)	% of Each Disease†
Lymphoma	29	25	33	40	57
CML	16	8	11	20	39
Hemoglobinopathy	7	25	6	20	38
Myelofibrosis	10	9	21	20	100
Acute leukemia	8	8	4	0	20
CLL	10	0	11	0	50
Hemolytic anemia	8	4	6	0	33
Preleukemia	3	0	3	0	33
Polycythemia vera	6	0	4	0	33
Other‡	2	13	0	0	0
MDS or MPD	2	8	2	0	25
Total	100	100	100	100	47

CLL = chronic lymphocytic leukemia, CML = chronic myelocytic leukemia, MDS = myelodysplastic syndrome, MPD = myeloproliferative disease, SFGH = San Francisco General Hospital Medical Center, UCSF = University of California, San Francisco, School of Medicine

*Data are given as the percentage of patients at UCSF and SFGH.
†% of Each Disease indicates massive splenomegaly as a percentage of the total number of patients with splenomegaly.
‡Other indicates hypereosinophilic syndrome (2 patients), malignant histiocytosis (1 patient), Diamond-Blackfan syndrome (1 patient), and idiopathic thrombocytopenic purpura (1 patient).

Table 4 shows the infectious diseases in diagnostic detail. At SFGH, AIDS was much more frequently associated with both splenomegaly and massive splenomegaly than at UCSF. The commonest infectious disease associated with massive splenomegaly was *Mycobacterium avium* complex, found in 7 (47%) of 15 patients. The commonest non-AIDS–related disease associated with splenomegaly was endocarditis, which was usually found (>90%) in injection drug users.

Two patients at SFGH had a splenic friction rub, and one patient at UCSF had a splenic bruit. One patient with a friction rub had myelofibrosis with a splenic infarct and the other patient had disseminated tuberculosis. The patient with the splenic bruit had an arteriovenous malformation of the splenic blood vessels.

Table 5 shows progressive enlargement of the spleen during clinical observation for six hospital series of splenomegaly, three from UCSF and one each from SFGH, Santa Clara Valley Medical Center, San Jose,[4] and the Stanford University Medical Center, Palo Alto, California (unpublished observations February 1994). The overall incidence was 117 of 2,822 patients, or 4.1%. Hematologic diseases accounted for most of these patients (98 [84%] of 117 patients), especially hematologic malignancy. The other 19 patients were in the following disease groups: 6 with infectious disease (4 with tuberculosis, 1 with subacute bacterial endocarditis, and 1 with schistosomiasis), 5 with hepatic disease (2 with chronic liver disease, 1 with biliary cirrhosis, 1 with alcoholic liver disease, and 1 with acute hepatitis), 5 with primary splenic disease or other (2 with cystic disease, and 1 patient each with splenic hemangioma, metastases to the abdominal viscera, and histiocytosis X), and 3 with congestive or inflammatory diseases (2 with Felty's syndrome and 1 with congestive heart failure). The highest incidence of progressive splenic enlargement (>5%) occurred in those series with a high incidence of hematologic diseases: patients at UCSF from 1937 to 1962, those at UCSF from 1963 to 1995, and patients at Stanford University Medical Center.

Table 6 shows the patients who had splenectomy for all the series at UCSF plus those at SFGH. The incidence of splenectomy was 7% (170 of 2,505 patients). The disease group with the highest incidence of splenectomy was hematologic disease (110 patients [65%]), followed by hepatic disease (34 patients [20%]). The commonest indication for splenectomy was amelioration or a curative operation, particularly for hematologic diseases like hemolytic anemias. Splenectomy for hypersplenism occurred in 37 patients (22%), particularly patients with hepatic and hematologic diseases. Splenectomy was performed in 20 patients (12%) for diagnosis, generally for splenomegaly of unknown cause. A diagnosis was established in all 20 of these patients: 6 with hepatic disease (4 with PVT, 1 with chronic liver disease, and 1 with alcoholic liver disease); 5 with hematologic disease (2 with CML, 1 with CLL, 1 with lymphoma, and 1 with myelofibrosis); 5 with infectious disease (2 with tuberculosis, 1 with endocarditis, 1 with syphilis, and 1 with respiratory tract disease); and 1 patient each with sarcoidosis, Letterer-Siwe disease, thyrotoxicosis, and splenic cyst. Thirty patients (18%) had a splenectomy associated with massive splenomegaly. Most of these patients had hematologic diseases, especially 13 with hereditary spherocytosis.

