Influenza A (H1N1)

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In March 2009, an outbreak of human-infected swine influenza occurred in Mexico, with reports of deaths. Soon afterward, such cases were reported worldwide, namely, a pandemic outbreak. The prevailing disease is then defined as an acute respiratory infectious disease caused by swine-origin influenza A (H1N1) virus, a new variant of influenza virus. Its viral strains contain gene segments of three types of influenza viruses, namely swine influenza virus, avian influenza virus and human influenza virus. And the virus is mainly transmitted among humans via direct and indirect contact or respiratory tract.

This new virus is originated from pigs. Initially, WHO nominated such influenza as "human-infected swine influenza." However, such a nomination may cause misunderstandings about intake of pork and pork products. And such a nomination may even involve certain issues about religions and beliefs. Therefore, the influenza is known as "North American Influenza" by the World Organisation for Animal Health, "New Influenza Virus" by the European Union, "Mexican Virus" by South Korea and Israel, and "Mexican flu" by New Zealand. In China, it was initially nominated as "human-infected swine influenza," and "New H1N1 influenza" in Taiwan. In order to avoid misleading the public, the WHO declared on 30 April 2009 in Geneva that the nomination of "swine influenza" is terminated and the disease is renamed as "Influenza A (H1N1)."

On 11 June 2009, the WHO raised the pandemic alert level of influenza to Phase 6. By 21 March 2010, according to the WHO official website, the laboratory confirmed cases of influenza A (H1N1) had been reported from more than 213 countries and regions including at least 16,931 deaths. By 7 March 2010, according to data from China, 127,427 confirmed cases had been reported from 31 provinces in mainland, including 8320 severe and critical cases, and 796 deaths. The death rate of the pandemic of influenza A (H1N1) is 0.4–6.77 %, being higher than that from common influenza.

4.1 Etiology

The main pathogen causing influenza is the influenza virus, which can be categorized into the family of Orthomyxoviridae and the genus of influenza virus. Influenza viruses are composed of envelope and segmental single-stranded negative RNA. The virus consists of three parts, namely, from the outside to the inside, the envelope, matrix protein (M protein), and the core. According to matrix protein antigens, genetic characteristics, and virus nucleoprotein particles, the influenza viruses can be classified into type A (A), type B (B), and type C (C). Influenza A can cause seasonal epidemics in certain regions and may even lead to a worldwide pandemic outbreak.

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Influenza A (H1N1) virus is a single-stranded RNA virus which is categorized into the family of Orthomyxoviridae and the genus of influenza A virus. According to different antigenic characteristics of hemagglutinin (HA) and neuraminidase (NA) on the surface of virus, influenza A viruses can be classified into several subtypes. HA acts like a key to unlock the door of the host cells for the invading viruses, while NA contributes to destroy the cell receptor, which renders free transmission of the viruses in the body of the host. Both enzymes are highly variant, and the defined influenza A viruses, so far, are nominated based on different combinations of 16 types of HA (H1-16) and 9 types of NA (N1-9), such as H1N1, H1N2, H5N1, etc. Among all the subtypes, HA 1–3 can cause pandemic of human influenza, and H1N1, H1N2, and H3N2 are common and fixed virus phenotypes causing human influenza. In human history, three pandemic outbreaks of influenza occurred in 1918, 1957, and 1968. The prevailing influenza virus in the pandemic of 1918 was influenza A (H1N1) virus. Due to common existence of most influenza A (H1N1) virus strains in pigs, the WHO once nominated the influenza as swine influenza at the beginning of its outbreak.

Typical influenza A (H1N1) virus particle is enveloped and spherical whose diameter is 80–120 nm. Many raised glycoproteins (spikes) are radially arranged on the surface of lipid envelope. These spikes are 10–14 nm of erythrocyte hemagglutinin (HA), neuraminidase (NA), and matrix protein M2. Matrix protein (M1) is located inside the envelope of the virus. The nucleocapsids inside the viral particle are spirally symmetrical whose diameter is 10 nm. Such nucleocapsid contains RNA segments and polymerase proteins (PB1, PB2, PA). Certain enzymes (including glycoproteins hemagglutinin and neuraminidase) play a vital role in the entire life cycle of the virus.

The genome of influenza A (H1N1) virus is approximately 13.6 kb and is composed of eight unequally sized independent RNA segments which separately encode ten kinds of proteins: NA, HA, PA (RNA polymerase subunit PA), PB1 (RNA polymerase subunit PB1), PB2 (RNA polymerase subunit PB2), M (matrix protein, including M1 and M2, encoded by the same RNA segment), NS (nonstructural proteins, including N1 and N2, encoded by the same RNA segment), and NP (nucleoprotein). Influenza A (H1N1) virus is composed of three kinds of gene segments from swine influenza virus, avian influenza virus, and human influenza virus, which is a new mutant strain of swine influenza virus (SIV).

Influenza A (H1N1) virus is sensitive to heat and can be inactivated at 56 °C for 30 min. It is also sensitive to ultraviolet rays. But the UV-inactivated swine influenza virus can induce multiple reactivation of the virus. Swine influenza virus is an enveloped virus and is sensitive to ethanol, iodophor, iodine tincture, chloroform, acetone, and other organic solvents.

4.2 Epidemiology

4.2.1 Introduction

In human history, pandemic outbreak of influenza occurred for several times. It has a high incidence, and populations are generally susceptible to it. Its global infection rate is 5–20 % and its mortality rate is 0.1 %. Within the twentieth century, five pandemic outbreaks of influenza occurred in respective years of 1900, 1918, 1957, 1968, and 1977. The pandemic outbreak of influenza A (H1N1) in 1918 in Spain is the most serious, with about 500 million people being infected worldwide and a mortality rate of 2.5 %.

In the year of 2009, an outbreak of influenza firstly occurred in Mexico City. On 18 March 2009, a significant increase of influenza-like cases was reported by the local health agency. On 30 March 2009, a 10-year-old boy in California, USA, experienced fever, cough, and vomiting. Two days later, his conditions deteriorated and the boy was sent to an emergency clinic for treatment. One week later, the boy was cured. On 15 April 2009, the CDC of the USA received the clinical specimens of this boy and then defined a new swine-origin influenza virus, influenza A (H1N1) virus. The WHO and the CDC indicated that the influenza cases in Mexico and the USA were infected by the same strain of H1N1 subtype of swine influenza virus.

After large-scale prevalence of a new influenza virus in human being, persons with a history of infection or vaccination can acquire certain resistance to such virus. When such influenza virus prevails again, its transmissibility and infectivity can be greatly reduced. The influenza A (H1N1) virus has no exception. Its gradually weakened transmissibility and infectivity have changed influenza A (H1N1) into a seasonal flu, and the virus is currently the dominant strain of influenza. The prevalence of influenza A (H1N1) is currently characterized by decreased epidemic intensity and range as well as low incidence rate of severe cases, which have been shown by data from the prevalence of influenza A (H1N1) in 2013.

Influenza A (H1N1) is mainly transmitted via respiratory tract. Its transmission route is various and its transmission is rapid. The virus can survive and spread in densely populated places with poor ventilation and spread widely along with flow of population to cause prevalence of the disease.

4.2.2 Source of Infection

The main source of infection is patients with influenza A (H1N1) and infected asymptomatic person. Although the influenza A (H1N1) virus has been found in the body of pigs, no evidence has been found to prove that the animal is the source of infection.

The infective stage of the patient with influenza A (H1N1) is the period from 1 day prior to the onset of symptoms to

day 7 after the onset or to 24 h after the absence of symptoms (the longer one should be defined as the infective stage). The infective stage may be longer in patients of young children, patients with compromised immunity, and patients critically/seriously ill. In some cases, the virus-carrying persons experience no onset of symptoms but can still infect others.

4.2.3 Route of Transmission

The virus is mainly transmitted via respiratory tract after inhalation of virus-containing droplets or aerosols from sneezing or coughing of infected persons. The virus can also be transmitted via direct or indirect contacts to the mucosa of oral cavity, nose, and eyes. Contacts to respiratory secretions, body fluids, and contaminated utensils of the patients can also cause infection. In addition, the fecal-oral transmission should be taken into account, because many patients experience diarrhea, and fecal detoxification is possible. Humans cannot be infected by influenza A (H1N1) virus via contacts to pork or intake of pork products.

On 12 April 2009, a Canadian farm worker feeding pigs experienced some influenza symptoms after traveling Mexico. He was then diagnosed with influenza A (H1N1). The pigs in this farm began to have influenza symptoms since 24 April 2009. On 2 May 2009, Canadian government officially announced that about 220 pigs in this farm were infected by influenza A (H1N1) virus. The swine infection indicated that human-infected swine influenza can be transmitted to pigs.

4.2.4 Susceptible Population

Populations are generally susceptible to influenza A (H1N1), with no specific immunity. Youngsters aged 9–19 years have a high incidence, with clustering cases in affected school within short period of time.

The following are the high-risk populations of influenza A (H1N1), and these populations are likely to develop into severe cases after onset of influenza symptoms. Therefore, these populations should be highly concerned.

- Pregnancies;
- Obese people (BMI ≥40 means a high risk, BMI between 30 and 39 means a risk factor);
- Children under the age of 5 years (young children patients aged under 2 years are more likely to develop serious complications);
- Elderly people >65 years old;
- The patients with the following underlying diseases or conditions: chronic respiratory disease, cardiovascular disease (except hypertension), kidney disease, liver disease, hematological disease, neurological and neuromuscular disease, metabolic and endocrine system disease, and immune suppression (including those with compromised immunity due to use of immunosuppressor or HIV infection); and the patients aged under 19 years with long-term intake of aspirin.

The abovementioned populations with influenza-like symptoms should receive viral nucleic acid test for influenza A (H1N1) and other necessary examinations as early as possible.

4.3 Pathogenesis and Pathological Changes

4.3.1 Pathogenesis

The influenza A (H1N1) virus responsible for the pandemic of influenza in Mexico and southwestern America is a subtype of influenza A virus that is categorized into the family of Orthomyxoviridae. Influenza A (H1N1) is a zoonotic respiratory disease caused by influenza A (H1N1) virus. As a new mutate of influenza virus, influenza A (H1N1) virus differs from those causing human seasonal H1N1 influenza for years in many aspects, such as genetic and antigenic properties. Evolutionary analysis has revealed that the virus is composed of gene segments from three different influenza viruses: avian influenza virus, swine influenza virus, and human influenza virus. The eight different gene segments are originated from different strains of influenza virus, showing genetic properties of NA and M segments of Asian swine influenza virus, PB2, PB1, PA, HA, NP, and NS segments of North American triple reassortant swine H1 influenza. Humans are generally susceptible to influenza A (H1N1) that can spread from human to human. In vitro experiments have demonstrated that influenza A (H1N1) virus cannot only affect respiratory epithelial cells but also infect dendritic cells (DC) and mononuclear macrophages (MC). The pathogenesis of influenza A (H1N1) may involve of the virus itself, the host immune system, and the interaction between them.

Influenza A (H1N1) can be complicated by multiple organ dysfunction (MODS). Its mechanism is as the following: (1) the influenza A (H1N1) virus can invade the lungs to cause severe pulmonary inflammation. And in some cases, the condition may rapidly progress into acute respiratory distress syndrome (ARDS). (2) The patients with influenza A (H1N1) sustain different degrees of hypoxemia, which enhances anaerobic metabolism of tissue cells and reduces the production of ATP and cAMP. Therefore, the energy metabolism in organs is disturbed. Hypoxia can also lead to decreased cardiac output, insufficient circulating blood volume and reduced organ or tissue perfusion. (3) Secondary infection may occur.

