Leptospirosis

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Leptospirosis, also known as field fever, is an acute infectious zoonosis with natural focus caused by various pathogenic leptospiras. Rodents and pigs are the major sources of its infection, which has an acute onset. At its early stage, the symptoms include high fever, fatigue and weakness, systemic pain soreness, conjunctival congestion, calf tenderness, as well as swelling of superficial lymph nodes. At its middle stage, it is clinically characterized by diffuse pulmonary bleeding and apparent lesions at the liver, kidneys, and the central nervous system. At its advanced stage, most patients can be cured, but some rare patients may further develop fever, ocular uveitis, and occlusive cerebral arteritis. Leptospirosis is a globally distributed disease, more commonly affecting the tropical and subtropical areas.

14.1 Etiology

Leptospira is categorized into the order of Spirochaetales, the genus *Leptospira*, and the family of Treponema. Currently, the genus *Leptospira* is divided into two species: *Leptospira interrogans* and *Leptospira biflexa. Leptospira interrogans* is pathogenic to humans and animals while *Leptospira biflexa* leads a free life. The pathogen of leptospirosis, belonging to the genus *Leptospira,* is pathogenic to humans, livestock, and wild animals. The pathogenic *Leptospira* is slender and cylinder shaped, with 12–18 fine treponemas twining delicately and regularly around. The appearance is just like a watchband with regularly arranged coils. With no flagella, the thallus is curved in a C or S shape, since either or both of its ends bend like a hook. The length of thallus varies from 4 to 20 μm, with a mean length of 6–10 μm and a mean diameter of 0.1–0.2 μm. The leptospira has active movements, which rotates steadily around the long axis with both soft ends and rigid middle part. And the penetrating strength is strong. *Leptospira*, composed of the type-specific antigen and the group-specific antigen, has a complex antigenic structure.

Leptospira is Gram negative. In the past, the bacteria were stained black by the silver staining and light red by the Giemsa staining. Currently, the bacteria can be observed after immunofluorescence and immunoenzyme staining. *Leptospira* has a strong resistance to the environment and can be survive in a cold, humid, and weak base environment for a long period of time. It is very sensitive to dryness, heat, acid, alkali, and disinfectants.

14.2 Epidemiology

14.2.1 Distribution

Leptospirosis affects many areas around the world, mainly prevailing in tropical and subtropical areas. It can be found in 31 provinces, cities, and autonomous regions in mainland China, especially the southwestern area and the southern area of mainland China.

14.2.2 Source of Infection

Rodents and pigs are two major sources of its infection. And they can excrete the bacteria along with urination for a long period of time.

14.2.3 Route of Transmission

There are three major routes of its transmission. In most cases, contract to leptospira-contaminated water is the most important route of its transmission.

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H. Li (ed.), *Radiology of Infectious Diseases: Volume 2*, DOI 10.1007/978-94-017-9876-1_14

14.2.3.1 Contact Transmission

Leptospiras can survive in the body of wild animals for a long period of time. It can spread from livestock to humans and from livestock via wild animals to humans. The urine carrying leptospiras discharged by rats and pigs can contaminate their external environment (e.g., water and soil). Humans with common contacts to the contaminated water or soil are at a high risk of invasion by the bacteria via wounded skin.

14.2.3.2 Transmission via the Nasal Mucosa and Gastrointestinal Mucosa

Leptospiras can be transmitted via mucosa at the gastrointestinal tract, respiratory tract, and reproductive system.

14.2.3.3 Others

Leptospira can infect humans via breast feeding and congenital infection. Humans are rarely infected by bacteria-containing urine from patients.

14.2.4 Susceptible Population

Populations are generally susceptible. Farmers, fishermen, drainage workers, slaughterhouse workers, and animal raisers have higher occurrence of infection due to their common contacts to contaminated water. The persons traveling in the epidemic area are more susceptible than local residents due to their weak immunity. After the infection, the immunity against the same type of pathogens can be acquired. Sporadic cases can be found all year round in high-temperature areas, slaughterhouses, and mining areas.

14.2.5 Epidemic Features

14.2.5.1 Age of Onset

Leptospirosis commonly occurs in young and middle-aged adult farmers, with a peak incidence in the group aged 10–39 years. Male patients account for above 80 % due to their increased chances of infection.

14.2.5.2 Prevailing Season

Leptospirosis commonly prevails in July, August, and September, with a peak incidence in August and September.

14.2.5.3 Types of Prevalence

Prevalence with Rainfall

During the rainy seasons, water tends to deposit both inside and out of the villages. In addition to overflow of feces and urine containing the bacteria discharged by animals, the environment is contaminated with the following possible occurrence of outbreak.

Prevalence in Rice Field

Rats are the major sources of the disease in this prevailing type. When rats eat the rice in the rice field, they may urinate in the field. Thus, farmers working then in the field are more likely to contract the disease via their contact with the contaminated water.

Prevalence with Flood

Flood may wash away the livestock sheds with leptospiras and therefore be contaminated for spreading of the disease. In such prevailing type, outbreak commonly occurs with pigs as the major source of infection.

Sporadic Prevalence

As a variety of animals carrying leptospiras are distributed widely, many areas and places may be contaminated by the bacteria.

14.3 Pathogenesis and Pathological Changes

Leptospira can be divided into several types, all of which have both variant-specific surface antigen and common internal antigen. Different variants have different pathogenicity to humans, with different human organs involved. The relationship between its variants and clinical typing is complex. The same variant may cause different types of clinical symptoms, while the same clinical type of symptoms can be induced by different variants.

14.3.1 Pathogenesis

After invading the organism via skin or mucosa, the leptospiras grow and reproduce rapidly in the blood. In the first week of after onset, the pathogens can be found in the peripheral blood, which are then eliminated by the reticular endothelial system. In the organism, endothelial injuries develop in the small blood vessels and cause vascular bleeding and migration of the leptospiras into the tissues, resulting in relative hypoxia of the tissues. The incubation period usually lasts for 1–2 weeks, followed by the onset of systemic symptoms caused by the toxins released after the reproduction and disintegration of the bacteria.

14.3.1.1 Route of Invasion, Reproduction in the Organisms, and Systemic Toxic Symptoms

After invading into human body via skin wound or mucosae at the oral cavity, nose, intestinal tract, and eye conjunctiva, the leptospiras spread into the blood circulation and different organs (including the cerebrospinal fluid and eyes) via the

lymph vessels and small blood vessels, resulting in bacteremia after rapid reproduction.

14.3.1.2 Organ Damages

The severity of the organ damages depends on the type and virulence of leptospiras as well as the body reactions. Clinically, the conditions are characterized by different clinical types due to prominent symptoms of one certain organ, such as diffuse pulmonary bleeding, icteric bleeding, renal failure, and meningoencephalitis.

14.3.1.3 Nonspecific and Specific Responses at the Middle and Late Stages

The initial response of human body to invasion of leptospiras is characterized by an increased count of neutrophils in the blood and mild inflammatory responses, with no infiltration of white blood cells and no suppuration. The reticular endothelial cells are subject to apparent proliferation with a distinct phagocytic ability. The swelling of superficial lymph nodes can be observed in the groin and other parts of the body. And these responses are nonspecific.

About 1 week after the onset, specific antibodies can be detected, firstly IgM and following IgG. The titers of specific antibodies peak in the first month of the whole illness course. After the emergence of specific antibodies, the symptoms of leptospiremia gradually disappear. However, leptospiras can still survive, reproduce, and be excreted along with urination without being affected by the specific antibodies in the blood. After the immune response is triggered to decrease or eliminate the pathogens in the human body, some patients may experience late-onset fever and late-onset symptoms of the eyes and the nervous system. These manifestations are possibly related to hypersensitivity or the pathogen itself, leptospiras. Some scholars believe that these manifestations are symptoms of remnant infection.

14.3.2 Pathological Changes

The changes of leptospirosis are pathologically categorized into acute systemic toxic lesions, mainly affecting the systemic capillaries and resulting in bleeding and circulatory disturbance of different levels. Meanwhile, severe functional disturbance is caused by extensive degeneration of parenchymal organs and necrosis. The inflammatory responses are commonly mild, with following organ lesions.