TABLE 4.—*Infectious Diseases Associated With Splenomegaly and Massive Splenomegaly**

Disease	Splenomegaly, %		Massive Splenomegaly, %		
	UCSF (n = 48)	SFGH (n = 53)	UCSF (n = 8)	SFGH (n = 9)	% of Each Disease† 17
AIDS Related	(n = 8)	(n = 30)	(n = 3)	(n = 7)	
AIDS only	75	47	33	29	15
Mycobacterium avium complex	25	43	67	71	47
Opportunistic‡	0	10	0	0	0
Total	100	100	100	100	26
Non-AIDS-Related	(n = 40)	(n = 23)	(n = 5)	(n = 2)	
Endocarditis	12	43	20	0	7
Acute§	23	9	0	50	9
Chronic‖	10	26	0	0	0
Infectious mono	10	0	0	0	0
Injection drug use	10	0	0	0	0
Hypoglobulinemia	10	0	0	0	0
FUO	9	0	20	0	25
Malaria	8	0	20	0	33
Tuberculosis	5	4	20	0	33
Schistosomiasis	3	9	20	50	67
Sarcoidosis	0	9	0	0	0
Total	100	100	100	100	11

AIDS = acquired immunodeficiency syndrome, FUO = fever of unknown origin, mono = mononucleosis, SFGH = San Francisco General Hospital Medical Center, UCSF = University of California, San Francisco, School of Medicine

*Data are given as the percentage of patients at UCSF and SFGH for 1963 to 1995.
†% of each disease indicates massive splenomegaly as a percentage of the total number of patients with splenomegaly.
‡Opportunistic refers to disseminated histoplasmosis, cryptococcosis, or cytomegalovirus.
§Acute refers to conditions such as sepsis, viral syndromes in children, aspiration pneumonia, urosepsis, and fever and thrombocytopenia in a child.
‖Chronic refers to conditions such as abscesses, recurrent skin infections, recurrent respiratory tract infections, urinary tract infections, bronchiolitis, or chronic infections of several organs.

Discussion

Lymphoma

Lymphoma was again the leading hematologic cause of splenomegaly in this series at UCSF (29%, 1963-1995), as it was in the earliest series (24%, 1913-1936) at UCSF. The patients with lymphoma and splenomegaly in all three series had a high incidence of lymphadenopathy: 98% (50 of 51), 97% (37 of 38), and 68% (20 of 29), respectively. The percentage of these patients with generalized lymphadenopathy was 11% (6 of 51), 55% (21 of 38), and 7% (2 of 29), respectively. Massive splenomegaly occurred in 37% (19 of 57), 39% (15 of 39), and 59% (17 of 29), respectively. Chylous ascites occurred in six patients in all the series at UCSF: two with lymphoma in the earliest series (1 also with chylous hydrothorax), two with lymphoma in the next series, and one with lymphoma in the third series (1963-1995), and 1 patient with CLL in the second series. Chylous ascites is usually associated with extensive involvement of the retroperitoneal lymph nodes by a slow-growing lymphoproliferative malignant disease such as lymphoma and CLL.[6]

