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Vascular complications of liver abscess: A literature review

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Abstract

Extensive vascular network and proximity to the gastrointestinal tract make the liver susceptible to abscess formation. While pyogenic liver abscesses account for the majority of liver abscesses in the Western world, amebic liver abscesses are more prevalent in tropical and developing nations. Most liver abscesses heal without complications. However, various vascular complications can occur in these patients, including compression of the inferior vena cava, thrombosis of the portal vein and/or hepatic veins, hepatic artery pseudoaneurysm, direct rupture into major vessels or the pericardium, and biliovascular fistula. These complications can present significant clinical challenges due to the potential for haemorrhage, ischemia, and systemic embolism, thereby increasing the risk of morbidity and mortality. Mechanical compression, flow stasis, inflammation, endothelial injury, and direct invasion are some of the proposed mechanisms that can cause vascular complications in the setting of a liver abscess. For the diagnosis, thorough assessment, and therapeutic planning of vascular complications, more sophisticated imaging techniques such as multidetector computed tomography angiography or magnetic resonance angiography may be necessary. Although most vascular complications resolve with abscess treatment alone, additional interventions may be required based on the nature, severity, and course of the complications. This article aims to provide a systematic update on the spectrum of vascular complications of liver abscesses, offering insights into their pathogenesis, diagnosis, and management strategies.

INTRODUCTION

A liver abscess (LA) is a significant infectious complication of the liver parenchyma that requires accurate diagnosis and targeted treatment. Most LAs are classified as amebic liver abscesses (ALA), caused by the anaerobic protozoan *Entamoeba histolytica,* or pyogenic liver abscesses (PLA), caused by various bacteria. Rarely, an LA can be of fungal or tubercular origin. ALA is usually a non-suppurative liver infection with thick brown, odorless, and sterile acellular debris[1]. In contrast, PLA is a pus-filled, suppurative liver infection that is usually culture-positive. PLA is mostly polymicrobial with certain organisms, including Klebsiella, Escherichia coli, Anaerobes, Streptococcus, and Staphylococcus being more frequently noted[2]. There has been a perceptible global trend in the incidence of LA[3]. Certain conditions, such as diabetes mellitus, male gender, advanced age, and impaired immune systems, render individuals more susceptible to LA[2]. The incidence and forms of LA differ geographically, with higher ALA prevalence in tropical regions and developing countries such as the Indian subcontinent, Africa, Central and South America, and Mexico.[4] ALA constitutes over 80% of all LA cases in India[5]. The predominant form of LA in the Western world is PLA, with an incidence rate of 2.3 per 100,000 population in North America[6]. Males over 60 have a higher prevalence of PLA.

The liver is vulnerable to both ALA and PLA due to its complex vascular network and close relationship with the gastrointestinal (GI) tract. The dual blood supply of the liver, comprising the portal vein (PV) and hepatic artery (HA), is unique among visceral organs[7]. The liver's proximity to many vessels increases its vulnerability to the hematogenous dissemination of infections and potential vascular complications[8]. These complications arising from LA encompass a wide spectrum, including vascular thrombosis, thromboembolism, rupture into large vessels, and pseudoaneurysm, underscoring the intricacy of the condition. Pulmonary thromboembolism and trans-diaphragmatic rupture into the heart, resulting in cardiac tamponade, are among LA's

potentially fatal complications[9-12]. Patients with PLA and ALA have both been reported to have vascular complications. In a large study from India, vascular complications were reported in 93 of 1630 LA patients (5.7%)[13]. However, up to 69% of ALA patients had venous thrombosis, in a recent study specifically designed to identify vascular complications using a multidetector CT scan[14]. Several proposed mechanisms can lead to vascular complications in the context of LAs, including vascular compression, flow stasis, inflammation, endothelial damage, and direct invasion[4,15-17]. Further, chronic inflammation can weaken the HA wall, making it vulnerable to the development of hepatic artery pseudoaneurysm (HAPA) and its eventual rupture[18,19]. This article aims to provide an update on the spectrum of vascular complications of LA, including their pathophysiology, diagnostic approach, and therapeutic considerations. A systematic literature search up to February 2024 was performed using PubMed and Google Scholar database for the purpose of this article.