14.3.2.1 Lung

Bleeding is the major lesion of the lungs, which is mainly diffusive bleeding with common occurrence in the subpleural area. During recent years, it constitutes the main cause of death in the cases of anicteric leptospirosis. At the surface of lungs, spots and flakes of bleeding can be observed, with mucosal bleeding at the tracheae and bronchi and even interstitial and alveolar bleeding as well as apparent pulmonary edema. Diffuse pulmonary bleeding primarily occurs in the capillaries, which develops gradually from spots to patches and masses. Histological examination demonstrates that intact capillaries in the lung tissues are subject to serious congestion and bleeding. The bronchial lumen and alveolus are filled by red blood cells. In some cases, some alveoli may contain air, possibly with a small quantity of serous fluid exudation. With a purplish-black color, the infected lung is twice or three times as heavy as the normal lung. The section surface is dark red, with overflow of bubble-shaped or dark red bloody fluid.

14.3.2.2 Kidney

The changes of kidneys are pathologically characterized by interstitial nephritis, with swollen kidneys, widened renal cortex, and medullary congestion. Bleeding spots can be observed at the renal pelvis and subcapsular cortex of the kidneys, with blood clots in the renal pelvis in some cases. By microscopy, the main lesions are found at the renal tubules, mostly at the distal convolution and the ascending branch of Henle loop. The epithelial cells at the renal tubules are subject to degeneration and necrosis, with some shedding in the lumen. Lumen obstruction of the renal tubules occurs due to basilar membrane rupture of some renal tubules, dilated renal tubules, and filling of blood cells or hyaline casts in the lumen. By electron microscopy, no changes can be observed in the endothelial cells of the glomerulus, with immune complexes and complement depositing at the basilar membrane of the glomerulus. Edema can be found in the interstitial tissue around the renal tubules, with accompanying infiltration of large monocytes, lymphocytes, as well as rare eosinophils and neutrophils. Leptospiras can be detected in most renal tissues.

14.3.2.3 Liver

The damages to hepatic tissue can vary from mild to severe. The long illness course results in serious damages. In the cases with mild lesions, no apparent changes can be found from the appearance of the liver. By microscopy, mild interstitial edema and vascular congestion as well as sporadic focal necrosis can be observed. In some serious cases, jaundice, bleeding, hepatomegaly, and even hepatic failure occur. Under a microscope, cell infiltration (mainly the neutrophils), swollen hepatocytes, fatty degeneration, and deranged hepatocytes can be observed around the portal area, with accompanying focal necrosis of hepatocytes. Some changes of the liver are pathologically characterized by excretion disturbance of the bile, with hepatocytic necrosis as the less serious lesion. In such cases, slight elevation of serum transaminase can be detected. The occurrence of jaundice may be caused by hepatic inflammation and necrosis as well as obstructed capillary bile ducts and hemolysis.

14.3.2.4 Heart

Myocardial damage is believed to be the major lesion of leptospirosis. Rare bleeding spots and focal necrosis can be observed at the pericardium of patients. By examinations, the myocardium can be demonstrated with hyaline or granular degeneration of the myocardial fibers, usually hydropic degeneration of the myocardial fibers as well as sometimes focal myocardial necrosis and fibrolysis of myocardial fibers. The conditions are commonly accompanied by interstitial inflammation and edema. Electron microscopy demonstrates swollen and empty myocardial mitochondria, with absence of the cristae, blurry and broken muscular filament fibers, as well as absence of the intercalated disk. Vascular damages mainly involve systemic capillaries.

14.3.2.5 Other Organs

Spleen

Generally, the spleen has a normal size but commonly with congestion and small spots or patches of bleeding. The normal structure of the spleen is commonly destroyed.

Adrenal Gland

Bleeding lesions can be frequently observed in the cortex, occasionally with infarct lesions. In most cases, the cortex lipids may be subject to decrease or even absence. Focal or diffuse inflammatory infiltration can be observed at the cortex and medulla.

Pancreas

In the pancreas, necrosis possibly occurs, with surrounding infiltration of neutrophil cells and lymphocytes.

Lymph Nodes

Congestion or bleeding can be discovered in the cervical, supraclavicular, inaugural, and mesenteric lymph nodes, with apparent phagocytosis.

Bone Marrow

The bone marrow can be demonstrated with proliferation of granulocytic system.

Reproductive System

Apparent bleeding can be found at the endometrium, and a small quantity of bleeding is observed at the testis and prostate glands.

Bladder and Ureteral Wall

Spots of bleeding can be observed.

Gastrointestinal Tract

Bleeding occurs at the mouth mucosa, with diffuse congestion and bleeding at the mucosa of the stomach and intestines.

Meninges and Brain Parenchyma

There are congestion, edema, bleeding, infiltration of inflammatory cells, and degeneration of the neurocytes. In addition, cerebral arteritis, infarction, and atrophy may occur.

Skeletal Muscle

The gastrocnemius is observed with swelling, absence of striations, and bleeding, with accompanying sarcoplasmic vacuolation and fusion, only remnant fine particles in the myoplasm, as well as absence of myoplasm and myofibril. The only remained sarcolemma has changed contour due to lytic necrosis. Bleeding and leptospiras can be found in the muscular interstitial tissues. Electron microscopy can demonstrate well-defined structure of the myofilaments as well as swollen mitochondria.

14.4 Clinical Symptoms and Signs

The incubation period generally lasts for 2–20 days, commonly 7–12 days. The clinical symptoms of leptospirosis are extremely complex, ranging from mild with no apparent symptoms to severe with occurrence of death. Factors affecting clinical manifestations include not only the bacterial types or the strain virulence of a same bacteria type but also individual difference as well as immunity of the infected patients. According to Edward and Domm, leptospirosis can be divided into two stages: the septic stage and the immune response stage. In China, Cao divided the illness course into three stages: the early stage, the middle stage, and the advanced stage. The staging of the disease is important to guide the clinical practice, especially the early diagnosis and treatment.

14.4.1 The Early Stage (The Leptospiremic Stage)

The early stage is usually within 3 days after the onset, with the following clinical manifestations.

14.4.1.1 Fever

Its onset is sudden and acute, with accompanying aversion to cold and chills. The body temperature can increase up to 39 °C in a short period of time. Remittent fever is common at this stage.

14.4.1.2 Headache

Headache is apparent, with accompanying systemic myalgia. Gastrocnemius is the most commonly involved muscle.

14.4.1.3 Systemic Upset

Feebleness of legs is commonly observed at this stage.

14.4.1.4 Conjunctival Congestion

Conjunctival congestion is characterized by no secretion, pain or photophobia, and persistent congestion which may persist even after the body temperature returns to normal.

14.4.1.5 Systemic Superficial Lymphadenectasis

It is commonly observed at the groin and armpit. The enlarged lymph nodes are commonly in a size of soybean or horsebean, with tenderness but no congestion, inflammation, and suppuration.

14.4.1.6 Symptoms of the Digestive System

The symptoms include nausea, vomiting, anorexia, and diarrhea.

14.4.2 The Middle Stage (The Organ Lesion Stage)

During days 3–14 after the onset, organ lesion-induced clinical manifestations can be found, including hemoptysis, diffuse pulmonary bleeding, jaundice, extensive bleeding of the skin mucosa, proteinuria, hematuria, cylindruria, renal insufficiency, and meningoencephalitis. The clinical manifestations at this stage constitute the main basis for typing of leptospirosis, which is categorized into pulmonary bleeding type, hemorrhagic icterus type, renal type, and meningitis type.

14.4.2.1 Influenza and Typhoid Type

About 60–80 % of the cases of leptospirosis can be categorized into this type, which is mostly characterized by systemic symptoms. With an acute and sudden onset, the patients experience chills, fever (38–39 °C), headache, conjunctival congestion, and systemic myalgia that is prominently gastrocnemius soreness and pain. There are also symptoms of nasal obstruction, pharyngalgia, and coughs. The clinical manifestations resemble the symptoms of influenza, upper respiratory infection (URI), or typhoid fever. The natural course is usually 5–10 days.

14.4.2.2 Pulmonary Bleeding Type

In addition to the symptoms of leptospiremia, the patients experience coughs, bloody sputum, and hemoptysis. This clinical type can be further divided into common pulmonary bleeding and diffuse pulmonary bleeding according to the range and severity of lesions demonstrated by X-ray radiology as well as the cardiopulmonary manifestations.

Common Pulmonary Bleeding

The clinical symptoms resemble those of leptospiremia, with accompanying hemoptysis and bloody sputum of different degrees. The physical signs of the chest are inapparent. X-ray radiology demonstrates increased pulmonary markings.

