Scintigraphic Functional Hyposplenism in Amyloidosis

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Functional asplenia or hyposplenism may predispose patients to spontaneous splenic rupture and potentially increase the risk of serious infection. In addition, hyposplenism may be a marker of more extensive systemic amyloidosis and has been correlated to a reduction in survival. Decreased splenic function is generally diagnosed by the presence of abnormal red blood cell morphology and decreased splenic uptake on ^{99m}Tc-sulfur colloid or microlite scans. We compared liver spleen scans with red cell morphology and anatomic imaging results in all patients with biopsy-proven amyloidosis who presented to the nuclear medicine department over a 12-yr period. Patients were referred from a center for amyloid disease for work-up of suspected hepatic involvement. **Methods:** Between 1983 and 1995, 23 liver spleen scans from 21 patients (one patient had three scans) with known amyloidosis were referred for the assessment of degree of hepatic involvement with amyloid. All scans were retrospectively reviewed, and the degree of splenic uptake was graded. Medical records were reviewed for evidence of splenomegaly on physical exam. Extent of splenic involvement also was assessed by anatomical imaging (CT or MRI) in 45% of cases. Peripheral smear reports were reviewed for the presence of abnormal red cell morphology consistent with hyposplenism. **Results:** Splenic activity was moderately or markedly reduced in 22 of 23 liver spleen scans (21 patients). Eight of these scans had correlative anatomic splenic imaging: four were abnormal and four were normal. Forty-one percent of available peripheral smears contained abnormal red cell morphology. Nine patients had palpable splenomegaly at the time of the liver spleen scan. Splenic pathologic studies were available for three patients (two autopsy, one surgical) and demonstrated diffuse splenic infiltration with amyloidosis. One patient had spontaneous splenic rupture. Fourteen patients died, four of overwhelming infection. **Conclusion:** Reduced splenic uptake on liver spleen scans for patients with suspected hepatic infiltration with amyloid is a common finding. Liver spleen scanning appears to be a more sensitive marker of splenic amyloidosis than clinical parameters or anatomical imaging.

Key Words: hyposplenism; amyloidosis; liver imaging; spleen imaging

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Systemic amyloidosis comprises a group of diseases characterized by the extracellular deposition of amyloid fibrillar proteins in one or more organs. Progressive organ infiltration with amyloid can lead to organ failure and death, most commonly due to renal and/or cardiac involvement. The three most common forms of systemic amyloidosis are primary amyloidosis (AL), secondary amyloidosis (AA) and hereditofamilial amyloidosis (HF). They are distinguished by a particular precursor protein. The primary form is characterized by amyloid deposits composed of light chain fragments. The secondary form is characterized by AA proteins and the hereditofamilial form by mutant transthyretin protein.

The diagnosis of functional hyposplenia in amyloidosis is infrequently discussed in the literature. There are discrepant reports of the comparative sensitivity of peripheral smears and liver spleen scan findings for the presence of splenic infiltration with amyloid (*1,2*).

Splenic infiltration with amyloid is, however, a common finding in systemic amyloidosis; amyloid proteins were identified in 41% of 142 cases of systemic amyloidosis at the time of autopsy (*3*). Hyposplenism in amyloidosis has been associated with reduced survival (*1*). Splenic rupture is a known rare complication of splenic involvement with amyloid (*3–7*). Since surgical or congenital asplenia is a predisposing condition for overwhelming sepsis (*8*), we hypothesized that functional hyposplenism or asplenia also may predispose amyloid patients to infection.

MATERIALS AND METHODS

Subjects

We retrospectively reviewed 23 studies in 21 individuals (14 men, 7 women; aged 39–69 yr) with biopsy-proven amyloidosis who were referred to the nuclear medicine department for liver spleen scans from 1983–1995. Cases were referred for evaluation of degree of hepatic involvement with amyloidosis. A single patient had been excluded from analysis as he had a premorbid splenectomy for trauma. Duration of disease at time of liver spleen scan study was 2 mo–7 yr (mean = 2 yr). Of the 21 individuals, 19 were classified as AL, one as AA and one as HF. At the time of review, 14 of 21 patients had died; the cause of death was available for 11 of the 14 patients. None of the patients had known underlying liver disease or hemoglobinopathies.

