Liver Abscesses as Pseudotumoral Lesions

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Abstract

An important hepatic lesion that produces masses that may mimic cancer is pyogenic liver abscess. Liver abscesses are caused by diverse bacterial organisms, but certain bacteria are prominent inducers of liver abscesses, such as *Klebsiella* and *Staphylococcus*. The spread of bacteria to the liver follows hematogenous or ascending routes, sometimes associated with infectious pylephlebitis. Pyogenic liver abscesses exhibit a characteristic macroscopic presentation, with a purulent center followed to the periphery by a belt of granulation tissue and a hyperemic demarcation zone. In the curse of fibrous repair, pyogenic abscesses can collapse and leave a scar-like lesion. Distinct variants of bacterial liver abscesses and related lesions are caused by *Salmonella* species. In case of infection with anaerobic germs, and in particular *Clostridium* species, complex morphologies ensue, in part with prominent gas formation.

Classical Pyogenic Liver Abscess

Introduction

Pyogenic liver abscess (PLA) is a potentially life-threatening disorder that may, owing to the invasive and destructive mode of presentation in the liver, be confounded with malignancy. PLA develops in a wide variety of patients (Branum et al. 1990; Huang et al. 1996; Seeto and Rockey 1996; Johannsen et al. 2000; Alvarez Perez et al. 2001).

Epidemiology

PLA is usually found in elderly patients with biliary tract disease, and males predominate in all major studies (Frey et al. 1989; Kurland and Brann 2004; Chan et al. 2005). There are marked differences in epidemiology and etiology between western countries and tropical countries, in particular what regards the contribution of amebic infections. A study performed in India has shown that 51.2 % of all abscesses were amebic, 23.2 % were PLA, and 25.6 % had unknown causes (Mohan et al. 2006). In contrast, most liver abscesses in the West are in fact PLA. The epidemiology of PLA has markedly changed in recent years, in that the incidence of PLA is rising in numerous countries and that the etiology is changing (Land et al. 1985; Seeto and Rockey 1996). This is also specifically due to the emergence of *Klebsiella*-associated PLA, a distinct syndrome (Lederman and Crum 2005). Whereas PLA formerly was mainly associated with preexisting hepatobiliary disease and polymicrobial infections, dominated by *Escherichia coli*, more and more patients with PLA have no preexisting hepatobiliary disease, but suffer, e.g., from diabetes mellitus and have PLA caused by *Klebsiella*. A nationwide analysis of PLA in Taiwan from 1996 through 2004 showed that the annual incidence of PLA increased steadily from 11.15/100,000 population in 1996 to 17.59/100,000 in 2004. Diabetes mellitus, malignancy, renal disease, and pneumonia were associated with a higher risk for PLA (Tsai et al. 2008).

Clinical Features

Malaise, anorexia, abdominal pain (mainly focal abdominal tenderness), and night sweats are the leading symptoms in patients with PLA. Up to 60 % of patients present with these nonspecific features, which have been specified in numerous reports, while fever was noted in up to 80 % (less often chills), and a variable number of patients show hepatomegaly and weight loss. Jaundice is usually only present in case of simultaneous biliary obstruction (Warren and Hardy 1968; Young 1976; Perera et al. 1980; Rubin et al. 1981; Kandel and Marcon 1984; Beaumont and Davis 1985; Gyorffy et al. 1987; Hau and Hartmann 1987; Bansal and Prabhakar 1988; Frey et al. 1989).

In PLA not caused by *Klebsiella* (see below), the most common coexisting diseases are diabetes mellitus, followed by biliary stone disorders and other types of biliary tract disease (Rockey 2001),

and intra-abdominal infectious and neoplastic disease (Lin et al. 2011a; Law and Li 2012), in particular colonic disease (McDonald et al. 1984), including colorectal cancer (Lonardo et al. 1992; Yokota et al. 2005; Pisano et al. 2007, Lee et al. 2008). Silent colorectal cancer (CRC) can manifest as PLA in the absence of metastasis (Teitz et al. 1995; Fernandez Ruiz et al. 2007; Giuliani et al. 2007; Hiraoka et al. 2007; Chen et al. 2012; Jeong et al. 2012; Qu et al. 2012), a constellation which is an important cancer-inflammation syndrome (the CRC-PLA syndrome, as I tend to call it). PLA has also found to be the initial manifestation of hepatocellular carcinoma (Yeh et al. 1998; Lin et al. 2011a). Diabetes mellitus is a very important risk factor for PLA, as poorly controlled diabetic patients are immunocompromised and are susceptible to bacterial infections. In a large study, persons with diabetes mellitus had a 3.6-fold increased risk of experiencing PLA in comparison with a control population, and patients with PLA who had diabetes mellitus had a higher 30-day post-discharge mortality rate, compared with patients with PLA who did not have diabetes (Thomsen et al. 2007; Tian et al. 2012). On one study, 10–16 % of patients with PLA had diabetes mellitus (McDonald et al. 1984). There are less common predisposing conditions for PLA, such as pylephlebitis in pancreatitis (Rustagi et al. 2012) and Crohn's disease (McGreal et al. 2012). In case no infectious cause is identified, the term cryptogenic liver abscess is used (Stokes 1960).

PLA are usually more often solitary than multiple lesions; among 483 patients with PLA, 343 PLA were single lesions, 140 multiple abscesses. In this study, single abscesses were usually larger than 5 cm, whereas multiple abscesses were usually smaller than 5 cm. Solitary abscesses were predominantly located to the right liver lobe. Multiple PLA were more often associated with preexistent biliary tract disease (Chou et al. 1997). Abdominal pain was more frequent in case of single PLA than with multiple PLA, but jaundice was more often found in multiple PLA. However, there are also series where solitary and multiple PLA had about the same prevalence (Strong et al. 2003).

