Radiological findings of pneumonia in patients with swine-origin influenza A virus (H1N1)

Aspetti radiologici della polmonite da influenza suina (virus H1N1)

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Abstract

Purpose. During spring 2009, a pandemic swine-origin influenza A (H1N1) virus (S-OIV) emerged and spread globally. We describe the chest X-ray and computed tomography (CT) findings of 40 patients with pneumonia due to S-OIV observed in our institution.

Materials and methods. Among 534 patients with S-OIV, according to the US Centers for Disease Control and Prevention case definition, seen between June and November 2009, 121 underwent chest X-ray and 40 (median age 44 years, range 16–79) had pneumonia. The initial chest radiographs were evaluated for pattern, distribution and extent of lung abnormalities. Unenhanced chest CT scans were performed in two patients and were reviewed for the same findings. Underlying medical conditions were present in 42% of patients (17/40).

Results. Our patients had predominantly mild illness, and pneumonia was observed in 40 individuals (40/121 patients who had chest X-rays, 33%; and 40/534 patients with S-OIV, 7.5%). However, S-OIV can cause severe illness requiring admission to the intensive care unit for advanced mechanical ventilation and extracorporeal life support, including adult respiratory distress syndrome (ARDS) and death. The major radiological abnormalities observed were interstitial changes (60.0%), with (22.0%) or without patchy ground-glass appearance, mostly bilateral, and located in the lower lung zones (7.5%). Extensive disease was seen in 37.5% (15/40), and ARDS was observed in three individuals (0.30%) with underlying medical conditions. Subtle pleural effusion was noted in four patients.

Riassunto

Obiettivo. Scopo dello studio è quello di descivere i quadri di presentazione radiologica della polmonite determinata dal virus influenzale A (H1N1), durante la pandemia sviluppatisi nella primavera del 2009.

Materiali e metodi. Nel periodo compreso tra giugno e novembre 2009 abbiamo identificato, mediante radiografia del torace, 40 polmoniti in pazienti con influenza A (H1N1), (età mediana 44 anni, range 16–79 anni). I radiogrammi relativi all’esame del torace effettuato al momento del ricovero e la tomografia computerizzata, eseguita in due casi, sono stati valutati relativamente al quadro di presentazione, alla distribuzione e all’estensione delle anormalità identificate. Il 42% dei pazienti (17/40) con polmonite presentava comorbilità.

Risultati. Nella nostra casistica, i pazienti hanno presentato prevalentemente un quadro clinico di media gravità e la polmonite ha complicato l’influenza in 40 di essi (40/121 [33%] pazienti con radiografia del torace e 40/534 [7,5%] pazienti con influenza A). In questi casi può rendersi necessario il ricovero presso reparti di rianimazione, poiché l’influenza può provocare complicazioni gravi fino alla acute respiratory distress syndrome (ARDS) e alla morte. Il quadro di presentazione radiologica più frequentemente osservato è stato l’impegno interstiziale (60%), con (22%) o senza consolidamenti multifocali a vetro smerigliato, bilaterali (70%) e localizzati nei campi polmonari inferiori (70%). Alterazioni parenchimali diffuse sono state identificate nel 37,5% dei casi (15/40) e la ARDS si è manifestata in tre pazienti (7,5%), tutti con comorbilità. Il versamento pleurico era presente in quattro casi.
Conclusions. In our series, the most frequent pneumonia patterns observed during S-OIV (H1N1) virus were interstitial changes and patchy ground-glass appearance, mostly bilateral, and located in the lower lung zones. CT, performed in severely ill patients, confirmed the ARDS identified with chest X-rays, better depicting the features and extent of lung abnormalities.

Keywords S-OIV A (H1N1) · Viral pneumonia · Chest radiograph · CT

Introduction

Swine-origin influenza A virus (S-OIV) (H1N1) was first reported in Mexico in late March 2009, and rapidly spread throughout the world. Epidemiological data suggest that the newly emerged H1N1 virus had relatively low virulence [1]. It is believed that the mechanism of transmission of S-OIV is predominantly by droplet secretions [2]. The clinical manifestations mostly consist of mild illness [3], even though, as in the case of seasonal influenza [4, 5], S-OIV can cause severe illness and death, above all in persons with underlying medical conditions. The role of radiological imaging is identifying pulmonary complications and depicting severe cases early in the course of the disease. In this paper, we review the chest radiographic and computed tomography (CT) findings observed in 40 individuals with pneumonia and S-OIV H1N1 infections.

