Granulomatous Liver Diseases

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Abbreviations

BCG Bacillus Calmette-Guerin
HIV Human immunodeficiency virus
PBC Primary biliary cholangitis

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14.1 Introduction

The liver is the largest parenchymal organ in the body and a prime target for the formation of granulomas because of its large population of fixed macrophages, the Kupffer cells. Granulomas are defined as circumscribed collections of inflammatory cells, such as activated macrophages, lymphocytes, histiocytes, and plasma cells. The diagnosis of granulomatous liver diseases is made by histological examination of liver specimens. However, the presence of the disease cannot be predicted by clinical symptoms and signs or serological data. The clinical manifestations are due to cytokines released by activated macrophages and lymphocytes. Symptoms are pyrexia, anorexia, night sweats, weight loss, and nonspecific constitutional symptoms. Liver manifestations are hepato-

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megaly and deranged liver function such as elevated alkaline phosphatase. It is often asymptomatic and discovered as an incidental finding.

14.2 Etiology

Granuloma formation is due to bacterial, mycobacterial, rickettsial, chlamydial, fungal, viral, or parasitic infection, immunological disease, hypersensitivity, foreign materials, neoplasm, and other miscellaneous factors (Table 14.1). Sarcoidosis, infection, drug reactions, and primary biliary cholangitis are the four most common causes, accounting for >80% of cases. The incidence of the different etiologies, however, varies according to geographic region, characteristics of the patient population, and biopsy habits of clinicians. Diagnosis of granulomatous liver diseases is determined by its histological findings of caseous or non-caseous necrosis, location in acini, and bile duct injury. Thus the importance of hepatic granulomas lies in the opportunity to diagnose the underlying disease, which dictates prognosis and treatment. [1–3]

14.3 Diagnostic Evaluation

Hepatic granulomas have been classified into four morphologic types [4]. The first type is foreign body granuloma. The second one is lipogranuloma, which forms when histiocytes ingest fat droplets released by ruptured steatotic hepatocytes or in mineral oil lipidosis. The third is an epithelioid type which consists of activated macrophages. These macrophages secreted a large amount of cytokines and are often multinucleated and surrounded by lymphocytes and plasma cells. The fourth is an inflammatory (lymphohistiocytic) type, composed of lymphocytes, plasma cells, and occasionally eosinophils and neutrophils without epithelioid cells.

Pathologically significant granulomas involve the formation of epithelioid cells. However, if the host is immunocompromised, the reaction may take the form of aggregates of foamy macrophages, without the formation of epithelioid cells and with little inflammatory response. Examples include lepromatous leprosy and Mycobacterium avium-intracellulare infection in AIDS patients. Besides epithelioid granulomas, other types of granulomas may not be clinically significant. Kupffer cell granulomas (or microgranulomas) are small and round clusters of unmodified histiocytes and are usual nonspecific findings resulting from the cleanup of necrotic hepatocytes or other debris by Kupffer cells. Bile granulomas, resulting from small clusters of bile-laden and foamy histiocytes, are often associated with surrounding extracellular bile or evidence of cholestasis [5].

The pathologist plays a key role in etiological diagnosis. Infections may often be identified morphologically, even before culture results are available. In suspected drug reactions, the finding of granulomatous hepatitis may serve to confirm the diagnosis. Thus, careful and systematic examination of the pathological specimen is important. This includes assessment of the features described below [6–8].

Table 14.1 Etiology of hepatic granuloma

Infectious		Mycobacteria
		Tuberculosis
		Mycobacterium leprae
		Mycobacterium avium-intracellulare
		BCG immunotherapy
		Brucellosis
		Systemic mycoses
		Candidiasis
		Histoplasmosis
		Parasitic infections
		Schistosomiasis
		Toxoplasmosis
		Rickettsial infections
		Viral infections
		Hepatitis C
		EBV
		CMV
Noninfectious	Immunology disorder	Sarcoidosis
		Primary biliary cholangitis
		Common variable immunodeficiency
	Drugs and chemicals	Beryllium, thorotrast, allopurinol, sulfonamides, phenytoin, carbamazepine, chlorpropamide, quinidine, methyldopa, nitrofurantoin, isoniazid, amiodarone, diazepam
	Malignancy	Lymphoma
		Renal cell carcinoma
	Other cause	Foreign materials

14.4 Distinctive Features of Granulomas

Sarcoid granulomas are characteristically large and noncaseating. They contain Schaumann bodies, asteroid bodies, or calcium oxalate crystals. They often coalesce to form conglomerates and undergo fibrosis. Epithelioid granulomas with a caseous or necrotic center are suggestive of an infective etiology, such as tuberculosis (Fig. 14.1). Associated

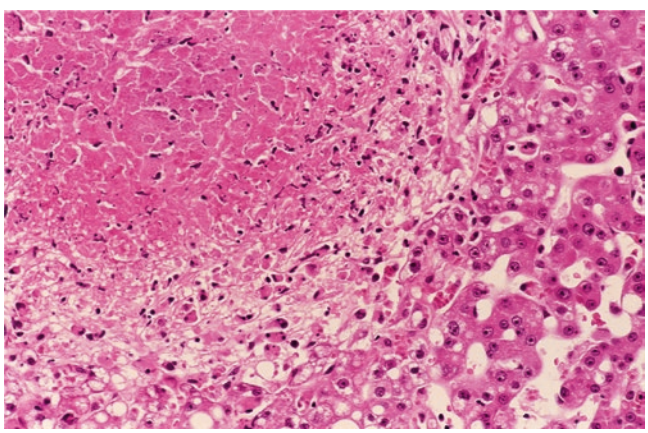

Fig. 14.1 Tuberculosis. Caseous necrosis is commonly present in tuberculous granuloma, and epithelioid cells and lymphocytes are present in the surrounding area

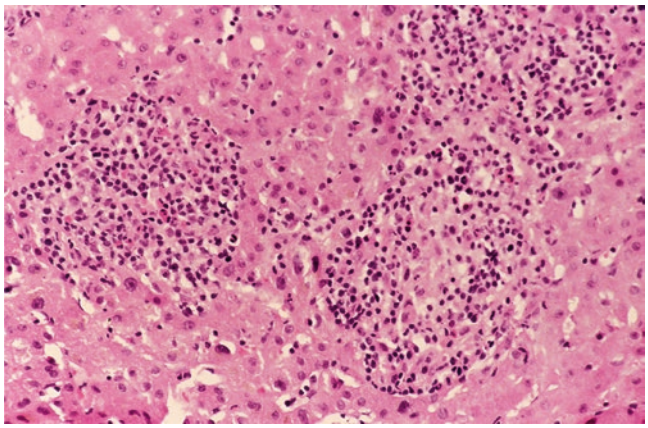

Fig. 14.2 Chlorpropamide-induced liver injury. Abundant eosinophils are seen in granulomas induced by chlorpropamide administration