Diffuse Pulmonary Bleeding (Massive Pulmonary Hemorrhage)

After invasion of leptospiras into human body, the infected individuals commonly experience an incubation period and a transient period of early infection that commonly lasts for 2–3 days. After that, the patients sustain sudden onset of facial paleness, accelerated heart and breath rate, palpitation and irritation. The conditions may further develop into circulation failure and respiratory failure. At this time, moist rales are overwhelmingly heard at both lungs, and hemoptysis progressively deteriorates. In recent years, they are the common causes of death in the cases of anicteric leptospirosis. X-ray radiology demonstrates diffuse spots and flakes of shadows in both lungs.

14.4.2.3 Hemorrhagic Icterus Type

Most cases are caused by the icterohemorrhagic serotype of leptospira. The clinical manifestation is characterized by hemorrhagic icterus and its mortality rate is high. Jaundice commonly occurs at days 3–7 after the onset and accompanying bleeding of different degrees occurs in 80 % of the cases. This type also features renal and hepatic lesions, with 70–80 % of the cases experiencing involvement of the kidneys. The renal lesions vary from mild symptoms including proteinuria, hematuria, as well as a small quantity of WBC and casts in the urine to severe symptoms including renal insufficiency, oliguria or anuria, acidosis, uremic coma, and even death. Renal failure is the common cause of death in the cases of this type.

14.4.2.4 Renal Failure Type

The clinical symptoms are characterized by prominent renal damages, with manifestations of proteinuria, hematuria, cylindruria, oliguria, anuria, azotemia of different levels, and acidosis. As icterus does not occur in the cases of this type, renal failure in this case can be differentiated from that in the cases of hemorrhagic icterus type. In severe cases, death occurs due to renal failure.

14.4.2.5 Meningoencephalitis Type

The clinical symptoms are characterized by encephalitis or meningitis, with severe headache, systemic pain and soreness, vomiting, gastrocnemius pain, diarrhea, irritation, unconsciousness, neck rigidity, and Kernig sign positive. Before the immune responses, the cell count in the cerebrospinal fluid is not subject to increase, commonly varying from ten to several hundreds per cubic millimeter. In some rare cases, the cell count can reach 1,000/mm^3. In addition, the CSF is also demonstrated with weakly positive protein response and normal levels of sugar and chlorides. The clinical manifestations resemble those of aseptic meningitis.

14.4.3 The Convalescence or Late-Onset Symptoms Stage

After the body temperature returns to normal, various symptoms gradually regress. However, in some rare cases, fever recurs after several days to 3 months to show symptoms, which are known as late-onset symptoms.

14.4.3.1 Late-Onset Fever

After the body temperature returns to normal for 1–5 days, fever may recur, with a body temperature of 38–38.5 °C. In about 50 % of the cases, the count of eosinophil granulocytes in peripheral blood is subject to increase. After being treated or untreated, the patients experience return of the body temperature to normal within 1–3 days.

14.4.3.2 Ocular Late-Onset Symptoms

Such symptoms are commonly found in the cases in northern regions of China. Ocular symptoms commonly occur 1 week to 1 month after the onset of disease and are mainly characterized by uveitis, iridocyclitis, and choroiditis. In addition, episcleritis and retrobulbar neuritis may also occur.

14.4.3.3 Neurological Late-Onset Symptoms

Reactive Meningitis

In some rare cases, the patients experience late-onset fever concurrently with meningitis. However, the cerebrospinal fluid examination bears normal findings. And the symptoms may be self-cured.

Occlusive Cerebral Arteritis

Occlusive cerebral arteritis, also known as moyamoya disease, can be observed in the cases caused by *Leptospira pomona*. It is one of the most common and the most severe neurological complications of leptospirosis. And the cases account for 0.57–6.45 % of all the leptospirosis cases. About 90 % of the patients are children aged below 15 years, and about 10 % of the patients are young and middle-aged adults. The incidence has no significant gender difference, with a delayed incidence peak for more than 3 months after local prevalence of leptospirosis. The symptoms occur within 9 months after the onset of leptospirosis, including hemiplegia, aphasia, and repeated transient paralysis.

Pretibial Fever

In some extremely rare cases, nodular erythema occurs in the convalescence stage at the skin of bilateral anterior tibia, with accompanying fever that regresses within 2 weeks. Its occurrence is closely related to the immune responses.

14.5 Leptospirosis-Related Complications

Generally, complications occur in the early or middle stage of a disease, while late-onset symptoms occur in the advanced stage. The complications of leptospirosis are characterized by ocular and long-term neurological complications.

Uveitis is the most common ocular complication of leptospirosis, mostly anterior uveitis (iridocyclitis) with manifestation of vitreous opacity and white precipitates at the surface of the iris. The second common complication includes retina lesions and optic nerve lesions. Some patients may also experience complications of sclera, pupil, and ocular muscle. Most symptoms occur within 2–8 weeks of the illness course, with favorable prognosis in most cases. However, some rare cases have prolonged illness course or repeated occurrence.

The neurological complications are characterized by advanced cerebropathies, whose occurrence is probably related to disturbance of blood supply to brain tissues caused by narrowed or occlusive cerebral vascular lumen due to anaphylactic reactions. The patients may experience persistent headache, dizziness, and limb numbness after the acute stage. The neurological symptoms, characterized by central nerve-related paralysis and motor language impairment, may occur 2–5 months after the onset. Some patients may experience psychiatric symptoms.

14.6 Diagnostic Examinations

14.6.1 Routine Test and Blood Biochemical Test

14.6.1.1 Routine Blood Test

In the cases with no jaundice, the WBC count and the neutrophil granulocyte count are normal or increase slightly. However, in the cases with jaundice, the WBC count mostly increases, about 50 % of the cases being $(10–20)\times10^9$/L and the highest level being 70×10^9/L. In some rare cases, leukemoid reactions occur, such as increased neutrophil granulocyte count, mostly at a level of 81–95 %. The patients with bleeding may experience anemia and thrombocytopenia, which may have the lowest level of 15×10^9/L. Accelerated erythrocyte sedimentation rate (ESR) is a characteristic laboratory finding of the disease, which may persist for 2–3 weeks.

14.6.1.2 Liver Function Test

In the cases with jaundice, the bilirubin level increases, which fluctuates with the severity of jaundice. In about 2/3 of the cases, the bilirubin level is lower than 342 μmol/L, and the highest level of bilirubin can be up to 1,111 μmol/L. Generally, the bilirubin level continues to increase at week 1 and 2 of the illness course, with following

decrease at week 3 and 4. The serum transaminase level may be found with an increase, whose degree is not parallel to the severity of the conditions. Therefore, the increase of serum transaminase level fails to be a direct indicator for assessment of liver damages. In addition, about 50 % of the cases are demonstrated with increased CPK, whose average value is five times as high as the normal level.

14.6.1.3 Urine Test and Renal Function Test

As leptospiras cause common and severe damages to the kidneys, renal dysfunction of different severities is demonstrated in most patients. By routine urine test, 70 % of the cases is demonstrated with mild proteinuria, RBC, WBC, or casts.

14.6.2 Specific Detection

14.6.2.1 Pathogen Isolation

As leptospiras can be hardly stained, they cannot be directly observed via common microscope. Instead, dark field illumination can be applied for their detection. At week 1 of the illness course, pathogen can be detected in the blood. During this period of time, the blood specimen can be collected from the patient to inoculate in Korthof medium for the culture of pathogens. In such a way, leptospiras are more likely to be detected. Since week 2, the antibodies are gradually produced in the infected human body, with absence of pathogens in the blood. Therefore, detection of pathogen at this time in the blood is almost impossible. However, since week 2, along with gradual increase of the antibody titer in the blood, the positive rate by serological test is increasing. During this period of time, the pathogens are excreted along with urination, which can, therefore, be detected in the urine. Recently, pathogens are directly detected by direct microscopy, immunofluorescence, silver staining, and toluidine blue staining after the bacteria are concentrated by ultracentrifugation. In such ways, fast diagnosis can be achieved, with a positive rate of 50 %, which facilitates the early diagnosis.

Animal inoculation is another reliable way to isolate the pathogens. The blood or other body fluid specimens can be collected from the patient, with following inoculation into the abdominal cavity of experimental animals, such as young guinea pigs or golden hamsters. For the cases at the advanced stage, the urine specimens can be inoculated into subcutaneous area of the abdomen of the experimental animals. Three to five days after the inoculation, the peritoneal fluid should be collected for dark field examination. Otherwise, the blood specimens should be collected from the heart of animals for examination. The positive rate by animal inoculation is comparatively high. However, such an examination needs more time and is costly.