Materials and methods

Between June and November 2009, 534 patients fulfilling the US Centers for Disease Control and Prevention (CDC) clinical criteria for the diagnosis of S-OIV [6] were observed in our institution. Among 121 of these individuals who underwent chest radiography on admission, 40 had findings consistent with pneumonia. These patients formed our study population. S-OIV was subsequently confirmed by polymerase chain reaction (PCR) in all these individuals. The study population included 24 men, median age 44 years (range, 16–79 years); in all cases S-OIV was confirmed with the identification of the virus mediante polymerase chain reaction (PCR) dedicata. Tutti i pazienti avevano febbre con temperatura superiore a 38°C e uno o più sintomi clinici di malattia respiratoria. In 17 soggetti coesistevano una o più condizioni di comorbilità (obesità, infezione da virus per l’immunodeficienza umana [HIV], chronic obstructive pulmonary disease [COPD], asma bronchiale, fibrosi, diabete).

Gli esami radiografici del torace eseguiti al momento del ricovero sono stati effettuati nelle 2 proiezioni standard,
The admission chest radiographs in the standard posteroanterior and lateral views were obtained with Opera G 650 rad-RT20 radiographic equipment (General Medical Merate, Seriate, Italy) at 110–140 kV, 12 mAs and 200–cm film-focus distance. The anteroposterior bedside radiographic examinations were performed with portable equipment TMXR plus (General Electric Medical System, Milwaukee, WI, USA) using 90 kV, 5 mAs and 150-cm film-focus distance. Images were evaluated on high-resolution monitors (2,048×2,560 pixels, display gradation 1,021, 10-bit), maximum brightness 750 cd/m², LCD display device 54 cm) of the Picture Archiving and Communication System (PACS 5.1, Kodak Carestream, Rochester, NY, USA).

Two patients underwent unenhanced helical CT with a HiSpeed scanner (General Electric Medical System). CT was performed at a table speed of 15 mm/s, 5-mm collimation and a 5-mm reconstruction interval. CT scans were displayed on monitors with window setting appropriate for lung parenchyma and mediastinum (2,048×2,560 pixels, display gradation 1,021, 10-bit), maximum brightness 750 cd/m², LCD display device 54 cm) of the PACS system. Three experienced, board-certified radiologists (LR, EBR, VS) independently reviewed the radiographs obtained on admission, and consensus was reached in all cases.

The chest radiographs and CT scan were assessed for the presence and distribution of the following findings: (1) reticular opacities, (2) ground-glass opacities, (3) nodular opacities, (4) parenchymal consolidation, (5) pleural effusion, and (6) adenopathies. In accordance with the Fleischner Society Glossary [7, 8], reticular opacities were defined as linear opacities forming a mesh-like pattern, which may be thin or thick and coarse. Ground-glass opacities were defined as hazy areas of increased attenuation with preservation of bronchial/vascular markings and without obscuration of the ribs. Nodular opacities were defined as focal round opacities, with a diameter no greater than 7 mm. Consolidation was an opacification of the parenchyma with obscuration of the underlying anatomical structures. A mixed pattern denoted a combination of ground-glass opacities, dense consolidations and reticular opacities. Distribution was categorised as bilateral or unilateral, focal, patchy or diffuse. Focal was defined a single focus of abnormality, patchy as more than one focus and diffuse when abnormalities involved three or more lung zones. The predominant distribution was also assessed as being in the upper (above the level of the anterior end of the third rib), middle (between the third and fifth anterior ribs) or lower (below the level of the anterior end of the fifth rib) lung zones.
Results

All chest radiographs obtained on admission were interpreted prospectively and retrospectively as abnormal. The imaging findings are summarised in Table 1. The predominant chest radiographic findings were interstitial changes (Fig. 1), which constituted the sole finding in 37.5% (15/40).

