

Splenic Infarction and Infectious Diseases in Korea

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Abstract

Background

Although the etiology of splenic infarction (SI) is multi-factorial, the nature of its relationship with infectious diseases is not well understood. We thus aimed to investigate the relationship between SI and infection using a retrospective approach.

Methods

We reviewed the hospital records of patients with SI who visited Inha University Hospital (Incheon, Republic of Korea) between January 2008 and December 2018. We collected and analyzed data on the patients' clinical presentation, causative pathogens, risk factors, and radiologic findings.

Results

Of the 353 patients with SI, 101 patients with infectious conditions were enrolled in the study and their data were analyzed to identify an association between SI and infection. Ten patients were diagnosed as having infective endocarditis (IE), and 26 patients had bacteremia without IE. Twenty-seven patients had systemic infection due to miscellaneous causes (negative result on conventional automatic blood culture), such as the following intracellular organisms: parasites (12 cases of malaria and 1 case of babesiosis), bacteria (five cases of scrub typhus), viruses (one case each of Epstein–Barr virus infection and cytomegalovirus infection) or not identified pathogen (seven cases). Splenomegaly was more common among patients with miscellaneous systemic infection, and infarction involving other organs was rare. Twenty-one patients had localized infections (e.g. respiratory, intra-abdominal, or skin and soft tissue infection), and most of them (18 of 21) had other risk factors of SI.

Conclusions

In this study, various infectious conditions were found to be associated with SI, and intracellular organisms were the most common pathogens observed. Further studies are needed to examine other possible etiologies and the underlying pathophysiologic mechanisms.

Background

Although splenic infarction (SI) is generally asymptomatic, it may occasionally result in severe complications such as bleeding, rupture, pseudocyst formation, and death [1]. SI is mainly caused by thrombosis or vascular injury [2] mediated by arrhythmia, cancer, liver cirrhosis, pancreatitis, trauma, vascular procedures, infective endocarditis (IE), and coagulopathy [3].

In clinical practice, SI is often detected incidentally when abdominal computed tomography (CT) scan is performed to identify the cause of fever. While several studies have shown that various pathogens can cause SI [4–8], comprehensive studies on the association between SI and infection are limited. One retrospective study showed that 4 of 32 patients with SI had infections [3], whereas another study identified infection as the causative factor in 11 of 89 patients with SI [9]. As can be seen from the results of the previous studies, assessing the etiology of SI has the following limitations: (i) there is a lack of extensive information on the relationship between SI and infection, and (ii) there is a lack of a sufficient number of cases to allow for an in-depth analysis.

Therefore, to bridge this gap in knowledge, we sought to investigate the relationship between SI and infection by conducting a retrospective analysis of the clinical and demographic data of patients with SI and coexisting infections.

Methods

Overall design and study population

This study was designed as a retrospective investigation of patients who were diagnosed with both SI and infectious disease at the Inha University Hospital between January 2008 and December 2018. Data on the patients' demographic and clinical characteristics were collected from medical records. The inclusion criteria for this study were a diagnosis of SI and evidence of pathogenic infection. Since the differentiation between SI due to various metastatic cancers is limited, patients with solid organ malignancy were excluded from this study. We investigated the patients' medical records for risk factors of SI such as trauma, vasculitis, pancreatitis, pancreatic tumor, surgical technique, invasive procedures, hematologic malignancy, liver cirrhosis with portal hypertension, atrial fibrillation, atherosclerotic disease, and hypercoagulable status (5). SI-associated radiologic findings were analyzed in the context of splenomegaly with signs of obstruction/infarction in other organs. Patients with liver cirrhosis and/or hematologic malignancy were excluded from the sub-group analysis of patients with splenomegaly because splenomegaly can occur as a result of these conditions.

Case Definition

SI was diagnosed on the basis of one or more of the following findings on a CT scan: (1) peripheral wedge-shaped lesion with low attenuation, (2) multiple heterogeneous lesions with patchy enhancement, or (3) lesions with extensive or complete low attenuation [10].