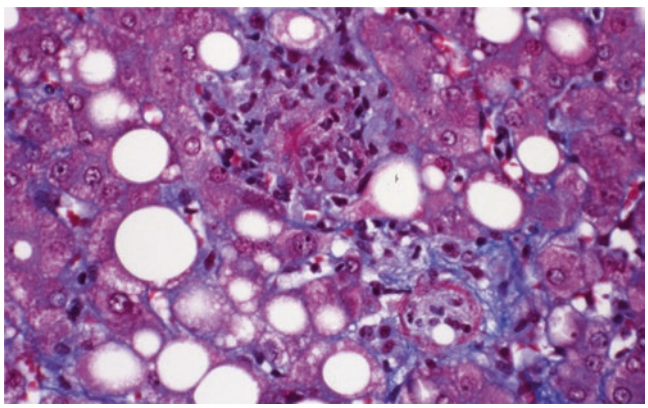

Fig. 14.3 Allopurinol-induced liver injury. Biopsied specimen of liver stained by Masson-Trichrome shows an eosinophilic ring of fibrin in granuloma

suppurative inflammation is commonly due to fungal infection or chronic granulomatous disease. Abundant eosinophils within or at the periphery of the granulomas are observed in acute drug reactions (Fig. 14.2) or parasitic infestation. The presence of fibrin-ring granulomas is characteristic of Q fever [9], but it is also reported in allopurinol-induced injury (Figure 14.3) [10], Epstein-Barr virus [11], cytomegalovirus [12], toxoplasmosis [13], leishmaniasis [14], and Hodgkin's disease [13].

14.5 Acinar Distribution

Sarcoid granulomas are diffusely distributed, though often portal or periportal in location. Granulomas in primary biliary cholangitis and schistosomiasis are mostly portal-based and are related to damaged bile ducts in the former (Figure 14.4) and obliterated portal venous branches in the latter. Granulomas caused by tuberculosis and drug reactions are randomly present in the parenchyma.

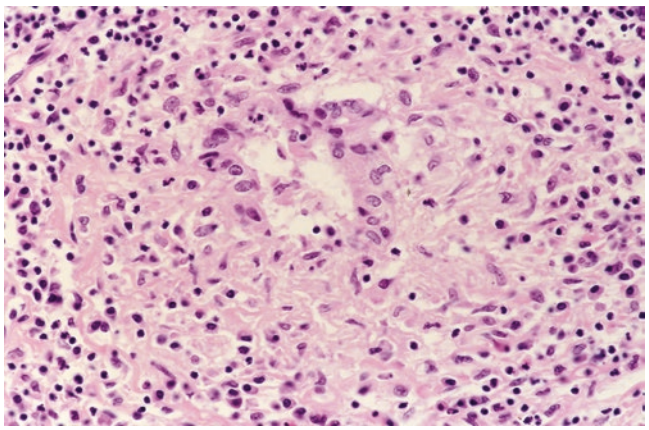

Fig. 14.4 Primary biliary cholangitis. An epithelioid granuloma surrounds damaged bile duct and is accompanied by lymphocytes, plasma cells, and neutrophils in the periphery

14.6 Associated Parenchymal Changes

Infective and drug-induced granulomas may be associated with a true hepatitis-like background. Fungal infection with angioinvasion can cause confluent necrosis or infarction. Bile duct damage and destruction are noted in primary biliary cirrhosis, sarcoidosis, and some drug reactions (Table 14.2).

14.7 Identifiable Etiological Agents

Apart from careful investigation at multiple levels, special histochemical and immunohistochemical stains for microorganisms are invaluable in the evaluation of granulomas. Polarization microscopy should be used to detect foreign bodies. **Polymerase chain reaction** can also be performed on liver specimens for infectious agents.

In many cases of granulomas, however, there are no morphological clues to the diagnosis. Hence, a complete workup needs to be done. Culture should be taken from suitable specimens from the patient, and a detailed drug history must always be taken. Other investigations, such as skin tests and serology, are performed as a diagnostic tool. In spite of these measures, the cause cannot be established in 10–25% of patients.

14.8 Immunological Disease

14.8.1 Sarcoidosis

Sarcoidosis is an inflammatory disorder of unknown etiology characterized by noncaseating granulomas [15]. There is usually no subjective complaint, and in the acute stage, high fever is generally found. Lung and intrathoracic lymph nodes are always affected, and extrathoracic organs are frequently involved. The

Table 14.2 Pathological features of granuloma and liver injury

		Non-necrotizing	Caseating	Location	Giant cell	Bile duct injury	Remarks
Infectious cause	Tuberculosis		+	Randomly present	+		HIV coinfections, drug abuser, multidrug resistance, and immunocompromised host
	Fungal infection		+		± (candidiasis)		Candidiasis - suppurative central necrosis and giant cells
							Aspergillosis - neutrophilic infiltration in granuloma
							Cryptococcosis - inflammatory reaction or granuloma
Sarcoidosis		+		Portal or periportal	+	±	Portal hypertension (±)
PBC		+		Portal		+	Anti-mitochondrial antibody(+) chronic nonsuppurative destructive cholangitis
Drugs and chemicals		+		Randomly present		±	Liver injury(+); hepatocellular, cholestatic, or mixed type
Malignancy		+					