Table 1

| Pattern of radiographic abnormality | No. patients = 40 | Percent |
|-----------------------------------|-------------------|---------|
| Interstitial changes               | 15                | 37      |
| Ground-glass opacities (GGO)       | 5                 | 12      |
| Centrilobular nodules              | 2                 |         |
| Consolidation                      | 2                 |         |
| Dystelectasis                      | 5                 |         |
| GGO + consolidation               | 3                 |         |
| GGO + interstitial changes         | 9                 | 22      |
| Mixed pattern                      | 6                 | 15      |
| Acute respiratory distress syndrome| 3                 | 0.7     |

Distribution

| Distribution                      |         |
|-----------------------------------|---------|
| Unilateral involvement            | 11      |
| Bilateral involvement             | 28      |

Extent on initial imaging

| Extent on initial imaging          |         |
|-----------------------------------|---------|
| Focal                             | 4       |
| Patchy                            | 5       |
| Diffuse (3 or more involved zones)| 15      |

Predominance

| Predominance                      |         |
|-----------------------------------|---------|
| Upper zones                       | 2       |
| Middle zones                      | 5       |
| Lower zones                       | 28      |
| Pleural effusion                  | 4       |

Distribution

| Distribution                      |         |
|-----------------------------------|---------|
| Unilaterale                       | 11      |
| Bilaterale                        | 28      |

Table 1 Segni radiografici e di TC in pazienti con polmonite e influenza suina

| Quadrhi radiologici               | Numero pazienti = 40 | Percentuale |
|-----------------------------------|----------------------|-------------|
| Impegno interstiziale             | 15                   | 37          |
| Opacità a vetro smerigliato (VS)  | 5                    | 12          |
| Nodali centrilobulari             | 2                    |             |
| Consolidamenti                    | 2                    |             |
| Distelectasie                     | 5                    |             |
| Consolidamenti + VS               | 3                    |             |
| Impegno interstiziale + VS        | 9                    | 22          |
| Quadri misti                      | 6                    | 15          |
| Acute respiratory distress syndrome| 3                   | 0.7         |

Distribution

| Distribution                      |         |
|-----------------------------------|---------|
| Unilaterale                       | 11      |
| Bilaterale                        | 28      |

Extent nel primo esame radiografico

| Extent                             |         |
|-----------------------------------|---------|
| Focale                            | 4       |
| Multifocale                       | 5       |
| Diffusa (3 o più zone)            | 15      |

Predominanza

| Predominanza                      |         |
|-----------------------------------|---------|
| Campi polmonari superiori         | 2       |
| Campi polmonari medi              | 5       |
| Campi polmonari inferiori         | 28      |
| Versamento pleurico               | 4       |
of the patients. Ground-glass opacities (Fig. 2) associated with interstitial changes were the second most common predominant finding, found in 22.5% (9/40). A mixed pattern (Fig. 3), a combination of ground-glass opacities, dense consolidations and reticular opacities, was observed in 15% (6/40). The lung abnormalities were bilateral in 70% (28/40) and most commonly found in the lower lung zones 70% (28/40) (Fig. 4). Extensive disease (Fig. 4) was seen in 37.5% (15/40), and acute respiratory distress syndrome (ARDS) (Figs. 5, 6) was observed in three individuals (7.5%). Significant lymph node enlargement was not identified in any chest X-ray. Subtle pleural effusions were seen in four patients.

Two patients with severe illness and ARDS identified on chest radiography were also studied with CT, which confirmed the ARDS pattern, better depicting the features and extent of lung abnormalities. One of the patients, despite showing improvement of lung disease at subsequent CT, unfortunately died from cerebral ischaemia confirmed at the postmortem examination. Follow-up radiographs (F-Ur) were never performed in individuals with rapid clinical recovery. Among the F-Ur available, advanced improvement of the abnormalities were always depicted. In our series, the influenza virus infection did not lead to secondary bacterial pneumonia in any individual.