Hyposplenism

Functional hyposplenia was scintigraphically defined as reduced intensity of splenic uptake of nuclide on liver spleen scan in the absence of a prior history of splenectomy. In a normal study, splenic uptake in the posterior view is approximately equal to hepatic uptake (*9*). Functional hyposplenism is classically diagnosed hematologically by the presence of abnormal red cell morphology (Howell-Jolly bodies, target and burr cells) on peripheral smear.

Data Collection

The analog images of liver spleen scans were evaluated for organ size, uptake and evidence of shift of nuclide to bone marrow. Splenic size was estimated by measurement of vertical span in the posterior projection (normal vertical span was defined as $\leq$ 12 cm). The degree of splenic uptake was classified as normal, slightly decreased, moderately decreased, markedly reduced (only faint uptake) and absent. Splenic scan findings were correlated with CT and MRI results when available, the presence or absence of Howell-Jolly bodies, target and burr cells on peripheral smears, available splenic pathology results and cause of death. Splenic scan findings also were correlated with hepatic findings. Hepatic size was estimated by measurement of right lobe vertical span (normal vertical span was defined as $\leq$ 19 cm). Hepatic uptake was graded

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TABLE 1
Imaging and Clinical Data in Patients with Amyloidosis

Patient no.	Type	Splenic uptake	Clinical splenomegaly	RBC smear	Anatomic imaging
1	AL	None	Y	—	Normal spleen, fluid in capsule (CT)
2	AL	Moderate	N	—	Moderate splenomegaly (CT)
3	AL	None	Y	+	Normal (CT)
4	AL	Faint	Y	—	Normal (CT)
5	AL	Normal	Y	+*	Normal (CT)
6	AL	Faint	—	—	
7	AL	Faint	Y	—	
8	AL	None	N	+	Splenic infarct (CT)
9	AA	Moderate	Y	—	
10	AL	Faint	N		
11	AL	Faint	N		
12	AL	Faint	N	+*	
13	AL	None	N	—*	
14	AL	None	N	+*	
15a	AL	Moderate	N		
15b	AL	Faint	Y		
15c	AL	None	—		
16	AL	Moderate	N	—	
17	AL	Faint	—	+	Normal (CT)
18	AL	Faint	N	—*	
19	AL	None	N	—	
20	HF	Faint	Y	—	Moderate splenomegaly, splenic infiltration (MRI)
21	AL	None	Y	—	Spleen present, subcapsular hematoma (CT)

*Studies that were performed manually.
AL = primary amyloidosis; AA = secondary amyloidosis; HF = hereditofamilial amyloidosis.

as normal start on resolve or mildly, moderately or markedly heterogeneous. Shift of nuclide to bone marrow was classified as absent, mild (spine faintly visualized), moderate (spine and ribs clearly visualized) or marked (intense uptake in spine, ribs and pelvis).

Peripheral smear results for red blood cell pathology were classified by an automated or manual method, since it is known that routine automatic analysis is less sensitive than manual analysis for cellular pathology. The presence or absence of palpable splenomegaly proximate to the liver spleen scan was recorded from the patients' charts.

RESULTS

Imaging and Laboratory Results

Average hepatic vertical span on nuclear imaging was 20 cm (range = 16–28 cm). Average splenic vertical span was 6 cm (range = 0–12 cm). Table 1 contains imaging, laboratory and clinical measurements of splenic size and function; 22 of 23 splenic scans demonstrated reduced uptake of nuclide in 21 patients. Of these 21 patients, splenomegaly was diagnosed on physical exam in 7 of 18 patients. Of the available peripheral smears, 5 of 17 (41%) demonstrated abnormal red blood cell pathology consistent with hyposplenism. Most smears were analyzed by machine, five smears were performed manually and three of these five smears were abnormal (one in a patient with normal splenic uptake on liver spleen scan). Of the eight patients who had anatomical imaging (seven by CT, one by MRI) four studies were abnormal. Of the four abnormal studies only two demonstrated splenomegaly and/or evidence of infiltrative disease. Unfortunately, most of the studies were performed at outside institutions and re-review of these images was not possible. Sixteen of 20 studies with moderate-to-severe reduction of splenic uptake had normal uptake or minimally or mildly abnormal hepatic uptake on scintigraphic studies. Assessment of bone marrow uptake demonstrated absence of shift in eight studies, mild shift in three, moderate in eight and marked shift in two cases. Although there was a trend toward a greater degree of bone marrow shift in cases of moderate-to-marked organ involvement, results were highly variable, and the degree of shift did not appear to be organ specific.