Complications

Portal and/or hepatic vein thrombosis can be caused by PLA (Syed et al. 2007). Sometimes, the classical Budd-Chiari develops (Karadag et al. 2005). Such thrombotic events can extend into the inferior vena cava and/or the right atrium (Bagri et al. 2013). Abscess rupture causes subdiaphragmatic abscess (specifically, this is an empyema per definition), and such a process can penetrate through the diaphragm and pericardial wall to induce pyopericardium (Chong et al. 2010). PLA can cause septic pulmonary embolism (Lin and Chang 2008). This complication is more common in patients with diabetes mellitus (Yang et al. 2008). A subset of PLA is characterized by gas formation (gas-containing PLA; Hayashi et al. 1989; Ukikusa et al. 2001; Chen et al. 2008a; Chong et al. 2008; Huang et al. 2009; Oh et al. 2011; Safe et al. 2013). In part of these PLA, the bacteria causing the infection express formic hydrogen lyase, leading to mixed acid fermentation and gas formation. Etiologically, classical gas-forming bacteria may be involved (such as Clostridia; Kahn et al. 1972; Ogah et al. 2012), but at least 75 % of all gas-containing PLA have been found to be caused by *Escherichia coli* and *Klebsiella* (Zhang et al. 2013). Other germs inducing gas-forming PLA are *Salmonella enteritidis* (Tee Yu et al. 2013) and diverse anaerobic bacteria. Gas-forming PLA, which are rare variants of liver abscesses, most often occur in patients with diabetes mellitus (Yang et al. 1993) and are associated with a high mortality rate. In case a gas-forming PLA ruptures, pneumoperitoneum ensues (Matsuyama et al. 1994; Ukikusa et al. 2001).

There is evidence that patients with PLA have a higher rate of primary liver cancer than matched controls, suggesting that PLA is a warning sign for liver cancer (Huang et al. 2013). In a study of 1257 PLA patients from Taiwan, 186 were diagnosed with cancer after a median follow-up of 3.33 years, including 56 liver cancer, 22 biliary tract cancer, and 40 colorectal cancer patients: The highest standard incidence ratio/SIR of all cancers, hepatocellular carcinoma, biliary tract

cancer, and colorectal cancer, occurred within 90 days of follow-up (Kao et al. 2012).

Pathology

Macroscopy

Non-gas-containing PLA are usually spherically, wedge-shaped or irregular mass-producing lesions varying in diameter from few millimeter to more than 20 cm (Figs. 1, 2, 3, and 4). PLA can present as solitary or multiple lesions, sometimes involving both liver lobes. In case the PLA extends to the liver capsule, the capsule may be thinned, a yellowish or hemorrhagic mass being visible through the transparent capsule, and the capsular surface can be eroded or covered by an exudate (fibrinous or fibrinopurulent), or coagulated blood. On cut surfaces, the center of PLA is occupied by thick, viscous, or liquefied pus that flows off the cut surface and sticks to the knife. In contrast to tuberculosis, the purulent material is never cream white, but has several shades of yellow to yellow green, a greenish tinge being caused by neutrophil myeloperoxidase, a green enzyme, or by pyocyanin in case of *Pseudomonas*

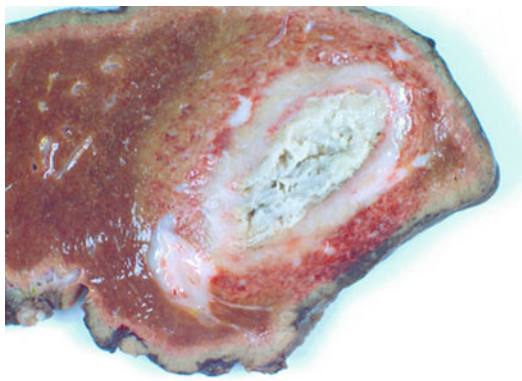

Fig. 1 Pyogenic liver abscess. On cut surfaces, hepatic abscesses frequently show a distinct concentric structure, as in this case. The innermost part is occupied by pus (whitish-yellow mass), followed by a zone of granulation tissue and scar tissues (white rim) and a peripheral hyperemic zone

Fig. 2 Pylephlebitic liver abscess. The pyogenic abscess in this case displays the distribution of portal veins with infectious pylephlebitis, through which the pyogenic infection has spread to the liver substance

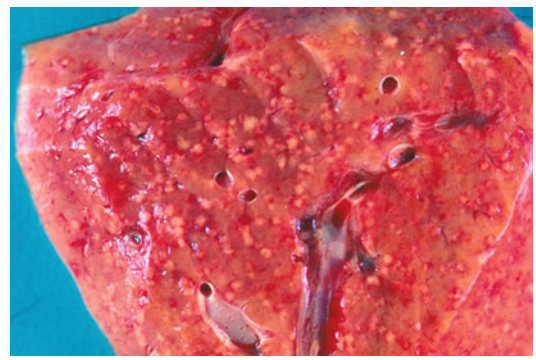

Fig. 3 Multiple miliary abscesses of the liver in a patient with septicemia. The lesions are evenly distributed

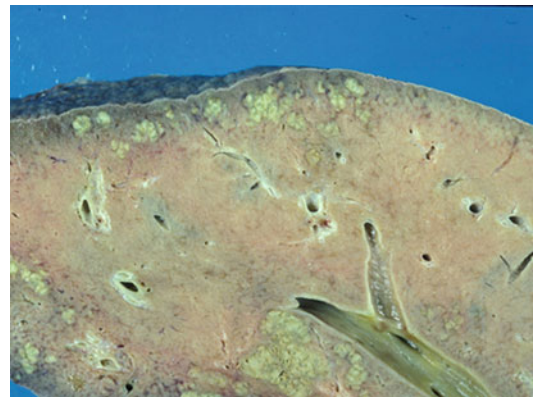

Fig. 4 In this case, small or miliary abscesses accumulated in terminal ramifications of the intrahepatic portal venous system

aeruginosa infection. In some cases, the central part of the abscess exhibits a fluid-filled cyst in which purulent exudate flakes may float. Part of PLA contain hemorrhagic pus. In acute PLA, the purulent material directly contacts the adjacent liver substance, while older lesions show a dark-red demarcation zone mainly consisting of a wall of granulation tissue. In PLA undergoing contraction, this vessel-rich zone collapses and shows a wavy contour. The parenchyma surrounding a PLA may contain spotty hemorrhage and sometimes a perifocal steatosis. PLA may destroy the walls of intrahepatic bile ducts and discharge the pus into the ductal lumina. Bile may flow back into the abscess cavity, greenishly discoloring the purulent exudate. PLA can break through the organ's limits and give rise to fistulae entering diverse tissues and organs in the vicinity of the liver. In PLA caused by gas-forming bacteria, the tissue may produce a blistering or crackling sound on palpation, and the cut surface shows a foamy or spongy appearance due to the presence of gas bubbles. Sometimes, gas bubbles float within the pus, an effect difficult to distinguish from artificial air entering upon cutting the tissue.

Macroscopically, the etiology of PLA is difficult to assess. A foul and feculent odor indicates *E. coli* infection, while in case of *Pseudomonas aeruginosa* infection, the pus may have a bluish-green tinge due to accumulation of pyocyanin. Gas production suggests anaerobic infections.