4.3.2 Pathological Changes

The influenza A (H1N1) virus can cause acute respiratory infectious disease, which may progress into interstitial pneumonia in some severe cases, with a mortality rate of about 0.1–0.2 %. The pathological changes of severe influenza A (H1N1) mainly include severe pulmonary disease, multiple organ dysfunction, and secondary infection. The main causes of death include (1) progressive respiratory failure induced by diffuse alveolar lesion; (2) the complication of multiple organ dysfunction including the liver, kidney, and heart; and (3) secondary infection.

4.3.2.1 Respiratory System

Observation by Naked Eyes

The pathological changes noticeable by naked eyes include: increased volume of both lungs with increased weight but decreased air content, consolidation of both lungs, and dark reddish lungs with fibrinous exudates on their surfaces.

Observation by Light Microscopy

Under a light microscope, diffuse alveolar lesion can be observed at both lungs, which is mainly acute diffuse exudates with presence of pulmonary tissue necrosis (Fig. 4.1). The alveolar cavity is demonstrated with edema and/or fibrinous and inflammatory exudates (Fig. 4.2), with formation of pulmonary hyaline membrane. In some alveolar cavities, hemorrhages can be observed, with hyperplasia of type II alveolar epithelial cells. Neither megakaryocytes nor inclusions in nucleus or cytoplasm can be observed. Some alveolar septa are demonstrated to be slightly widened, with vascular dilatation, congestion, and necrosis (Fig. 4.3), as well as thrombus in some cases. Pulmonary interstitial fibrosis is present.

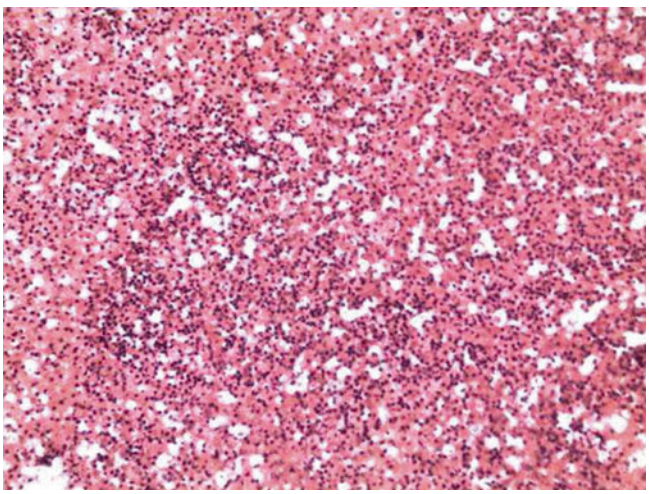

Fig. 4.1 Necrosis of pulmonary tissue and infiltration of inflammatory cells H&E ×100

Observation by Electron Microscopy

Virus particles can be observed both within and out of the infected cells in alveolar cavity of pulmonary tissue. The virus is round or oval in shape with a diameter of averagely about 88 nm, and some viruses are surrounded by spikelike structure in a length of about 12 nm.

4.3.2.2 Other Major Systems

Cardiovascular System

The heart is slightly heavier. Under a light microscope, myocardial cells are degenerated, with myocardial breakage, myocardial interstitial edema, infiltration of small quantity or no inflammatory cells, and degeneration of atrial ganglion cells (Figs. 4.4, 4.5, and 4.6).

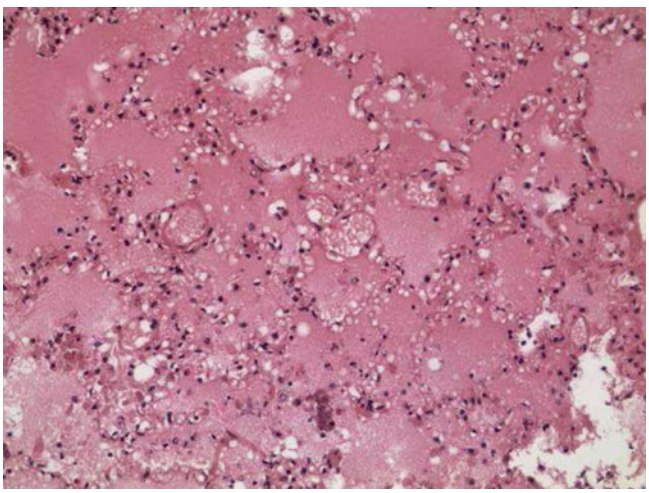

Fig. 4.2 Pulmonary edema, with the alveolar cavity filled by homogeneous acidophilic exudates H&E ×100

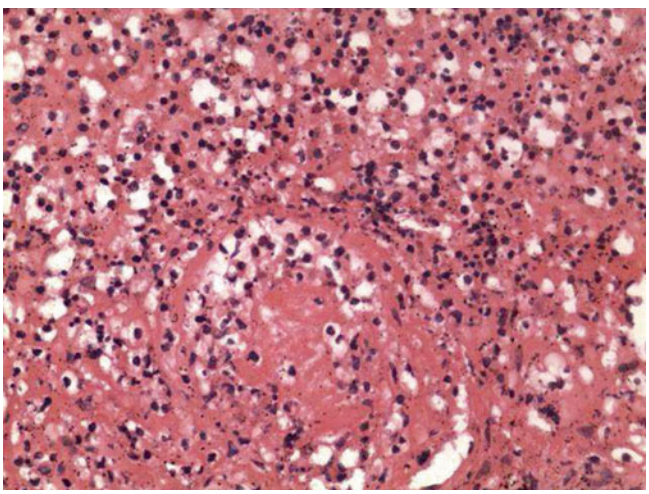

Fig. 4.3 Necrosis of pulmonary vascular wall and infiltration of inflammatory cells H&E ×200

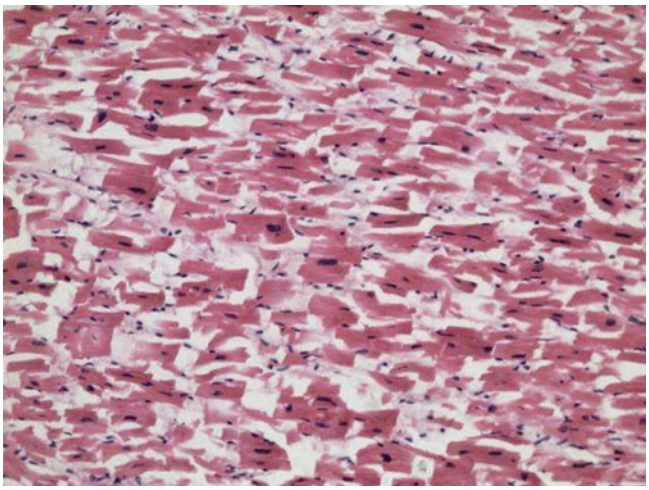

Fig. 4.4 Myocardial breakage, degeneration of myocardial cells, and myocardial interstitial edema H&E ×400

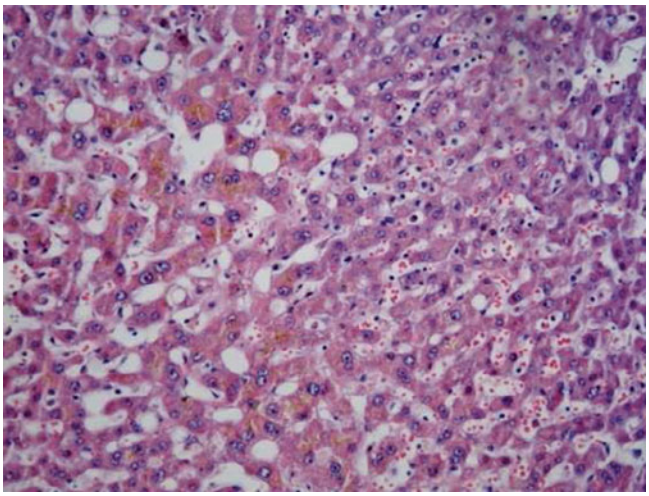

Fig. 4.7 Bullous fatty degeneration of hepatocytes, cholestatic hepatocytes, and dilated hepatic sinus H&E ×200

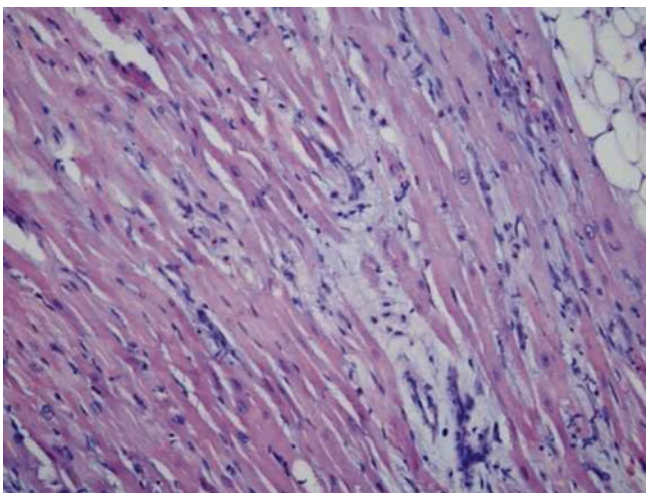

Fig. 4.5 Infiltration of inflammatory cells at the myocardial tissue space H&E ×200

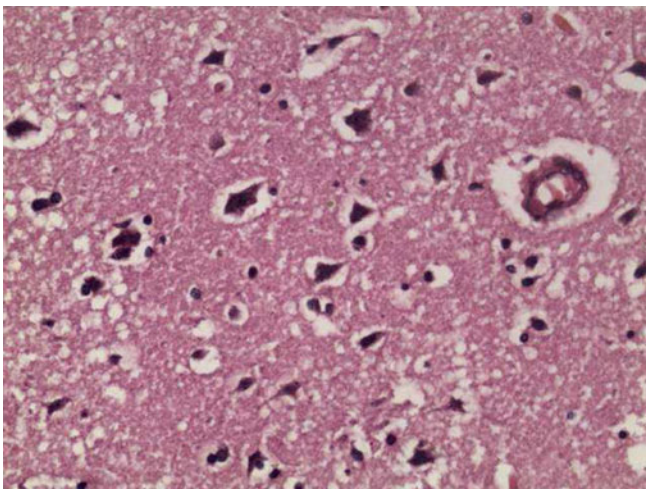

Fig. 4.8 Degeneration of brain nerve cells H&E ×400

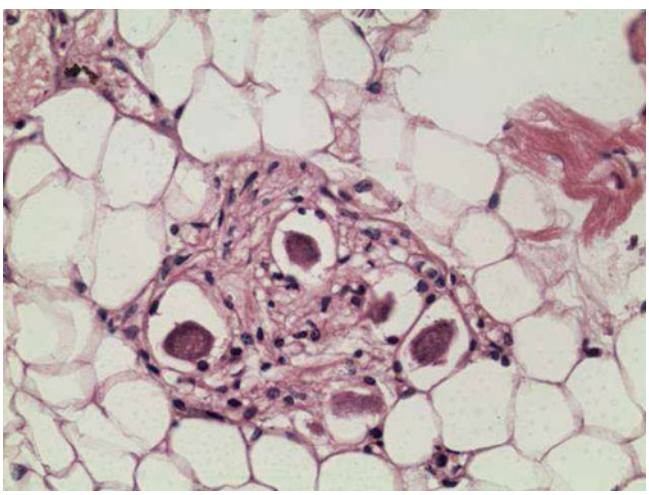

Fig. 4.6 Degeneration of atrial ganglion cell H&E ×200

Digestive System

The liver can be observed with congestion, focal hepatocytic swelling and fatty degeneration, and infiltration of small quantity mononuclear cells at the portal area. Erythrocytophagy can be observed (Fig. 4.7).