14.6.2.2 Serological Test

Agglutination Lysis Test

Despite high specificity and sensitivity, the agglutination lysis test requires different types of living bacteria for its operation. Generally, lectin occurs 7–8 days after the onset and increases gradually then. A titer of above 1:400 as positive, it can persist for several months to years. The cases with a titer of paired sera every 2 weeks with above four times increase are defined positive.

ELISA

A positive finding by ELISA is earlier than that by the agglutination lysis test, indicating a higher sensitivity. The total consistent rate of agglutination lysis test and ELISA reaches 86.2 %. In recent years, the leptospira-specific IgM antibody technique has been commonly applied, which is characterized by its high specificity.

Indirect Hemagglutination Test (IHT)

IHA has genus specificity for pathogen detection, but with no group or serotype specificities. Compared to the agglutination lysis test, IHT has an earlier positive result. In addition, IHT requires simple operation and no complicated equipment, and it is appropriate to be widely adopted in community-oriented hospitals.

Indirect Hemolysis Test

Indirect hemolysis test has a higher sensitivity than IHA.

Indirect Immunofluorescence

Compared to hemagglutination test, both the detection of antibody and the negative conversion are earlier, which is more valuable for the early diagnosis.

Since the known antigens of leptospiras are applied to detect the corresponding antibodies in the blood specimens, the early diagnosis cannot be defined by these examinations. The following techniques can be applied for the early diagnosis.

DNA Probe for Leptospiras

In 1984, Schoone et al. have demonstrated that DNA probe is a highly sensitive way for the early diagnosis of the disease. Thereafter, it has been clinically applied. The probe is prepared with DNA of Wijnberg strain, Copenhagen type, and icterohemorrhagic group of leptospiras; the homologous DNA of 2 pg can be detected at cellulose nitrate membrane, with cross hybridization to pathogenic leptospiras of Patoc I strain of different serogroups.

Gene Amplification Technique (GAT)

In 1989, VanEys et al. examined bovine urine specimens after their infection by Hardjo leptospiras with PCR

amplification technique. Their conclusion was that PCR DNA amplification technique by PCR is a novel method for the diagnosis of leptospirosis. Such a way has simple operations and is appropriate for large-scale epidemiological investigations.

14.6.3 Diagnostic Imaging

14.6.3.1 Ultrasound

Ultrasound is appropriate for the detection of hepatic, splenic, and renal lesions as well as the examination of heart, lymph nodes, and gastrocnemius.

14.6.3.2 X-Ray Radiology and CT Scanning

X-ray radiology and CT scanning are commonly applied to assess pulmonary lesions.

14.6.3.3 MR Imaging

MR imaging is clinically applied to assess abdominal and neurological lesions.

14.7 Imaging Demonstrations

14.7.1 Lung

14.7.1.1 X-Ray Radiology

In the cases of leptospirosis being classified as pulmonary bleeding type, chest X-ray demonstrates variant lesions at different clinical stages. The lesions are demonstrated chronologically as thickened lung markings, miliary shadows, nodular shadows, patches of shadows, and flakes of fused shadows.

The Early Stage

X-ray demonstrates no obvious abnormalities, with only increased and blurry lung markings and occasional scattered small nodular blurry lesions (Fig. 14.1).

The Middle and Advanced Stages

X-ray demonstrates miliary and nodular shadows diffuse in both lungs, mainly in the middle and lateral parts of the middle and lower lung fields. Most shadows are densely contributed at the lateral parts. The lung apex is commonly well defined. Along with progress of the conditions, pulmonary bleeding increases and the nodular shadows fuse together to form small and large flakes of high-density shadows with extremely blurry boundaries. The lesions may involve the lung apex (Fig. 14.2).

In some cases, pleural effusion is demonstrated as unilateral pleural effusion in a large quantity or bilateral pleural effusion in small quantities. The lesions are symmetrically distributed, with concurrent shallow bilateral costophrenic angles. In some cases, interlobar fissure effusion can be demonstrated as long stripes of shadows.

The Convalescence Stage

Reexamination by X-ray after 1 week medication of sensitive penicillin, the patients demonstrated with spots and flakes of hemorrhagic lesions absorbed.

The summary of imaging demonstrations is as follows:

1. Lesions are more likely to be distributed in the lateral parts of both lungs than in the middle and medial parts, namely, positive splay sign.
2. Multiple nodular shadows can fuse into flakes of shadows. And the primary nodular shadows (the bleeding spots) can be defined via the uneven flakes of shadows.
3. The lung apex and base are well defined, and the lesions are rarely distributed around the hilum.
4. In most cases, the transparency of both lung fields is evenly decreased to produce ground glass opacities, which are caused by pulmonary bleeding due to toxic damages of the pulmonary capillaries induced by toxins produced by leptospiras or direct damages from leptospiras.
5. The development and absorption of the lesions are rapid, with daily changes.
6. In some cases, X-ray demonstrations are inconsistent with severity of clinical symptoms.

Case Study 1

A male patient aged 53 years experienced high fever with a body temperature of 40 °C, coughing up little sputum, myalgia, and headache. After hospitalization, he experienced septic shock and respiratory failure. Serological test demonstrated leptospira positive, with a leptospira titer of 1:1,600.

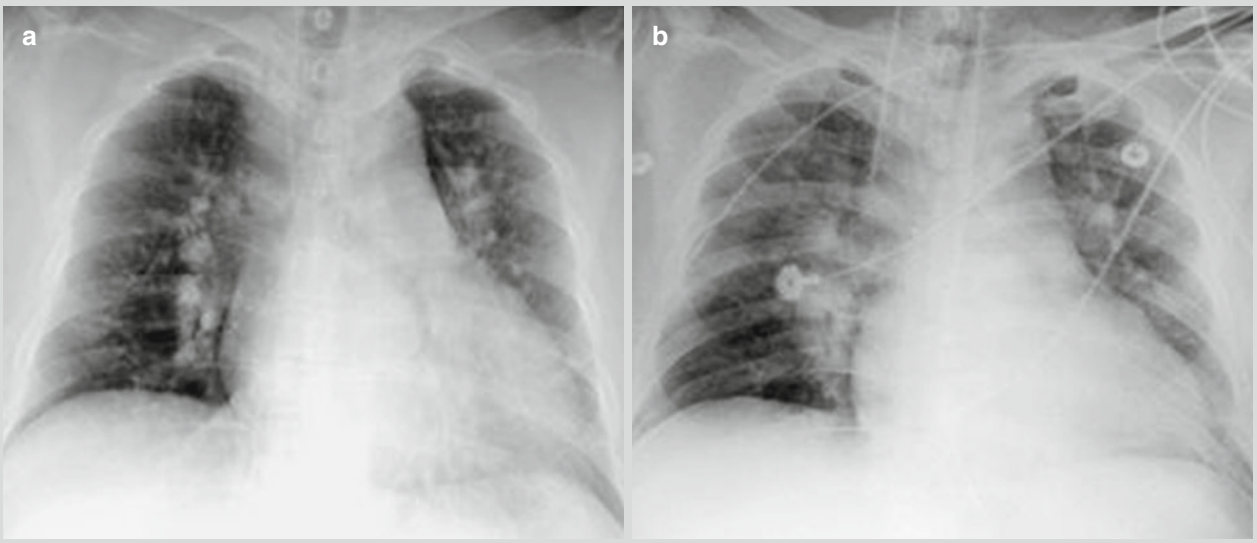

Fig. 14.1 Leptospirosis with pulmonary bleeding. (**a**) X-ray at day 1 of hospitalization demonstrates enlarged heart shadow and small patches of shadows in the left upper lung. (**b**) X-ray at day 2 of hospitalization demonstrates development of the conditions, with patches of blurry shadows in both lungs (Reprint with permission from Wei YF, et al. *J Microbiol Immunol Infect*, 2012, 45 (3): 251)

Case Study 2

A 46-year-old male vagrant reported a history of sleeping in a forest and eating food bitten by rats 5 days ago. He experienced nausea, diarrhea, myalgia, dizziness, headache, hemoptysis, and high fever with a body temperature of 39 °C. Leptospira was detected in his blood.

For case detail and figures, please refer to Luks AM, et al. *Chest*, 2003, 123 (2): 639.)

Case Study 3

Two cases of adult males were diagnosed with leptospirosis with pulmonary bleeding.