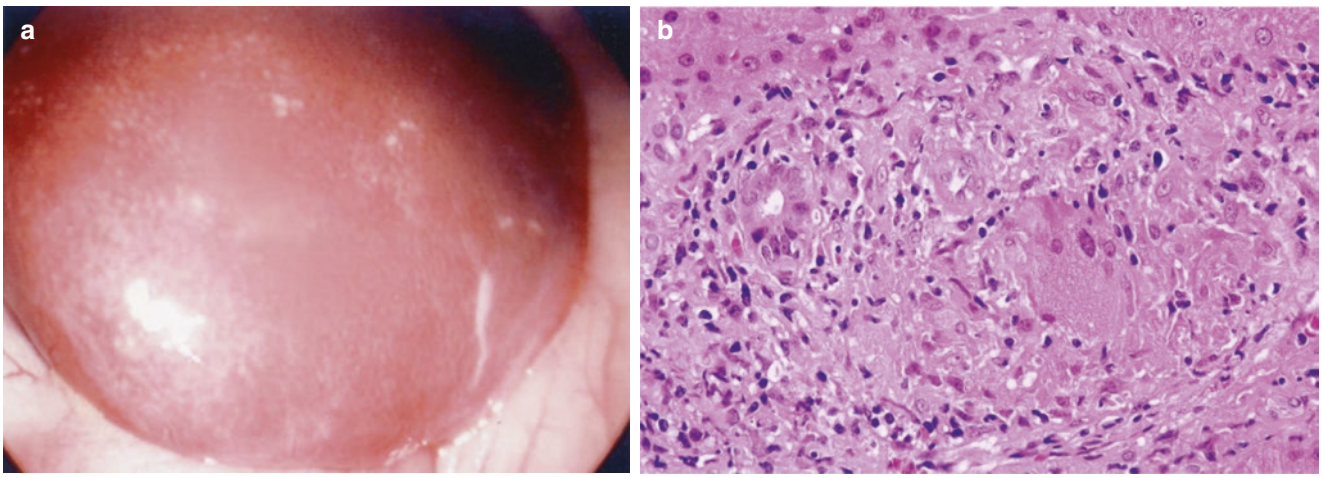

Fig. 14.5 Sarcoidosis. (**a**) Peritoneoscopy shows enlarged liver with granular formations. (**b**) Granuloma is seen in portal tract, and a giant cell is visible in the center, and lymphocytes and histiocytic cells are observed

incidence of hepatic involvement is reported to be 17–90%. Sarcoidosis is often associated with serum elevation of angiotensin-converting enzyme and calcium levels [16], and its diagnosis is frequently established by peritoneoscopy or liver biopsy [17, 18]. Sarcoid granulomas are epithelioid type and are diffusely distributed and tend to be more frequent in portal tracts or periportal area. They consist of aggregated epithelioid cells with multinucleated giant cells surrounded by lymphocytes and macrophages [18]. They often coalesce to form conglomerates, undergo fibrosis, and may be complicated by portal hypertension in 6–8% of patients and primary biliary cholangitis-like lesions. Cirrhotic change can occur by portal inflammation and fibrosis, associated with phlebitis and thrombosis of portal or hepatic veins [19], though it is uncommon [20]. It is necessary to make a diagnosis of hepatic sarcoidosis in the early phase by biopsy. Evidence for the treatment of hepatic sarcoidosis is lacking. Sarcoidosis does not respond well to therapeutic drugs, and corticosteroid administration does not prevent the development of liver lesions; however, it is recommended to treat hepatic sarcoidosis in symptomatic patients by its administration [21]. Liver transplantation is done in some cases complicated with liver cirrhosis, but the disease may recur in the allograft.

Case 14.1

A 26-year-old male complained of high fever. Chest radiograph revealed swelling of bilateral hilar lymph nodes. Uveitis was present. Serum angiotensin-converting enzyme was 33.7 mU/mL. Peritoneoscopy showed white granulomas on the liver surface, while liver biopsy showed granulomas in portal tract; giant cells were surrounded by fibrous tissues with epithelioid cells and rimmed by lymphocytes and macrophages (Figure 14.5).

Case 14.2

Granular shadow in the lower field of bilateral lung was detected in a 28-year-old male by chest CT several years ago (Fig. 14.6a), and his laboratory data showed AST 18 IU/L, ALT 14 IU/L, CRP 0.1 mg/dL, WBC 6100/μL, PLT 27 × 10^4/μL, KL-6425 U/mL, Quantiferon (−), and ACE 15.6 U/L. CD4/