Progressive Splenic Enlargement

Splenomegaly is a nonspecific finding caused by so many diseases that comprehensive lists are clinically useless.[7] Yet, splenomegaly of any size warrants evaluation as to its cause. *Progressive* splenic enlargement observed clinically or radiologically demands diagnostic study because these patients usually have a hematologic cancer.[8] In fact, 84% of the patients at UCSF (Table 5) had hematologic cancers. Past reports on progressive splenic enlargement in hematologic malignancy include chronic myeloproliferative syndromes,[9] particularly patients in whom thrombosis of the major abdominal veins developed,[10] and evolving CLL dominated by hypersplenism.[11] In AIDS patients with disseminated *M avium* complex[12] or disseminated histoplasmosis,[13] rapidly progressive splenomegaly developed. Even patients with inflammatory diseases like progressive systemic sclerosis had the abrupt development of massive splenomegaly and Felty's syndrome.[14] Splenic cysts often enlarged rapidly and caused acute splenomegaly within a few weeks, as occurred in one of the patients of the second series at UCSF.[15] In Gaucher's disease, even partial splenectomy accelerated the disease and resulted in the recurrence of splenomegaly.[16] In all, progressive splenic enlargement for nonhematologic diseases occurred in 19 patients, 18 of whom had benign disease. Thus, progressive splenic enlargement in hematologic patients was usually malignant and in nonhematologic patients was usually benign, albeit often of serious consequence.

TABLE 5.—*Progressive Splenic Enlargement in Six Series of Splenomegaly**

Series	Patients, No.	Hematologic	Infectious Diseases	Hepatic	Primary Splenic or Other	Congestive-Inflammatory	Total Series	% of Series
UCSF								
1913 to 1936	621	3	3	3	0	0	9	1.4
1937 to 1962	1,435	70	1	2	4	2	79	5.5
1963 to 1995	301	14	0	0	1	1	16	5.3
SFGH								
1979 to 1994	148	2	1	0	0	0	3	2.0
Stanford								
1986 to 1994	147	8	0	0	0	0	8	5.4
Santa Clara VMC	170	1	1	0	0	0	2	1.2
Total	2,822	98	6	5	5	3	117	4.1

SFGH = San Francisco General Hospital Medical Center, UCSF = University of California, San Francisco

*Data are the number of patients at UCSF. Stanford refers to Stanford University Medical Center, Palo Alto, California (unpublished data). Santa Clara VMC refers to Valley Medical Center, San Jose, California.

Splenic Cysts

Of the ten patients at UCSF with splenomegaly and cystic masses of the spleen, nine were in the second and third decades of life. Five of the cystic masses were congenital or true cysts, two were tumors (1 cystic hemangioma and 1 cystic lymphangioma), one infectious (echinococcal), one a traumatic or false cyst, and one a cyst of unstated origin.[17] Four of the ten patients had left upper quadrant pain, two had left upper quadrant tenderness, and one had both left upper quadrant pain and tenderness; three were asymptomatic. Massive splenomegaly was present in eight (80%) of the ten patients. Two patients had progressive splenic enlargement: one had the traumatic cyst, and the other had the cystic hemangioma. One patient with an epithelial cyst had fever, massive splenomegaly, and a splenic friction rub. The echinococcal cyst was calcified. One cyst was aspirated percutaneously; the fluid was not diagnostic. The surgical indications for cystic disease included massive cysts, those with an infectious cause, involvement of the splenic hilum, and infected cysts.[18] Seven patients at UCSF with massive splenomegaly and the patient with the echinococcal cyst had a splenectomy. The cyst that was percutaneously aspirated was localized to one splenic pole, and the patient had a partial splenectomy. The one remaining patient had a small asymptomatic epithelial cyst and came to autopsy. The Armed Forces Institute of Pathology reviewed 52 patients with true and false splenic cysts and could not find reliable radiologic distinctions between the two.[19] Thus, etiologic uncertainty of cystic masses of the spleen may be another factor that dictates a diagnostic splenectomy for almost all these patients.

Splanchnic Vein Obstruction

Portal vein thrombosis occurred in 21 patients: 7 in this series and 14 during the second period of the study at UCSF (from 1937 to 1962). Splenic vein thrombosis occurred in 14 patients: 8 in the third period at UCSF

TABLE 6.—*Indications for Splenectomy in Patients With Splenomegaly**

Disease	Patients, Total No.	Indication for Splenectomy: Amelioration No. (%)	Hypersplenism No. (%)	Diagnostic No. (%)	Symptomatic No. (%)	% of Total
Hematologic	110	86	16	5	3	(65)
Hepatic	34	10	18	6	0	(20)
Infectious	10	3	2	5	0	(6)
Primary splenic	9	7	0	2	0	(5)
Other,† congestive, inflammatory	7	3	1	2	1	(4)
Total	170	109 (64)	37 (22)	20 (12)	4 (2)	(100)

*Data are for patients of all 3 series at UCSF plus those at SFGH. % of Total refers to percentage of total number of splenectomies for each disease group.
†Other refers to hepatic, infectious, and carcinomas.