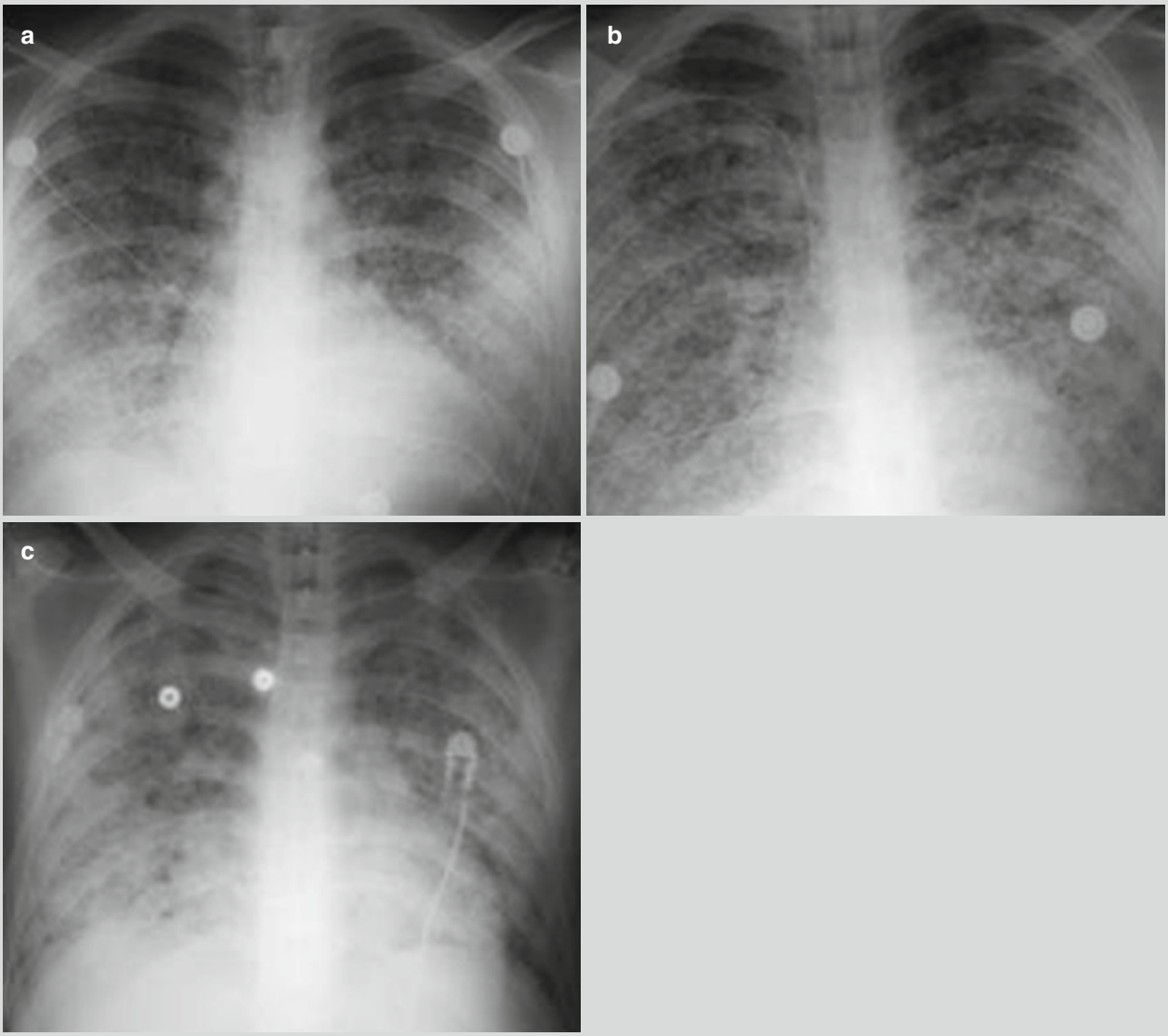

Fig. 14.2 Leptospirosis with pulmonary bleeding. (**a**) X-ray demonstrates nodular shadows with poorly defined boundaries in the lateral parts of both lower lungs. Some nodular shadows are demonstrated with fusion and the lung apex is comparatively well defined. (**b**) At the development stage, both lungs are demonstrated with diffuse nodular shadows. (**c**) Another case of leptospirosis with pulmonary bleeding at the middle or advanced stage. The nodular shadows are demonstrated with fusion in both longs to form diffuse patches of shadows (Reprint with permission from Ketai L, et al. *Thorac Imaging*, 2006, 21 (4): 265)

14.7.1.2 CT Scanning

CT scanning is superior to X-ray in demonstrating bleeding lesions. By CT scanning, the bleeding lesions are demonstrated as fine spots of shadows due to small volume of bleeding. Along with the increased volume of bleeding, the fine spots of shadows gradually fuse and are enlarged to form small patches, cotton-like, mass-like, and even patches of shadows with extremely blurry boundaries (Figs. 14.3 and 14.4). Meanwhile, in the cases with larger range of bleeding but rare intra-alveolar bleeding, CT scanning demonstrates lesions as ground glass opacities. As bleeding is dynamic and progressive, early demonstrations by radiology may be shadows with uniform morphology. However, in the advanced stage, shadows of various morphologies are demonstrated with mixed existence.

Case Study 4

A male patient aged 19 years experienced headache, neck pain, muscular pain, fever, nausea, vomiting, hemoptysis, and respiratory failure.

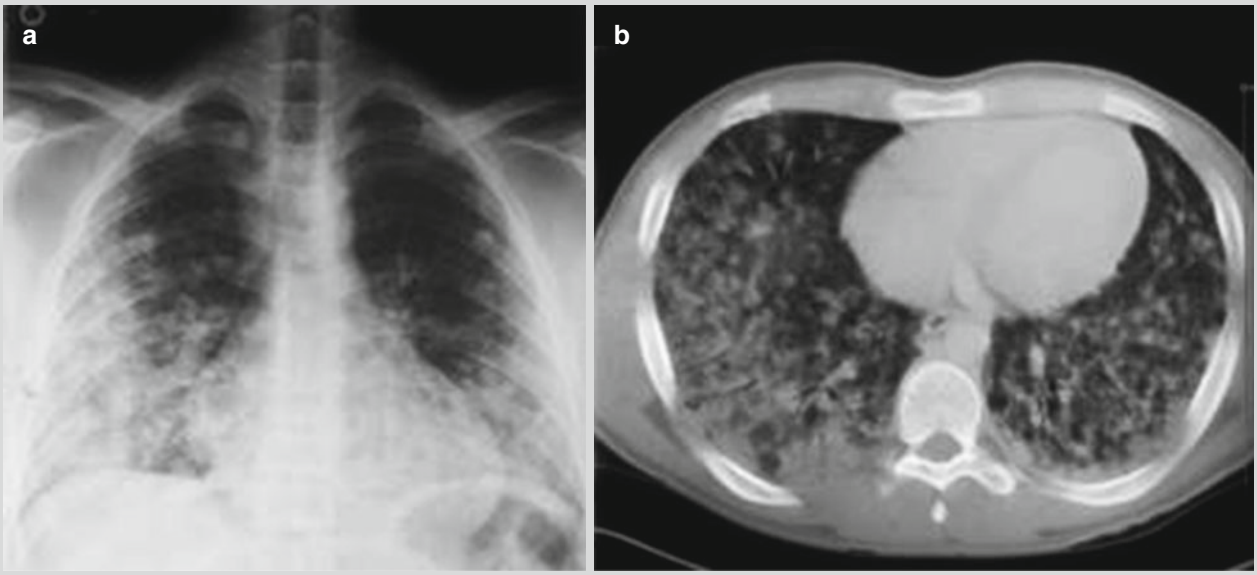

Fig. 14.3 Leptospirosis with pulmonary bleeding. (**a**) X-ray demonstrates patches of blurry shadows in bilateral middle and lower lung fields. (**b**) CT scanning demonstrates alveoli and interstitium of both lungs with infiltrative inflammation (Reprint with permission from Kishimoto M, et al. *Am J Med Sci*, 2004, 328 (2): 116)

Case Study 5

A male patient reported a history of contact to contaminated water by infected rats. He experienced high fever, headache, myalgia, hemoptysis, and jaundice. Bronchoalveolar lavage (BAL) demonstrated pulmonary bleeding. Serological test demonstrated positive.

For case detail and figures, please refer to Marchiori and Müller. *J Thorac Imaging*, 2002, 17 (2): 151.)

Case Study 6

A male patient reported a history of contact to contaminated water by infected rats. He experienced high fever, headache, myalgia, hemoptysis, and icterus. Autopsy demonstrated the diagnosis of leptospirosis.