Histopathology

Histologically, the purulent exudate reveals the classical composition of neutrophils and macrophages in all stages of decreasing viability. Many of the phagocytes remain only as shadow cells or nuclear debris, specifically in the central, older parts of the abscess. Bacteria are shown by use of bacterial stains and are either present as free organisms or bacteria located within phagocytic cells. Viable phagocytic cells are usually seen at the periphery of the lesion, where active leukodiapedesis from blood vessels of the granulation tissue takes place. The granulation tissue itself is nonspecific and lacks an epithelioid cell reaction of granulomas. At the parenchymal face of granulation tissue, dilated blood vessels entering the parenchyma are seen. The sinusoidal vascular bed is usually hyperemic in the area surrounding the PLA. The suppurative process may cause damage of adjacent intrahepatic bile ducts, followed by bile leakage (Fig. 5). Abscesses may be associated with peliosis hepatis (Van Schil et al. 1988). In healing PLA, the purulent exudate becomes more viscid and histologically dense, with less and less phagocytes being visible. The wall of granulation tissue transforms into a less vascular scar tissue, associated with focal hemosiderosis. Through organization, the exudate may completely vanish at the end, but in large PLA, a cyst may remain, as the granulation tissue is unable to form a bridge through large exudate masses.

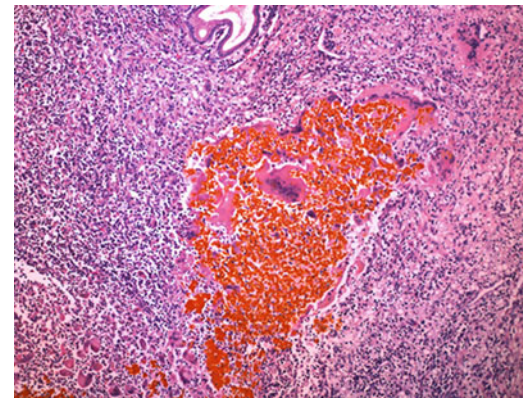

Fig. 5 Intrahepatic bile duct damage due to purulent inflammation. There is marked bile leakage with induction of a foreign body reaction (multinucleated giant cells; hematoxylin and eosin stain)

Differential Diagnosis

Radiologically, PLA can mimic massively necrotic primary liver cancer or necrotic metastases (Klotz and Penn 1987), in particularly those of tumors with a high tendency of necrosis, such as colorectal, pancreas, and bronchopulmonary primaries. It is important to note that PLA may hide a primary malignant liver tumor, in particular necrotic HCC (Yeh et al. 1998).

Biology of Disease

The Acute Physiology and Chronic Health Evaluation II (APACHE II) classification system (Knaus et al. 1985; Knaus 2002) has been evaluated in patients with PLA and found to be useful in predicting in-hospital mortality of PLA (Levison and Zeigler 1991; Hsieh et al. 2006). In a multivariate analysis, it turned out that the mortality from PLA was associated with gas-forming abscess, multidrug-resistant isolates, anaerobic infection, APACHE II score > or = 15, and blood urea nitrogen level > 7.86 mmol/l (Chen et al. 2008b). The cumulative recurrence rates of PLA were lower in both the cryptogenic and diabetic groups than in the underlying biliary tract disease group (Cheng et al. 2008).

Pathogens Causing PLA

Worldwide, causative agents of PLA mostly include *Escherichia coli* (*E. coli*), *Klebsiella pneumoniae*, *Enterococcus* species, *Staphylococcus* species, *Streptococcus* species, *Bacteroides* species, and a large group of other organisms (Gyorffy et al. 1987; Chou et al. 1997), but *E. coli* and *Klebsiella* are by far the most common pathogens, with *Klebsiella* having a specific role in that it causes as distinct syndrome of invasive infection.

Over the past years, a new type of invasive *Klebsiella pneumoniae* disease (*Klebsiella* liver abscess syndrome, KLAS; invasive *Klebsiella pneumoniae* liver abscess syndrome), which typically manifests as a community-acquired primary liver abscess associated with bacteremia, has been identified, first in Taiwan (Wang et al. 1998; Rahimian et al. 2004; Lee et al. 2010), but then also in other countries (Saccente 1999; Lederman and Crum 2005; Gomez et al. 2007; Keynan and Rubinstein 2007; Casella et al. 2009; Frazee et al. 2009; Pope et al. 2011; Fung et al. 2012; Moore et al. 2013). KLAS is caused by the *Klebsiella* capsular phenotype K1, magA KP, which confers a unique hypermucoviscous phenotype to the bacterium (see below). Community-acquired primary liver abscess caused by *K. pneumoniae* or KLAS mainly occurs in diabetic patients without previous hepatobiliary or intra-abdominal infection. Patients with this type of infectious syndrome can present with or without hepatic metastatic complications, but the development of metastatic infections is a typical feature in part of the patients, and 10–20 % of reported cases developed metastatic meningitis, endophthalmitis, endocarditis, and metastatic manifestations in other organs (Wang et al. 1998; Fung et al. 2002; Chan et al. 2007, Cheng et al. 2007; Chen et al. 2008a). There are certain clinical differences between KLAS patients from Eastern Asia, South Africa, and western countries (Ko et al. 2002). *Klebsiella pneumoniae* causing this syndrome has several distinct microbiologic features and a distinct genomic signature based on complete genome sequencing (Wu et al. 2009a). The main feature is the HMVKp (hypermucoviscous *Klebsiella pneumoniae*) phenotype, caused by the capsular serotype K1, magA + Kp. The mucoviscous phenotype is seen when contacting a bacterial colony in culture with a probe, resulting in the production of a viscous thread between the probe and the colony. The mucoviscosity-associated gene A, magA (wzy_K1), is the K1 polymerase gene, which encodes a 43 kDa outer membrane protein involved in the synthesis of exopolysaccharides (Fang et al. 2010; Yeh et al. 2010). *Klebsiella pneumoniae* isolates causing KLAS carry three rmpA/A2 genes, two large-plasmid-carried genes (p-rempA and p-rampA2), and one chromosomal gene (c-rmpA) (Hsu et al. 2011). Hyperviscosity, an extremely sticky phenotype of K. pneumonia, is associated with this destructive abscess syndrome (Kawai 2006; Lee et al. 2006; Yu et al. 2006; Pan et al. 2008). The K antigen, a capsular polysaccharide, is a very important virulence factor for *K. pneumoniae*. Expression of the rmpA and magA genes is associated with the hypermucoviscous phenotype and is linked to *Klebsiella* virulence and an aggressive clinical presentation (Yu et al. 2006). Capsular polysaccharide production leading to the hypermucoviscous phenotype is linked to the expression of genes regulating *Klebsiella* biofilm formation, treC (encoding trehalose-6-phosphate