(after 1962) and 6 in the second period. Portal vein thrombosis occurred in 11 children and 10 adults, whereas SVT occurred in 11 adults and only 3 children. Only 2 of the 21 patients with PVT showed an underlying cause (1 polycythemia vera and 1 alcoholic liver disease), and 3 had abnormal results on liver function tests. Recent imaging studies of PVT in children showed a characteristic shape of the portal vein and suggested a congenital basis for the disease,[20] but another recent study showed an ongoing prothrombotic state in the portal circulation and suggested an acquired basis for PVT.[21] Hypersplenism was found in 13 of 21 patients with PVT and in 8 of 14 patients with SVT, for a total of 21 (60%) of 35 patients. A review back to the turn of the century of patients with isolated SVT found 66% with splenomegaly but only 9% with hypersplenism.[22] Massive splenomegaly occurred in 5 patients with PVT and 2 with SVT at UCSF, for a total of 7 (20%) of 35 patients. Gastrointestinal bleeding occurred in only 4 patients with PVT and 2 patients with SVT at UCSF, for a total of 6 (17%) of 35 patients. Ascites occurred in 2 patients each with PVT and SVT at UCSF, for a total of 4 (11%) of 35 patients. Clearly, these patients at UCSF were relatively asymptomatic.[23]

Splenectomy was performed in 14 of 21 patients with PVT at UCSF; 6 did not have a splenectomy, and 1 died and was examined at autopsy. Splenectomy was performed in 9 of 14 patients with SVT; 4 did not have a splenectomy, and 1 died and was examined at autopsy. Thus, splenectomy was performed with almost the same frequency (67%) in PVT as in SVT (64%), even though the operation is contraindicated in patients with PVT.[23] The main procedure used in PVT to prevent recurrent variceal bleeding was a portal-systemic shunt operation.[23] It was used only once at UCSF, however, in a patient with many bleeding episodes from esophageal varices. Three of the four patients with SVT who did not have a splenectomy or who were examined at autopsy had apparent surgical contraindications: one patient had severe mental retardation, one was pregnant, and one had a history of multiple pulmonary emboli. The response to splenectomy in SVT was excellent: the surgical mortality was 0% and no postoperative complications or long-term gastrointestinal bleeding occurred. The overall mortality for all the patients with SVT was only 7%.[24]

Only 1 of the 14 patients with SVT at UCSF had pancreatitis, whereas in most reported series, the rate is more than 50%.[25] Splenic vein thrombosis with the classic triad of splenomegaly, gastrointestinal bleeding, and normal liver function test values occurred in only three patients (21%), all of whom had hypersplenism as well. One patient with SVT had an arteriovenous malformation of the splenic artery with an audible splenic bruit.[26] Another patient with SVT had an associated small aneurysm of the splenic artery, massive splenomegaly, and hypersplenism.[27] One patient with SVT had gastric varices without esophageal varices on endoscopy, the classic left-sided localized portal hypertension.[28] One patient at UCSF who bled after splenectomy had another classic finding of SVT, massive enlargement of the left gastroepiploic vein.[28] Thus, SVT has two different systems of collateral veins: the short gastric veins with gastric varices and the gastroepiploic veins with varices in the small or large bowel that can bleed. Most authors recommend splenectomy as the treatment of choice for SVT,[25] but others recommend a conservative approach in asymptomatic patients unless hemorrhage occurs.[29] If the SVT developed acutely—for example, after splenectomy or pancreatitis—anticoagulant drugs were recommended for the duration of obstruction.[29]