The evidence for infectious disease was as follows: (1) fever, with temperature above 37.7 °C; (2) increased levels of inflammatory markers (C-reactive protein levels of > 0.05 mg/dL or leukocyte counts of > 10000/ μ L); and (3) general clinical signs and symptoms of infection. The diagnosis of infection was confirmed by blood culture studies, polymerase chain reactions, serologic examinations, microscopic examinations, and histopathologic studies. IE was defined using the Duke criteria [11]. Bacteremia was defined as a positive result on blood analysis using an automated blood culture system (BACTEC™). Miscellaneous systemic infection was defined as systemic infection in the absence of IE or bacteremia, assessed using a conventional automatic blood culture system. Localized infections were defined by the presence of typical features indicative of the involvement of a single organ system observed during physical examination, laboratory tests, or radiologic examination at the time of admission. Respiratory, urinary, or gastrointestinal tract infections; skin and soft tissue infections; and intra-abdominal, hepatobiliary, or central nervous system infections are some examples of localized infections involving a single organ system.

Data Analyses

Fisher's exact test was used for the comparison of the risk factors and radiologic findings of SI. A P-value of < 0.05 was considered statistically significant. All data analyses were performed using SPSS statistical software, version 18 (SPSS Inc., Chicago, IL, USA).

Ethics Statement

Ethical approval was obtained from the Institutional Review Board of Inha University Hospital (Incheon, Korea) approved this study (IRB No.: 2019-06-009). Individuals are not identified by the indirect information listed in the manuscript.

Results

Demographic characteristics of patients

Among the 353 patients with SI, 252 patients with no evidence of infection or a history of solid cancer(s) were excluded from the study. The data of the remaining 101 patients were analyzed to assess the relationship between infection and SI. The mean age of the patients was 59.1 ± 17.3 years, and 49.5% of the cohort were women. Thirty-nine patients reported abdominal pain, and 25 patients died—1 because of splenic rupture; 8, sepsis; 2, cardiogenic events; 5, acute respiratory distress syndrome; 3, hypovolemic shock; and 1, liver failure. Splenic rupture was suspected in three patients, and one of these patients died.

Causes Of Infection With Splenic Infarction

Table 1 shows the etiology of infection in the study population. Ten patients (9.9%) had IE, 26 patients (25.7%) had bacteremia without IE, 27 patients (26.7%) had miscellaneous systemic infection, and 38 patients (37.6%) had a localized infection. The most common isolated bacterial pathogens were as follows: *Staphylococcus aureus* (n = 7, 6.9%), *Escherichia coli* (n = 6, 5.9%), viridans group *Streptococcus* (n = 3, 3.0%), and *Enterococcus faecalis* (n = 3, 3.0%).

Of the patients with miscellaneous systemic infection, *Plasmodium vivax* was the most commonly isolated pathogen (n = 12), followed by *Orientia tsutsugamushi* (n = 5), *Babesia microti* (n = 1), cytomegalovirus (CMV, n = 1), and Epstein–Barr virus (EBV, n = 1). Pathogens could not be identified in the remaining 7 patients.

In the 38 patients with localized infection, the most common clinical presentation was respiratory infection (n = 11), followed by intra-abdominal infection (n = 9), hepatobiliary infection (n = 8), skin and soft tissue infection (n = 8), and urinary tract infection (n = 2).

Risk Factors For Splenic Infarction In Patients With Infection

Among the 101 patients, 63 had one or more risk factors for SI, whereas 38 patients did not have any risk factors. Among the patients with risk factors, 27 had a condition that could directly affect the pancreatic vessel(s) (hematologic malignancy in 12 patients, pancreatitis/pancreatic tumor in 8 patients, connective tissue diseases in 3 patients, portal vein thrombosis in 3 patients, and history of trauma in 1 patient). Of the remaining 38 patients (excluding conditions capable of directly affecting the splenic artery), the most common comorbidities were atherosclerotic diseases (n = 22), followed by atrial fibrillation (n = 13), liver cirrhosis (n = 8), and hypercoagulable status, when including duplication (n = 8, Table 2). Among the patients without any risk factors, miscellaneous systemic infection was most commonly observed (n = 21).

Of the 38 patients with localized infections, 35 had one or more risk factors. This is probably because infection alone is unlikely to cause SI. Three of the patients with localized infections developed SI but did not possess any of the risk factors. One patient had necrotizing fasciitis due to *Streptococcus pyogenes*, the second had liver abscess due to *Klebsiella pneumoniae*, and the third had cellulitis with no proven pathogenic cause (a patient with end-stage renal disease).