Urinary System

The kidney can be observed with congestion. Under a light microscope examination, glomerular congestion is observed, with edema of renal tubular epithelial cells but no microthrombus and renal tubular necrosis.

Central Nervous System

The pathological changes include cerebral edema and congestion, with visible hemorrhagic focus, focal liquefactive necrosis at the capsule, and neuronal degeneration (Fig. 4.8).

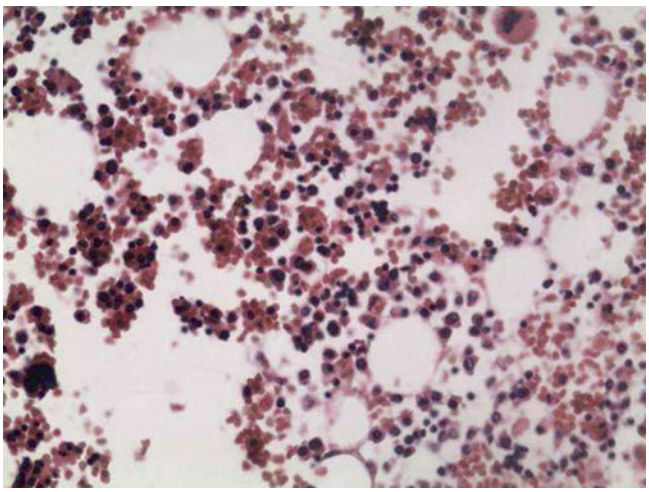

Fig. 4.9 Prominent hemophagocytic phenomenon at bone marrow H&E ×200

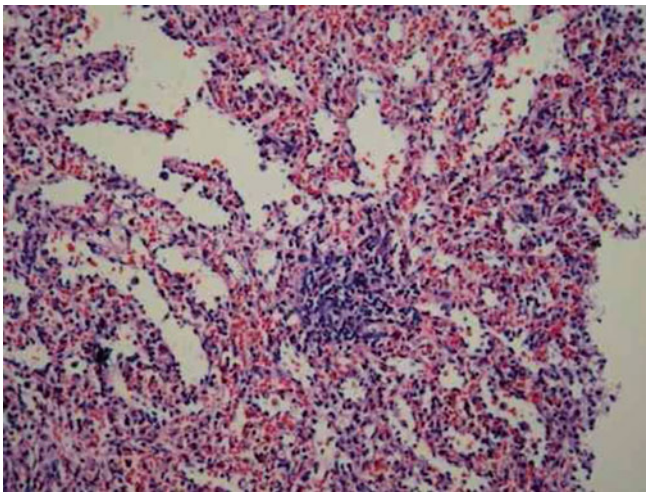

Fig. 4.10 Dilation and congestion of splenic sinus, atrophy of splenic corpuscle, and decreased lymphocytes H&E ×200

Lymphoid Hematopoietic System

Hemophagocytic phenomenon can be observed at some lymph nodes and bone marrow (Fig. 4.9). The spleen can be observed with reduced lymphocytes, histiocytosis, and hemophagocytic phenomenon (Fig. 4.10).

4.3.2.3 Secondary Infection

The patients with influenza A (H1N1) can develop secondary bacterial and fungal infections. The pathogenic bacteria are mainly gram-positive coccus.

4.3.2.4 Molecular Pathology

The nucleoprotein antigen of influenza A (HIN1) virus is located at the nucleus and cytoplasm of infected cells, including epithelial cells at airway, submucosal glands of airway, and detached and lining epithelial cells at alveolus. In addition, the antigen can also be found at the hyaline membrane and rarely vascular endothelial cells. Double labeling has revealed that the target cell of viral infection is pulmonary epithelial cells, predominantly type II alveolar epithelial cells (co-labeled with cytokeratin) and occasionally macrophages.

No viral antigen of influenza A (H1N1) virus is immunohistochemically detected in nonrespiratory tissue. By RT-PCR, the nonrespiratory tissue is also detected negative for influenza A (H1N1) virus.

4.4 Clinical Symptoms, Signs, and Laboratory Tests

Influenza A (H1N1) is a self-limited respiratory disease. Its clinical manifestations resemble to those of seasonal influenza, being mild in most patients. However, the patients from high-risk populations are more likely to develop into severe cases and even death.

4.4.1 Incubation Period

The incubation period of influenza A (H1N1) generally lasts for 1–7 days, mostly 1–3 days, which is longer than that of common influenza and avian influenza.

4.4.2 Clinical Symptoms and Signs

The patient usually experiences influenza-like symptoms, including fever (axillary temperature ≥37.5 °C), sore throat, runny nose, nasal congestion, cough, expectoration, headache, general soreness, and fatigue. In some cases, the patients experience vomiting and/or diarrhea. In rare cases, the patients only experience mild upper respiratory symptoms with no occurrence of fever.

The signs mainly include pharyngeal congestion and swollen tonsils.

4.4.3 Laboratory Tests

4.4.3.1 Peripheral Blood Test

Total WBC count is commonly within or lower than normal range. In some severe pediatric cases, the total WBC count may increase. The common cases commonly show normal or lower WBC count, while the severe cases show normal or increased peripheral WBC count. The increase of WBC count in severe cases may be related to complicated infections. It should be paid close attention that, compared to common cases, the severe cases have obviously decreased percentage and absolute count of peripheral blood lymphocytes. Peripheral blood lymphocyte count <800 cells/ml is a high-risk factor for patient with influenza A (H1N1) to develop respiratory failure. The decrease of both percentage

and absolute count of peripheral lymphocytes is an indicator for early prediction.

4.4.3.2 Blood Biochemistry

Blood Biochemistry

The blood biochemistry for liver function is commonly normal in most patients. Only in rare cases, the levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), and lactate dehydrogenase (LDH) can be tested with increase.

Myocardial enzyme of creatine kinase (CK) exists in the cytoplasm and mitochondria of skeletal muscle, heart, brain, and other tissues, which is an important kinase directly related to intracellular energy transformation, muscle contraction, and ATP regeneration. Its level increases in the cases with myocardial damage.

The blood glucose level in both critical cases and death cases is higher than that in severe cases, which may be related to responses of host to stress.

Electrolyte

In some cases, hypokalemia or hypocalcemia occurs. Relevant studies have demonstrated that hypocalcemia is an important indicator predicting poor prognosis of influenza A (H1N1).

4.4.3.3 Assay for Cellular Immunity

The infection of influenza A (H1N1) virus can cause allergic reaction. In critical cases, the serum cytokine significantly increases, with increased permeability of pulmonary and cerebral vascular vessels, to cause respiratory failure and pulmonary edema. Therefore, the test for serum cytokines plays an important role in assessing conditions of influenza A (H1N1) and guiding clinical prevention and treatment.

4.4.3.4 Etiological Examination

Test for Viral Nucleic Acid

The test for viral nucleic acid is currently the main diagnostic examination for influenza A (H1N1). The respiratory specimens, including throat swabs, nasal swabs, nasopharyngeal or tracheal extracts, and sputum, are tested by using RT-PCR (more favorably real-time RT-PCR). The cases of influenza A (H1N1) show positive results.

Virus Isolation

In the cases of influenza A (H1N1), the pathogenic virus can be isolated from respiratory specimens. In the cases with influenza A (H1N1) complicated by viral pneumonia, the virus can also be isolated from the lung tissue.

Serum Antibody Test

In the cases of influenza A (H1N1), dynamic tests of double sera specimens show at least four times increase of the neutralizing antibody specific to influenza A (H1N1) virus. The result may facilitate to define the diagnosis and the retrospective diagnosis.

4.5 Clinical Diagnosis

The patients with influenza A (H1N1) experience different degrees of fever, cough, expectoration, chest distress, shortness of breath, fatigue, headache, and myalgia, all of which are collectively referred to as the flulike symptoms. Although the influenza A (H1N1) virus is a new mutant of influenza virus, the symptoms of infected patients can be hardly distinguished from infections of respiratory syncytial virus, parainfluenza virus, rhinovirus, adenovirus, *Coronavirus*, and *Legionella pneumophila*. Therefore, the diagnosis cannot be defined based only on the symptoms, but needs to combine findings of specific laboratory tests, such as serological test, viral nucleic acid test, and pathogen isolation.

4.5.1 Suspected Cases

The case with the following ONE condition can be diagnosed as a suspected case:

1. The patient has a history of close contact to patient suspectively or definitively diagnosed with influenza A (H1N1) at its infectious stage within 7 days prior to the onset of influenza-like symptoms. Close contact refers to attending to patients with influenza A (H1N1) in its infectious stage with no effective protection; living together with the patient and exposure to the same environment with the patient; and direct contact to the airway secretions, body fluids, and other contaminated utensils from the patient.
2. The patient has a history of visiting the country or region with epidemic of influenza A (H1N1) (continuous spread of virus from person to person and community-based prevalence and outbreak) within 7 days prior to the onset of influenza-like symptoms.
3. The patient experiences influenza-like symptoms and shows positive to test for influenza A (H1N1) virus, but infection of previous influenza virus subtypes has not been further excluded.

The cases with ONE of the above three conditions should be etiologically tested for influenza A (H1N1), if possible.

4.5.2 Clinically Diagnosed Cases

The clinical diagnosis should be made based only on the following condition. During the same epidemic event of

influenza A (H1N1), the patient with influenza-like symptoms has not definitively diagnosed by laboratory test but has been excluded from other diseases with influenza-like clinical manifestations. Such patients can be clinically diagnosed as influenza A (H1N1).

Outbreak of influenza A (H1N1) refers to abnormally increased occurrence of influenza-like disease in one region or unit within a short period of time, and the disease is defined to be influenza A (H1N1) by laboratory tests.

If possible, the clinically diagnosed patients should receive etiological examination.

4.5.3 Definitively Diagnosed Cases

The cases with influenza-like symptoms and at least ONE of the following laboratory findings can be definitively diagnosed as influenza A (H1N1).

1. The viral nucleic acid of influenza A (H1N1) virus is tested positive by real-time RT-PCR or RT-PCR.
2. The serum level of neutralizing antibody specific to influenza A (H1N1) is tested with at least four times increase.
3. The influenza A (H1N1) virus is isolated.

4.5.4 Diagnosis of Severe and Critical Cases

4.5.4.1 Severe Cases

The severe cases can be defined based on ONE of the following conditions.

1. Persistent fever lasting from more than 3 days, accompanied by severe cough, purulent and/or bloody sputum, or chest pain
2. Rapid respiratory rate, dyspnea, cyanotic lips
3. Consciousness changes, including delayed response, drowsiness, restlessness, and convulsions
4. Severe vomiting and diarrhea, dehydration
5. Radiological findings of pneumonia-like signs
6. Rapid increases of myocardial enzyme levels, such as creatine kinase (CK), creatine kinase M isoenzyme (CK-MB), etc.
7. Obviously aggravated previous underlying disease

4.5.4.2 Critical Cases

The critical cases can be defined based on ONE of the following conditions:

1. Respiratory failure
2. Septic and toxic shock
3. Multiple organ dysfunction
4. Other severe clinical conditions in need of monitoring treatment

4.6 Selection of Radiological Modalities

Influenza A (H1N1) is commonly complicated by diseases of respiratory and central nervous system. The selection of radiological modalities is mainly based on the two systems.