AIDS and Splenomegaly

Infections with HIV and splenomegaly at SFGH occurred in 44 (30%) of the total 148 patient, and in 30 (57%) of 53 patients with infectious disease. Of these 30 patients, 7 (23%) had massive splenomegaly, 5 of whom had infection with *M avium* complex. At UCSF, infections with HIV and splenomegaly occurred in only 8 (3%) of 301 patients. Three (38%) of these 8 patients had massive splenomegaly, two of whom had infection with *M avium* complex. The one patient at Santa Clara Valley Medical Center with HIV infection and massive splenomegaly also had infection with *M avium* complex.[4] Thus, 8 (73%) of the 11 patients with AIDS and massive splenomegaly had an associated infection with *M avium* complex. The greater incidence of infections with *M avium* complex at SFGH probably reflected a patient population with more advanced AIDS because infections with *M avium* complex occur only when the CD4 cell count is less than 0.10×10^9 per liter (<100 per μl).[30]

Human immunodeficiency virus infection resides in the lymphatic system and causes lymphadenopathy.[31] In the combined UCSF-SFGH series, lymphadenopathy occurred in 30 (79%) of the 38 patients with AIDS and splenomegaly. In addition, five of the eight patients with lymphoma at SFGH were infected with HIV.[32] Five of the AIDS patients at SFGH and Santa Clara Valley Medical Center[4] had diseases that occur particularly in immunocompromised hosts: disseminated histoplasmosis, cryptococcosis, cytomegalovirus disease, and disseminated *Pneumocystis carinii* disease.[33] One patient with AIDS at Santa Clara Valley Medical Center[4] had disseminated cat- scratch disease, and one patient with AIDS at SFGH had bacillary angiomatosis, diseases that have been redefined by the recent discovery of the protobacterium Rochalimaea.[34]

Hemoglobinopathy and Splenomegaly

Of the 13 patients with hemoglobinopathy and splenomegaly, 7 were adults. Five (38%) patients had massive splenomegaly, and nine patients (69%) had hypersplenism. Six patients (46%) had a splenectomy: two with thalassemia for hypersplenism and massive splenomegaly, two with hemoglobin SC disease for painful splenic infarctions, and two for splenic sequestration (1 with hemoglobin SS and 1 with hemoglobin SC disease).[35] Splenic sequestration has been reported in

adults with hemoglobin SC and sickle cell–thalassemia disease.[36] The two patients with splenic infarcts were both adults and had hemoglobin SC disease, which is being reported more frequently.[37] The patient with β^o-thalassemia–hemoglobin E had massive splenomegaly, a finding more frequent with β^o-thalassemia and absent production of hemoglobin A.[38]

Splenomegaly With Tumors Not Metastatic to the Spleen

Many of the patients with solid tumors and splenomegaly in this and all the series at UCSF (36 [92%] of 39 patients) did not have metastases to the spleen even on microscopic examination at autopsy or splenectomy. Yet, these tumors, mostly carcinomas of several different organs—kidney, pancreas, lung, breast, and hepatic metastases with unknown primary—seemed to be associated with splenomegaly as a component of the host response to cancer.[39] Clinical reports on this association were readily found in the literature,[40] particularly for patients with malignant melanoma.[41] With removal of the primary site of the malignant melanoma, the splenomegaly usually regressed.[42] In mice injected with tumor cells, colonies of cancer cells regularly developed, accompanied by expansion of their reticuloendothelial system and by splenomegaly.[43] Thus, the splenomegaly of tumors remote to the spleen could reflect an immunologic response of the host to the tumor.[44]

Splenectomy

The incidence of splenectomy in patients with splenomegaly at UCSF increased markedly over time: 4% from 1913 to 1936, 9% from 1937 to 1962, and 26% from 1963 to 1995. The low incidence of splenectomy in the earliest period at UCSF may reflect the initial development of the operation primarily for specific hematologic diseases.[45] The higher incidence of splenectomy in the later series may reflect the wider use and more liberal indications for the operation as its mortality rate dramatically declined. By 1910, Sutherland and Burghard successfully treated two patients with hereditary spherocytosis with splenectomy because "the spleen is actively engaged in the destruction of blood cells."[46 p1822] In 1916, Kaznelson, a precocious medical student in Prague, successfully applied this theory to the blood platelets by inducing his professor of surgery to perform a splenectomy in a patient with idiopathic thrombocytopenic purpura (ITP).[47] Before 1928, even the Mayo Clinic had a 10% mortality for 500 patients with splenectomy performed except in the "triumph of splenectomy" for ITP and hereditary spherocytosis (<5% mortality).[48] Now, the mortality for splenectomy, even for massive splenomegaly, is less than 1%.[49] Currently, ITP is the commonest hematologic indication for splenectomy.[45] The low incidence of splenectomy for ITP in all the series at UCSF (3 of 2,056 patients) partially reflects the low incidence of splenomegaly in ITP, about 2%.[50] The commonest disease for splenectomy at UCSF was hereditary spherocytosis: 16 (57%) of 28 patients from 1913 to 1936 and 59 (44%) of 133 patients from 1937 to 1962.