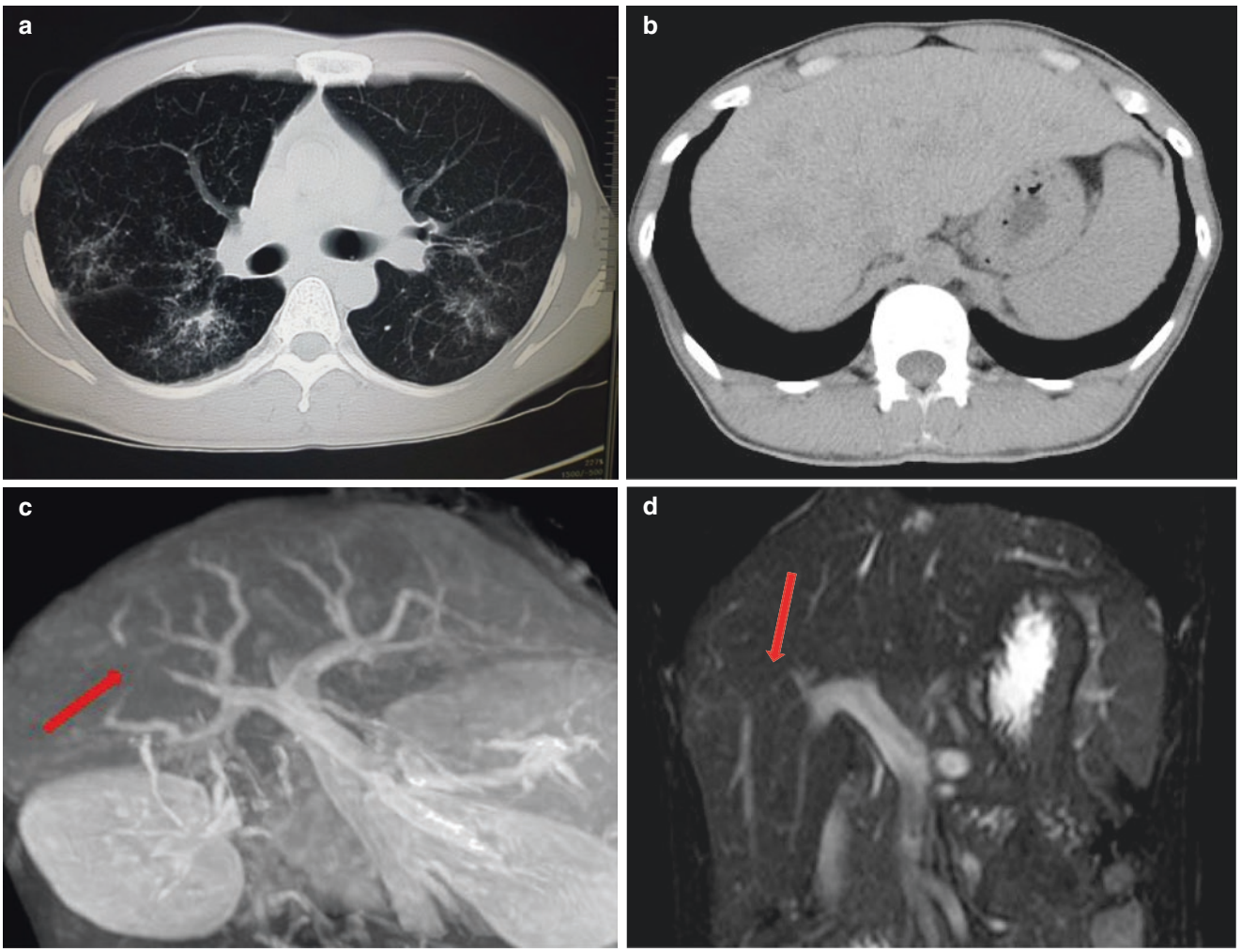

Fig. 14.6 Sarcoidosis. (**a**) Chest CT shows high-density area in lower field of bilateral lung, and granular shadows are detected. (**b**) Abdominal CT without contrast medium shows presence of multiple low-density area in the right lobe. (**c**) MRI with contrast medium shows stenotic area in S8-branch of the portal vein (arrow). (**d**) MRI shows partial interruption of the right hepatic vein (arrow)

CD8 was proved to be high in aspiration tissue taken by bronchofiberscope. Abdominal CT without contrast medium showed presence of multiple low-density area in right lobe (Fig. 14.6b), and low-density area was faintly enhanced by contrast medium in early phase, and enhancement was remained in late phase, and low-density area was seen in enlarged spleen. MRI with contrast medium showed stenotic area in S8-branch of portal vein (Fig. 14.6c), and right hepatic vein is partly interrupted with presence of developing collateral vein (Fig. 14.6d). Liver biopsy under US guidance showed granulomatous lesions with central non-caseous necrosis with giant cells surrounded by mononuclear cells (Fig. 14.7a), and pseudolobular formation was established (Fig. 14.7b).

14.9 Primary Biliary Cholangitis (PBC)

PBC targets the small intrahepatic bile ducts. Chronic nonsuppurative destructive cholangitis is histologically characteristic of PBC. Noncaseating granuloma is seen in about 25% of patient with PBC and is a requisite component of the florid duct lesion in the early stage [22]. Granuloma involves damaged interlobular or septal bile duct in the center surrounded by infiltration of epithelioid cells, plasma cells, lymphocytes, and eosinophils (Fig. 14.4).

14.10 Infectious Cause

14.10.1 Hepatic Tuberculosis

The liver involvement in tuberculosis is histologically classified into miliary, nodule (tuberculoma), and abscess. Miliary pattern is the most common form in the liver and part of generalized or localized disease. Patients with chronic liver diseases due to hepatitis B or C virus, HIV, or alcohol and with a past history of tuberculosis should be examined by biochemical test including albumin/globulin ratio and alkaline phosphatase. Granulomas in hepatic tuberculosis are due to

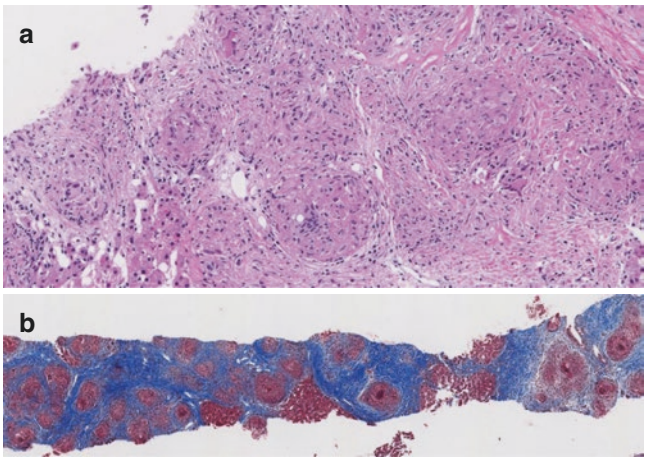

Fig. 14.7 Sarcoidosis. (**a**) Liver biopsy shows multiple non-necrotizing granulomas with giant cells and intermixed mononuclear cells, and granulomatous lesions are cohesive and associated with fibrosis. (**b**) Serial section stained with Masson-Trichrome shows pseudolobular formation

cell-mediated immunological response to tuberculosis antigens; they are well-demarcated and composed of epithelioid cells, lymphocytes (Fig. 14.5), and multinucleated Langhans giant cells. Central caseous necrosis may be observed in large granulomas. Granulomas in AIDS patients are typically absent or poorly formed and lack necrosis due to a dysfunctional immune system. Liver specimen for the diagnosis of hepatic tuberculosis should be stained for acid-fast bacilli or examined by PCR for mycobacterial DNA. Combination of isoniazid, rifampicin, pyrazinamide, and ethambutol is used for the treatment of hepatic tuberculosis. [23–26]

14.10.2 Immunotherapy in Bacillus Calmette-Guerin

Local immunotherapy using an attenuated live strain of *Mycobacterium bovis*, Bacillus Calmette-Guerin (BCG), is effective for bladder cancer. However, intravesical BCG administration sometimes induces granulomatous hepatitis with high value of serum alkaline phosphatase or gamma-glutamyl transpeptidase as a rare and serious systemic side effect, as well as sepsis and pneumonitis after its hematogenous dissemination [27–29]. Formation of granulomas in the liver is considered to be due to hematogenous infection of *Mycobacterium bovis* or its hypersensitive reaction. Granulomatous hepatitis should be treated by combination of isoniazid, rifampicin, and ethambutol. Corticosteroid should be administered when interstitial pneumonia is complicated [30].

Case 14.3

A 65-year-old male suffered from superficial bladder cancer. He was administered bladder instillations with BCG. At the second administration, fever and general malaise developed, and his liver function tests showed TBIL 2.38 mg/dL, AST 195 IU/L, ALT 235 IU/L, ALP 813 IU/L, GGT 340 IU/L, CRP 0.8 mg/dL, and WBC 5900/μL. CT showed hepatomegaly, but neither low-density areas nor dilatation of intrahepatic bile ducts could be detected. Peritoneoscopy showed small, white macular patches on liver surface, with white capsule; liver biopsy showed proliferation of Kupffer cells in sinusoids, a few microvesicular fat vacuoles in hepatocytes and scattered granulomas; and granulomas were noncaseating and comprised epithelioid cells and giant cells, surrounded by lymphocytes or macrophages (Fig. 14.8). A 6-month course of isoniazid plus rifampin was recommended, with administration of pyrazinamide for the first 2 months [31]. His liver function tests returned to normal values, and fever disappeared.