Clinical Course

One patient with functional asplenia by liver spleen scan and subcapsular hematoma developed sudden rupture of the spleen requiring surgical removal. Fourteen of 21 of the patients died by the time of this published article; 4 of 14 patients died from overwhelming viral or bacterial infection (cytomegalovirus, gram-negative sepsis, pneumonia and sepsis of unknown pathogen, and disseminated mycobacterium).

DISCUSSION

Technetium-99m-sulfur colloid is composed of radiolabeled colloidal particles measuring approximately 3–5 μ in diameter. The particles are phagocytized by reticuloendothelial cells. The amount of hepatic and splenic uptake of ^{99m}Tc-sulfur colloid is dependent on the integrity of blood supply and on the presence of functioning reticuloendothelial cells. Although the finding of functional hyposplenism in amyloidosis is rarely reported in the literature (*1,2*), in a single series six patients collected over 9 yr demonstrated functional asplenia by laboratory results or liver spleen scans (*8*). We were able to accumulate 21 cases over the 12 yr of this review. Conventionally, abnormal red blood cells in peripheral smears have been the means for diagnosis of hyposplenia or asplenia. In Boyko et al.'s series (*8*) all six patients had abnormal smears. In our series, only 30% of 17 available smears in patients with hyposplenism on liver spleen scans had abnormal peripheral smears; only two of the four smears that were analyzed manually were abnormal. A single case demonstrated an abnormal peripheral smear in the pres-

ence of a normal liver and spleen scan, CT scan and palpable splenomegaly. The reduced sensitivity of the peripheral smears overall may be due in part to the reduced sensitivity of the automated analysis for rare cellular pathology.

A single case report on CT findings in hepatic and splenic amyloidosis demonstrated low attenuation and poor contrast medium enhancement (*10*). In our series, 50% of the available anatomic imaging studies in patients with abnormal liver spleen scans demonstrated normal splenic anatomy on CT and MRI studies by report; however, attenuation measurements were not available.

Splenic abnormalities in our study were generally more extensive than liver abnormalities on liver spleen scan, as 16 of 20 studies with moderate-to-severe reduction of splenic uptake had normal uptake or minimally or mildly abnormal hepatic uptake. It is, therefore, likely that the degree of splenic infiltration with amyloid precedes hepatic infiltration.

Hyposplenism or asplenia in liver spleen scans can be secondary to arterial or venous obstruction, small vessel invasion or parenchymal infiltration (with eventual compression and obliteration of small vessels). Organ failure in amyloidosis is generally due to the latter process. Pathology was available on all six cases studied by Boyko et al. (*8*) and demonstrated extensive amyloid deposition in splenic cords. Pathology available on three of the cases in our series (one surgical, two autopsy) demonstrated extensive parenchymal infiltration as well.

Spontaneous splenic rupture is a known consequence of splenic amyloidosis (*3–6*). One patient in our series suffered this complication. Congenital and surgical asplenia are known to be associated with fatal systemic infections due to a limited number of organisms. The primary cause of death in 4 of 14 patients was determined to be secondary to overwhelming infection, although most of the causative pathogens are not classically associated with postsplenectomy infections. The isolated pathogens that are known to occur in the presence of hyposplenism are restricted to streptococcus pneumoniae, hemophilus influenza, staphylococcus and meningococcus. Further exploration into the significance of this finding with a larger series of patients is warranted.

Hyposplenism diagnosed by abnormal peripheral smear has been associated with a reduced duration of survival not apparently due to splenic rupture or infection (*1*). Liver spleen scans may, therefore, function as a useful standard examination for amyloid patients for diagnostic as well as prognostic information.

CONCLUSION

Functional hyposplenia is likely underdiagnosed in systemic amyloidosis. Liver spleen scanning should be considered the modality for assessment of splenic involvement with amyloid as it appears to be a more sensitive test for functional hyposplenia than peripheral smear evaluation, and standard anatomic imaging. Potential complications from splenic infiltration with amyloid include spontaneous splenic rupture and systemic infection. The presence of hyposplenism also may be associated with reduced length of survival.

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