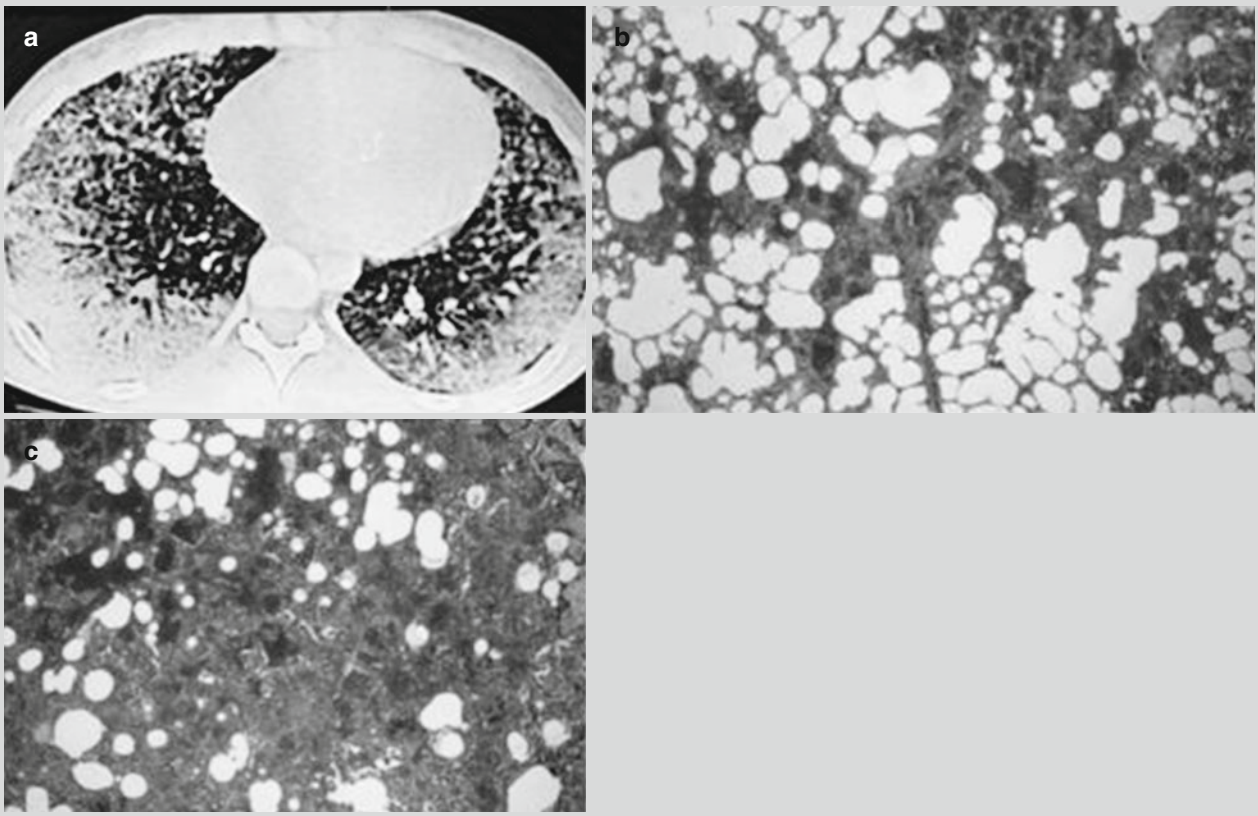

Fig. 14.4 Leptospirosis with pulmonary bleeding. (**a**) HRCT demonstrates ground-glass and nodular shadows in both lungs and consolidation shadows in the subpleural area. (**b**) Autopsy under low-power microscope demonstrates extensive pulmonary bleeding (Reprint with permission from Marchiori and Müller, J *Thorac Imaging*, 2002, 17 (2): 151)

14.7.2 Liver

14.7.2.1 Color Doppler Ultrasound

Color Doppler ultrasound demonstrates mild to moderate hepatomegaly, smooth liver capsule, and weakened and unevenly distributed echoes from the liver, with quite clearly defined vascularization.

14.7.2.2 CT Scanning

CT scanning demonstrates enlarged liver and multiple low-density lesions in the liver (Fig. 14.5).

Case Study 7

A 61-year-old male farmer experienced fatigue, right upper abdominal pain, and hepatomegaly. Endoscopy demonstrated ulceration at the transverse and ascending colon. Abdominal CT scanning demonstrated multiple low-density lesions in the liver, with slight ring-shaped enhancement. The initial diagnosis was hepatic metastasis of colon carcinoma. However, no malignancies were detected by biopsy of colon and liver tissue. Thereafter, the patient reported a history of close contacts to pigs. The antibody titer of leptospiras was then detected high.

For case detail and figures, please refer to Granito A, et al. *World J Gestroenterol*, 2004, 10 (16): 2455.

Case Study 8

A male patient aged 62 years experienced fever with a body temperature of 39 °C, icterus, nausea, vomiting, fatigue, and dizziness. By dark field microscopy, leptospiras were observed.

For case detail and figures, please refer to Kaya E, et al. *World J Gestroenterol*, 2005, 11 (28): 4447.

Case Study 9

A boy aged 10 years complained of headache, fever with a body temperature of 37 °C, abdominal pain, and fatigue for 10 days as well as language impairment for 6 days. Physical examination demonstrated hepatosplenomegaly. He was also detected leptospira positive.

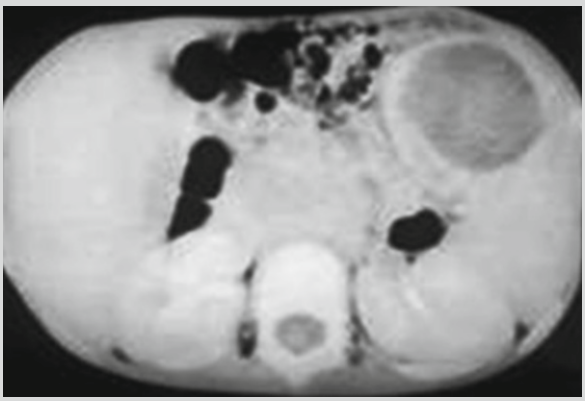

Fig. 14.5 Leptospirosis with hepatic and splenic lesions. CT scanning demonstrates the swelling of spleen, with a size of 6 cm × 4 cm

14.7.3 Brain

Cerebral leptospirosis is a series of clinical symptoms with manifestations of neurological damages caused by leptospiras. The illness course can be divided into the organ lesion stage (the middle stage or complications stage, hereinafter referred to as the cerebral lesions in the complications stage) and the convalescence stage (the late-onset symptoms stage, hereinafter referred to as the cerebral lesions in the late-onset symptoms stage). The lesions of these two stages may coexist, and their clinical manifestations can be hardly distinguished. The relationship between the imaging demonstrations and clinical symptoms is analyzed as the following.

14.7.3.1 Cerebral Lesions at the Complications Stage

The clinical manifestations are characterized by symptoms of encephalitis and meningitis, with severe headache, vomiting, irritation, unconsciousness, neck rigidity, and Kernig sign positive. The imaging demonstration features diffuse cerebral lesions. CT scanning demonstrates normal density, slightly low density, or diffuse cerebral edema. MR imaging demonstrates diffuse multiple spots and flakes of low or equal T1WI signal and high T2WI signal. The signs of demyelination are sometimes demonstrated.

14.7.3.2 Cerebral Lesions in the Late-Onset Symptoms Stage

The symptoms are clinically characterized by reactive meningitis or occlusive cerebral arteries, with manifestations of hemiplegia, aphasia, and multiple repeated transient paralysis. Cerebral angiography demonstrates stenosis of the involved vascular vessels. The imaging demonstrations feature diffuse or focalized lesions. Multiple diffuse lesions are commonly distributed in different areas of unilateral blood vessels, with equal or low T1WI as well as high T2WI signals. Occasionally, the lesions can be found at the interface of cortico-white matters, with typical manifestation of infarction. Local lesions are mostly characterized by signs of cerebral infarction (Fig. 14.6).

Case Study 10

A female patient aged 13 years complained of headache and irritation for 7 days as well as unconsciousness for 3 days. Her body temperature was 36.9 °C. Leptospira was detected positive.

For case detail and figures, please refer to Kurtoğlu MG, et al. *Tohoku J Exp Med*, 2003, 201 (1): 55.