Case 14.4

A 66-year-old male received BCG immunotherapy for early cancer of urinary bladder 13 times for 3 years, and he was admitted because of high fever and general malaise. Liver function test showed AST 46 U/L, ALT 52 U/L, ALP 558 U/L, γ-GTP 148 U/L, and CRP 12.7 mg/dL, and abdominal US and CT showed hepatosplenomegaly (Fig. 14.9a). Liver biopsy showed non-caseous granuloma with presence of giant cells (Fig. 14.9b), and BCG immunotherapy was considered to induce granulomatous hepatitis. INH, EB, and RFP were administered, and liver function test gradually reverted to normal value with alleviation of fever. However, dyspnea developed and CT of chest showed interstitial pneumonia (Fig. 14.9c). Lung biopsy under guidance of bronchofiberscope showed non-caseous granuloma with giant cells (Fig. 14.9d). Thereafter, PSL pulse therapy improved his dyspnea.

14.11 Syphilis Infection

Hematogenous dissemination of the pathogen, *Treponema pallidum*, which causes syphilis takes place in the primary and secondary stages of the disease. Syphilitic hepatitis is found in 10% of those infected.

In secondary syphilis, there is focal liver cell necrosis infiltrated with lymphocytes, eosinophils, and granulocytes, portal inflammation with numerous neutrophils around bile ductules, and epithelioid granulomatous formation. Vasculitis is sometimes seen in portal tract [32].

In the tertiary stage, lesions are gumma-necrotizing granulomas accompanied by plasma cells and endarteritis obliterans leading to fibrous scarring and hepar lobatum. Diagnosis is derived from serological tests for specific antigens, and administration of penicillin is recommended for treatment.

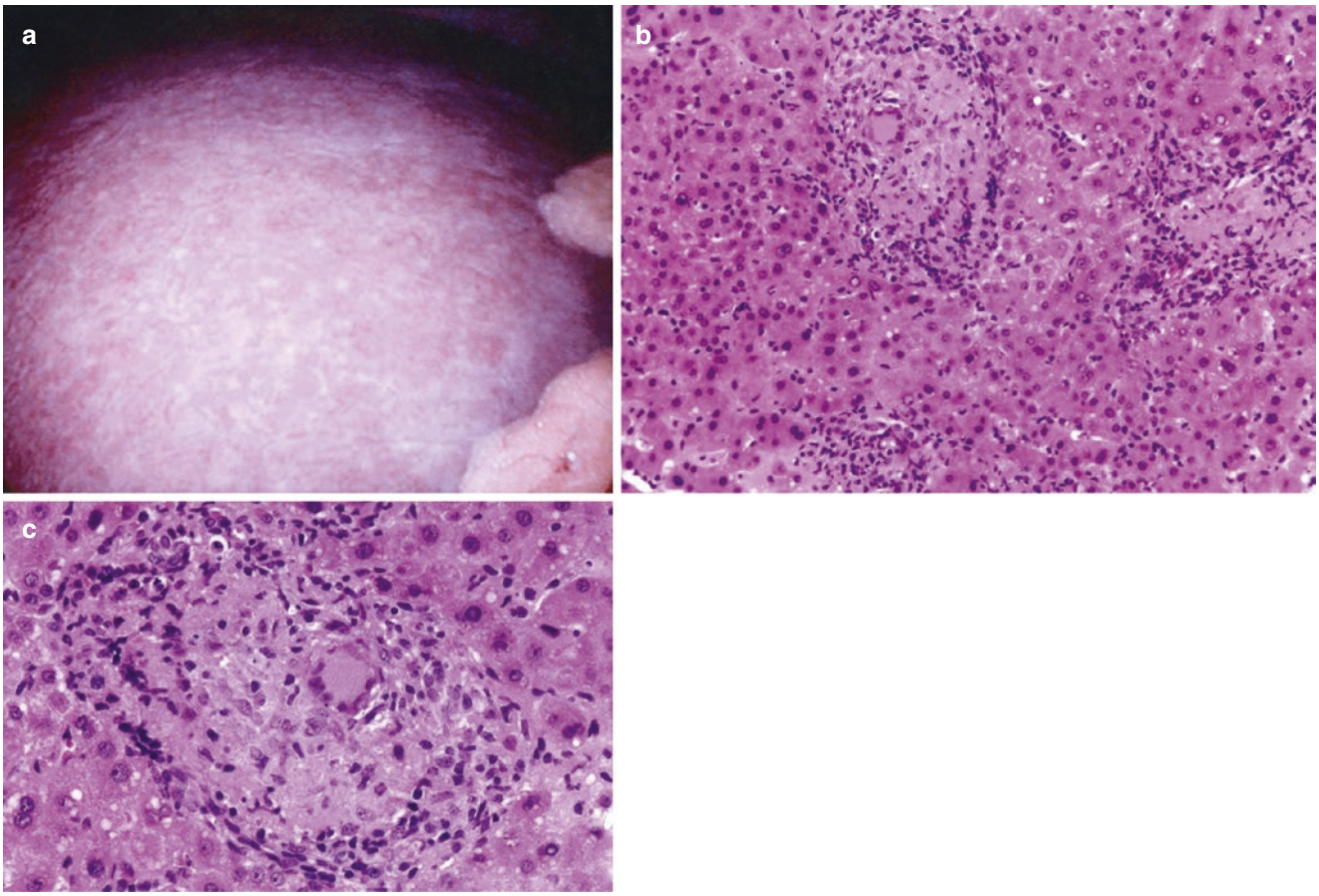

Fig. 14.8 Bacillus Calmette-Guerin immunotherapy-induced liver injury. (**a**) Peritoneoscopy shows diffuse presence of granules on liver surface. (**b**) Granulomatous lesions are visible in the liver. (**c**) Giant cells and epithelioid cells are seen in the center, and lymphohistiocytic infiltrates are observed in peripheral area of granuloma

Case 14.5
An 18-year-old female complained of general malaise, and jaundice was seen. Physical examination showed tonsillitis and erythematous lesions on the foot. Liver function test showed TBIL 5.3 mg/dL, AST 744 IU/L, ALT 678 IU/L, LDH 694 IU/L, ALP 659 IU/L, and GGT 260 IU/L. Rapid plasma reagin and *Treponema pallidum* haemagglutination tests were positive with a titer of 1:16 and 1:1280, respectively. Liver histology showed many inflammatory cells and vasculitis in portal tract, with numerous neutrophils and lymphocytes (Fig. 14.10).