VASCULAR ANATOMY OF THE LIVER IN RELEVANCE TO LA

The development of LA is significantly influenced by the liver's vascular architecture. The liver is divided into eight segments, each with a separate vascular supply. Based on the blood supply to particular hepatic segments, LA may be the site of localization. Comprehending this segmental blood flow facilitates the understanding of the mechanisms by which infections enter the liver parenchyma. The amebic trophozoites of colonize the cecum, invade the mucosa, and enter the liver through the portal circulation to cause ALA[4]. The right lobe of the liver is more frequently affected by ALA because the superior mesenteric vein, which drains the area of the intestine where trophozoites invade, is the main conduit for portal blood flow to the liver. In the case of PLA, where bacterial invasion can occur through the venous, arterial, or biliary systems, such lobar preference is not shown. Generally, biliary tract infections or ascending cholangitis cause right lobe PLA, whereas diverticulitis or colonic cancer can cause PLA in the left lobe[2]. The inferior vena cava (IVC) is more susceptible to compression and thrombosis from the LA of the caudate lobe due to its proximity[20]. The liver is an

important defense against microbial invasion. Therefore, bacteria may evade the hepatic filtration mechanisms in situations of portal vein thrombosis (PVT), raising the risk of infections, including PLA.[2]

MECHANISMS OF VASCULAR INVOLVEMENT IN LA

Several factors contribute to vascular involvement in LA, including the followings:

Hemodynamic changes due to compression: An expanding LA exerts pressure on nearby vessels, compromising their integrity and functionality, leading to alterations in blood flow[16,21]. The resultant pockets of stagnant blood can foster the development of thrombi. These thrombi can further impair blood flow and affect the cellular function and viability of the hepatic cells around the LA by preventing the delivery of oxygen and nutrients[22].

Inflammation and Endothelial Damage: Within the liver parenchyma, microbial invasion sets off a series of inflammatory reactions. The inflammatory mediators generated in response impact the surrounding vasculature, besides the abscess site. Vascular endothelial cells are essential for maintaining structural integrity. The inflammatory processes sparked by microbial invasion cause endothelial injury in nearby blood vessels, jeopardizing the structural integrity of vessels[23,24]. A pro-thrombotic surface created by damaged endothelial cells encourages platelet adhesion and activation. The coagulation cascade that leads to thrombus formation is initiated when platelets attach to the exposed subendothelial matrix[25]. The thrombus can impede blood flow in the involved vessels, worsening the compromised blood flow. In a recent study, 69% of ALA patients had venous thrombosis, and 53% showed a zone of perilesional ischemia[14]. Despite extensive thrombosis of the IVC and HV, underlying thrombophilia states were found negative in a study, highlighting the thrombogenic potential of ALA[26]. Besides thrombotic complications, inflammatory damage to nearby arteries may cause the accumulation of blood between tunica media and tunica adventitia of the arterial wall, leading to the formation of a pseudoaneurysm[18,19].

Direct invasion: Rupture into nearby structures is one of the most common complications of LA[4]. LAs of the left lobe and the caudate lobe are more vulnerable to cardiovascular complications due to their proximity to the heart and major vessels. ALA has been reported to directly invade the IVC[15,17]. Concomitant injury to the bile ducts and HV may cause a biliovascular fistula, which raises serum bilirubin levels rapidly[27].

SPECTRUM OF VASCULAR COMPLICATIONS AND CLINICAL PRESENTATION

The spectrum of vascular complications in LA patients is depicted in Figure 1. It includes the following:

Vascular compression

The complication due to vascular compression is more common with large LAs located in the caudate lobe (Figure 2). Huddle *et al*.[16] and Sharma *et al*.[21] reported a case of caudate lobe ALA causing extrinsic compression of the IVC without evidence of thrombosis. Mehrotra *et al*.[28] reported a large staphylococcal PLA causing IVC compression and presenting as acute Budd-Chiari syndrome (BCS). Karadag O *et al*.[29] have also reported a case of PLA compressing the IVC and HVs, causing acute BCS.

Venous thrombosis

Venous thrombosis contributes to the intricate cardiovascular landscape associated with LA (Figure 3). The reported frequency of thrombotic consequences varies widely, from 3.7% to as high as 69%[14,28,30]. Venous thrombosis has been reported in LAs of both amebic and pyogenic origin (Tables 2 and 3).

Venous thrombosis in ALA patients: Krishnan *et al*.[15] found IVC thrombosis in 8% of cases and HVT in all but one of the 95 ALA patients in a comprehensive autopsy study. In another autopsy series, Aikat *et al*.[31] reported PVT in 27.5%, HVT in 29.5%, and IVC thrombosis in 4% of ALA cases. Sarda *et al*.[32] reported three cases of ALA-

induced IVC obstruction that was resolved after percutaneous drainage and antibiotic treatment. Three cases of ALA extending into the IVC and causing its thrombosis were recently reported by Marak *et al*[17]. Hodkinson *et al*.[33] reported another case of a 50-year-old man with ALA who developed an IVC thrombus that spread to the right atrium. Sodhi *et al*. reported a 57-year-old man whose ALA was complicated by HVT and IVC thrombosis[34].