4.6.1 Radiology of the Respiratory System

4.6.1.1 Chest X-Ray

The suspected cases should receive upright posterior-anterior chest X-ray. For the severe cases of inability going to the radiology department, a bedside chest X-ray can be performed to assess the condition at a posture of sitting or lying. If possible, a special stand for upright chest X-ray or seated chest X-ray can be used. The children patients capable of standing should receive upright chest X-ray. For patients unable of standing due to severe conditions, seated chest X-ray is preferred.

Indications for Bedside Radiological Examination

The indications for bedside radiological examination are as the following:

1. Persistent fever lasting for at least 3 days
2. Cough with/without expectoration
3. Positive finding in viral nucleic acid test for influenza A (H1N1)
4. Signs of pulmonary inflammation by the first radiological examination

When a patient with suspected diagnosis of influenza A (H1N1) experiences above conditions 1, 2, and 4, a bedside radiological examination should be performed. If a patient with suspected diagnosis of influenza A (H1N1) experienced the above condition 3, the bedside radiological examination is NOT necessary.

Protection Principles During Bedside Radiological Examination

The patients, radiological technicians, and other healthcare workers should be protected against radiohazards. Data revealed that the average radiation dose at the chest surface of the patient by a bedside X-ray machine is 1.45 mGy/time, and its maximum dose is 3.39 mGy/time. The radiation dose by other digital chest X-ray machines is about (0.36 ± 0.05)

mGy/time. The radiation dose of bedside X-ray machine is significantly different from that of other digital chest X-ray machine.

Protective Measures Against Cross-Infection

Before entering into the isolation ward, the radiological technicians should receive training for knowledge and skills about disinfection and isolation. The procedures should be constantly improved.

The patients with influenza A (H1N1) experience rapid changes of lung lesions. Therefore, reexamination of chest X-ray within a short period of time facilitates to assess the condition. During the convalescent stage, chest X-ray should be regularly performed to assess the absorption of lesions and the residual lesions.

4.6.1.2 Chest CT Scan

In recent years, based on the application of new detectors and new algorithm for image reconstruction, the low-dose CT scan can be routinely performed. CT scans are favorable in detecting chest lesions and their characteristics, which can be applied for patients whose diagnosis cannot be defined by chest X-ray. CT scan can display occult lesions posterior to the heart shadow and at the posterior costophrenic angle, which can effectively avoid misdiagnosis and increase the detection rate of the lesions.

4.6.2 Radiology for the Central Nervous System

MRI has the absolute advantage in displaying lesions at the central nervous system due to its capabilities in multiparameter imaging, 3D imaging, and functional imaging. Therefore, MRI is the choice of radiological modalities for the examination of central nervous system. CT scan is applied only when MRI is inapplicable.

Influenza A (H1N1) may be complicated by aseptic meningitis, encephalitis, and acute necrotizing encephalopathy. MRI should be performed with conventional plain imaging and contrast imaging. FLAIR and DWI sequences should be additionally performed during contrast imaging to more favorably display meningeal lesions.

When MRI is performed for young children, some measures should be used to keep him/her warm and limit his/her movement. In addition, due to the loud noise generated during MRI, a pair of soundproof earplugs should be plugged into the ears of pediatric patient so as to avoid awakening the child and to prevent hearing damage. For the pediatric patient with poor compliance, oral/enema use of chloral hydrate can be administered to calm down the child prior to MRI.

4.7 Radiological Demonstration

4.7.1 Radiological Demonstrations of the Respiratory System

Influenza A (H1N1) is a new respiratory infectious disease. And respiratory complications, such as pneumonia and pulmonary edema, are important and common. Death may occur in critical cases due to respiratory failure.

For the patients with influenza A (H1N1), abnormalities displayed by chest radiological examinations are always in inpatients and severely ill patients receiving intensive care. The common complications mainly include pneumonia, pleural effusion, pulmonary edema, pneumothorax, and mediastinal emphysema.

4.7.1.1 Pneumonia

Influenza A (H1N1) is commonly complicated by pneumonia, with multiple lesions. Its radiological demonstrations share some commonalities with common pneumonia, such as exudative lesions, lung consolidation, pulmonary edema, and pleural effusion. Meanwhile, pneumonia complicating influenza A (H1N1) is characterized by commonly bilateral lesions as well as rapid change and exacerbation of the lesions and its range.

Radiological Demonstrations

The most common radiological demonstrations are ground-glass opacities and consolidation opacities at lungs. The two types of opacities may be separately or jointly present, commonly with reticular and nodular opacities. In rare cases, the lesions are demonstrated as consolidation opacities at pulmonary segments or lobes with air bronchogram, accompanied by or no segmental atelectasis. The lesions are commonly found at bilateral lower lung fields, which are focal, multiple, or diffusely distributed. Intrapulmonary nodular opacities, interlobular septal thickening, peribronchial patchy opacities, and pleural effusion are rarely found radiological signs (Fig. 4.11).

CT Scan Demonstrations

1. The common chest CT scan demonstrations are unilateral or bilateral ground-glass opacities, with or without singular consolidation or multiple fused consolidations.
2. The intrapulmonary lesions have lobular, segmental, or lobar distribution and often manifest as light thin small flaky or multiple patchy integrated lesions. By HRCT, the ground-glass opacities are commonly distributed at the peribronchovascular or subpleural region. The lesions are mostly located at both lower lung lobes or multiple lobes and segments of both lungs. In severe cases, the

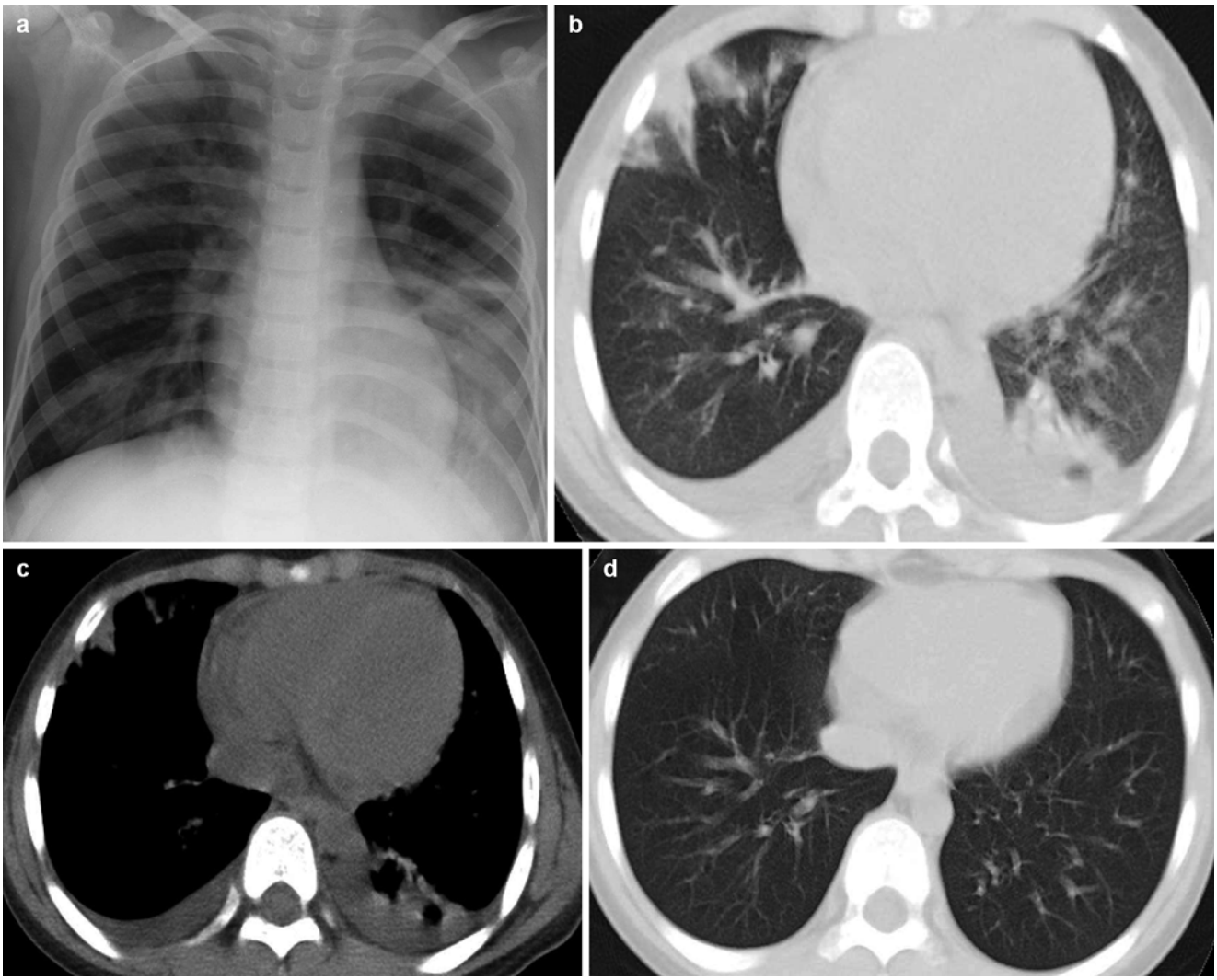

Fig. 4.11 (**a**–**d**) A boy aged 6 years with a diagnosis of influenza A (H1N1) complicated by pneumonia. (**a**) At d 4 since onset, chest X-ray showed large high-density opacities at the left lower lung field, poorly defined left diaphragmatic surface and absence of left costophrenic angle, and patchy ground-glass opacities at the right lower lung field. (**b**, **c**) At d 5 since onset, plain CT scan (**b** lung window; **c** mediastinal window) displayed flaky consolidation opacities at the basal segment lateroposterior to the left lower lung lobe and subpleural patchy ground-glass opacities at the right middle lung lobe and small quantities of pleural effusion at both lungs. (**d**) At d 16 since onset (1 day before discharge), reexamination by CT scan demonstrated absorption of lesions at both lungs

lesions are always shown as multifocal and integrated consolidation at both lungs with air bronchogram. Otherwise, the severe cases can be demonstrated with atelectasis.

3. The lung lesions can be completely absorbed within a short period of time, generally within 7–15 days. The absorption of lesions commonly lags behind the improvement of clinical conditions. At the early stage of the disease, ground-glass opacities may be integrated as multiple scattering consolidation opacities. Some of the consolidations are not integrated at the onset, but will be integrated within the following several days. The multiple scattering patchy opacities can change into light thin small flaky opacities and gradually disappear.
4. In some cases, the above lesions are accompanied by small quantity of pleural effusion and mediastinal lymphadenectasis (Fig. 4.12).