14.12 Schistosomiasis

The great majority of schistosomal liver diseases are caused by *Schistosoma mansoni* in Africa and South America, by *S. japonicum* in Asia, and by *S. mekongi* in Laos and Cambodia [33]. Other species mainly involve bladder or bowel and cause minor non-symptomatic hepatic lesions [34]. Fever, chills, headaches, arthralgia, pain in the right epigastrium, diarrhea, protein-losing enteropathy, weight loss, lymphadenopathy, and urticaria may rarely be manifested in acute infection, due to hypersensitivity [35].

However, the cardinal characteristic manifestations of advanced hepatic disease are related to the development of presinusoidal portal hypertension. Eggs are produced by mature worms in the mesenteric veins, carried to the liver, and trapped in the small portal venules, eliciting a granulomatous reaction. The granulomas consist of lymphocytes, histiocytes, eosinophils, and multinucleated giant cells with ova. The end result is marked portal and periportal fibrosis, described as "clay pipestem fibrosis," and occasionally leads to distortion and scarring simulating hepar lobatum [36]. The obstruction of portal venules due to eggs and portal fibrosis leads to presinusoidal portal hypertension. Egg-laying worms are sometimes present in the intestinal microvasculature of the inferior mesenteric venous plexus, and deposition of eggs in the large intestine induces exudative granuloma resulting in formation of inflammatory polyps, and fibrosis and wall thickening cause stenosis [37]. Clinical features are bloody diarrhea, anemia, and protein-losing enteropathy [35]. Praziquantel or oxamniquine should be administered to prevent schistosomiasis [38, 39].

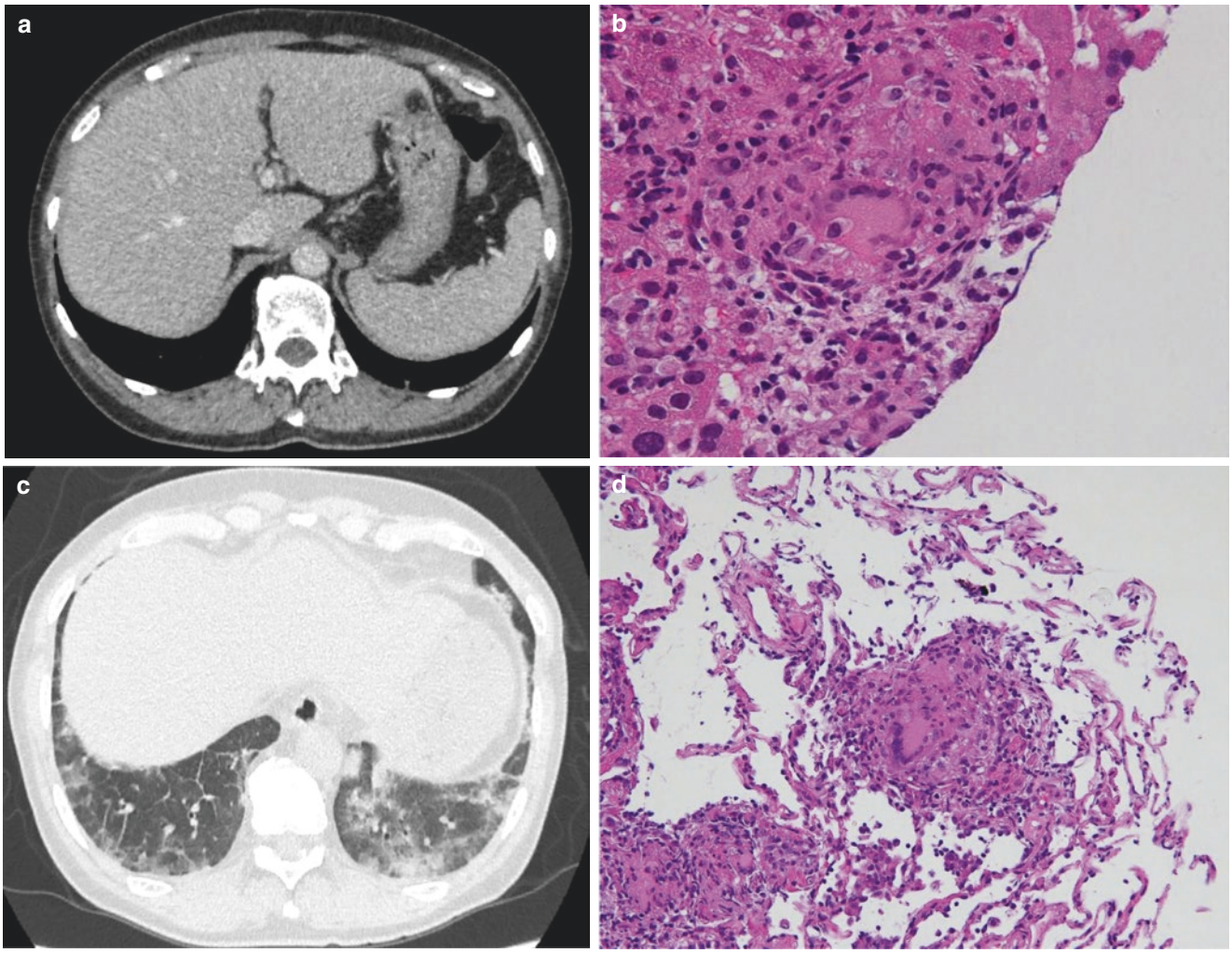

Fig. 14.9 Bacillus Calmette-Guerin immunotherapy-induced liver injury. (**a**) Abdominal CT with contrast medium shows hepatosplenomegaly. (**b**) Liver specimen shows a granulomatous lesion with giant cell. (**c**) Chest CT shows high-density shadows in lower field of both lungs. (**d**) Lung specimen shows a non-caseating granuloma with giant cell