Venous thrombosis in PLA patients: In a study by Syed MA *et al*.[35], 28 out of 67 patients (42%) with PLA had venous thrombosis. PVT was present in 24%, HVT in 22%, and combined PVT + HVT in 4% of patients. Venous thrombosis resolved in 37% of 27 patients after 6 months and persisted in 63% during the 3- to 38-month follow-up period. Yang *et al*.[30], in a retrospective analysis of 81 PLA patients, reported PVT in three patients (3.7%), and one patient also had extrinsic compression of the IVC. In a study, PLA due to Klebsiella pneumoniae was identified as the most common (37%) cause of thrombophlebitis of the portal venous system (pylephlebitis)[36]. PLA due to various other bacterial causes such as Lactococcus lactis, *Fusobacterium nucleatum, and* Clostridium clostridioforme has been reported to be complicated by PVT[37-39]. In a retrospective analysis of 169 patients with Klebsiella pneumoniae-associated PLA, Molten J *et al*.[40] found that 53 patients (31.4%) had thrombophlebitis of the PV or HV. In follow-up scans, 73% (30/49) of patients showed spontaneous recanalization in a mean duration of 44 days. Thrombosis of the cerebral venous sinus and superior mesenteric vein has also been reported in association with PLA[41,42].

Clinical consequences of vascular obstruction

Thrombosis of segmental hepatic vessels appears to aggravate the severity of LA. Priyadarshi *et al*. found that hepatic ischemia caused by venous thrombosis increased the severity of LA, and more patients with hepatic ischemia experienced an aggressive clinical course necessitating interventional therapy[14]. LA patients with IVC thrombosis are at risk of thromboembolic phenomena. Several studies, including those by Prendki V *et al*.[9], McKenzie D etal.[10], and Jesrani G *et al*.[43], have reported cases

of ALA complicated by pulmonary thromboembolism. A high index of suspicion is required to diagnose these complications in LA patients who might have hemodynamic instability and respiratory distress. Thrombosis of the HV and IVC may introduce additional signs such as pedal edema, ascites, and hepatomegaly, indicating possible venous congestion and impaired venous return. Thus, LA can rarely result in the development of secondary BCS. The development of portal hypertension poses an additional challenge and reflects the systemic impact of a complicated LA. There are many reports of neonatal PLA complicated by PVT with subsequent formation of portal cavernoma[44-46]. Shah *et al*.[44] reported the appearance of PVT in a neonate after 16 days of treatment for LA, who subsequently developed portal hypertension. Aggarwal *et al*.[45] and Sethi *et al*.[46] also reported PVT and cavernoma in association with neonatal PLA. One key clinical indicator that points to the presence of PVT in patients with LA is unexplained abdominal pain, particularly if it is severe and persistent. Patients with pylephlebitis may develop severe sepsis, including septic shock and decreased cognitive function.

HAPA

HAPA, although uncommon, are the second most prevalent type of pseudoaneurysm involving the splanchnic artery. They are usually extrahepatic in location (75%) and traumatic in origin[47]. Nonetheless, HAPA, in association with LA, are generally intrahepatic and can also be intracavitary (Figure 4). HAPA have been reported more often in association with ALA than PLA (Table 3). The first incidence of HAPA linked to an ALA was reported by Gopanpallikar A *et al*.[48] in 1997. Silvestri V *et al*.[49] reviewed 6 cases of HAPA associated with ALA. The mean age of patients was 44.8 ± 8 years, and all were male. The most common presentation was fever, abdominal pain, and GI bleeding. The aneurysm ruptured in two cases, while it regressed spontaneously in two others after treating ALA. With available follow-up data in 5 patients, all had uneventful recoveries. Qi X *et al*.[50] reported HAPA in association with PLA due to Listeria monocytogenes in a 50-year-old woman. While HAPA may be asymptomatic in

patients with LA, symptoms such as persistent abdominal pain, bleeding manifestations, or signs of hemodynamic instability should raise suspicions about this complication. Rupture of the HAPA into the biliary system can lead to hemobilia presenting as GI bleeding[18,51]. Importantly, in patients with ALA, concurrent ileo-colonic ulcerations caused by amebic trophozoites frequently result in GI hemorrhage[52]. Early detection and prompt management of HAPA are important, considering that its complications are catastrophic.