Typology of Radiological Demonstrations

Pneumonia demonstrated as flaky opacities confined within the lungs is defined as mild. That demonstrated as intrapulmonary flaky opacities with more than two lung lobes involved are defined as moderate. And that demonstrated as intrapulmonary lesions with at least three lung lobes involved are defined as severe. For the patients with mild to moderate pneumonia, pulmonary inflammation can be gradually absorbed after the use of effective therapy. The radiological demonstrations are not necessarily

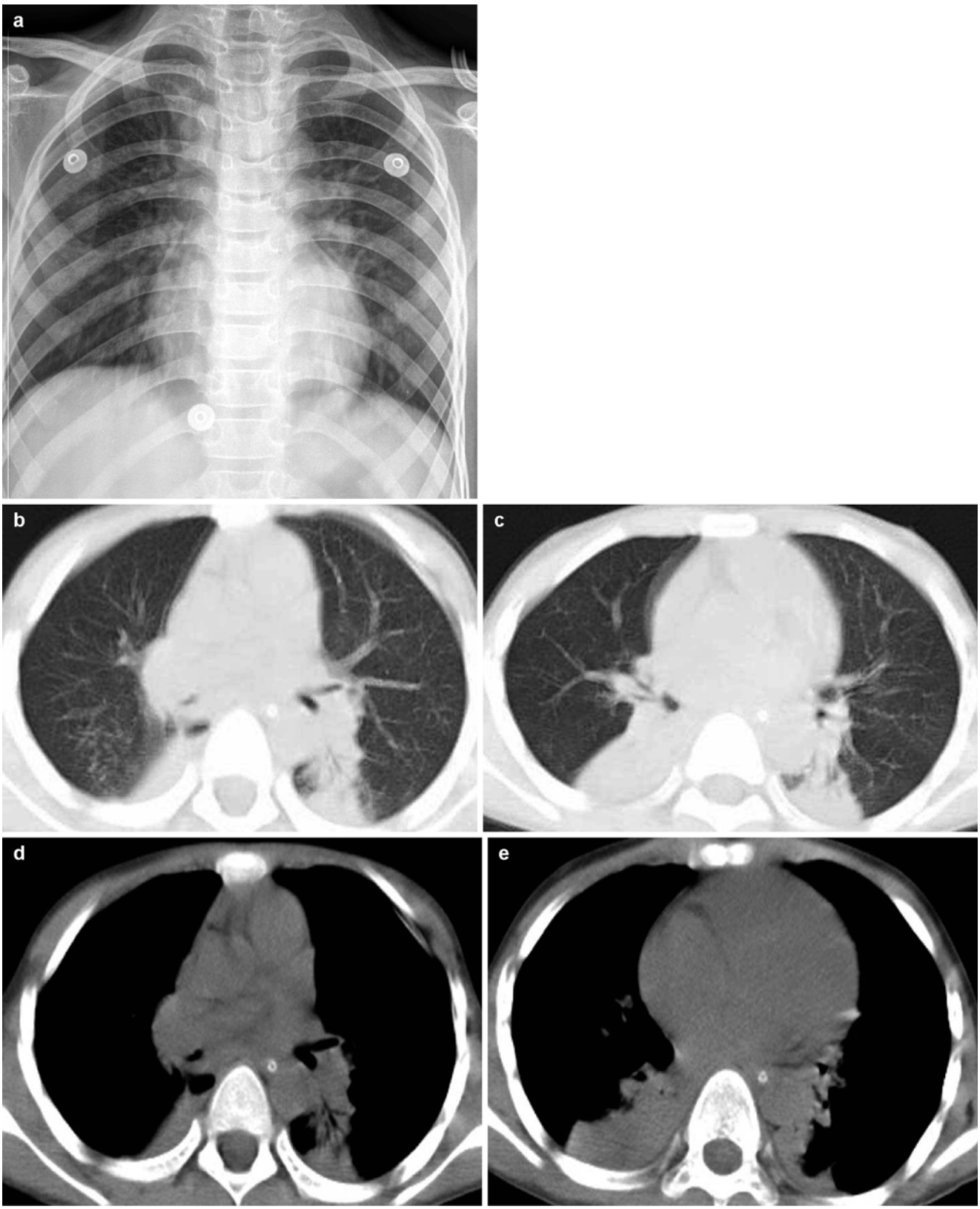

Fig. 4.12 A boy aged 9 years with influenza A (H1N1) complicated by pneumonia. (**a**) At d 3 since onset, chest X-ray showed thickened markings at both lungs and no consolidation opacities at bilateral lung fields. (**b**–**e**) At d 5 since onset, chest CT scan (**b**, **c**: lung window; **d**, **e**: mediastinal window) showed flaky high-density opacities at the dorsal and lateroposterior basal segments of both lower lung lobes, air bronchogram at the dorsal segment of left lower lung lobe, slightly increased transparency of the right middle lung lobe, and segmental atelectasis at the right lower lung lobe. (**f**) At d 7 since onset, chest X-ray displayed high-density flaky opacities at the middle and inner zone of the right middle and lower lung fields, partial atelectasis at the right lower lung lobe, and basic absorption of inflammation lesions at the left lung

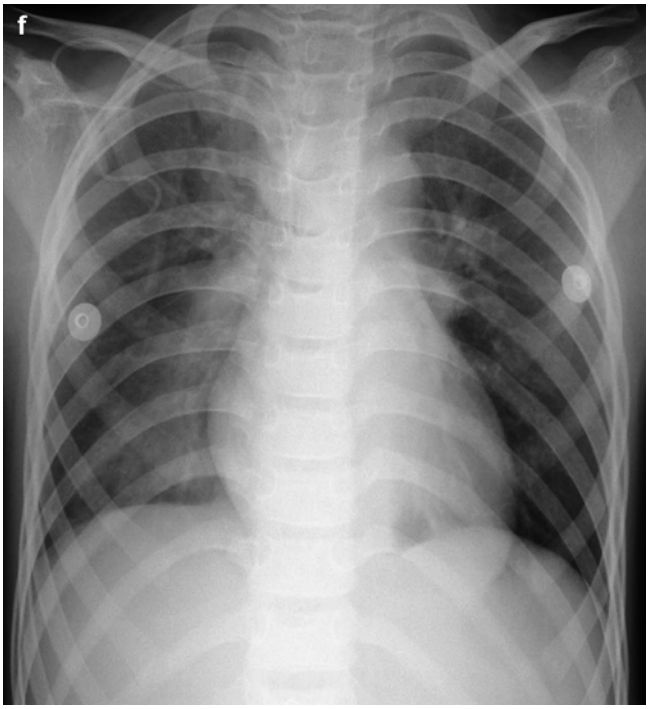

Fig. 4.12 (continued)

correspondent to the clinical symptoms. For severe pediatric cases, radiological examination should be performed to monitor the changes of pneumonia lesions. For the pediatric patients and the patients with severe lung lesions, radiological examination should be performed to assess the short-term absorption of lesions, any delayed absorption, and residual lesions in order to provide the basis for clinical treatment.

The Relationship Between Influenza A (H1N1)/ Complicated by Pneumonia and Viral Load

According to a study of viral load in 20 patients with influenza A (H1N1) whose chest CT scans were normal, the minimum viral load is 2.4 copies/ml, while the maximum viral load is 5.5 copies/ml, with a mean of 4.2 copies/ml. In this study, the dynamic viral load was also measured in 21 patients with influenza A (H1N1) whose chest CT scans demonstrated pneumonia. The average viral load is 7.7 copies/ml. The viral load has statistical difference ($P < 0.05$) between the group without pneumonia and the group with pneumonia. The findings primarily indicated that pneumonia does not occur to complicate influenza A (H1N1) in the cases with a viral load lower than 5.5 copies/ml (Fig. 4.13).

The same study also demonstrated that the severity of pneumonia complicating influenza A (H1N1), with an indicator of CT semiquantitative score, is not significantly related to the viral load. In general, the level of viral load indicates the degree of infection. However, by dynamic chest CT scoring (Radiology, 2003) in 21 cases of influenza A (H1N1) complicated by pneumonia and their viral load measures, it has been found that the severity (chest CT semiquantitative score) of pneumonia complicating influenza A (H1N1) is not related to the viral load, because no statistically significant difference was found ($P > 0.05$). That is to say, a high level of viral load does not necessarily indicate severe lesions of pneumonia.

Influenza A (H1N1) Complicated by Pneumonia in Perinatal Women

1. Location of lesions: commonly at the middle (lingular segment) and lower lobes of both lungs.
2. Morphology of lesions: mostly large or small flaky opacities.
3. Density of lesions: mainly high-density consolidation opacities, light thin opacities, or ground-glass opacities.
4. The lesions are mostly accompanied by unilateral/bilateral pleurisy or pleural effusion or other changes. The pathomechanism underlying pleurisy remains unknown, which may be related to hypoalbuminemia, direct effects of viruses, or endocrine factors.
5. After clinical treatment, the ground-glass opacities at the lungs can be completely absorbed within a short period of time; large high-density consolidation opacities can be obviously absorbed; the residual lesions in the advanced stage can be absorbed slowly (Fig. 4.14).

4.7.1.2 Pleural Effusion

It may develop due to pulmonary edema or pneumonia with the pleura involved. In severe pediatric cases of influenza A (H1N1), the incidence of pneumonia complicated by pleural effusion is relatively higher. By CT scan, the lesions are mostly located at the peripheral lung with the subpleura involved and pleurisy may be demonstrated.

4.7.1.3 Pneumothorax, Mediastinal Emphysema

Pneumothorax and mediastinal emphysema may occur in patients with underlying asthma, and their occurrence is possibly a result of increased intrapulmonary pressure due to shortness of breath caused by influenza A (H1N1) virus. The risk of developing pneumothorax and mediastinal emphysema in severe cases receiving intensive care can be increased due to mechanical ventilation (Figs. 4.15 and 4.16).

4.7.1.4 Mediastinal and Axillary Lymphadenectasis

As a result of inflammatory responses, mediastinal and axillary lymphadenectasis occurs, with no necrosis and integration.

