The virus-drug-host dynamics in the tomographic charaterization of pulmonary influenza A (H1N1) infection – a clinical-radiological-pathological view

O trinômio vírus-droga-hospedeiro na caracterização tomográfica da infecção pulmonar por influenza A (H1N1) – uma visão clínico-radiológico-patológica

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Common cold and flu refer to different clinical entities. Common cold is a benign and self-limited syndrome comprising a group of diseases caused by different virus families[1]. Approximately 200 virus subtypes are associated with common cold. Rhinovirus, with more than 100 serotypes, is collectively the most common virus (30% to 50% of the cases), while coronavirus accounts for 10% to 15% of the cases. The symptoms predominate in the upper airways and there is little systemic repercussion. Complications or death are not common[1].

Flu, or seasonal influenza, is caused by the influenza A and B viruses, and predominates in the winter in the form of outbreaks or epidemics. It manifests with signs and symptoms in the upper and lower airways and remarkable systemic involvement. The non-complicated condition, although followed by acute and debilitating symptoms, is usually self-limited. For susceptible individuals, the seasonal influenza brings greater risk for morbidity and mortality (complicated presentation). The incubation period ranges from 1 to 4 days[2]. Seasonal influenza is responsible for 200,000 hospital admissions and 41,000 deaths per year in the United States of America (seventh cause of deaths)[3].

The seasonal influenza viruses are included in the Orthomyxoviridae family and are classified into A, B, or C. The influenza A virus can be found in humans, other mammals, and in birds, and, among them, is the only historically responsible for pandemics. The B and C types, although previously identified only in humans, were also isolated in seals and pigs, respectively. Influenza A and B viruses are more relevant than influenza C virus for human beings and cause more severe infections. The latter may cause respiratory infections in children with less than 6 years of age. Usually, the exposure to influenza C virus during the childhood usually causes protection against new infections in adulthood[2].

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Influenza A virus is an obligate intracellular parasite classified according to the surface glycoproteins, namely, hemagglutinin and neuraminidase. While hemagglutinin binds to the sialic acid of the host's cells so that the virus is incorporated and starts controlling cell metabolism promoting its destruction, the neuraminidase is important for its release and propagation. Thus the HxNx nomenclature derives from the specific number of the hemagglutinin and of the neuraminidase. There are currently 16 types of hemagglutinins (H1-H16) and 9 of neuraminidases (N1-N9), all of them already identified in domestic and wild birds. Three types of hemagglutinins (H1-H3) and two types of neuraminidases (N1-N2) cause disease of great epidemiological impact in human beings (H1N1, H2N2, H3N2). Sporadic cases or outbreaks of H7N3, H7N7, H9N2 and H10N7 have occurred in human beings. Currently, two subtypes of influenza A rage among human beings: H1N1 and H3N2. Such a nomenclature is extremely important as changes occurred in the antigens of hemagglutinins and, to a lesser scale, of neuraminidases, result in exposure to strains against which the population has little or no immunity[2].

Although several flu epidemics were recognized in the 20th century, three well-defined pandemics caused by antigenic subtypes of influenza A were described, whose probable original foci were identified[4]. The Spanish flu (1918), caused by H1N1 was responsible for more than 40 million deaths; the Asian flu (1957), caused by H2N2, for 2 million deaths; and the Hong Kong flu (1968), associated with H3N2, caused 700 thousand deaths[4]. In March 2009, the first influenza A pandemic of the 21st century occurred, originating from Mexico and caused by H1N1 of swine origin[5]. The clinical signs ranged from a mild and self-limited infection to rapidly evolving pneumonia. In more severe cases, respiratory failure manifested at the first 48 hours. By December 2009, 208 countries had reported cases of the pandemic, and 10,000 deaths were recorded. In August of 2010, the World Health Organization announced the control of the pandemic with recorded 18,500 fatal victims. The highest number of deaths occurred in those cases of

obese individuals and in those with comorbidities[6]. Curiously, 6.4% of the cases and 4.3% of the deaths occurred in pregnant patients[7]. Although the pandemic was controlled and the population is more protected as a result from previous exposure to the virus and vaccination, the infection by influenza A (H1N1) virus is still producing victims around the world.

The characterization of tomographic patterns of pneumonia caused by influenza A (H1N1) depends directly on histopathological changes which, on their turn, result from interactions between the pathogen virulence and the immune response from the host. Furthermore, the effective management and the early institution of therapy can reduce symptoms, abbreviate the course of the disease and reduce the rates of mortality and complications, possibly producing significant impact on imaging studies. Bacterial coinfection that is present in most cases impairs the interpretation of tomography findings.