Radiologic Findings Of Splenic Infarction In Patients With Infection

We found several differences in the type of infection depending on the presence or absence of splenomegaly. After excluding patients with liver cirrhosis and/or hematologic malignancy, we included 77 patients in the sub-group analysis for assessment of features associated with splenomegaly. The 59 patients without splenomegaly had various types of infections: 6 had IE, 20 had bacteremia without IE, 12 had miscellaneous systemic infections, and 21 had localized infections. However, most patients with splenomegaly (15 of 18 patients, 83.3%) had miscellaneous systemic infections. Only 3 patients had splenomegaly (two patients with culture-negative IE and one patient with both urinary tract infection and polycythemia vera) in the non-miscellaneous systemic infections group.

SI caused by miscellaneous infections tended to involve only the spleen, rather than multiple organs. However, on comparing the incidence of miscellaneous infections between patients with SI alone and those with multiple organ infarction/obstruction, there was no statistically significant difference.

Discussion

The purpose of this study was to examine the different clinical scenarios encountered in patients having an infection and concurrent SI. To this end, we investigated various etiologies in order to elucidate the overall relationship between infection and SI and found that the etiologies were largely divided into i) thrombotic events due to IE or sepsis, ii) events due to the presence of intracellular organism, and iii) events due to synergy of localized infection and other risks.

Thrombogenic events can be considered as the main mechanism underlying infection-induced SI (35.3% in this study). Infection can cause thrombosis by various mechanisms. Under inflammatory conditions, increased cytokine production due to sepsis disrupts the coagulation system [12], activating platelets by the action of the pro-inflammatory mediators, such as platelet-activating factors [13], as well as the action of P-selectin, which increases systemic inflammation and leads to platelet adhesion [14]. The functioning of the elements of the anti-coagulation mechanism, including anti-thrombin, the protein C system, and inhibitors of the tissue factor pathway, can be compromised by infection [15]. In IE, vegetation occurs in the damaged endothelium. The degree of adhesion may vary depending on the type of organism involved [16]. The common pathogens involved include *Staphylococcus*, *Streptococcus* and *Enterococcus* as well as other fungal species. The occurrence of antiphospholipid syndrome or disseminated intravascular coagulation in association with severe infection can also be considered a thrombogenic event.

In this study, 27 patients (26.7%) were classified as having miscellaneous systemic infections; the causative pathogens in most of these cases were intracellular organisms. Malaria and babesiosis have previously been shown to cause SI [17, 18]. Both are parasitic diseases in which the parasites infect the red blood cells (RBCs). In these diseases, parasitemia and destruction of RBCs result in hemostasis and cytokine-induced thrombosis, which serve as the main causes of SI; however, the exact mechanism by which SI occurs in these diseases remains unclear. *Orientia tsutsugamushi* infection was frequently identified in several of our patients. This organism is known to cause endothelial dysfunction, leading to triggering of fibrin formation and platelet adhesion and aggregation by endothelial cells [14]. Additionally, endothelial dysfunction contributes to the impairment of the protein C system [14]. Antiphospholipid syndrome is another cause of endothelial dysfunction [19]. In addition to the conditions revealed in this study, Q fever, herpes infection, brucellosis, typhoid, and murine typhus [20] are other conditions that cause SI due to endothelial dysfunction. When physicians encounter cases of SI, they must take into consideration the possibility of infection with different pathogens capable of causing endothelial dysfunction. It is worth noting that most of the patients in this group (miscellaneous systemic infection) also have splenomegaly. In addition to endothelial dysfunction, vessel compression accompanying splenomegaly may be considered as one of the causes of splenomegaly, but there are no clear studies on this. Identifying the presence or absence of splenomegaly in SI patients may be helpful in differentiating those patients with intracellular organism from other patients with SI. In addition, the fact that the patients in the miscellaneous systemic infection group did not show multi-organ occlusion can help differentiate them from other SI patient groups.