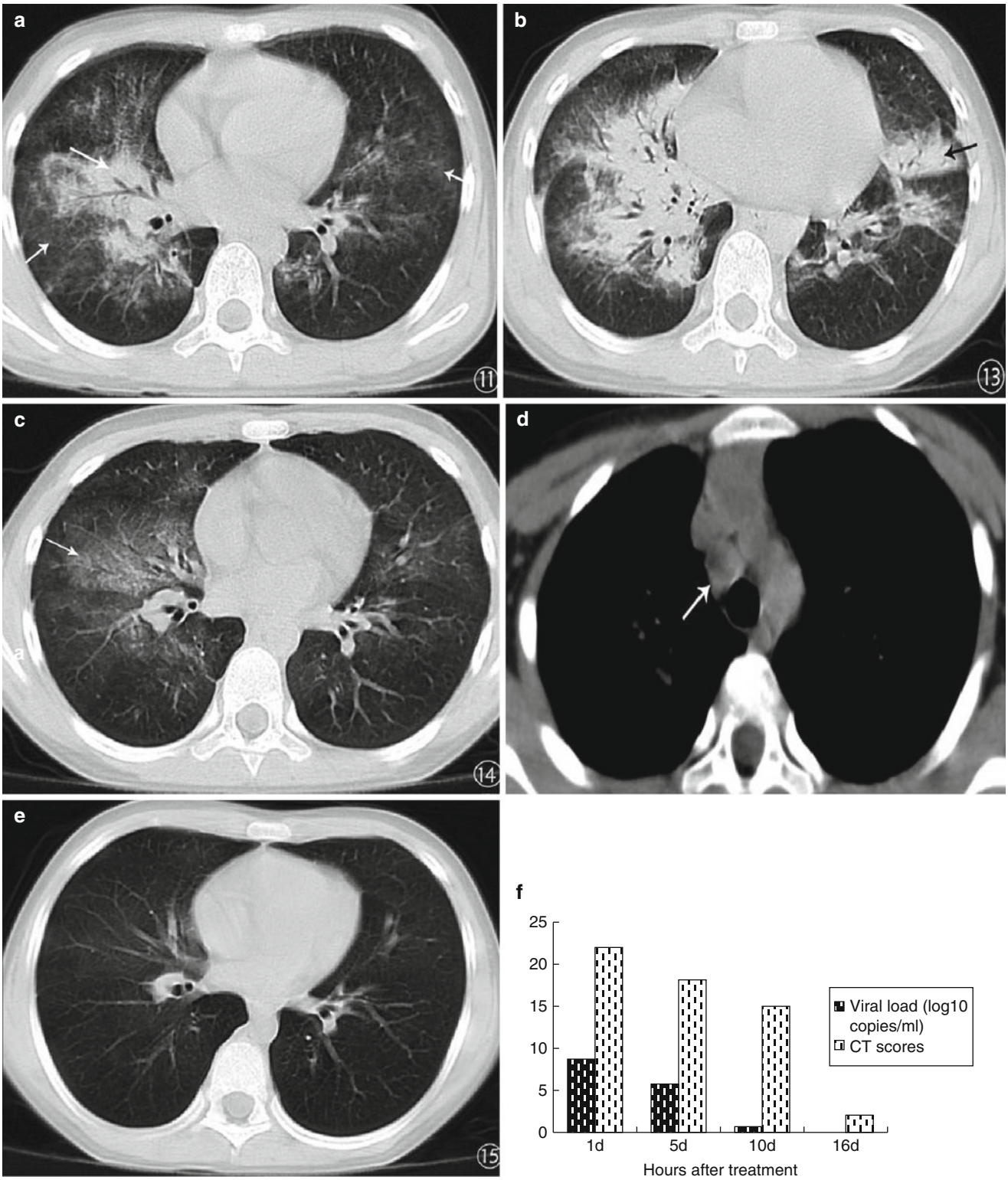

Fig. 4.13 (**a**–**f**) *A boy aged* 11 years with influenza A (H1N1) complicated by pneumonia. (**a**) At d 4 since onset, chest CT showed scattering ground-glass opacities (*short arrow*) at both lungs, integration of some lesions into flaky consolidation opacities at the right hilum (*long arrow*) with air bronchogram. (**b**) The same CT scan at d 4 also displayed a swollen lymph node (*white arrow*) anterior to the trachea and posterior to the superior vena cava, with uneven density. (**c**) At d 6 since onset, CT scan showed obviously more integrated lesions at both lungs and new patchy integrated lesions at the lingular lobe (*black arrow*) and lower lobe of left lung. (**d**) At d 8 since onset, CT scan demonstrated the obviously smaller range with lesions at both lungs, obviously decreased density of the lesions as ground-glass opacity (*white arrow*). (**e**) At d 14 since onset, CT scan displayed absorption of lesions at both lungs. (**f**) Dynamic changes CT scoring along with changes of the viral load

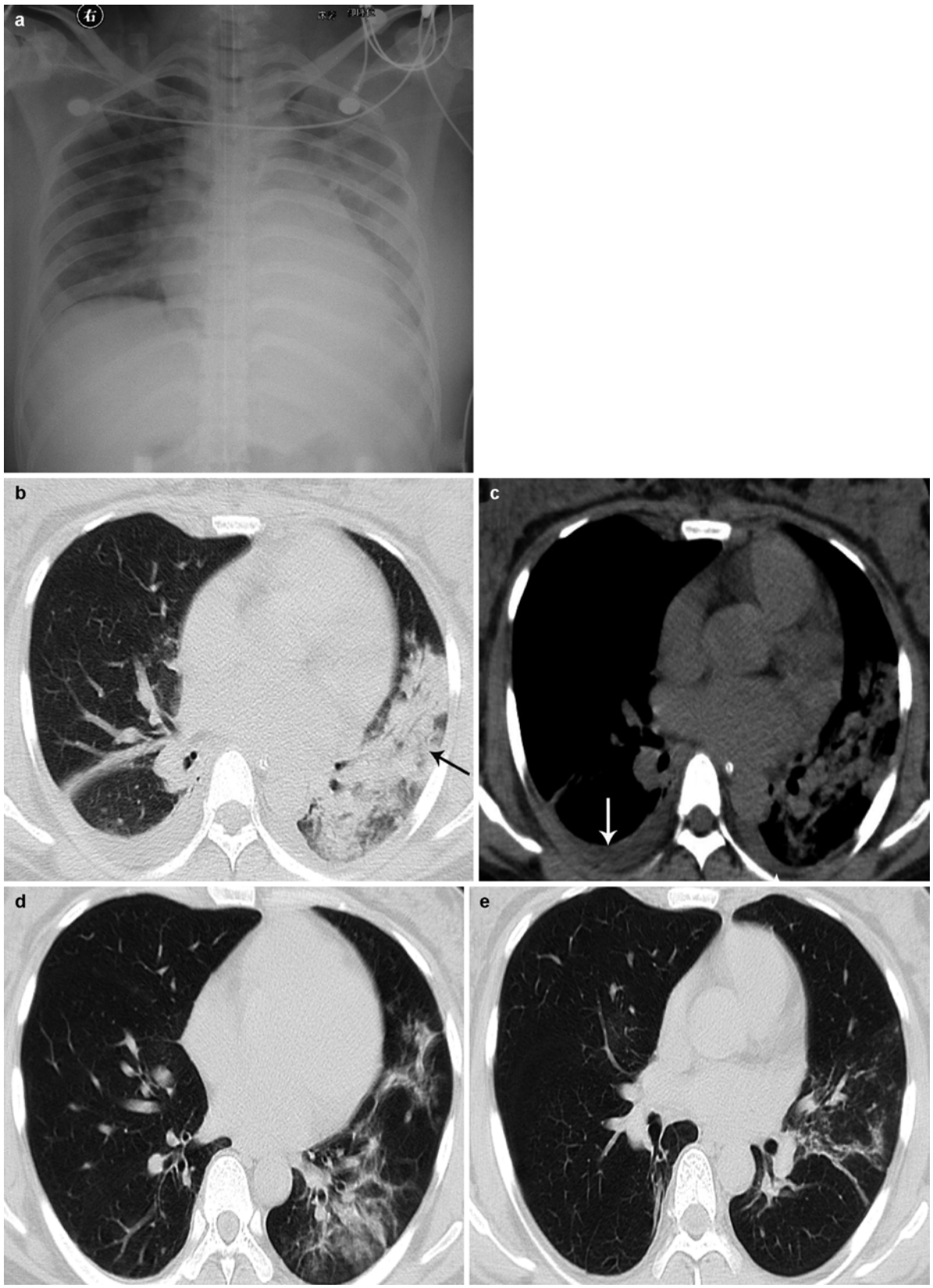

Fig. 4.14 (**a**–**e**) A pregnant woman aged 26 years with influenza A (H1N1) complicated by pneumonia. (**a**) At d 3 since onset, bedside chest X-ray showed large blurry opacities at left lung, small flaky opacities at the right lower lung near cardiac border, and poorly defined bilateral inferior costophrenic angles. (**b**) At d 5 since onset, the lung window of chest CT displayed large dense consolidation opacities (*black arrow*) at the lingular and lower lobe of left lung, with air bronchogram. (**c**) The same chest CT scan at d 5 demonstrated small quantities of liquid (*white arrow*) in bilateral pleural cavities and right oblique fissure pleura by the mediastinal window. (**d**) At d 7 since onset, chest CT showed decreased density of lesions at the lingular and lower lobes of left lung, and some lesions as ground-glass opacities. (**e**) At d 9 since onset, CT scan displayed obviously smaller range of the lesions and rare ground-glass opacities and cord-like opacities

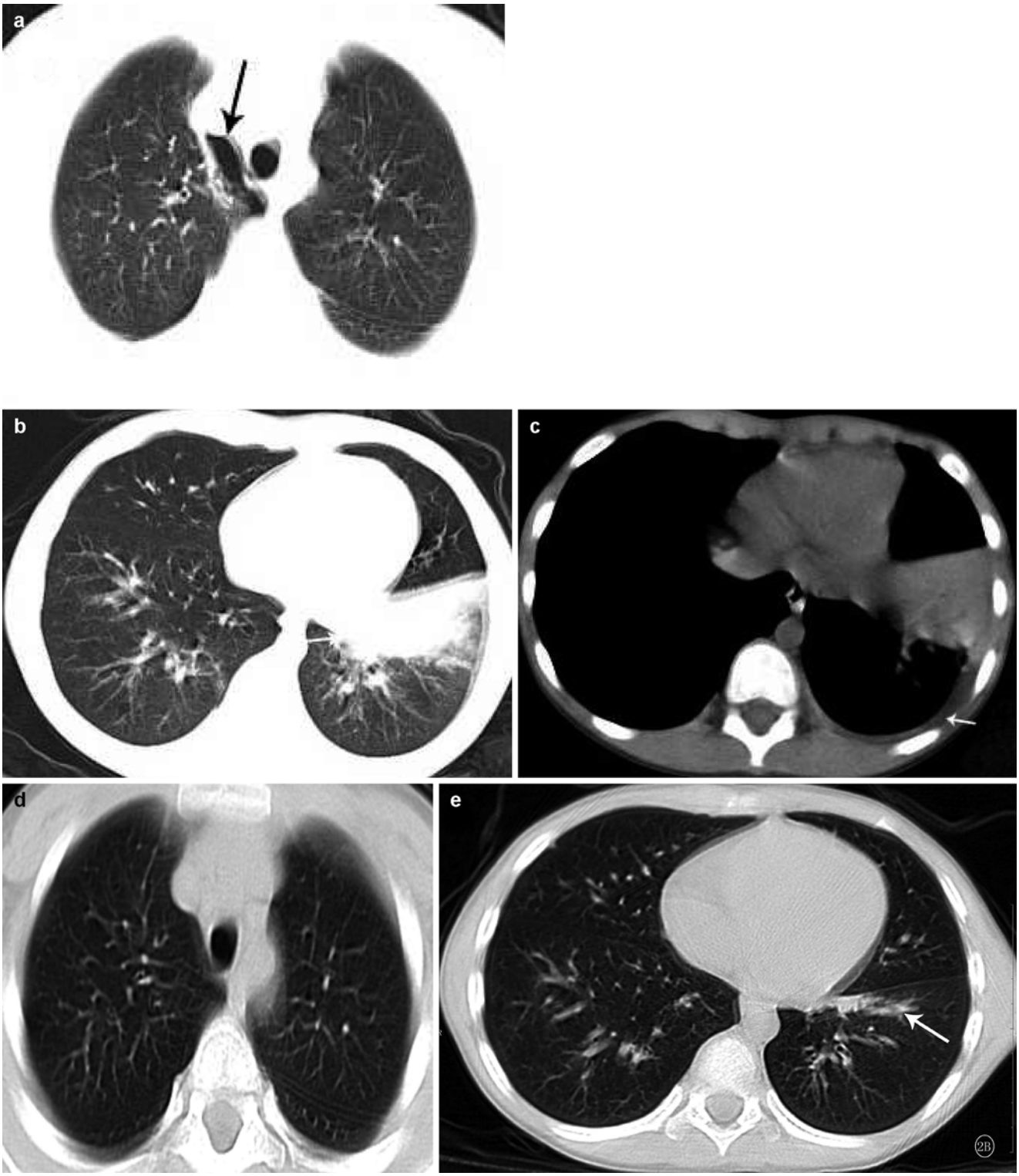

Fig. 4.15 (**a**–**e**) A boy aged 7 years with influenza A (H1N1) complicated by pneumonia. (**a**) At d 7 since onset, chest CT showed a strip-like area (*black arrow*) next to upper right mediastinum with no lung markings, which was preliminarily diagnosed as right pneumomediastinum; (**b**–**c**) The same chest CT at d 7 displayed large dense consolidation opacities (*black arrow*) at the left lower lung lobe immediately nearby the oblique fissure pleura, poorly defined border of the dorsal part, a small quantity of liquid (*white arrow*) at the left pleural cavity in the mediastinal window. (**d**) At d 14 since onset, reexamination by CT scan showed absorbed pneumatosis next to upper right mediastinum. (**e**) The same CT scan at d 14 demonstrated rare cord-like opacities (*white arrow*) at the left lower lung lobe

4.7.1.5 Plastic Bronchitis

Plastic bronchitis has an extremely rare occurrence whose diagnosis can be defined by bronchoscopy based on suction of branch-like bronchial casts. Pathologically, it is fibrinous exudation or fibrinous exudation with necrosis and may be accompanied by infiltration of neutrophils, eosinophils, and lymphocytes. Chest X-ray demonstrates some indirect signs, like lung consolidation and atelectasis. Airway reconstruction after CT scan shows higher-density opacities in the cavity (Fig. 4.17).