hydrolase) and sugE (Wu et al. 2011). The pathogenic mechanism by which this distinct *Klebsiella* phenotype is related to the unique clinical presentation is only partially known. Expression of K1 antigen hampers complement- and neutrophil-mediated killing of *Klebsiella*, a mechanism thought to promote an invasive phenotype (Lin et al. 2010; Fung et al. 2011). In fact, capsular serotypes K 1 and K2 impair *Klebsiella* phagocytosis in type 2 diabetic patients (Lin et al. 2006), and phagocytosis-resistant *Klebsiella* serotypes are highly prevalent in PLA (Lin et al. 2004). Antibodies directed against capsule polysaccharide protect the host from magA+ *Klebsiella pneumoniae*-induced lethal disease by evading Toll-like receptor 4 signaling (Wu et al. 2009b). Other virulence factors that markedly influence the aggressiveness of *Klebsiella* include the expression of FimH as an adhesive subunit of type 1 enterobacterial fimbriae (Stahlhut et al. 2009). Fimbriae play an important role in target cell adhesion and invasion of the host. The expression of *Klebsiella* fimbriae is highly associated with K1 serotype isolates. The genome of *Klebsiella pneumoniae* contains nine fimbrial gene clusters, comprising type 1 and type 3 fimbriae and a group of fimbriae termed Kpa, Kpb, Kpc, Kpd, Kpe, Kpf, and Kpg. The Kpc fimbriae are regulated by the site-specific recombinase Kpcl (Wu et al. 2010). *Klebsiella pneumoniae* must acquire iron for replication; for this, it utilizes iron-scavenging siderophores, such as enterobactin, glycosylated enterobactin (salmochelin), and yersiniabactin. Siderophore-dependent iron acquisition systems are implicated in *Klebsiella* virulence, and three are upregulated in *Klebsiella* strains causing KLAS, *Yersinia* high-pathogenicity island, lucABCDiutA, and iroA(iroNDCB) (Hsieh et al. 2008). Yersiniabactin is a virulence factor that is prevalent among *K. pneumoniae* carbapenemase (KPC)-producing strains (Bachman et al. 2011). Hypervirulent *K. pneumoniae* secretes more and more active iron-acquisition molecules than classical *K. pneumoniae*, and this enhances virulence (Russo et al. 2011). The uptake of iron from extrabacterial compartments is regulated by the ferric uptake regulator Fur, which also modulates *Klebsiella* capsular polysaccharide biosynthesis via repression of the expression of rmpA, rmapA2, and rcsA (Lin et al. 2011b). Another *Klebsiella* species that much less commonly causes PLA is *K. ozaenae*, which is generally considered an opportunist of low virulence and colonizer of the respiratory tract implicated in atrophic rhinitis/ozaena (Chowdhury and Stein 1992).

PLA Caused by *Escherichia coli*

In an investigation of 72 patients with *E. coli* PLA, the majority of the abscesses were solitary, involved the right lobe of the liver, and comprised polymicrobial infections. The local cause of PLA involved the biliary tract in 66.7 % of the patients, and the most concomitant diseases were diabetes mellitus (30.6 %) and underlying malignancy (30.6 %) (Chen et al. 2005). Among 202 patient with PLA, there was no significant difference in mortality between patients with *E. coli* and those with *Klebsiella pneumoniae* infections, although for patients with PLA caused by *E. coli*, the APACHE II score at admission, malignancy, and right lobe abscess were significant predictors of death (Chen et al. 2007).

PLA Caused by Other Bacteria

Less common bacteria causing or having been isolated from PLA comprise *Staphylococcus aureus* (Smith et al. 2007), *Pseudomonas aeruginosa* (Goldani et al. 2005), *Enterococcus* species (Thomas et al. 1983), *Bacteroides fragilis* (Lonardo et al. 1992), *Streptococcus mitis* (Sarthe and DiBardino 2013), *Streptococcus anginosus* (Giuliano et al. 2012), *Aeromonas sobria* (Kamano et al. 2003), *Citrobacter koseri* (Gupta et al. 2013), *Aggregatibacter aphrophilus* (Tsui et al. 2012), *Yersinia enterocolitica* (Pulvirenti et al. 2007), *Fusobacterium necrophorum* (Hagelskjaer and Pedersen 1993; Athavale et al. 2002; Thatcher 2003), periodontal bacteria (*Fusobacterium nucleatum*, *Treponema denticola*, *Prevotella intermedia*, *Porphyromonas*

gingivalis; Ohyama et al. 2009), several anaerobic bacteria (Sabbai et al. 1972; Ogah et al. 2012), and a large number of other germs, which have in part been observed in immunocompromised patients.

Staphylococcus aureus is a well-known cause of solitary or multiple pyogenic liver abscesses and is estimated to account for 7 % of infectious liver abscess in case of non-mixed infection. Also other *Staphylococcus* species, e.g., *S. epidermidis*, were identified as causative agents, but much less often. Pyogenic liver abscess may be caused by mixed bacterial infections, a frequent partner of *S. aureus* being *Escherichia coli*. Staphylococcal liver abscesses are commonly medium-sized to large solitary lesions with indistinct ("invasive") borders, but multiple smaller abscesses or even a miliary abscess pattern (so-called microabscesses) has also been encountered. Multiple hepatic microabscesses caused by *S. aureus* can radiologically mimic *Candida* abscesses. An increasing number of hepatic abscesses is caused by the highly virulent methicillin-resistant *Staphylococci*/CA-MRSA, which can cause liver abscesses also in previously healthy adult individuals and in children. PLA caused by *Staphylococcus aureus* seems to be more common in patients with schistosomiasis (Teixeira et al. 2001). An association between schistosomiasis and *Salmonella* infection is also well documented (Lambertucci et al. 2001). In rare instances, PLA contained *Ascaris lumbricoides* (Hamid et al. 2013), a parasite which either induces PLA or moved into an abscess cavity.

Liver Abscesses in Crohn's Disease

Perforating Crohn's disease is characterized by the formation of intra-abdominal abscesses which develop in 20–24 % of patients. However, liver abscess represents a rare complication of Crohn's disease (Fagge 1870; Taylor 1949; Lerman et al. 1962; Watts 1978; Macpherson and Scott 1985; Mir-Madjlessi et al. 1986; Vakil et al. 1994; Kreuzpaintner et al. 2000). In a review of 59 cases (Kreuzpaintner et al. 2000), 72.9 % were men. 62.2 % of the patients suffered from active and 37.8 % from inactive Crohn's disease. In 52.9 % of the patients with active disease, the liver abscess presented as the initial manifestation of Crohn's disease. 47.2 % had a solitary abscess, 9.4 % double abscesses, and 43.4 % multiple abscesses. Microbiological analyses revealed that *Streptococcus milleri* was the dominating pathogen, followed by other streptococci, anaerobes, and enterobacteriaceae.