Case Study 11

A male patient aged 43 years experienced gradual progressive instability, respiratory tract infection (RTI), ataxia, and dysarthria. He reported to have a working environment close to ditch. Examinations of the blood and cerebrospinal fluid demonstrated leptospira positive and he was clinically diagnosed with chronic leptospiral vasculitis.

For case detail and figures, please refer to Brinar and Habek. *Clin Neurol Neurolsurg*, 2010, 112 (7): 625.

Case Study 12

A male patient aged 51 years experienced fever with a body temperature of 38 °C.

For case detail and figures, please refer to Babamahmoodi and Babamhmoodi. *Casereport Med*, 2011, 2011: 504308.

Case Study 13

A male patient aged 17 years experienced multiple organ failure and hematemesis. ELISA demonstrated leptospira IgM positive.

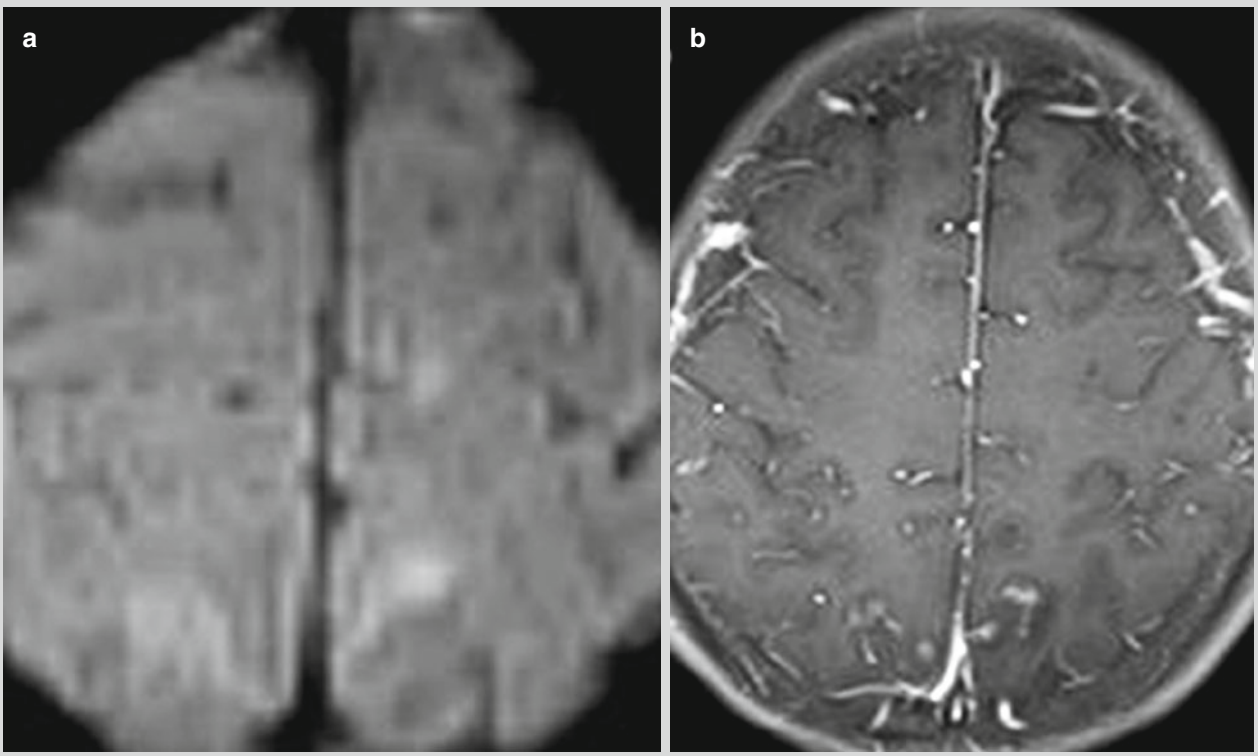

Fig. 14.6 Leptospirosis with cerebral lesions. (**a**) DWI demonstrates strips of high signals at the bilateral parietal lobes, suggesting restricted diffusion and subacute infarction. (**b**) Contrast imaging demonstrates gyri-like enhancement. (**c**–**d**) SWI demonstrates multiple spots of low signals at the supratentorial white matter, basal ganglia, callosum, pons, and cerebellum, suggesting slight bleeding (Reprint with permission from Naphadeps, et al. *J Infect*, 2012, 64 (5): 538

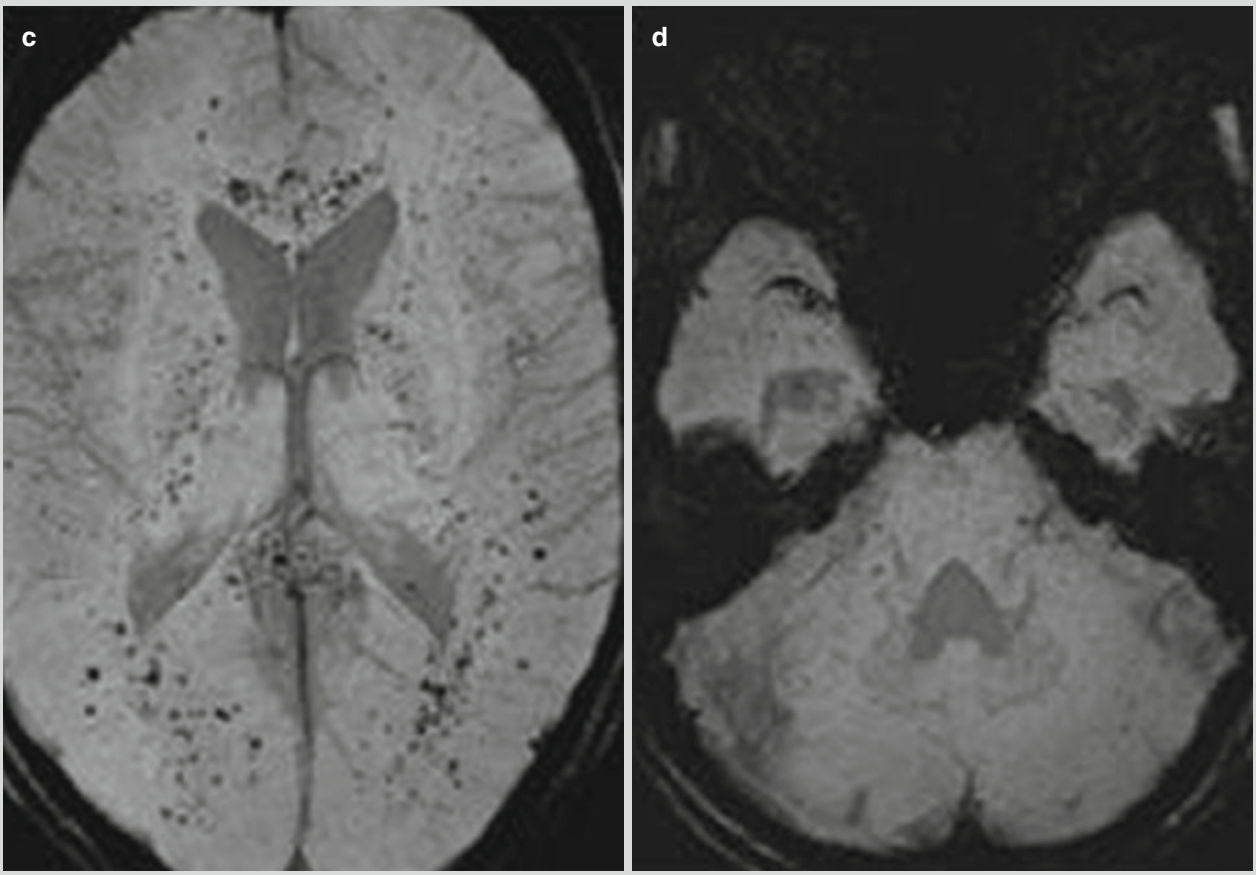

Fig. 14.6 (continued)

Case Study 14
A patient was diagnosed with neurological leptospirosis. He/she experienced acute fever, aversion to cold, headache, and vomiting. Serological test demonstrated leptospira antibody positive.

For case detail and figures, please refer to Matthew T, et al. *Indian J Med Res*, 2006, 124 (2): 15.

14.7.4 Imaging Demonstrations of Lesions at Other Organs

14.7.4.1 Spleen
Color Doppler ultrasound demonstrates enlarged spleen with weakened and even echoes. The splenic artery and vein are subject to slight thickness, with increased blood flow volume. More vascular distributions can be observed in the spleen.