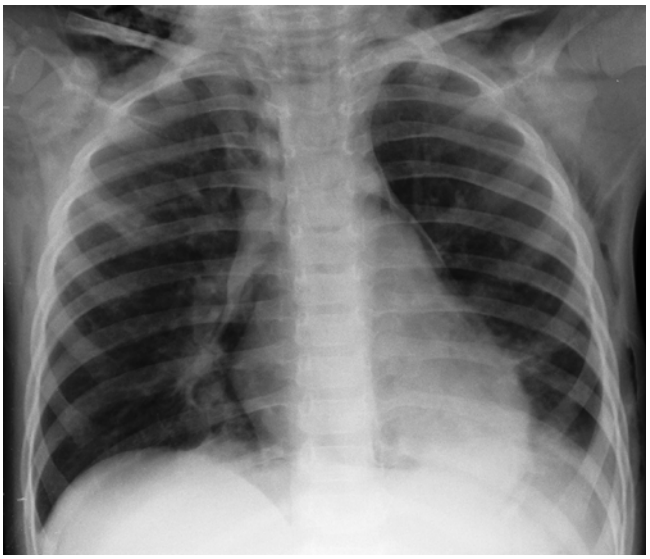

Fig. 4.16 A girl aged 3 years with influenza A (H1N1) complicated by pneumonia. Chest X-ray showed pneumomediastinum, subcutaneous pneumatosis at the neck, and pneumatosis at the left thoracic wall

4.7.1.6 Secondary Fungal Infection

The critical and severe pediatric cases of influenza A (H1N1) with respiratory complications are radiologically characterized by multiple patchy ground-glass opacities and consolidation opacities at both lungs, high incidence of pleural effusion, the more common complications of pneumonia, and pulmonary cryptococcal infection (Fig. 4.18).

4.7.2 Radiological Manifestations of the Central Nervous System

Some critical and severe pediatric patients with influenza A (H1N1) develop diseases of the central nervous system. The common complications of the central nervous system include influenza-related encephalopathy, aseptic meningitis, encephalitis, acute necrotizing encephalopathy, and secondary intracranial fungal infection.

4.7.2.1 Influenza-Related Encephalopathy

Influenza-related encephalopathy has symptoms of the central nervous system and abnormalities on EEG. However, no abnormality can be found by CSF and cranial radiology. The disease is often clinically diagnosed and radiological examination is performed to exclude other possible complications. MRI shows bilaterally symmetrical lesions at the deep white matter and basal ganglia (including the thalamus and brainstem tegmentum) of cerebral hemisphere.

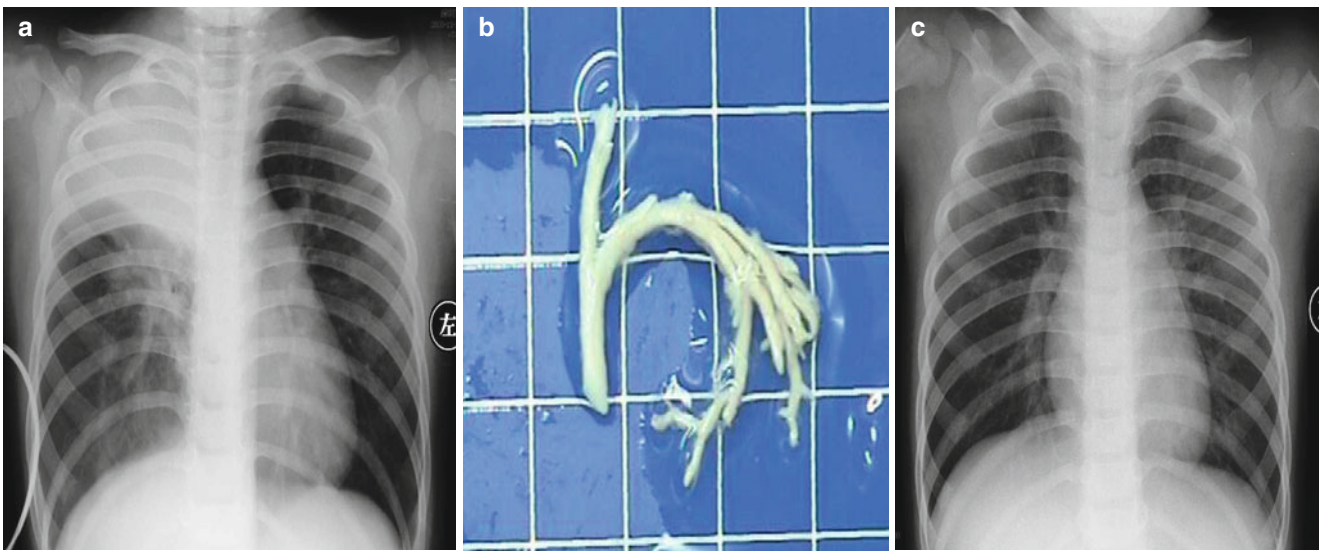

Fig. 4.17 (**a**–**c**) A boy aged 3 years with influenza A (H1N1) complicated by pneumonia. (**a**) At d 6 since onset, chest X-ray showed inverted triangle-shaped dense opacities at the right upper lung field, indicating lung consolidation and partial atelectasis. (**b**) At d 7 since onset, fibrobronchoscopy showed obstructed bronchi at the right upper lung lobe. Pathological examination of the suctions from bronchi demonstrated fibrinous exudation, large quantities of neutrophils and eosinophils, and no tumor cell, and the pathological diagnosis was plastic bronchitis. (**c**) At d 13 since onset, it was demonstrated that the original inverted triangle-shaped dense opacities at the right upper lung field disappeared

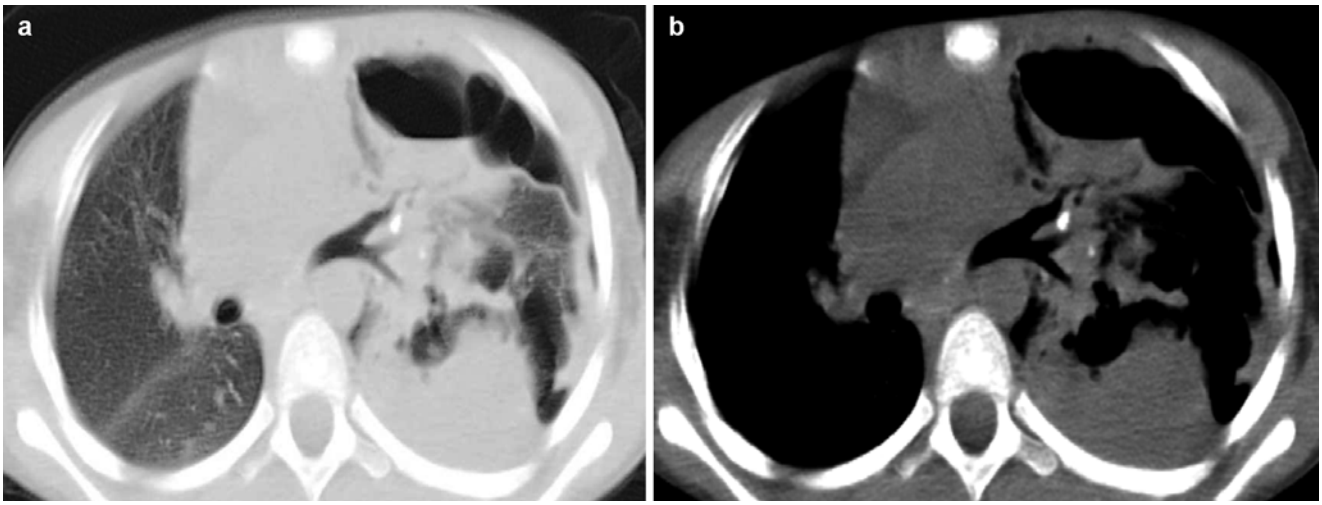

Fig. 4.18 (**a**, **b**) A girl aged 7 years with influenza A (H1N1) complicated by pneumonia and cryptococcal infection. (**a**) At d 7 since onset, plain chest CT scan showed left pneumothorax (*arrow*) in the lung window, shrinkage of the left upper lung lobe, and multiple large flaky high-density opacities at the left upper lung lobe with poorly defined borderline. (**b**) In the mediastinal window, it was demonstrated with flaky consolidation opacities at the dorsal segment of left lower lung lobe, archlike liquid-density opacities (a small quantity of left pleural effusion, *white arrow*) at the left thoracic cavity. Pleural effusion biopsy demonstrated cryptococcal infection

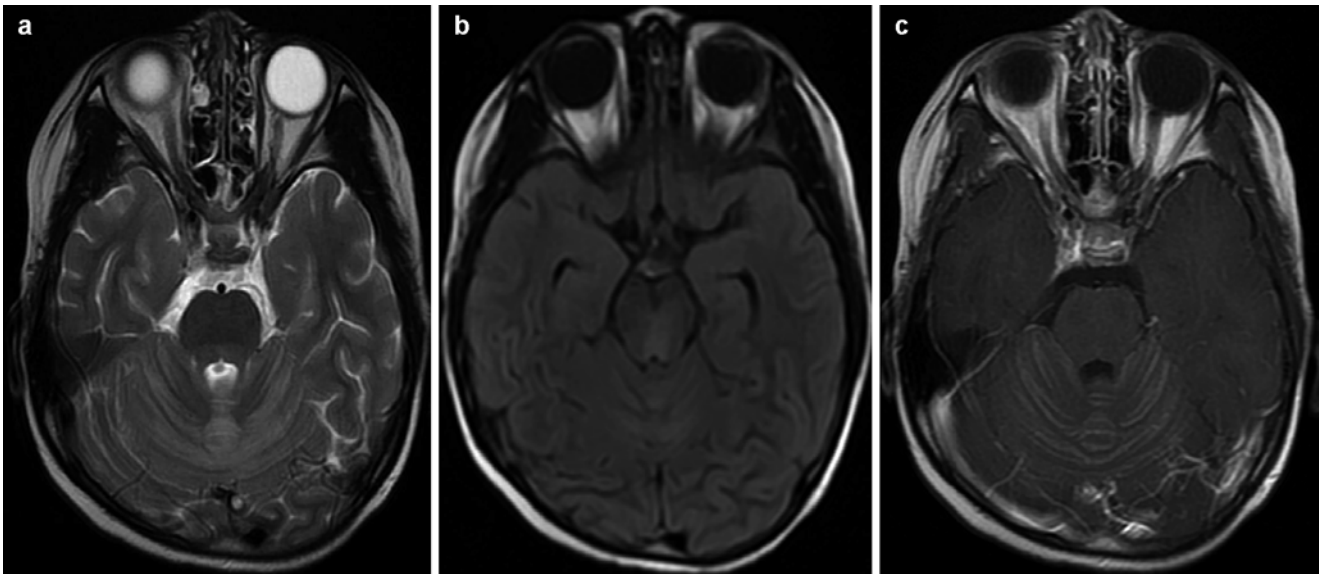

Fig. 4.19 (**a**–**c**) A boy aged 7 years with influenza A (H1N1) complicated by meningitis. (**a**) T2WI showed widened gyrus of the cerebellum. (**b**) FLAIR displayed increased signals at the sulci of cerebellum. (**c**) Contrast imaging demonstrated obvious enhancement of the cerebellar meninges

4.7.2.2 Aseptic Meningitis

Aseptic meningitis is often clinically diagnosed *Plain* MRI scan is often negative, and contrast MRI occasionally shows meningeal enhancement at both cerebrum and cerebellum that is nonspecific. The pediatric patients with aseptic meningitis commonly have a good prognosis (Fig. 4.19).