Most patients with localized infection and SI had at least one risk factor. The following risk factors – trauma, surgery, pancreatitis, pancreatic tumor, and portal vein thrombosis – which were seen at a rate of 11.9% in this study, are generally considered unrelated to infection, except for pancreatic abscess, splenic abscess, and pylephlebitis (liver abscess)[21, 22]. Hematologic malignancy, vasculitis, hypercoagulable status, and atrial fibrillation, however, are thought to lead to splenic infarction because of their varied associations with infection. Hematologic malignancy is thought to be associated with splenomegaly and/or hyperviscosity under acute leukemic conditions. However, infections due to an immunocompromised status should always be monitored, and attention should be paid to the increased tendency of thrombosis due to infections. Patients with connective tissue disorders may develop splenic infarction as a result of vasculitis, splenomegaly, and antiphospholipid syndrome (22). Infections in patients with vasculitis are generally thought to be secondary to an immunocompromised status, but the possibility of infection exacerbating connective tissue diseases should also be taken into consideration [23]. Exacerbation of atherosclerosis due to infection is sometimes ignored in clinical practice. Our findings revealed that atherosclerotic disease was the most common risk factor (22/101, 21.8%) for SI in patients with infection. Several studies have shown that infection exacerbates atherosclerosis [24]. However, acute infection alone is unlikely to cause a rapid enough aggravation of atherosclerosis to cause SI. Other studies suggest that occlusion may be associated with vasospasm. Arterial spasms can be caused by the increased production of the cytokine interleukin-1 and reduced bioavailability of nitric oxide during acute infection (19). In patients with atrial fibrillation, infections can promote SI by enhancing thrombogenic tendencies. Infection can lead to atrial fibrillation, but only two of our patients developed paroxysmal atrial fibrillation, and most patients with atrial fibrillation had had it before.

These above mentioned conditions must be differentiated using various approaches. First, it is important to differentiate between bacteremia and IE. Then, efforts should be made to identify the underlying diseases or risk factors. If no other risk factors are identified, infection by intracellular organisms should be ruled out. In this study, we found that the presence of intracellular

organisms was associated with splenomegaly without infarction in other organs. These findings may help differentiate the causes of various SI, but a comprehensive evaluation of the patient's underlying disease and history is important. Further, it is difficult to make a diagnosis of splenic infarction with a localized infection alone, and, in this case, the doctor must check whether the patient with SI has other risk factors.

Our study has a few limitations. First, this study was a retrospective investigation; however, a prospective study on this topic is difficult to perform because of the nature of SI. To overcome the drawbacks of a retrospective study design, we took into account various risk factors for SI and analyzed their potential correlations for the development of SI. Second, specific pathogen(s) could not be identified in some of the investigated cases. Third, the findings of this study are based on the experience at a single tertiary hospital, and it may be difficult to apply these findings elsewhere, particularly because diseases such as malaria and scrub typhus show significant regional variation in incidence. Nevertheless, the purpose of this study was to examine the nature of the relationship between infection and SI rather than to analyze the exact etiology of SI.

Conclusion

SI is associated with various infections. In addition to the well-known sepsis and IE, various intracellular organisms were implicated in the pathogenesis of infection-induced SI. The endothelial dysfunction caused by intracellular organisms may be a mechanism leading to SI, but further research is needed on this topic. Since various risk factors have a link with infections, we suggest considering both clinical and radiologic findings of SI patients when making a diagnosis.

Abbreviations

CT
computed tomography; IE:infective endocarditis; RBCs:red blood cells; SI:splenic infarction;

Declarations

Funding

This study had no funding.

Ethical approval

This study was approved by the local ethics committee, which waived the need for informed consent.

Competing interests

All authors declare that they have no competing interests.

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Author contributions

JHI: design and drafting the manuscript. MHC, HJL, HYK, and JHB: analysis of data and discussion. MHC, JHJ, and JSL: revising the manuscript. All authors read and approved the final manuscript.

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Tables

Table 3. Radiologic findings in patients withof splenic infarction

		Systemic infection			Localized infection	Total	χ^2	P-value
		Infective endocarditis	Bacteremia without infective endocarditis	Miscellaneous				
Splenomegaly (N=77)	No (Normal size spleen)	6	20	12	21	59	16.797	<0.001
	Yes (Splenomegaly)	2	0	15	1	18		
	Total	8	20	27	22	77		
Multiple site infarction (N=101)	No (Only splenic)	6	22	25	31	84	3.659	0.067
	Yes (Multiple organ)	4	4	2	7	17		
	Total	10	26	27	38	101		