In corrispondenza delle regioni medio-basali bilaterali consolidamenti parenchimali a stria, compatibili con ateleattasia, e impegno interstiziale. 

Vetro smerigliato (Fig. 2) associato ad alterazioni interstiziali è stato identificato nel 22,5% (9/40) dei casi. Il quadro di presentazione misto (Fig. 3), costituito da una combinazione di vetro smerigliato, consolidamenti parenchimali densi e opacità reticolari, è stato osservato nel 15% dei pazienti (6/40). L’impegno parenchimale è stato bilaterale nel 70% dei casi (28/40), più comunemente i campi polmonari interessati sono stati quelli inferiori 70% (28/40) (Fig. 4). L’impegno parenchimale è stato diffuso in 15 dei 40 pazienti (37,5%), con evoluzione in acute respiratory distress syndrome (ARDS) (Figg. 5, 6) in 3 casi (7,5%). Non abbiamo mai rilevato la presenza di adenopatia. In 4 pazienti abbiamo identificato un versamento pleurico di modesta entità.

Due pazienti con malattia clinicamente grave e ARDS identificato con la radiografia del torace, sono stati studiati anche con TC, che ha meglio rilevato la presenza e l’estensione delle anormalità polmonari già rilevate. Uno di questi soggetti, pur mostrando un miglioramento della patologia polmonare nella TC di controllo, è morto per ischemia cerebrale confermata dall’autopsia. Non abbiamo mai effettuato controlli radiografici nei pazienti con rapido miglioramento clinico e nei pazienti sottoposti a monitoraggio la guarigione radiologica è sempre stata rapida. Nessuna
Fig. 3 A 16-year-old man with swine-origin influenza virus. Chest X-ray shows patchy ground-glass opacity, interstitial changes and confluent centrilobular nodules. The lung abnormalities were unilateral and extensive, involving three lung zones.

Fig. 3 Maschio di 16 anni affetto da S-OIV. La radiografia del torace rileva la presenza di multipli focolai di consolidamento a vetro smerigliato associati a noduli centro-lobulari, anche confluenti, e impegno interstitialle. Le alterazioni sono unilaterali e impegnano tre campi polmonari.

Fig. 4 A 54-year-old man with swine-origin influenza virus. Chest X-ray shows patchy, bilateral areas of ground-glass opacity in both lower zones, associated with interstitial changes.

Fig. 4 Maschio di 54 anni affetto da S-OIV. La radiografia del torace mostra in sede basale bilaterale la presenza di multipli focolai di consolidamento a vetro smerigliato associati a impegno interstiziale.

Fig. 5 A 25-year-old man with swine-origin influenza virus and acute respiratory distress syndrome (ARDS). Chest X-ray shows bilateral areas of dense consolidation and ground-glass opacities. Lung involvement was extensive, consistent with ARDS.

Fig. 5 Maschio di 25 affetto da S-OIV e ARDS. La radiografia del torace identifica focolai di consolidamento parenchimale, densi e a vetro smerigliato. L’impegno polmonare è diffuso e compatibile con ARDS.

Fig. 6 A 58-year-old man with swine-origin influenza virus and acute respiratory distress syndrome (ARDS). Computed tomography scans shows the ARDS previously identified by radiography but better depicts the extent and pattern of the abnormalities.

Fig. 6 Maschio di 58 anni affetto da S-OIV e ARDS. La TC conferma la presenza di ARDS, già rilevata mediante la radiografia del torace, meglio rappresentandone l’estensione e gli aspetti semeiologici.
Discussion

Influenza virus belongs to the orthomyxovirus family of RNA viruses, and human disease is predominantly caused by type A, the most virulent, which can easily mutate [9]. Many subtypes of type A have been identified on the basis of the occurrence of surface glycoproteins, haemagglutinin (H) and neuraminidase (N). The 2009 H1N1 virus contained a unique combination of gene segments that had not previously been identified in humans or animals [10, 11].