14.7.4.2 Kidney
Color Doppler ultrasound demonstrates bilaterally enlarged kidneys with intact capsule and thickened cortex. The echoes from cortex are weakened with uneven distribution, which can be hardly distinguished from those of the medulla. Less vascular distributions can be observed in both kidneys, with increased resistance at the renal artery.

14.7.4.3 Myocardium

Color Doppler Ultrasound
Color Doppler ultrasound demonstrates enlarged left cardiac ventricle. The activities of the left ventricular wall and interventricular septum diffusively decrease, with shrunk and thickened myocardium. The heart rate decreases and the myocardium is demonstrated with uneven echoes. The range of mitral valve motion is decreased. CDFI demonstrates slight regurgitation signals at each valve orifice, with decreased velocity of the blood flow.

X-Ray Radiology
X-ray demonstrates enlarged heart shadow and existence of cardiac arch. The enlarged heart shadow can also be flask shaped, with absence of cardiac arch.

14.7.4.4 Superficial Lymph Node
Color Doppler ultrasound demonstrates inaugural and subaxillary swollen lymph nodes, with multiple round- or oval-shaped low-echo nodules that have clearly defined boundaries. The enlarged lymph nodes are demonstrated with thickened cortex, central location of the medulla, and more vascular distributions.

14.7.4.5 Gastrocnemius
Color Doppler ultrasound demonstrates thickened bilateral gastrocnemius and poorly defined running course of the striated muscle. The weakened echoes are unevenly distributed.

14.8 Diagnostic Basis

14.8.1 Epidemiology

In epidemic regions during summers and autumns, the acute infectious cases with similar clinical manifestations and a history of contact to contaminated water in recent 1–2 weeks should be suspected as leptospirosis. In non-epidemic regions, sporadic occurrence may be reported due to contact to secretions by infected rats and other host animals.

14.8.2 Clinical Manifestation

At the early stage, the disease is characterized by acute infection, with chills and fever, pain and soreness, fatigue, conjunctival congestion, myalgia, and lymphadenalgia. At the early stage, the patients may also experience digestive symptoms, respiratory symptoms, and bleeding tendency.

14.8.3 Laboratory Test

14.8.3.1 Peripheral Blood
The total count of WBC and the count of neutrophil granulocytes slightly increase, with accelerating ESR.

14.8.3.2 Serum Agglutination Test
The serum agglutination test is positive.

14.8.3.3 Blood Culture
The pathogen grows slowly by blood culture.

14.8.3.4 Urine Test
Urine test demonstrates mild proteinuria. Microscopic urinalysis demonstrates WBC, RBC, and casts. Most patients experience accompanying azotemia.

14.8.4 Radiology

14.8.4.1 X-Ray Radiology and CT Scanning
Patient with pulmonary bleeding is demonstrated with ground-glass opacities at both lungs. Otherwise, diffuse spots, flakes, or fused flakes of shadows are demonstrated at both lungs.

14.8.4.2 Ultrasound and CT Scanning
Patient is demonstrated with enlarged liver, multiple low-echo or low-density lesions in the liver, enlarged spleen, and enlarged kidneys.

14.8.4.3 CT Scanning and MR Imaging
CT scanning demonstrates normal-density, slight low-density, or diffuse cerebral edema. MR imaging demonstrates multiple diffuse spots and flakes of abnormal signals at the gray and white matters, which are low T1WI signals in most cases, equal signals in some rare cases, and high T2WI signals of all the cases. Demyelination can be occasionally observed.

14.9 Differential Diagnosis

As the clinical manifestations are complex, its early diagnosis is challenging and the disease tends to be misdiagnosed. Its clinical diagnosis requires positive result by etiological or serological test in combination to epidemiological data, early clinical manifestations, laboratory tests findings, and imaging demonstrations. The disease should also be differentiated from other diseases.

14.9.1 Fever

It should firstly distinguished from other diseases with acute fever, such as typhoid fever, influenza, upper respiratory infection, acute schistosomiasis, scrub typhus, pneumonia, epidemic hemorrhagic fever, and sepsis. In addition to the clinical symptoms, the epidemiological history commonly provides hint for the differential diagnosis. The occurrence of proteinuria and azotemia provides important basis for the differential diagnosis. For the cases of bronchopneumonia, chest X-ray demonstrates spots of shadows distributing in the middle and medial parts of bilateral middle and lower lungs along the lung markings, with poorly defined structure of the hilum, which facilitate the differential diagnosis.

14.9.2 Icterus

The disease should also be differentiated from icteric hepatitis. Generally, the cases of icteric hepatitis have a chronic onset, with prominent digestive symptoms such as poor appetite, but with no conjunctival congestion and gastrocnemius tenderness. The body temperature is usually normal or shows low-grade fever, with slightly low or normal WBC count in most cases and no accelerated ESR. ALT and AST levels indicating the hepatic function are obviously abnormal, with no increase of serum creatine kinase. However, leptospirosis has reverse manifestations. The epidemiological history and serological test also provide valuable evidence for the differential diagnosis. Concerning obstructive icterus, it commonly has no development course of acute infectious diseases with fever. CT scanning and MR imaging mainly demonstrate dilated biliary duct system above the obstruction or accompanying cholecystectasis. The diagnostic criteria include dilation of the intrahepatic bile duct by at least 3 mm or the diameter of common bile duct exceeding 10 mm, with acknowledged causes of obstruction such as neoplasm, calculus, and inflammation. Routine urine test and blood nonprotein nitrogen (NPN) test also facilitate the differential diagnosis from other icteric diseases. Renal changes commonly occur in the cases of leptospiral icterus, while the patients with other types of icteric diseases seldom experience renal changes.

14.9.3 Nephritis

For the cases of leptospirosis that show renal lesions but no icterus, it should be differentiated from nephritis. Leptospirosis has similar development course with other acute infectious diseases with fever, with conjunctival congestion, apparent myalgia, normal blood pressure, and no edema.

14.9.4 Myalgia

Myalgia should be differentiated from acute rheumatic fever (ARF). ARF features migrating joint pain, while leptospirosis features myalgia, prominently gastrocnemius.

14.9.5 Bleeding or Hemoptysis

Leptospirosis with bleeding should be differentiated from upper gastrointestinal bleeding, hematuria, as well as hemorrhagic hematosis such as leukemia, thrombocytopenia, and aplastic anemia via peripheral blood test, bone marrow examination, and GI examination. Other hemorrhagic sepsis commonly have severe illness course and a high mortality rate, which can be epidemiologically distinguished from leptospirosis. Leptospirosis with hemoptysis should be differentiated from tuberculosis, bronchiectasis, and tumors via chest X-ray radiology and CT scanning.

The key points for the differential diagnosis of pulmonary bleeding by X-ray radiology are as follows.

14.9.5.1 Acute Hematogenous Disseminated Pulmonary Tuberculosis

Acute hematogenous disseminated pulmonary tuberculosis has a long illness course, with mild symptoms and slow progress. In the cases of acute miliary tuberculosis, X-ray demonstrates three evens, even and wide distribution of the miliary lesions in both lungs, with even density and even size. In the cases of subacute hematogenous disseminated pulmonary tuberculosis, chest X-ray demonstrates widely distributed lesions with different sizes, which are mainly miliary lesions and mostly distributed in the middle and upper lungs.

14.9.5.2 Diffuse Alveolar Carcinoma

Alveolar carcinoma usually occurs in an elderly age group, which originate from bronchiolar epithelium. Chest X-ray demonstrates miliary nodules with different sizes that distribute diffusely in both lungs, with poorly defined boundaries and uneven density. Vacuoles can be observed between the nodules.

14.9.6 Meningoencephalitis

Both leptospirosis with meningoencephalitis and epidemic encephalitis B prevail in summers and autumns and can be hardly distinguished. With severe conditions, epidemic encephalitis B commonly occurs in children, with more obvious cerebral symptoms than leptospirosis, such as convulsion and comma. Patients with epidemic encephalitis B experience no apparent conjunctival congestion or gastrocnemius tenderness. The WBC count is relatively high, with normal findings by routine urine test and liver function examination. The patients usually have no case history of contact to contaminated water. Epidemic encephalitis B has characteristic CT demonstrations of low-density lesions at bilateral basal ganglia and hypothalamic area. In addition, the cerebral peduncle is commonly involved, but rare involvement of the cerebral cortex, brain stem, and callus. MR imaging demonstrates long T1 and long T2 signals at the corresponding positions, with slightly high FLAIR signals, mostly high DWI signals, and rarely slightly high DWI signals.

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