Pyogenic Abscesses and Necroses Caused by Gas-Forming Bacteria: *Clostridium* Liver Abscess

Introduction

Clostridium infections cover a broad spectrum of illnesses ranging from tetanus and severe and highly dangerous food intoxications to diarrheal disorders and highly aggressive organ and tissue lesions characterized by necrosis and gas-forming lesions (reviews: Maclennan 1962). Certain *Clostridium* species can cause large hepatic abscesses or abscess-like lesions that may mimic hepatic malignancy.

Liver Abscess

Clostridium species are a known cause of liver abscesses, in part with gas formation (Fiese 1950; Kivel et al. 1958; Sarmiento and Sarr 2002; Kurtz et al. 2005; Tabarelli et al. 2009; Ng et al. 2010; Rajendran et al. 2010; Huang et al. 2012; Ogah et al. 2012). Clostridial species causing liver abscess include *C. perfringens*, *C. clostridioforme*, *C. baratii*, *C. septicum*, and *C. welchii*. Among 83 patients with gas-forming pyogenic liver abscesses, 85.5 % of the patients had diabetes mellitus (Chou et al. 1995). The development of a clostridial liver abscess may be favored by the development of a hypoxic/anoxic hepatic area. For example, an abscess caused by *Clostridium perfringens* together with *Hafnia* and *Enterobacter cloacae* infection developed after obliteration of the portal vein by pancreatic cancer tissue (Tabarelli et al. 2009). Gas-forming hepatic abscess can develop as a complication of arterial

infusion chemotherapy (D'Orsi et al. 1979). Clostridial hepatic abscess may show a highly aggressive course, with extension of the abscess into adjacent organs (including the right kidney and the intestinal tract) and induction of portal vein thrombosis (Ogah et al. 2012). Liver abscess caused by C. perfringens can be followed by massive intravascular hemolysis (Kreidl et al. 2002; Au and Lau 2005; Ng et al. 2010), or intravascular hemolysis and septicemia (Rajendran et al. 2010).

Hepatic Gas Gangrene

Hepatic gas gangrene (gangrenous clostridial hepatitis) is an uncommon condition mainly caused by bacterial infection by *C. perfringens* (Fig. 6). It is a life-threatening disorder associated with a mortality rate (Ashley 1965; Birnbaum et al. 2012). The pathologic features of this rare disorder are characteristic. At autopsy, the liver is enlarged, pale, and fatty and feels crepitant. When this liver is put into water, it floats. On sections through the organ, multiple gas-filled spaces or cysts of variable sizes are noted, and sometimes the entire organ has a foamy aspect ("foamy liver"). Histologically, the liver exhibits separation of the hepatocyte plates, similar to far advanced autolysis. The gas-filled spaces are lined by flattened liver cells, and a leukocyte-mediated inflammatory reaction is lacking. Pressure exerted by the gas bubbles may cause crowding of the hepatocyte remnants, with formation of highly cellular areas without any lobular architecture. Gram-positive rods are present in this severely damaged tissue, sometimes in enormous numbers (Ashley 1965).

Clostridial Infection of Liver Metastasis

Colorectal liver metastases undergoing necrosis and forming an anaerobic niche can undergo infection with *Clostridium* followed by tumor abscess and eventually gas formation (Kahn et al. 1972; Saleh et al. 2009; Sucandy et al. 2012). Gas accumulating in the abscess may enter the peritoneal cavity and produce pneumoperitoneum (Urban et al. 2000; Fondran and Williams 2005; Sucandy et al. 2012). In one patient, infection of a hepatic CRC metastasis by *C. septicum* took place following alcohol injection into the liver lesion (Saleh et al. 2009). *C. septicum* infection presenting as a liver abscess has also been observed in a case of choriocarcinoma with liver metastasis (Lee and Hsieh 1999) and in metastases of breast carcinoma (Thel et al. 1994).

Microbiology

Clostridium is a genus of Gram-positive, rod-shaped bacteria belonging to the family *Clostridiaceae*, order *Clostridiales*. The genome of *C. perfringens* has been sequenced, and its genome analyzed in regard to toxin expression

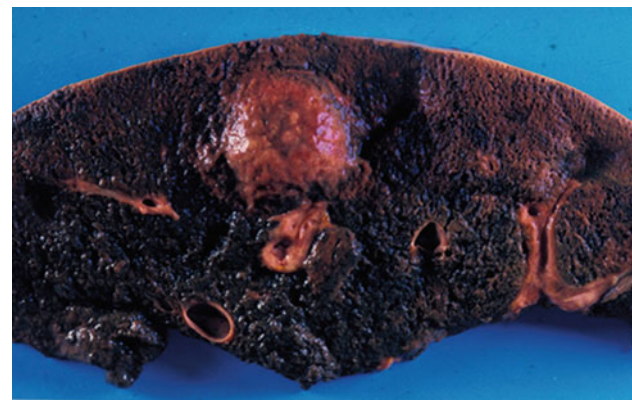

Fig. 6 Tumor-like, bulging, and hemorrhagic liver abscess associated with gas-forming *Clostridium* infection causing numerous gas bubbles in hepatic parenchyma

patterns (Myers et al. 2006). It is an obligate anaerobic group of microorganisms capable of developing endospores. There are about 100 clostridial species, of which a subset is pathogenic to humans, including *C. botulinum* (the cause of botulism), *C. tetani* (the causative agent of tetanus), *C. difficile* (bacterial diarrhea and antibiotic-induced enterocolitis), *C. perfringens/welchii* (gas gangrene), and *C. sordellii*. An increasing number of other *Clostridium* species have recently been isolated from humans, both with clinical manifestations and as isolates from apparently healthy individuals (*C. aldanense*, *C. amygdalinum*, *C. asparagiforme*, *C. baratii*, *C. celerecrescens*, *C. clostridioforme*, *C. fallax*, *C. glycolyticum*, *C. glycyrrhizinilyticum*, *C. hathewayi*, *C. intestinale*, *C. leptum*, *C. scindens*, *C. sphenoides*, and *C. symbiosum*. The clinically important taxon, *C. clostridioforme*, is now a mixture of three species that are different in terms of 16S rRNA sequences, phenotypic characteristics, and antimicrobial susceptibility (Finegold et al. 2005).