4.7.2.3 Encephalitis/Meningoencephalitis

Both have extremely rare occurrence. The lesions may be located at the frontal lobe, parietal lobe, occipital lobe, and other parts, which may involve cortical and subcortical tissues, corpus callosum, and the thalamus. The area with lesions is demonstrated with low density by CT scan, long T1 and long T2 signals by MRI, and slight or no enhancement by contrast imaging.

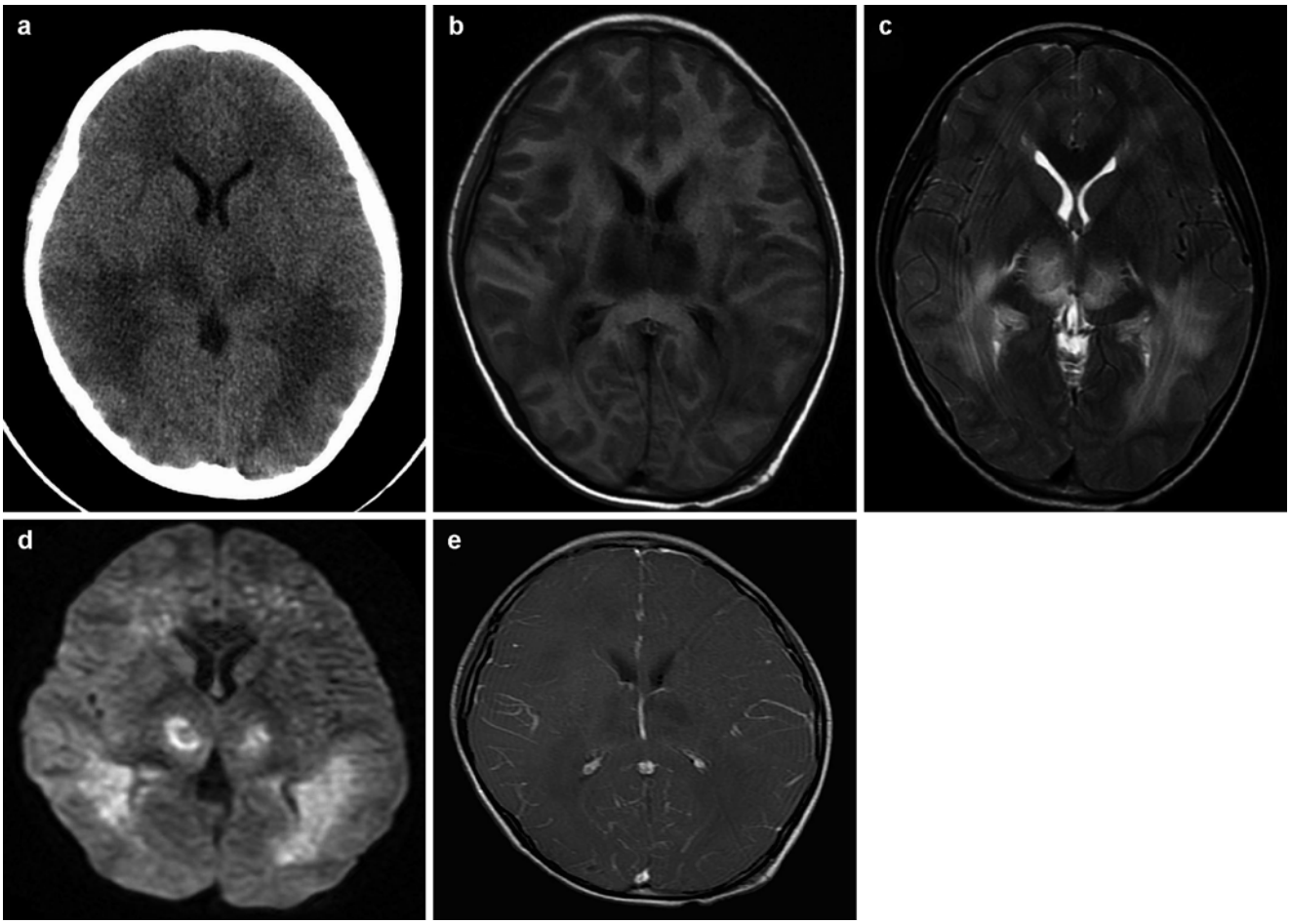

Fig. 4.20 (**a**–**e**) A boy aged 9 years with influenza A (H1N1) complicated by acute necrotizing encephalopathy. At d 4 since onset, the patient received CT and MRI scans. (**a**) Head CT scan showed symmetric low-density opacities at the bilateral thalami, posterior limb of internal capsule, lenticular nucleus, globus pallidus, optic radiation, and frontal white matters. (**b**) Head MRI showed symmetric slightly low T1WI signals at the bilateral thalami, posterior limb of internal capsule, lenticular nucleus, globus pallidus, optic radiation, and frontal white matters. (**c**) T2WI showed high signals of the above lesions;. (**d**) DWI showed centrally low signal and marginal ring-shaped high signal at the bilateral thalami and high signals of other lesions. (**e**) No enhancement of the lesions by contrast scans

4.7.2.4 Acute Necrotizing Encephalopathy

The radiological manifestations are characteristic, showing multifocal and symmetric brain lesions that are characterized by symmetric involvement of bilateral thalami. The internal capsule, lenticular nucleus, brain stem, and cerebral and cerebellar medullary substances can also be involved. The area with lesions is demonstrated with low density by CT scan, long T1 and long T2 signals by MRI, and high signals by FLAIR. By DWI, signals from the area with lesions are special, with centrally low signal and peripherally high signal of the bilateral thalami. ADC shows slightly high signal at the center that is surrounded by ring-shaped low signal (Fig. 4.20).

4.7.2.5 Secondary Intracranial Fungal Infection

Secondary intracranial fungal infection occurs in the pediatric patients mainly due to immunosuppression and long-term use of antibiotics or glucocorticoid. It may be mucor or cryptococcal infection, which is radiologically demonstrated as common fungal infection. MRI demonstrates fungal meningitis as obvious meningeal enhancement and fungal granulomas as round-like slightly long T1 and long T2 signals with marginal enhancement by contrast imaging (Fig. 4.21).

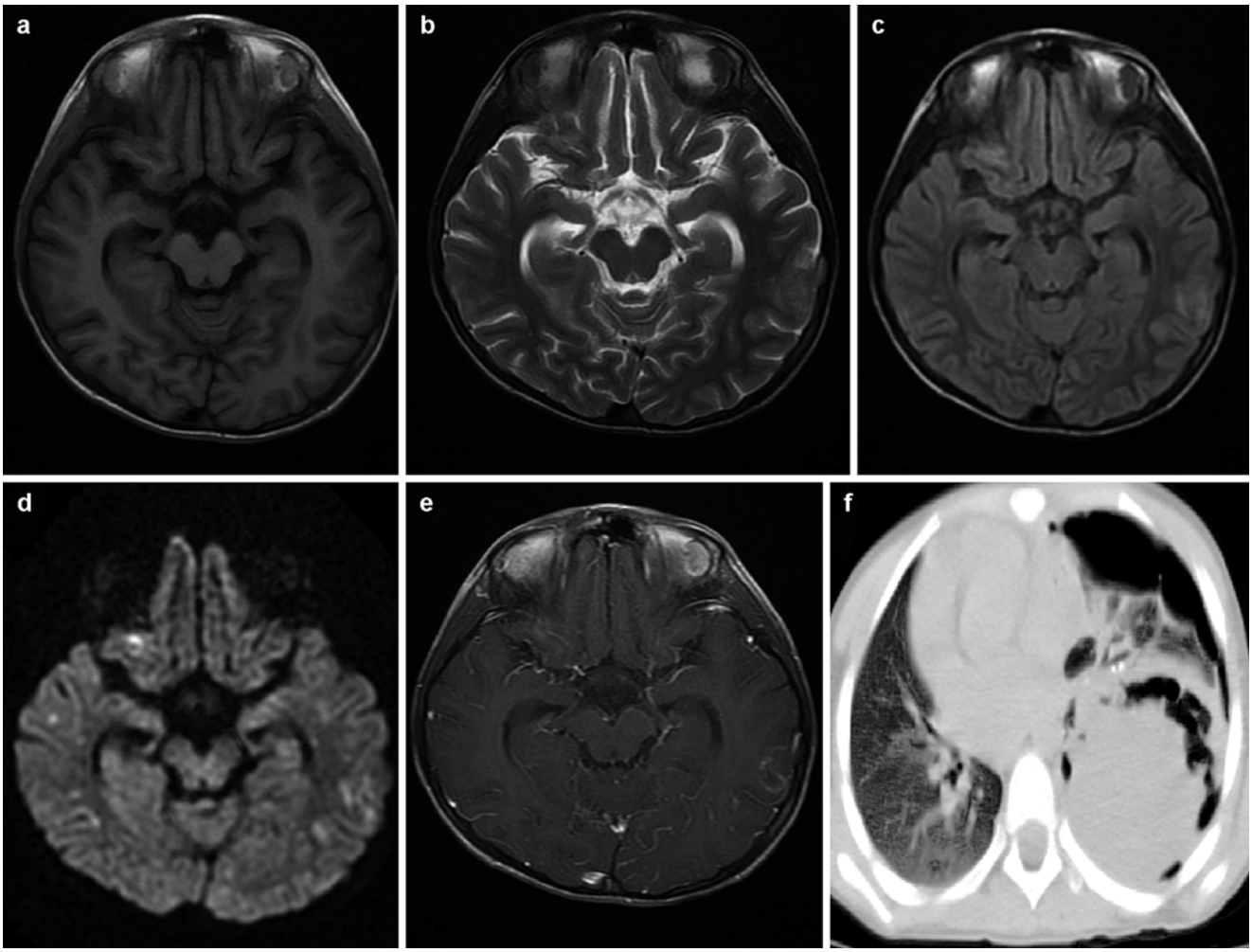

Fig. 4.21 (**a**–**f**) A boy aged 8 years with influenza A (H1N1) complicated by pneumonia and intracranial mucor infection. At d 21 since onset, the patient received head MRI. (**a**) Round-like low signal opacity at the left temporal lobe; (**b**) slightly high T2WI signals; (**c**) slightly high FLAIR signals; (**d**) high DWI signals and spotlike high signals at the right temporal lobe; (**e**) slight marginal enhancement at the left temporal nodules by contrast imaging. (**f**) The patient was diagnosed with fungal infection, with pneumothorax and large flaky opacities at the chest

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