In 2011, Sheng et al.[8] reviewed the clinical, pathological, bacteriological and virological findings of 68 fatal cases of North-American soldiers who were victims of the 1918 influenza pandemic (Spanish flu). In all of the cases there were histopathological evidences of bacterial pneumonia, and abundant Gram-positive bacteria in 94% of the cases (coinfection). *Streptococcus pneumoniae*, *Streptococcus pyogenes* and *Staphlyococcus aureus* were the most frequently found bacteria. The predominant histological findings were bronchitis, bronchiolitis and diffuse alveolar damage (acute, proliferative and chronic phases), besides the evidences of tissue repair and remodeling. Gill et al.[9] have analyzed autopsies of 34 proven fatal cases of influenza A (H1N1) infection occurred in the 2009 pandemic. Tracheitis, bronchitis and bronchiolitis with ulceration, epithelial denudation, inflammatory infiltrates in the submucosa and focal squamous metaplasia were the main histological findings in the airways. Diffuse alveolar damage – comprising edema, acute alveolar hemorrhage and formation of hyaline membrane – were found in most cases. Acute or organizing, diffuse alveolar damage was identified in individuals who were hospitalized for 3.7 and 11.7 days on average, respectively. Bacterial coinfection was present in 55% of the cases. Mauad et al.[10] have described clinical, laboratory and histopathological findings of 21 fatal cases of influenza A (H1N1) infection occurred in Brazil. Diffuse alveolar damage, necrotizing bronchiolitis and alveolar hemorrhage were the main histopathological changes observed. Also, cytopathic effect was identified in the bronchi and epithelial cells in the alveoli, as well as necrosis, epithelial hyperplasia and squamous metaplasia in the trachea and bronchi. The authors have also demonstrated prominent TLR-3 and IFN-g expression, besides great accumulation of T CD8 cells and granzymes in the lung tissue. Such findings reinforce the hypothesis that an aberrant immune response could be responsible for the clinical and histopathological behavior presented by some patients with pneumonia caused by influenza A (H1N1).

Modern investigation techniques have demonstrated the hybrid etiology of community-acquired pneumonia in 35% of the cases, commonly involving bacteria and viruses[11]. Bacterial infections occurred in all fatal cases in the 1918 influenza A (H1N1) pandemic[8], and in 34% of the cases admitted to ICUs in the 2009 pandemic[5]. An analysis of 683 cases treated in 35 North-American intensive care units demonstrated that bacterial coinfection usually occurs in the first six days of symptoms onset. *Staphylococcus aureus, Streptococcus pneumoniae* and *Streptococcus pyogenes* were the main isolated pathogens[12]. Tasher et al.[13] have demonstrated greater incidence of invasive infections by *Streptococcus pyogenes* and *Staphlyococcus aureus*, regardless of age, and by *Streptococcus pneumoniae* in children infected by influenza A (H1N1) in the 2009 pandemic. Rice et al.[14] have demonstrated that bacterial coinfection in individuals affected by pneumonia caused by influenza H1N1 in the first 72 hours after admission to ICU is a factor of poor prognosis.

Usually, the infection by influenza A (H1N1) presents a more severe clinical course and a worse prognosis than that observed in cases of seasonal influenza. Radiography performed at hospital admission in patients with H1N1 infection reveals pneumonia in more than 40% of the cases. Approximately 10% to 30% of individuals hospitalized with H1N1 infection require admission to ICU and mechanical ventilation[6].

The utilization of neuraminidases inhibitors[15], when instituted at the first 48 hours of symptoms, demonstrated to be advantageous as compared with those cases where therapy was late initiated more than 48 hours after symptoms onset[16]. According to data from the CDC[17], 98.6% of the H1N1-2009 viruses were sensitive to oseltamivir, and 100% to zanamivir. Additionally, 100% of the influenza A (H3N2) tested strains were sensitive to both drugs. Both H1N1 and H3N2 demonstrated high resistance against amantadine and rimantadine[17].

Studies approaching the characterization of tomographic patterns in pneumonias caused by influenza A (H1N1) are usually observational and retrospective, comprising reviews, case reports and small series[18–20]. New prospective and controlled studies are necessary for a better characterization of the findings and to define their clinical applicability. Considering the superiority of therapeutics with neuraminidase inhibitors over the influenza virus when the treatment is instituted within the first 48 hours from symptoms onset, it is possible to assume that the tomographic findings may differ between the groups with early and late treatment institution. Although the influenza A virus may isolatedly cause diffuse al-

veolar damage, hemorrhage and edema, which are responsible for the described tomographic changes, the bacterial coinfection that is present in many such cases is a puzzling variable in the interpretation of such findings. Considering the low accuracy of the criteria which would allow the differentiation of pulmonary changes associated with these etiologies (virus and bacteria), the tomographic characterization of pulmonary infection supposedly caused by the influenza A (H1N1) virus isolatedly, if not judiciously utilized, may result in therapeutic omission as monotherapy with neuraminidase inhibitors is prescribed without association with the required antibacterial coverage. Further studies with a higher number of immunocompetent and immunocompromised individuals, either with or without HIV, could demonstrate eventual distinctive findings according to the condition presentations. The definition and validation of tomographic severity scores, when applicable to clinical and laboratory parameters might constitute important allies in the management of the cases. Finally, in order to be able to uniformly characterize the tomographic patterns, it would be desirable to prospectively and systematically establish a technical standardization for the performance of exams, comprising types of equipment, slice thickness (1 mm), inclusion of images at inspiratory and expiratory apnea, as well as standards for images interpretation taking intra- and interobserver variations into account.

The review article published by Amorim et al.[21] in the present issue of **Radiologia Brasileira** is very much welcome, as it allows for the expansion and sedimentation of the knowledge on tomographic patterns in pulmonary infections caused by influenza A (H1N1), and for stimulating the discussion and the development of further studies to shed light on some still unresponded questions pointed above.

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