Pathogenic Pathways

Clostridium species are commonly found in soil, leaf litter, animal feces, and freshwater sediments, from where they can enter the human organism, either as complete viable bacteria or as spores. In the human host, they most commonly inhabit the intestinal tract.

Virulence Factors

C. perfringens has a variegated system of virulence factors, regulated at the transcriptional level by the products of the virR and virS genes that mainly comprise numerous extracellular toxins including alpha-toxin (phospholipase C), beta-toxin, theta-toxin (perfringolysin), kappa-toxin (a collagenase), and a sporulation-associated enterotoxin (reviews: Smith 1979; Rood and Cole 1991; Rood 1998). The global VirRS two-component signal transduction pathway regulates gene expression of alpha-toxin and perfringolysin O. In this regulatory pathway, the response regulator VirR regulates directly the expression of the theta-toxin/perfringolysin O gene and ccp, encoding the cysteine protease alpha-clostripain (which is not essential for *C. perfringens*-induced tissue necrosis), and indirectly regulates the expression of plce gene encoding the alpha-toxin, the colA gene (kappa-toxin of collagenase), and other genes. Alpha-toxin is a zinc-metallophospholipase C toxin mainly produced by *C. perfringens* and is responsible for necrosis and gas gangrene. It also possesses hemolytic activity and is the key virulence factor of *C. perfringens* infections. It induces the release of IL-8 from host cells through a dual pathway via tyrosine kinase A/TrkA acting on the ERK1/2/NF-kappaB and p38 MAPK pathways (Oda et al. 2012).

C. perfringens toxins affect the function of blood platelets and neutrophils and cause a reduction in blood supply to affected tissues (Hickey et al. 2008), a mechanism that may be important in the pathogenesis of *Clostridium*-induced tissue necrosis. *C. perfringens* beta-toxin is a necrotizing agent and is capable to release catecholamines from the host. The toxin forms potential-dependent, cation-selective channels in lipid bilayers and is a pore-forming agent with cytopathic effects. The *C. perfringens* iota toxin, only produced by type E strains, is an ADP-ribosyltransferase that induces ion-permeable channels in cells. The theta toxin of *C. perfringens* is also termed perfringolysin O. Perfringolysin O is a member of the cholesterol-dependent cytolysin family and a pore-forming agent that requires high concentrations of cholesterol to insert into host cell membranes. After binding to membrane cholesterol and transmembrane protein rafts, it oligomerizes into a prepore structure containing around 50 monomers followed by structural changes to create a rigid transmembrane beta-barrel (review: Nelson et al. 2010). *C. perfringens* epsilon-toxin is produced by type B and D strains and belongs to the aerolysin-like family of pore-forming toxins and is one of the most potent bacterial toxins that can cause fatal toxinemia in animals and eventually humans. Its expression is regulated by the agr operon (Chen et al. 2011). *C. perfringens* produces an

enterotoxin (CPE) which is responsible for the diarrheal signs and symptoms of *C. perfringens* type A food poisoning and antibiotic-associated diarrhea. CPE is 35 kDa polypeptide with an N-terminal toxicity domain that binds to tight junctions and damages their structure and function (McClane 2001). In tight junctions, CPE interacts with occludin, forming a complex that causes the internalization of occludin into the cytoplasm, followed by disruption of the normal paracellular permeability barrier (McClane and Chakrabarti 2004). CPE is a potent cytolytic agent and has been shown to rapidly and specifically destroy cancer cells expressing the CPE receptors, the tight junction proteins claudin-3 and claudin-4 (Kominsky et al. 2004, 2007; Kominsky 2006). *Clostridium* species produce several pore-forming toxins involved in the induction of host cell death and necrosis. The pore-forming alpha-toxin of *C. septicum* can induce programmed cellular necrosis, a distinct form of cell death described also in ischemia/perfusion injury and mediated by a disordered Ca^{2+} flux in target cells (Kennedy et al. 2009). Enterotoxic *C. perfringens* causing disease in birds and particularly in poultry produces a necrotic enteritis B-like toxin or NetB, a member of the beta-barrel pore-forming toxin family (Keyburn et al. 2010). *C. perfringens* strains also express up to three different sialidases which affect the host cell adherence and epsilon-toxin-induced cytotoxicity (Li et al. 2011), but as such are not decisive virulence factors (Chiarezza et al. 2009). Apart from the VirRS virulence factor system briefly discussed above, *C. perfringens* has a second important virulence effector and response regulator termed RevR, which affects cell morphology and regulates the expression of alpha-clostripain, hyaluronidase, and sialidase (Hiscox et al. 2011).

Liver Abscesses and Other Hepatobiliary Lesions in Salmonellosis

Introduction

Salmonella (S.) species cause both acute and chronic infections, depending on bacterial species, strains, virulence, and the host's immune defense system. Salmonellosis is the main cause of bacterial enteritis in humans and animals, and it is estimated that 1.4 million cases of salmonellosis occur among humans in the USA. Chronic infections increase the risk of inflammatory bowel disease and cancer. Typhoid (enteric) fever or *Typhus abdominalis* ("Typhus" in German, not to be confounded with the English term, typhus, which denotes a rickettsial disease) is a severe acute septicemic infectious illness caused by *S. typhi* (typhosa) and *S. paratyphi* A, less often by *S. paratyphi* B and C, and uncommonly by other S. species (review: Bhan et al. 2005). In typhoid fever, involvement of the liver can result in the development of focal lesions that may mimic hepatic malignancy.

Hepatobiliary Involvement

Pathologically, typhoid fever is characterized by a severe and diffuse enterocolitis, associated first with hyperplasia/hypertrophy of the intestinal (Peyer's patches) and lymphonodal lymphatic tissue (during the invasion phase) and then with necrosis and ulcerations of the Peyer's patches toward the end of the fastigium phase. In the course of typhoid septicemia, marked splenomegaly develops.

Salmonellosis and in particular typhoid fever can be associated with several forms of hepatobiliary disease (Table 1). These liver alterations were described in detail in the older literature, but have become uncommon due to the potent treatment modalities now available. The lesions can, however, be still encountered in

Table 1 Hepatobiliary involvement in salmonellosis

Miliary/submiliary typhoid nodules (so-called typhomas) and *Salmonella*-associated granulomatous hepatitis
Miliary hepatic necroses
Microabscesses
Macroabscesses
Typhoid hepatitis
Cholestatic typhoid hepatitis
Cholangitis typhosa (typhoid cholangitis)
Cholecystitis typhosa

regions with poor medical care and/or high exposition to *Salmonellae*.