Other vascular complications

On rare occasions, LA can lead to an intrahepatic connection between the biliary and venous systems, resulting in the mixing of bile and contents of the LA with blood in low-pressure intrahepatic veins. This leads to a rapid increase in the levels of bilirubin and bile acids in serum. Thus, biliovascular fistula is a unique and uncommon consequence of LA that may have significant clinical implications[27,53]. Singh V *et al.*[27] described the occurrence of biliovascular fistula in 12 ALA patients with hyperbilirubinemia. Interestingly, following biliary diversion with nasobiliary drainage, the hyperbilirubinemia in these patients returned to normal.

The heart is a vital component of the vascular system. Due to its proximity to the liver's left lobe, the heart may get involved in complicated left lobe LA. As rupture is a common complication of ALA, cardiac tamponade may result from the rupture of the left lobe of ALA into the pericardium[35,36]. PLA due to Actinomyces, which is a gram-positive anaerobic to microaerophilic bacterium, has been associated with purulent pericarditis with cardiac tamponade[54,55]. The presence of dyspnea, tachycardia, hypotension, and pulsus paradoxus can raise suspicions about this life-threatening complication of LA. Early diagnosis of this condition is necessary to avoid adverse outcomes. Rarely, right heart failure can occur in patients with LA due to a right atrial thrombus[56].

MANAGEMENT ISSUES: DIAGNOSTIC AND THERAPEUTIC CONSIDERATIONS

The initial presentation of LA with vascular involvement may be similar to that of uncomplicated LA. However, when LA patients develop persistent or worsening abdominal symptoms, ascites or pedal edema, gastrointestinal bleeding, dyspnea, or hemodynamic instability, vascular complications should be suspected. Appropriate imaging modalities should be used to diagnose these complications to enable timely intervention and improved patient outcomes. Doppler ultrasound can be the initial imaging modality to diagnose PVT. It has the advantages of being non-invasive, widely available, and good sensitivity to detect flow abnormalities in the PV. However, its role may be limited in patients with obesity or extensive thrombosis. More sophisticated imaging methods like multidetector CT angiography and magnetic resonance angiography provide better diagnostic precision and spatial resolution for identifying PVT and/or HVT and evaluating their severity and associated complications[57,58]. By providing a thorough assessment of collateral circulation, vascular patency, and cavernous changes, these modalities can aid in prognostication and therapeutic decision-making. Regarding HAPA, CT angiography is valuable for detecting, characterizing, and guiding treatment decisions[19,51]. Contrast-enhanced ultrasonography (CEUS) is a valuable diagnostic tool for LAs. It can also be used to differentiate LAs from other liver masses, characterize LAs, which may help with treatment decisions, and guide percutaneous catheter or needle drainage[59,60]. On CEUS, LAs commonly exhibit rim enhancement, a nonenhanced central necrotic region, enhanced internal septa, and transiently hyperenhanced liver parenchyma surrounding the lesions[61]. Treatment under Sonovue CEUS is associated with faster recovery, better treatment response, and a lower risk of complications in PLA patients[59].

Vascular complications of LA are managed through a multidisciplinary approach that considers multiple host- and disease-related factors. To navigate the intricacies of this clinical circumstance and provide optimal patient care, hepatologists, interventional radiologists, and surgeons must collaborate. Prompt initiation of antibiotic therapy

targeting probable microorganisms is essential to treat the underlying abscess; typically, drugs like metronidazole are combined with cephalosporins or fluoroquinolones.[59] Image-guided percutaneous catheter drainage (PCD) of the abscess is crucial to eliminate the infectious source. Drainage is important because it facilitates better penetration of antibiotics and clears necrotic material, bile, and blood clots that delay the abscess cavity healing[62]. The routine use of anticoagulant medication for venous thrombosis in the setting of LA continues to be debated. The benefits of preventing thrombus propagation must be weighed against the risk of hemorrhagic complications[63]. Anticoagulation therapy resolves venous thrombosis associated with both ALA[64-66] and PLA[67-69]. Nevertheless, many reports document spontaneous recanalization of vascular thrombosis after proper treatment of LA alone[30,63,70,71]. Surgical thrombectomy has also been performed in some cases; however, such aggressive treatment is often unnecessary[72,73]. Sarda *et al.*[32] reported recanalization of IVC obstruction in three ALA patients treated with percutaneous drainage and antibiotic therapy. Molton J *et al.*[40] reported spontaneous recanalization of vascular thrombosis in the majority (73%) of affected PLA patients without anticoagulant therapy. This implies that the underlying abscess should be the focus of treatment, rather than the thrombus. However, therapeutic anticoagulation should be considered in cases of severe IVC thrombosis, right atrial thrombus, or thromboembolism.