Whereas the elderly and young children are at high risk for seasonal influenza, H1N1-related illness predominantly affects young individuals. The possible explanation for this phenomenon includes the fact that the young have a greater susceptibility to the virus, as proven on the basis of serological studies [12, 13]. Another reason might be that elderly people have some level of cross-reactive neutralising antibodies to the H1N1 virus [14]. However, it is also possible that there is a case-ascertainment bias because more young people are tested as part of outbreak investigations in schools [15].

The majority of S-OIV infections reported has been mild illness. However, the pandemic strain of H1N1 virus can cause severe illness, including pneumonia and ARDS [16–19]. In a pattern similar to patients with seasonal influenza, patients with severe illness had a high prevalence of underlying medical conditions [20, 21]. Risk factors for severe S-OIV illness are obesity, pulmonary diseases, cardiac diseases, neurological diseases, immunosuppression and pregnancy [16–19]. One contributing factor for death during H1N1 infection may be delayed admission and/or delayed initiation of therapy [16, 19]. Concurrent bacterial infection does not appear to be a contributing factor to the severity of illness, and lung damage was mostly due to the primary effect of infection with influenza virus [16–19]. Possible mechanisms of damage include direct injury to the respiratory epithelium with a secondary cytokine storm [22].

The radiographic findings in viral pneumonia consist of interstitial changes, ground-glass opacities, centrilobular nodules and consolidation. These findings are variable and overlapping [23] and reflect the variable extent of the underlying histopathological features. The most prominent histological changes are seen in the bronchial epithelium and in the adjacent interstitial tissue. Necrosis and desquamation of the epithelial cells in the bronchial lumen, associated with endoluminal exudates, may produce obstructions. The mononuclear cells infiltrate the bronchial wall, and the inflammation may extend to the adjacent interstitial tissue. The radiological features of those changes are dystelectasis, with consolidations or air trapping [24, 25] and/or centrilobular nodules.

superinfezione polmonare batterica è stata identificata nella popolazione in studio.

Discussione

Il virus dell’influenza appartiene alla famiglia degli virus a RNA Orthomixovirus. La malattia umana è generalmente provocata dal tipo A, il più virulento, che può facilmente mutare [9]. Esistono una grande quantità di sottotipi del virus A, identificati per la presenza di glicoproteine, emoagglutinine (H) e neuraminidasi (N), sulla membrana di superficie. Il virus H1N1 identificato nel 2009 contiene una combinazione genetica mai identificata precedentemente nell’uomo e negli animali [10, 11].

L’influenza H1N1 colpisce prevalentemente soggetti giovani, al contrario dell’influenza stagionale per la quale i bambini e gli anziani sono le popolazioni a rischio più elevato di malattia. Una delle possibili spiegazioni di questo fenomeno, comprovata da studi sierologici, è la grande susceptibilità dei giovani al virus [12, 13]. Un’altra ragione potrebbe essere la presenza di livelli di anticorpi adeguati al controllo del virus prodotti dalle persone anziane [14]. I dati statistici potrebbero comunque essere inquinati per un errore di campionamento, che viene effettuato prevalentemente nei giovani, in corrispondenza dell’insorgenza di epidemie scolastiche [15].

La maggior parte delle influenze suine segnalate hanno presentato un decorso clinico di media gravità, ma il virus H1N1 è in grado di provocare malattia grave con polmonite e ARDS [16–19]. I pazienti con malattia grave hanno presentato un’alta prevalenza di comorbidità [20, 21], come accade in corso di influenza stagionale. I fattori di rischio correlati all’insorgenza di malattia grave sono: l’obesità, le malattie cardiache, neurologiche e polmonari pre-esistenti, l’immunosoppressione, la gravidanza [16–19].

Un ritardo nel ricovero e/o nell’inizio della terapia rappresentano un fattore prognostico negativo fino al decesso [16, 19]. In questi casi fatali le superinfezioni batteriche non hanno contribuito alla severità della malattia e il danno polmonare è stato essenzialmente provocato proprio dal virus. I possibili meccanismi di danno includono infatti l’azione del virus sull’epitelio respiratorio, diretta e indiretta per la successiva liberazione di citochine nell’ambito di complessi meccanismi flogistici [22].