Miliary Typhoid Granulomas and Salmonellotic Granulomatous Hepatitis

In the course of typhoid fever (*Typhus abdominalis*), submiliary or miliary nodules of whitish to gray-white color (so-called typhomas or typhoid pseudotubercles; Fig. 7) can develop in the liver, often in association with similar nodules in the subperitoneal tissue and the kidneys. In the original observation, these nodules were compared to "lymph follicles" owing to similarities in size, color, and shape (Friedreich 1857; Wagner 1860, as cited in Mallory 1898) and have been related to lymphomas ("miliary lymphomas"; Gruber 1916), but were later found to be specific nodular lesions not exclusively composed of lymphocytes (Fraenkel and Simmonds 1886), but histologically presenting two patterns, i.e., liver necroses surrounded by a neutrophil reaction (Reed 1895) or lesions resembling granulomas as seen in tuberculosis (Joest's "pseudotubercles"; Joest 1914).

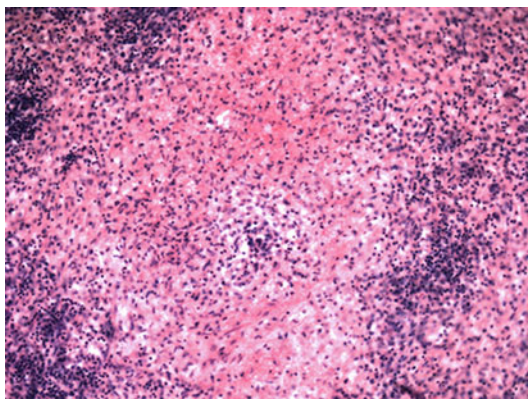

Fig. 7 Hepatic typhoid nodule (typhoid pseudotubercle; "typhoma") in *Salmonella typhi* infection. The granulomatous lesion shows central necrosis and exudation and a peripheral lymphocytic reaction (hematoxylin and eosin stain)

Histologically, these lesions chiefly consist of activated macrophages similar to those found in other tissues in the invasion and fastigium phases of disease (Mallory 1898). These macrophages are sometimes highly activated and enlarged. These are the so-called Rindfleisch cells which may phagocytose *Salmonellae* and/or erythrocytes. These large macrophages were originally described by Georg Eduard von Rindfleisch (1836–1908), a scholar of Virchow who was active in the then Breslau (now Wroclaw), Zurich, and Bonn and intensely worked on typhoid fever (Rindfleisch 1867). Stimulated macrophages may be associated with multinucleated giant cells (derived from macrophages), elements that occur in Peyer's patches, mesenteric lymph nodes, and liver, and detected by Billroth and Grohe in 1861 and Hoffmann in 1869 (cited in Mallory 1898). In the fastigium phase, and similar to Peyer's patches and mesenteric lymph nodes, the macrophage nodules undergo necrosis, sometimes with a central focus of coagulation necrosis, however without caseification, in contrast to tuberculosis. The necroses may a contain a filamentous, slightly eosinophilic network of fibrin-containing filaments, and the granulomas often show a peripheral infiltrate of lymphocytes in a rim of atrophic or decaying hepatocytes (Fraenkel and Simmonds 1886; McCrae and Klotz 1908; Büchner 1956). In case of septicemia and reduced monocyte activated, necrosis of the lesion can increase, associated with epithelioid cell loss, resulting in miliary hepatic necroses that may or may not contain bacteria (Kaiserling et al. 1972). In patients with an intact cell-mediated immunity, and in later stage disease, activated macrophages can form epithelioid cells and granulomas, usually without multinucleated giant cells or only very few giant cells. The granulomas may have direct contact with the lining of terminal vein ("nodular endophlebitis typhosa circumscripta"). These phlebocentric lesions can cause thrombosis of terminal veins and terminal vein obliteration.

Miliary Hepatic Necroses

In some patients with typhoid fever, small and round intra-acinar foci of coagulation necrosis are present in the absence of a significant macrophage reaction. These lesions may have pathogenesis similar to other so-called areactive necroses occurring in the setting of infections, e.g., peracute forms of tuberculosis, and are probably related to a distinct immune status of the host.

Hepatic Macroabscesses and Microabscesses in Typhoid Fever

Liver abscess is a rare, but well-known complication of both enteric typhoid fever and non-enteric *Salmonella* infections. In salmonellosis, liver abscesses are caused by *S. typhi* (Rodriguez and Undurraga 1955; Penaloza et al. 1974; Chogle et al. 1981; Rovito and Bonanno 1982; Petersen 1984; Matar et al. 1990; Soni et al. 1994; Ciraj et al. 2001; Rogers and Wadula 2001; Chaudhry et al. 2003; Chou et al. 2006; Kabra and Wadhwa 2006), *S. paratyphi* A (Rajagopal et al. 2002; Chaudhry et al. 2003; Jeans and McKendrick 2007), *S. enteritidis* (Hirschowitz 1952; Collazos et al. 1991; Elias et al. 1996; Vidal et al. 2003; Sheikh et al. 2011), *S. infantis* (Simmers et al. 1997), *Salmonella* group D non-typhi (Choi et al. 2006), *S. choleraesuis* (Luong and Fournier 1960), and *S. bareilly* (Allegra and Niutta 1957).

Salmonella abscess of the liver may develop within necrotic hepatic tumor metastases (Modol et al. 2006) or hepatocellular carcinoma (Elias et al. 1996; Lee et al. 2002), in intrahepatic hematoma (Cerwenka et al. 1997), via secondary infection of an amoebic liver abscess (Essien et al. 1965; Mansharamani et al. 1971; Marr and Haff 1971; Jeans and McKendrick 2007), and as a late complication of simple liver cyst infection (Gömceli et al. 2006; Sangwaiya et al. 2009). Hepatic *Salmonella* abscess can follow *Salmonella cholangitis* (Holler and Starlinger 1954) and may be combined with splenic abscesses (Chaudhry et al. 2003).

Typhoid Hepatitis

In the course of typhoid fever, a form of acute hepatitis may develop, mimicking viral hepatitis or leptospirosis and rarely ending up with fulminant hepatitis, liver failure, and encephalopathy (Ramachandran et al. 1974; Pais 1984; Ramanathan 1991; Husain 2011; Karoli et al. 2012).

Cholestatic Typhoid Hepatitis

A minority of patients with typhoid fever can develop cholestatic hepatitis, the pathogenic mechanism being unknown (Arabaci et al. 2003; Albayrak et al. 2011; Ratnayake et al. 2011).