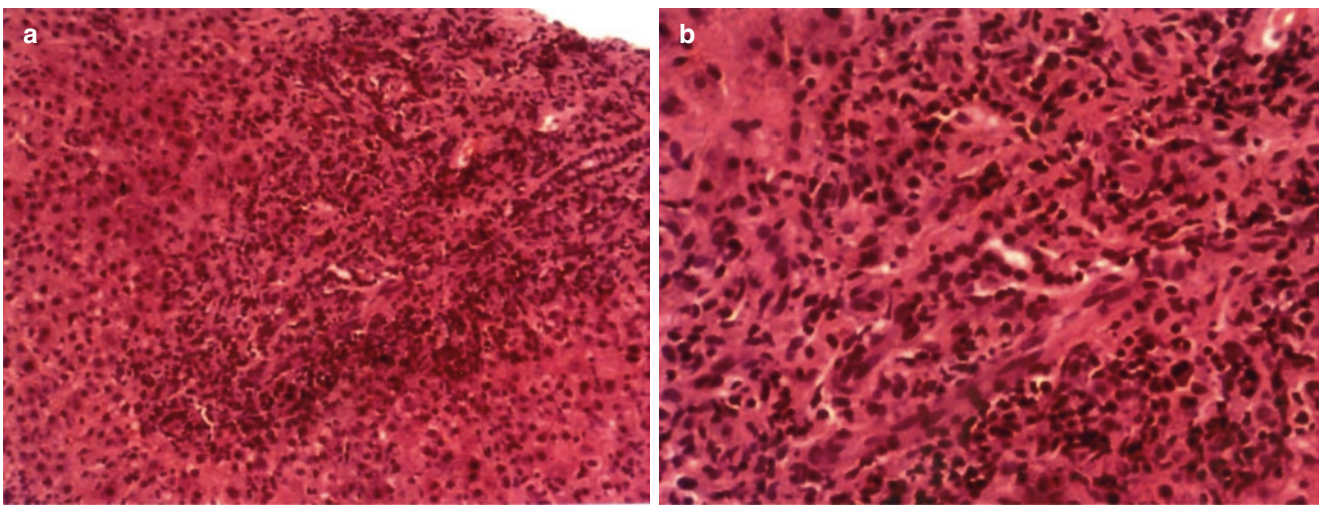

Fig. 14.10 Syphilis. (**a**) Inflammatory cells are present in portal tract, clustering around bile ductules. (**b**) Portal tract is infiltrated by polymorphs and lymphocytes, and vasculitis is seen

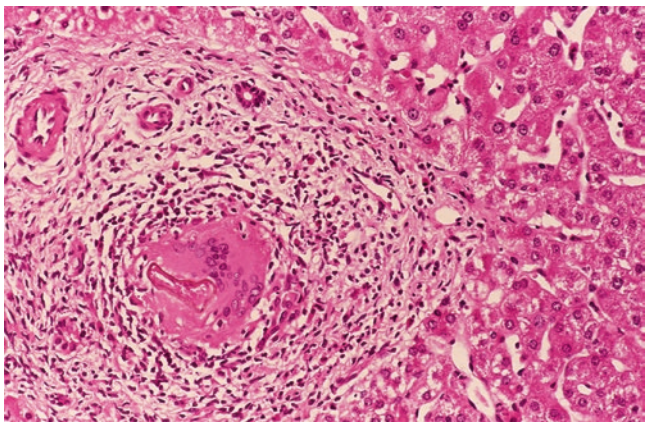

Fig. 14.11 Schistosomiasis. Granuloma is seen in portal tract, and a schistosome egg is ingested by multinucleated giant cell

Case 14.6
A 76-year-old man presented with repeated hematemesis. His liver function was normal. Endoscopy showed bleeding from abnormal vessels in gastric fundus. CT showed splenomegaly and normal-sized liver with no mass lesion. Laparotomy was required to control repeated bleeding from gastric varices. Splenectomy was also performed, and wedge liver biopsy was undertaken to find the underlying cause of portal hypertension. Biopsy showed normal architecture with no evidence of cirrhosis. Portal tracts were enlarged and fibrotic, and many portal venous branches were obliterated. Clusters of schistosome ova were deposited in region of obliterated veins, and an occasional foreign body-type granuloma was noted (Fig. 14.11).

Case 14.7
A 37-year-old female who had stayed in Southeast Asia when she was 18 years old was admitted because of right hypochondriac pain. Liver function test showed AST 123 U/L, ALT 84 U/L, ALP 113 U/L, γ-GTP 50 U/L, and CRP 0.6 mg/dL. Abdominal US showed hyperechoic edges of large or peripheral portal vein (Fig. 14.12a). Liver biopsy showed eggs in portal vein surrounded by fibrosis, and lobular structure is disarrayed (Fig. 14.12b). Colonoscopy showed atrophic mucosa, irregular yellow fleck, and telangiectatic spots (Fig. 14.12c). Colon mucosa showed the presence of eggs in venules, and mucosa was infiltrated by lymphocytes and eosinophils (Fig. 14.12d).

14.13 Drugs

Many drugs and chemicals induce hepatic granuloma with infiltration of eosinophils, and hepatitis, cholestasis, steatosis, ballooning of hepatocyte, and apoptosis are often seen in liver injury. Granulomas usually are small and present within hepatic lobule accompanied by a portal and lobular inflammation. Chemical materials of beryllium and thorotrast and phenylbutazone, allopurinol (Fig. 14.3), phenytoin, carbamazepine, chlorpromazine (Fig. 14.2), methyldopa, isoniazid, amiodarone, and diazepam are known to cause formation of hepatic granulomas [3]. It may be difficult to diagnose a relationship between drug usage and hepatic granuloma formation. However, the resolution of granulomas after discontinuation of the drug is helpful in establishing the diagnosis.

14.14 Lymphomas

Hepatic noncaseating epithelioid granuloma has been reported to occur in patients with Hodgkin's lymphoma and non-Hodgkin's lymphoma [40, 41]. Hepatic lesions are difficult to detect in image analysis. Liver biopsy sometimes demonstrates lymphoid aggregates with atypical cells or Reed-Sternberg cells and sinusoidal dilatation with or without infiltration of atypical cells. Macroscopic findings in the livers of non-Hodgkin's lymphoma patients are classified into disseminated infiltrate in sinusoids, multiple granulomas in the portal tract, multiple macronodules, and solitary tumor mass. The relationship between malignant lesions and the development of hepatic granuloma is not clear. Hepatic granuloma in lymphoma is non-necrotic, and atypical cells are almost present in granulomas and rarely not seen, and the presence of granuloma does not affect the prognosis of lymphoma [3].

Clinical manifestations of patients with malignant lymphomas include high fever, night sweats, weight loss, hepatosplenomegaly, and swelling of lymph nodes. Serum values of alkaline phosphatase and C-reactive protein are high, and lactate dehydrogenase is sometimes elevated. Liver biopsy is recommended for differential diagnosis and staging, and guidance under peritoneoscopy is essential to prevent bleeding. The diagnostic process is described in greater detail in Chap. 15.