I segni radiologici della polmonite virale consistono di alterazioni interstitiali, opacità a vetro smerigliato, noduli centrilobulari, consolidamenti, variamente rappresentati, e riflettono la presenza e l’estensione dei fenomeni istopatologici sottostanti [23]. Le principali alterazioni si osservano a livello dell’epitelio bronchiale e dell’adiacente tessuto interstiziale. Necrosi e desquamazione dell’epitelio nel lume bronchiale, in concomitanza con l’essudazione endoluminale,
Interstitial thickening may produce reticular or linear opacities. Parenchymal inflammation initially involves the air space adjacent to the terminal and respiratory bronchioles. Variable extension and amount of exudate occur. Imaging findings are ground-glass opacities or dense consolidations.

Rapidly progressive pneumonia may be seen, particularly in patients with underlying medical conditions; in these cases, the lung histologically shows diffuse alveolar damage, comprising interstitial lymphocyte infiltration, airspace haemorrhage, oedema and hyaline membrane formation [26, 27]. In these cases chest X-ray and CT show the ARDS pattern [25, 28]. Pleural effusion is rare.

The literature data [16–19] show that also in S-OIV-related pneumonia, the radiographic pattern is consistent with the nonspecific pattern of viral pneumonia. In our series, the major radiological abnormalities were interstitial changes, with or without patchy ground-glass opacities and centrilobular nodules, mostly bilateral and located in the lower lung zones. These data differ considerably from the literature data [16–19] in which the most prevalent pattern is patchy ground-glass opacities, more frequently bilateral and located in lower zones.

In our series, extensive lung abnormalities with involvement of three or more lung zones were observed in 37.5% of patients, and ARDS was observed in three patients, all with underlying medical conditions. CT was performed only three times in our series, as it is known that it does not add information in patients with evident radiographic abnormalities, leading to only a modest increase in diagnostic accuracy [29, 30]. On the contrary, incipient and/or overt ARDS should be further investigated with CT, which is more sensitive and specific than radiography for detecting thoracic abnormalities and may be useful for guiding treatment decisions in critical patients, providing a more accurate evaluation of the extent and distribution of the disease.

In conclusion, S-OIV-related pneumonia does not differ in radiographic presentation from the other viral pneumonias, and it may evolve into ARDS. Therefore, during S-OIV, recognition of the radiological findings of pneumonia is imperative for determining appropriate management. Chest radiograph is an effective and adequate tool for identifying S-OIV-related pneumonia, whereas CT is helpful in individuals with severe illness to depict incipient ARDS and to orient prompt therapeutic management.
References/Bibliografia