Previous reports cited lymphoma as the largest disease group for diagnostic splenectomy, usually about a third of these patients.[51] In the entire series at UCSF, only two patients had a diagnostic splenectomy for lymphoma. In the earliest series at UCSF in which lymphoma was the commonest hematologic disease associated with splenomegaly, none of those patients had a splenectomy. The current series had a 12% rate of diagnostic splenectomy (20 of 170 patients), similar to the 10% reported by others.[52] With detailed preoperative evaluation, the need for a diagnostic splenectomy could be reduced even further. Furthermore, the use of diagnostic splenectomy is tempered even more by the fear of overwhelming postsplenectomy infection and the frequent lack of a definitive diagnosis.[53] In this series at UCSF and SFGH of splenectomy for splenomegaly, 19% of the patients had massive splenomegaly. In a recent study from the National Institutes of Health of splenectomy for massive splenomegaly, the commonest disease group for which a splenectomy was done was overwhelmingly hematologic disease (96%),[54] compared with 61% at UCSF.

Hospital-based Patients and the Incidence of Splenomegaly: Why So Low?

The incidence of splenomegaly in the four series at UCSF was about 1% before 1963 and about 0.3% after 1963. In contrast, the incidence of splenomegaly in healthy first-year college students was found to be 3%.[55] Even in office-based prospective series on splenomegaly,[2,3] the incidence of splenomegaly was 2% and 5%, respectively. One explanation for this discrepancy is the nature of the study in the healthy college students: two expert hematologists were prospectively and specifically determining the incidence of splenomegaly. Similarly, Lipp and colleagues in their study[2] were prospectively "looking for" splenomegaly. At UCSF, the studies were retrospective tabulations of splenomegaly detected by physicians with no direct interest in the spleen or its enlargement. This underreporting of splenomegaly (the denominator) may explain the "high" incidence of massive splenomegaly (the numerator) in the studies at UCSF, particularly the average of 22% found for chronic liver disease in the four studies at UCSF and the 50% found for CML in the present series.

Diagnostic Evaluation of Unexplained Splenomegaly

Any patient who presents with unexplained splenomegaly should have an evaluation with respect to its cause, particularly if cancer is in the differential diagnosis. A complete history and thorough physical examination may establish the diagnosis.[56] The physician should review the laboratory test results, the imaging studies, and particularly the peripheral blood smear.[57] If benign disease is suggested by the evaluation, patients with splenomegaly can simply be observed periodically.[55] A lymph node biopsy should be done, particularly if lymphadenopathy is present and a malignant lesion is suspected.[58] For patients with hematologic associations, bone marrow

aspiration and biopsy may be the invasive procedure of choice; for hepatic associations, a percutaneous liver biopsy; and for infectious disease, a lymph node biopsy, before any consideration of a diagnostic splenectomy.[59] Percutaneous splenic procedures had been limited by the mortality associated with splenic biopsy and the lack of tissue architecture associated with fine-needle aspiration.[60] Paradoxically, percutaneous liver biopsy for splenomegaly was reported to be more valuable in the tropics than percutaneous splenic procedures.[61] If these invasive procedures fail to establish a cause for the splenomegaly, the ultimate diagnostic test of laparotomy and splenectomy may be required.[59] Splenic structure is virtually unchanged in its evolution from primitive fish, however.[62] So the spleen may be important for our survival and not be readily disposable, as evidenced by overwhelming postsplenectomy infections.[53]

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