Case 14.8
A 93-year-old man complained of unknown fever and had anemia. His liver function test showed AST 11 IU/L, ALT 7 IU/L, ALP 280 IU/L, TP 4.8 g/dL, and CRP 8.3 mg/dL. Peripheral blood examination showed Hb 6.5 g/dL, WBC 3800/μL, RBC 249 × 10^4/μL, and PLT 30.1 × 10^4/μL. Spike in fever remained, and serum test 2 weeks later revealed AST 58 IU/L, ALT 34 IU/L, ALP 3782 IU/L, GGT 110 IU/L, and CRP 17 mg/dL. Liver biopsy showed dilatation of sinusoids filled with red blood cells in middle zone to central area. Granulomas were seen in portal tract (Fig. 14.13), and many atypical lymphocytes were present in clusters. He was diagnosed with lymphoma.

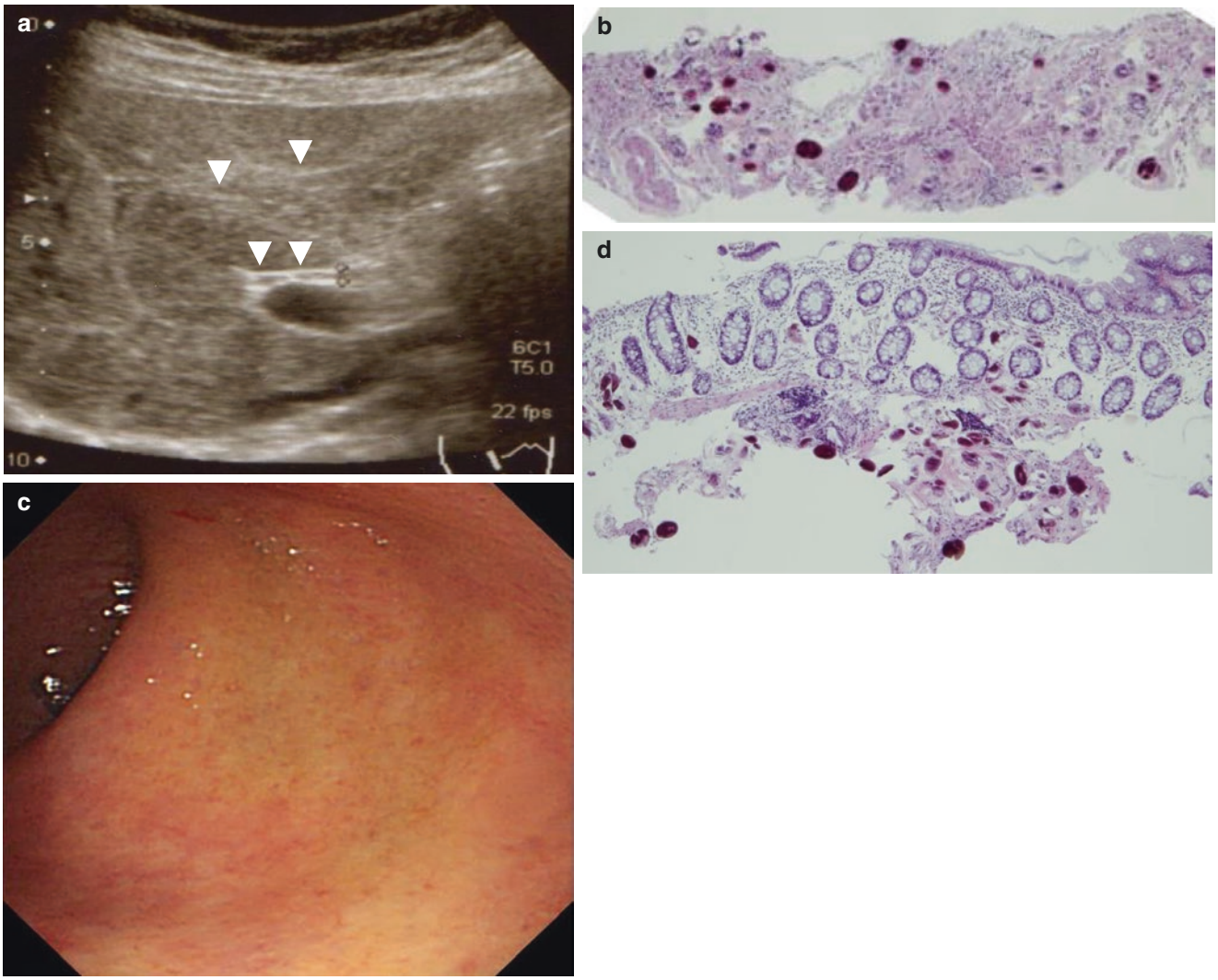

Fig. 14.12 Schistosomiasis. (**a**) Abdominal US shows hyperechoic edges (arrow) of portal vein. (**b**) Liver biopsy shows eggs in portal veins surrounded by fibrosis and infiltrated by inflammatory cells, and lobular structure is in disarray. (**c**) Colonoscopy reveals atrophic mucosa, irregular flecks, and telangiectatic spots. (**d**) Large intestinal biopsy shows presence of eggs in venules and infiltrate of lymphocytes and eosinophils in mucosa and submucosa

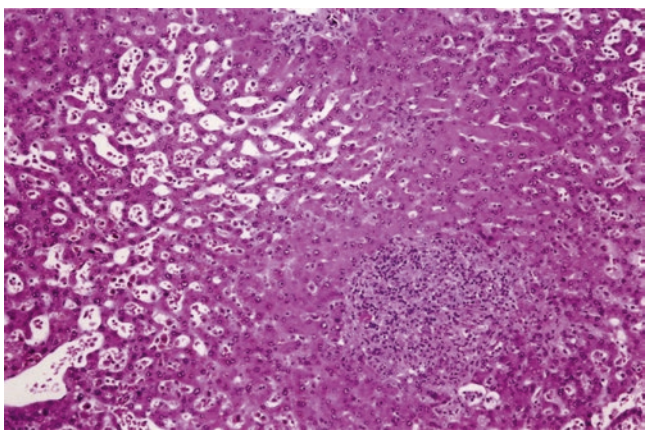

Fig. 14.13 Malignant lymphoma. Liver biopsy shows dilatation of sinusoids filled with red blood cells and atypical lymphocytes in midzonal to centrilobular areas and granuloma in portal tract

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