HAPA can be treated with endovascular embolization, surgical resection, or close observation. Due to its rarity and the paucity of knowledge thereof, there is still no consensus on the best treatment approach. Given the significant morbidity associated with surgical treatment, percutaneous trans-arterial embolization is currently recommended for intrahepatic aneurysms[18,51,74]. Metallic coils, non-absorbable polyvinyl alcohol particles, or liquid embolic agents like N-butyl cyanoacrylate are the most common types of embolic agents used. Coils are the most commonly used embolic agent when vascular anatomy is favorable. Nevertheless, with appropriate treatment of LA using antibiotics and PCD, spontaneous resolution of HAPA is possible[19,50,75]. Which patients should be chosen for expectant treatment is unclear. A small HAPA (< 2

cm) arising from the peripheral branch of the HA may resolve spontaneously[19]. Repeated ultrasonography with Doppler can help clinicians monitor these patients while adhering to expectant treatment. For patients with pericardial rupture of LA, immediate pericardiocentesis is the cornerstone of treatment[12]. LA complicated by biliovascular fistula may respond to biliary diversion using nasobiliary drainage[27].

Thus, many of vascular complications require care of only LA with antimicrobials and percutaneous drainage. Ultrasound guided percutaneous drainage of LA is quite safe procedure. No major complication related to PCD or needle aspiration have been reported in patients with either PLA or ALA 1,76-78]. The requirement of additional treatment will depend on the nature, severity and course of vascular complication.

UNUSUAL CAUSES OF LIVER ABSCESS

Occasional causes of LA include mycobacteria and fungi[79]. Sometimes, suppuration of cystic hepatic diseases, such as hydatid cysts, can also result in LA. In a cross-sectional study from India (n = 200), the etiology of LA was mycobacteria in 7.5% and candida in 1.5% of 200 consecutive LA patients[79]. Fungal liver abscesses can occur in onco-hematologic patients and hematopoietic stem cell transplantation recipients[80]. Generally, fungal liver infections are caused mostly by Candida species. Little information is available about vascular involvement in fungal LA. Paccoud O *et al*.[81] reported a case of chronic LA with PVT caused by Candida. Liver involvement is possible in endemic areas of tuberculosis; however, the presentation of hepatic tuberculosis as focal LA is extremely uncommon[82,83]. In a study, tubercular LA was found in the left liver lobe and smear positive for acid-fast bacilli. PVT has also been associated with hepatic tuberculosis rarely[84,85]. These cases have been successfully treated with antituberculosis medications and an anticoagulant[85]. A hepatic hydatid cyst can sometimes masquerade as LA[86]. Particularly, secondary bacterial infection of a hydatid cyst makes it difficult to differentiate from a PLA. In a large series of hepatic hydatid cysts, suppuration occurred in 7 of 328 cases (2.1%)[87]. Although vascular

involvement in the form of PVT and secondary BCS has been reported in cases of hepatic hydatid disease, no literature has specifically detailed this complication vis-a-vis an infected hydatid cyst[88-90].

CONCLUSION

Vascular complications due to LA occur with varying frequencies[14,19,28,30,91]. They include mainly thrombosis of PV, HV, IVC, and rarely HAPA; direct rupture into major vessels and pericardium; and biliovascular fistula. These vascular complications can increase morbidity and may cause mortality among affected patients. Mortality is usually associated with rare but serious complications such as septic shock, pulmonary thromboembolism, and cardiac tamponade. Suspicion of vascular complications should be high if patients with LA show persistent, worsening, or new symptoms, despite receiving the recommended antibiotic therapy. Hemodynamically unstable patients might need immediate imaging to rule out life-threatening complications. Vascular problems may not show up on traditional ultrasound imaging, necessitating abdominal CT or MRI with angiography. The majority of vascular complications resolve with antibiotics and drainage of LA. Drainage is particularly necessary in large LAs, which are more likely to cause vascular complications. Abdominal ultrasonography is generally used to guide percutaneous drainage. Serial ultrasound examinations can be useful in monitoring therapeutic responses, besides clinical signs. The requirement for additional treatment will depend on the nature, severity, and course of the vascular complication. Thrombotic complications appear to resolve with treatment of LA alone, and anticoagulation is not necessary. Nonetheless, a small proportion of PVT patients, especially those diagnosed early in life, may develop chronic portal hypertension. Thus, individualized treatment and vigilant monitoring are required to ensure favorable patient outcomes. Additional research is necessary to shed more light on the risk factors and natural history of vascular complications, the appropriate timing and indication of intervention, and ways to prevent such complications.

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