Cholangitis Typhosa (Typhoid Cholangitis)

Cholangitis associated with hepatic microabscesses was observed in infections with *Salmonella enteritidis* serovar Choleraesuis (Vogel et al. 2007).

Cholecystitis Typhosa (Typhoid Cholecystitis)

Cholecystitis caused by *Salmonella* is a rare but clinically important complication of *Salmonella typhi* infection (Bender 1946; Avalos et al. 1992; Lai et al. 2006; Ruiz-Rebollo et al. 2008; Ali et al. 2013).

Differential Diagnosis

The main differential diagnosis of hepatic *Salmonella* abscess is abscess formation caused by other bacterial species. In most cases, salmonellosis is nowadays promptly diagnosed, but there are rare situations where liver abscess caused by *Salmonella* may be attributed to other types of hepatic

mass-forming lesions. In patients with septic salmonellosis, hepatic malignancies may mimic (expected) liver abscesses, as the necroses that develop in malignant tumors may resemble cavitated *Salmonella* abscesses on CT images (Hagiwara et al. 2009). Conversely, liver abscesses in septic salmonellosis may be confounded with multiple hepatocellular carcinomas (Simmers et al. 1997).

Microbiology

Salmonella is a genus of rod-shaped, Gram-negative, chemoorganotrophic, predominantly motile bacteria of the family *Enterobacteriaceae*. The bacteria are peritrich, i.e., they have flagella all around their body. *Salmonella* is very closely related to *Escherichia* and occurs worldwide in the environment and in cold- and warm-blooded animals. Most species are facultative intracellular pathogens. There are about 2500 serotypes (serovars) of *Salmonella*, which are allocated to few species. The taxonomy and nomenclature of *Salmonella* species have evolved from an initial one serotype-one species concept, and each serotype was previously considered a separate species, but taxonomy has undergone several revisions. *Salmonella* species formerly included five species, namely, *S. arizonae*, *S. choleraesuis* (the type species of the genus), *S. enteritidis*, *S. typhi*, and *S. typhimurium*. According to the Centers for Disease Control and Prevention (CDC), the genus *Salmonella* contains only two species, each of which contains multiple serotypes. The two species are termed *S. enterica* and *S. bongeri*. *S. enterica* contains the subspecies referred to by a Roman numeral and a name: I, *S. enterica* subsp. *enterica*; II, *S. enterica* subsp. *salamae*; IIIa, *S. enterica* subsp. *arizonae*; IIIb, *S. enterica* subsp. *diarizonae*; IV, *S. enterica* subsp. *houtenae*; and VI, *S. enterica* subsp. *indica* (review: Brenner et al. 2000). Clinically well-known "species" are in part distinct serovars, e.g., the former *S. typhi* is now *S. enterica* subsp. *enterica* ser. Typhi.

What Is Typhoid Fever?

Typhoid fever may present as diarrhea followed by sustained fever, anorexia, vomiting, abdominal distention, headache, and apathy. The illness usually starts after an incubation of 10–14 days, but it ranges from 5 to 30 days, chiefly depending on the size of the infectious dose and the strain's virulence. In the classical medical literature, the first week of clinically manifest infection was termed *Stadium incrementi* ("stage of increase"), characterized by step-wise increase of fever, while the severe *Stadium fastigii* was defined as the stage with continuous high fever (typically 39–40 C). The *Stadium amphibolicum* (third week) was defined as disease with end of continuous fever, with high evening fever and low temperature in the morning. The *Stadium decrementi* ("stage of decrease") was typically in the fourth week of illness and was characterized by lytic fall of fever and decrease of splenomegaly. Today, untreated typhoid fever is usually classified to progress through five stages, i.e., incubation, invasion, fastigium, lysis, and convalescence. In the course of active invasion, patients experience a stepwise elevation in body temperature from day to day, and part of the patients develop rose-colored skin spots grossly resembling petechiae, the roseoles of typhoid fever which have a histologic substrate of perivascular cellular infiltrates, but only rarely minor bleedings. Symptoms and signs are maximum in the fastigium stage, which is also characterized by a continuous fever with only minor daily fluctuations (the well-known "febris continua" or briefly, "continua" of typhoid fever). In the lysis stage, the symptoms start to wane and the fever slowly falls, however still with sometimes extreme daily fever fluctuations. In the convalescence stage, the condition of the patient improves, but fatigue and weakness can continue for a long time period.

Typhoid fever can show several complications, including septic metastases in several organs, osteomyelitis typhosa, nephritis, meningitis, parotitis, orchitis, pneumonia, and hepatobiliary disease. About 3 % of patients develop chronic

typhoid cholecystitis after 1 year, the infected gallbladder forming a reservoir for viable *Salmonellae* (the carrier state).

Pathways of Infection

Salmonella species adhere to host cells through fimbrial adhesins. In the course of cellular invasion, *Salmonella* species interact in a complex manner with the actin cytoskeleton of host cells. Rearrangements of the actin cytoskeleton are brought about by elements of the bacterial type III protein secretion system, a virulence complex which activates the regulatory proteins, Cdc42 and Rac, to produce membrane ruffles that engulf the bacteria, while the pathogenicity island 2/SPI2 translocates effectors that promote intracellular survival and growth, associated with focal actin polymerization around the *Salmonella*-containing vacuole of the host cell (Guiney and Lesnick 2005). *Salmonellae* can also be taken up by host cells through macropinocytosis and phagocytosis, e.g., by luminal neutrophils in the inflamed gut during early infection (Loetscher et al. 2012). Replicating bacteria within host cells can counteract the autophagy pathway and evade elimination via the induction of aggresome-like induced structures through the action of a translocated virulence protein, deubiquitinase (Thomas et al. 2012).

The *Salmonella* type II secretion effector protein AvrA is a multifunctional enzyme having important roles in inhibiting inflammation, regulating apoptosis, and increasing proliferation. In a mouse model of salmonellosis, AvrA expression suppressed intestinal inflammation and inhibited the secretion of the cytokines, IL-12, IFN-gamma, and TNF-alpha. On the other hand, AvrA promoted the bacterium's invasion and was associated with *Salmonella* translocation to the gallbladder and liver abscess formation (Lu et al. 2010).

Host cell death plays a significant role in *Salmonella* infections (review: Guiney 2005). *Salmonella* species can induce cell death through apoptosis, a process dependent of the type III secretion system of the bacterium (Boise and Collins 2001). In particular, intestinal epithelial cells/enterocytes are killed by caspase-dependent apoptosis in salmonellosis, while macrophages undergo a caspase-1-dependent proinflammatory programmed cell death called pyroptosis (Monack et al. 2001; Fink and Cookson 2007).

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