1. Centers for Disease Control and Prevention (2009) Update: Novel influenza A (H1N1) virus infections - worldwide, May 6, 2009. MMWR Morb Mortal Wkly Rep 58:453–445
2. Han K, Zhu X, He F et al (2009) Lack of airborne transmission during outbreak of pandemic (H1N1) 2009 among tour group members, China, June 2009. Emerg Infect Dis 15:1578–1581
3. Centers for disease control and Prevention (2009) H1N1 flu situation update. www.cdc.gov/h1n1flu/casedef.htm. Accessed April 2010
4. Tillett HE, Smith JW, Clifford RE (1980) Excess morbidity and mortality associated with influenza in England and Wales. Lancet 1:793–795
5. Thompson WW, Shay DK, Weintraub E et al (2004) Influenza–associated hospitalizations in the United States. JAMA 292:1333–1340
6. Centers for Disease Control and Prevention (2009) Interim guidance on case definitions for swine influenza A (H1N1) human case investigations. http://www.cdc.gov/h1n1flu/casedef.htm. Accessed April 2010
7. Tuddenham WJ (1984) Glossary of terms for CT of the lungs: recommendations of the Nomenclature Committee of the Fleischner Society. AJR Am J Roentgenol 143:509–517
8. Austin JH, Muller NL, Friedman PJ et al (1996) Glossary of terms for CT of the lungs: recommendations of the Nomenclature Committee of the Fleischner Society. Radiology 200:327–331
9. García-García J, Ramos C (2006) Influenza, an existing public health problem. Salud Publica Mex 48:244–267
10. Novel Swine-Origin Influenza A (H1N1) Virus Investigation Team (2009) Emergence of a novel swine-origin influenza A (H1N1) virus in humans. N Engl J Med 360:2605–2615
11. Garten RJ, Davis CT, Russel CA et al (2009) Antigenic and genetic characteristics of swine-origin 2009 A (H1N1) influenza viruses circulating in humans. Science 325:197–201
12. Hancock K, Veguilla V, Lu X et al (2009) Cross-reactive antibody responses to the 2009 pandemic H1N1 influenza virus. N Engl J Med 361:1945–1952
13. Cate TR, Kassel JA, Couch RB et al (1977) Clinical trials of bivalent influenza A/New Jersey/76- A/Victoria/75 vaccines in the elderly. J Infect Dis 136[Suppl]:S518–S525
14. Dolin R, Wise TG, Mazur MH et al (1977) Immunogenicity and reactogenicity of influenza A/New Jersey/76 virus vaccines in normal adults. J Infect Dis 136[Suppl]:S435–S442
15. Jordan H, Mosquera M, Nair H, France A (2009) Swine-origin influenza A (H1N1) virus infections in a school - New York city, April 2009. MMWR Morb Mortal Wkly Rep 58:470–472
16. Perez-Padilla R, de la Rosa-Zamboni D, Ponce de Leon S et al (2009) Pneumonia and respiratory failure from swine-origin influenza A (H1N1) in Mexico. N Eng J Med 361:680–689
17. Mollura DJ, Aspis DS, Conetta R et al (2009) Imaging findings in a fatal case of pandemic swine-origin influenza A (H1N1). AJR Am J Roentgenol 193:1500–1503
18. Agarwal PP, Cinti S, Kazerouni EA (2009) Chest radiographic and CT findings in novel swine-origin influenza A (H1N1) virus infection. AJR Am J Roentgenol 193:1488–1493
19. Jain S, Kamimoto L, Bramley AM et al (2009) Hospitalized patients with 2009 H1N1 influenza in the United States, April-June 2009. N Eng J Med 361:1935–1944
20. Walsh EE, Cox C, Falsey AR et al (2002) Clinical features of influenza A in older hospitalized persons. J Am Geriatr Soc 50:1498–1503
21. McGeer A, Green KA, Plevneshi A et al (2007) Antiviral therapy and outcomes of influenza requiring hospitalisation in Ontario, Canada. Clin Infect Dis 45:1568–1575
22. Ng WF, To KF, Lam WW et al (2006) The comparative pathology of severe acute respiratory syndrome and avian influenza A subtype H5N1 - a review. Hum Pathol 37:381–390
23. Kim EA, Lee KS, Primack SL et al (2002) Viral pneumonias in adults: radiologic and pathologic findings. Radiographics 22:137–149
24. Han BK, Son JA, Yoon HK, Lee SI (1998) Epidemic adenoviral lower respiratory tract infection in pediatric patients: radiographic and clinical characteristics. AJR Am J Roentgenol 170:1077–1080
25. Palmer SM Jr, Henshaw NG, Howell DN et al (1988) Community respiratory viral infection in adult lung transplant recipients. Chest 113:944–950
26. Feldman PS, Cohan MA, Hierholzer WJ Jr (1972) Fatal Hong Kong influenza: a clinical microbiological and pathological analysis of nine cases: Yale J Biol Med 45:49–63
27. Yeldandi AV, Colby TV (1994) Pathologic features of lung biopsy specimens from influenza pneumonia cases. Hum Pathol 25:47–53
28. Cortese G, Nicali R, Placido R et al (2008) Radiological aspects of diffuse alveolar haemorrhage. Radiol Med 113:16–28
29. Hommeyer SH, Godwin JD, Takasugi E (1991) Computed tomography of air-space disease. Radiol Clin North Am 29:1065–1084
30. Kang E, Staples CA, McGuinness G et al (1996) Detection and differential diagnosis of pulmonary infections and tumors in patients with AIDS: value of chest radiography versus CT. AJR Am J Roentgenol 66:15–19